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CLINICAL RESEARCH
Epidemiology and prevention

SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe

SCORE2 working group and ESC Cardiovascular risk collaboration

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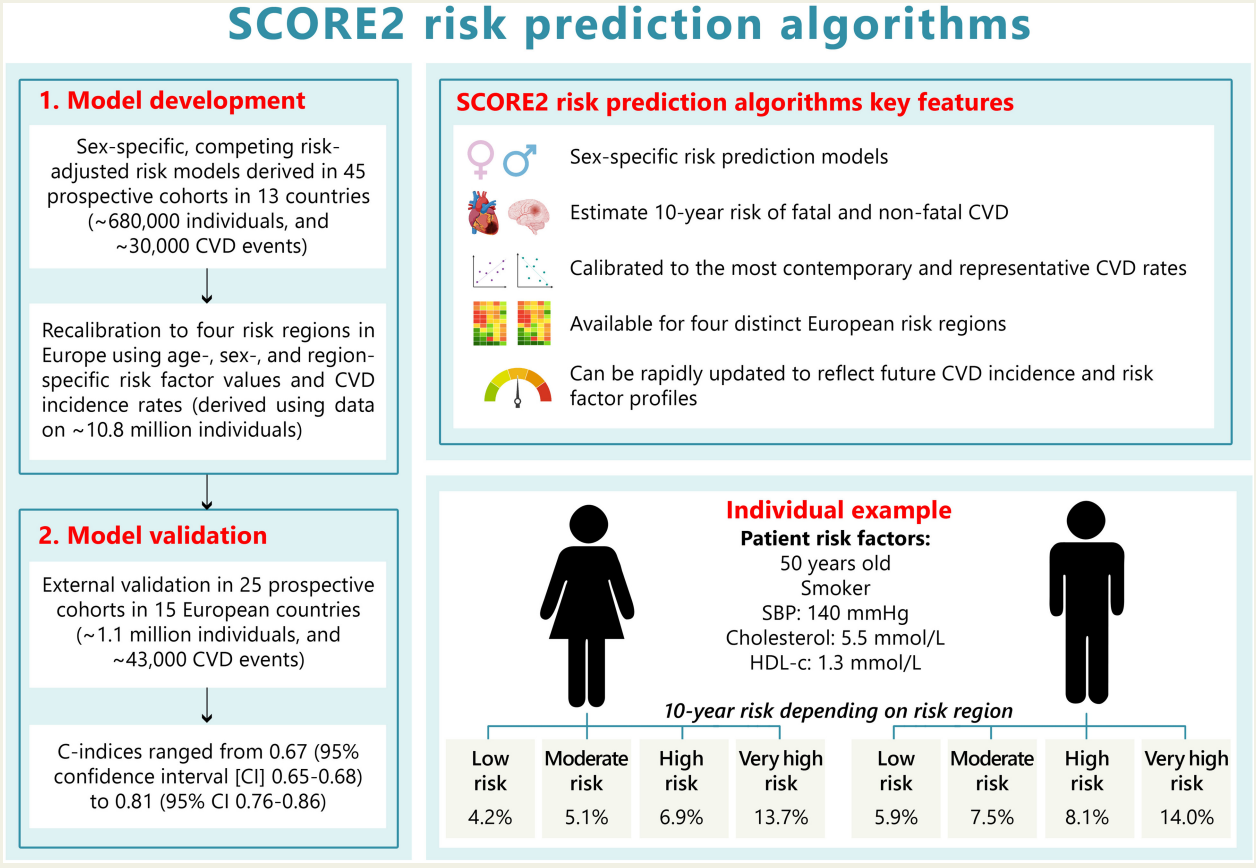
Aims The aim of this study was to develop, validate, and illustrate an updated prediction model (SCORE2) to estimate 10-year fatal and non-fatal cardiovascular disease (CVD) risk in individuals without previous CVD or diabetes aged 40–69 years in Europe.

Methods and results We derived risk prediction models using individual-participant data from 45 cohorts in 13 countries (677 684 individuals, 30 121 CVD events). We used sex-specific and competing risk-adjusted models, including age, smoking status, systolic blood pressure, and total- and HDL-cholesterol. We defined four risk regions in Europe according to country-specific CVD mortality, recalibrating models to each region using expected incidences and risk factor distributions. Region-specific incidence was estimated using CVD mortality and incidence data on 10 776 466 individuals. For external validation, we analysed data from 25 additional cohorts in 15 European countries (1 133 181 individuals, 43 492 CVD events). After applying the derived risk prediction models to external validation cohorts, C-indices ranged from 0.67 (0.65–0.68) to 0.81 (0.76–0.86). Predicted CVD risk varied several-fold across European regions. For example, the estimated 10-year CVD risk for a 50-year-old smoker, with a systolic blood pressure of 140 mmHg, total cholesterol of 5.5 mmol/L, and HDL-cholesterol of 1.3 mmol/L, ranged from 5.9% for men in low-risk countries to 14.0% for men in very high-risk countries, and from 4.2% for women in low-risk countries to 13.7% for women in very high-risk countries.

Conclusion SCORE2—a new algorithm derived, calibrated, and validated to predict 10-year risk of first-onset CVD in European populations—enhances the identification of individuals at higher risk of developing CVD across Europe.

Graphical Abstract



Development process, key features and illustrative example of the SCORE2 risk prediction algorithms for European populations.

Keywords Risk prediction • Cardiovascular disease • Primary prevention • 10-year CVD risk

Introduction

Cardiovascular diseases (CVD), which include coronary heart disease and stroke, are the most common fatal non-communicable diseases globally, responsible for an estimated 18.6 million deaths in 2019.[1,2] Cardiovascular diseases remains a major cause of morbidity and mortality in Europe. The European Society of Cardiology (ESC) provides guidelines and advocates the use of risk prediction models to enhance healthcare and population-wide prevention.[3,4] Risk models, which integrate information on several conventional CVD risk factors, typically estimate individual risk over a 10-year period. The goal is to identify people at higher risk of CVD who should benefit most from preventive action.

The ESC has convened an effort to revise its recommended risk prediction algorithm, known as the Systematic COronary Risk Evaluation (SCORE) model,[5] to address inter-related needs. SCORE includes only fatal CVD outcomes, meaning it underestimates total CVD burden, which in recent decades has shifted towards non-fatal outcomes, especially for younger people.[1] SCORE does not allow for substantial variations of risk across countries from the same risk region, meaning it may mis-estimate risk in these circumstances. SCORE was developed from cohorts recruited before 1986 and has not been systematically 'recalibrated' (i.e. statistically adapted) to contemporary CVD rates, meaning it is not ideal for use in contemporary European populations. Finally, risk prediction models recommended for other global regions,[6,7] may not be readily applicable to European populations because they typically include risk factors not available in routine European data sources needed for risk model recalibration.[6,8–10]

To address these limitations, we provide the development, validation, and illustration of SCORE2 to estimate 10-year fatal and non-fatal CVD risk in individuals in Europe without previous CVD or diabetes aged 40–69 years.

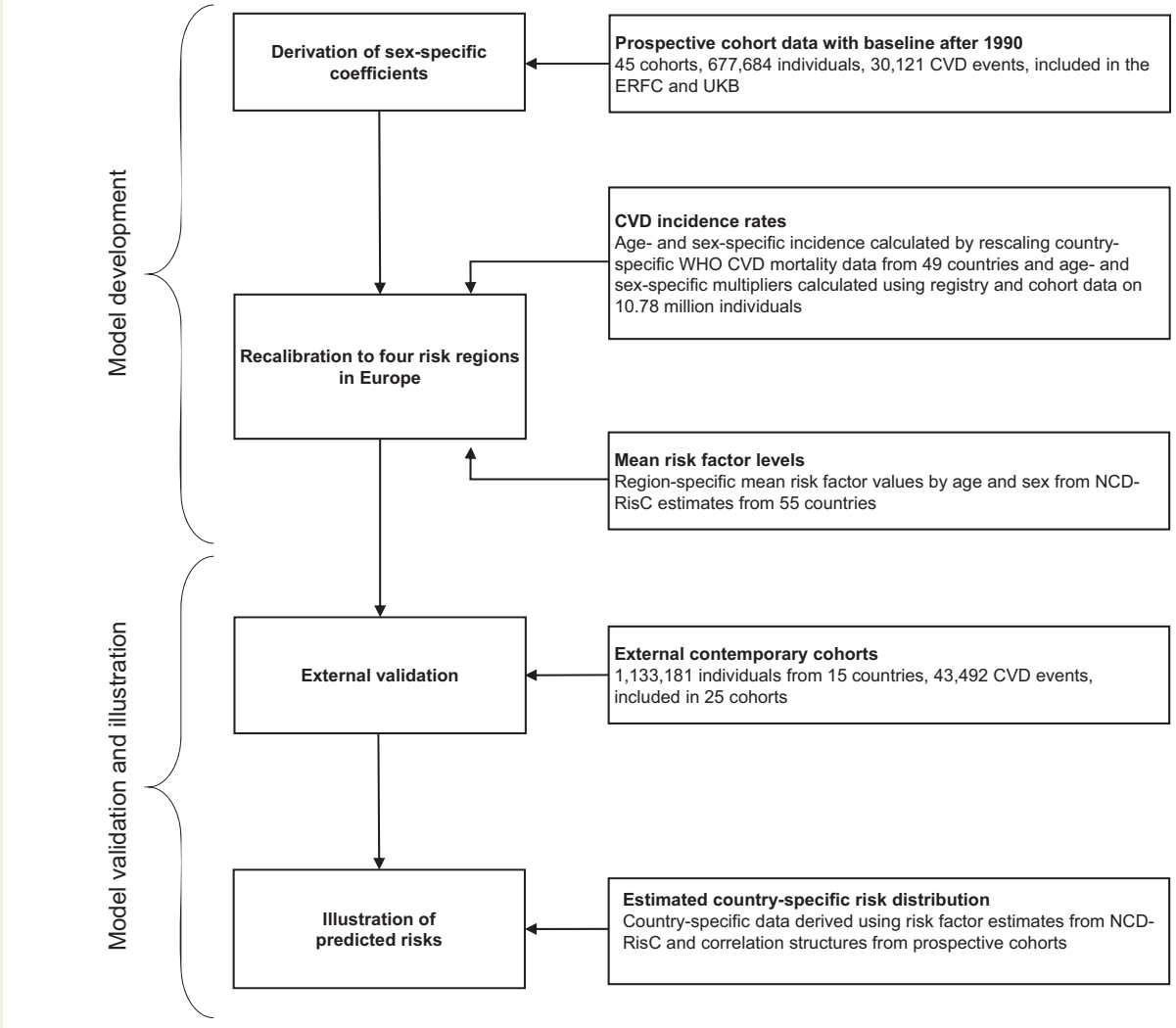
Methods

Study design

The SCORE2 project involved multiple data sources (*Figure 1*). First, to enable reliable estimation of age- and sex-specific relative risks, we derived prediction models for fatal and non-fatal CVD outcomes using individual-participant data from 45 prospective cohorts involving 677 684 participants in 13 countries. Second, to adapt risk prediction models to the circumstances of each European region, we recalibrated the derived risk models using estimated contemporary age- and sex-specific incidences and risk factor distributions. Third, to enhance validity and generalizability, we completed external validation using individual-participant data from a further 25 prospective cohorts (i.e. studies not in the model derivation) involving 1 133 181 individuals in 15 European countries. Fourth, to illustrate the variation of CVD risk across European regions, we applied the model to contemporary populations.

Data sources and procedures

For model derivation, we used individual-participant data from 44 cohorts included in the Emerging Risk Factor Collaboration (ERFC) and the UK Biobank (UKB).[11,12] The ERFC has collated and harmonized individual-participant data from many long-term prospective cohort studies of CVD risk factors and outcomes. Prospective studies in the ERFC were included in this analysis if they met all the following criteria: had recorded baseline information on risk factors necessary to derive risk prediction models (age, sex, smoking status, history of diabetes mellitus, systolic blood pressure, and total- and HDL-cholesterol); were approximately population-based [i.e. did not select participants on the basis of having previous disease (e.g. case-control studies) and were not active treatment arms of intervention studies]; had a median year of baseline survey after 1990; and had recorded cause-specific deaths and/or non-fatal CVD events (i.e. non-fatal myocardial infarction or stroke) for at least 1-year of follow-up. The UKB is a single large prospective cohort study with individual-participant data on approximately 500 000 participants aged



CVD, cardiovascular disease; ERFC, Emerging Risk Factors Collaboration; UKB, UK Biobank; WHO, World Health Organization; NCD-RisC, Non-Communicable Disease Risk Factor Collaboration

Figure 1 Study design.

>40 years recruited across 23 UK-based assessment centres during 2006–10, and followed-up for cause-specific morbidity and mortality through linkages to routinely available national datasets and disease-specific registers. Data selection for model derivation is shown in Supplementary material online, *Figure S1*. Details of contributing cohorts are provided in Supplementary material online, *Appendix S1* and *Table S1*.

For recalibration of models, we obtained country-specific CVD mortality rates reported by the World Health Organization (WHO),[13] and estimated fatal and non-fatal CVD incidences by using age- and sex-specific multipliers. Multipliers were derived in the Clinical Practice Research Datalink (CPRD),[14] the Finnish CVD register,[15] the Swedish population data (linked to the Swedish National Inpatient and cause of death registries),[16] the Estonian Biobank,[17] and the Health, Alcohol and Psychosocial factors In Eastern Europe (HAPPIEE) study.[18] Details of these data sources are provided in Supplementary material online, *Table S2* and *Appendix S1*. Age- and sex-specific risk factor values were obtained from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC).[19,20] The incidence rates predicted by the recalibrated models for low- and moderate-risk regions were then compared with 2018 incidence rates as reported in national registry data from the Netherlands, Denmark, UK, Germany, and Spain (Supplementary material online, *Table S3*).

For external validation of models, we included prospective cohort studies if they met the following criteria: did not contribute to the model derivation; met the same criteria as for the cohorts selected from the ERFC for the model derivation stage; and made individual-participant data available to our working group. The following consortia and individual studies were used for external validation: the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) project,[21] the Biomarker for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium,[22] the European Prospective Investigation into Cancer and Nutrition—cardiovascular disease (EPIC-CVD),[23] CPRD,[14] Heinz-Nixdorf Recall study (HNR),[24] Estonian Biobank,[17] HAPIEE study,[18] HUNT study,[25] DETECT study,[26] and Gutenberg Health Study (GHS).[27] Details of these cohorts are provided in the Supplementary material online, *Appendix S1* and *Table S4*.

The primary outcome was CVD, defined as a composite of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. The CVD mortality component of the primary outcomes corresponds to the endpoint definition of the original SCORE model and includes death due to coronary heart disease, heart failure, stroke, and sudden death.[5] Follow-up was until the first non-fatal myocardial infarction, non-fatal stroke, death, or end of the registration period. Deaths from non-CVD causes were treated as competing events. Details of the different ICD-10 codes included in both the fatal and non-fatal components of the endpoint are provided in Supplementary material online, *Table S5*.

Statistical analysis

Details of statistical analysis are provided in Supplementary material online, *Methods*. For model derivation, sex-specific associations [i.e. subdistribution hazard ratios (SHRs)] were estimated using Fine and Gray competing risk-adjusted models stratified by cohort. The sex-specific models included the following predictors: age, current smoking, history of diabetes mellitus, systolic blood pressure, and total- and HDL-cholesterol. The risk factors were selected due to their predictive ability as well as their availability in: derivation cohorts, target populations for screening, and population statistics needed for model recalibration. Since previous research showed that associations of these risk factors with CVD decline with increasing age, age-interactions were added for all predictors.[28] To maximize statistical power when estimating age-interactions, risk models were derived in participants aged 40–79 years at baseline without previous CVD. However, SCORE2 risk models are intended for use in people aged 40–69 years. In a parallel initiative, a risk score for individuals aged over 70, SCORE2-OP, has been developed using similar methods,[29] While the SCORE2 risk models are not intended for use in individuals with diabetes, participants with a history of diabetes were included at the model derivation stage (with appropriate adjustment for diabetes status), since it wasn't possible to exclude people with diabetes from population-level mortality statistics and risk factor data used in recalibration. There were no (or only very minimal) violations of the proportional hazards assumptions. Meta-regression was used to assess temporal and geographical heterogeneity.

Risk models were recalibrated to risk regions using age- and sex-specific mean risk factor levels and CVD incidence rates.[30] All European countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100 000 population (ICD 10 chapters IX, I00-I99).[13] The four groupings were low risk (<100 CVD deaths per 100 000), moderate risk (100 to <150 CVD deaths per 100 000), high risk (150 to <300 CVD deaths per 100 000), and very high risk (≥300 CVD deaths per 100 000) (Figure 2 and Supplementary material online, Table S6). Incidence rates were estimated by rescaling region-specific CVD mortality rates, by derived age-, sex-, and region-specific multipliers, estimated in contemporary representative cohorts from each region (Supplementary material online, *Table S2*). We assessed discrimination using external validation cohorts by calculating Harrell's C-index, adjusted for competing risks,[31] and in the case of EPIC-CVD weighting according to the case-cohort structure of the data.[32] Comparison of SCORE2 and SCORE in relation to discrimination and calibration was performed in CPRD, as the only nationally representative data source with both risk factor and outcome information available at the individual-participant level. To compare the proportion of the population at different levels of CVD event risk according to the SCORE2 models, predicted risk distributions were simulated using age- and sex-specific risk factor value means and prevalences from NCD-RisC and correlation structures observed in ERFC cohorts.

Approaches used to handle missing data are described in the Supplementary material online, *Methods*. We adopted analytical approaches and reporting standards recommended by the PROBAST guidelines[33] and TRIPOD.[34] Analyses were performed with R-statistic programming (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 15.1, StataCorp, College Station, TX, USA). The study was designed and completed by the SCORE2 Working Group in collaboration with the ESC Cardiovascular Risk Collaboration, the ERFC academic co-ordinating centre, and the MORGAM and BiomarCaRE co-ordinating centres. Data used for the current study are available upon reasonable request and approval of the individual cohorts or collaborative groups, please contact the individual cohorts used for the current study for details. Stata code for calculation of the SCORE2 algorithms is available on request from authors.

Results

Model derivation involved 677 684 participants from 45 cohorts without previous CVD recruited between 1990 and 2009. Mean age at recruitment was 57 (SD 9) years, 300 735 (44%) were male (*Table 1*). During median follow-up of 10.7 (5th, 95th percentile; 5.0, 18.6) years, a total of 30 121 CVD events and 33 809 non-CVD deaths were recorded. Subdistribution hazard ratios are shown in Supplementary material online, *Table S7*. The strength of associations of model predictors decreased with older age of participants (Supplementary material online, *Figure S2*). Associations of smoking and diabetes mellitus with CVD were stronger in women than men. Calibration and 'goodness of fit' for the prediction models were

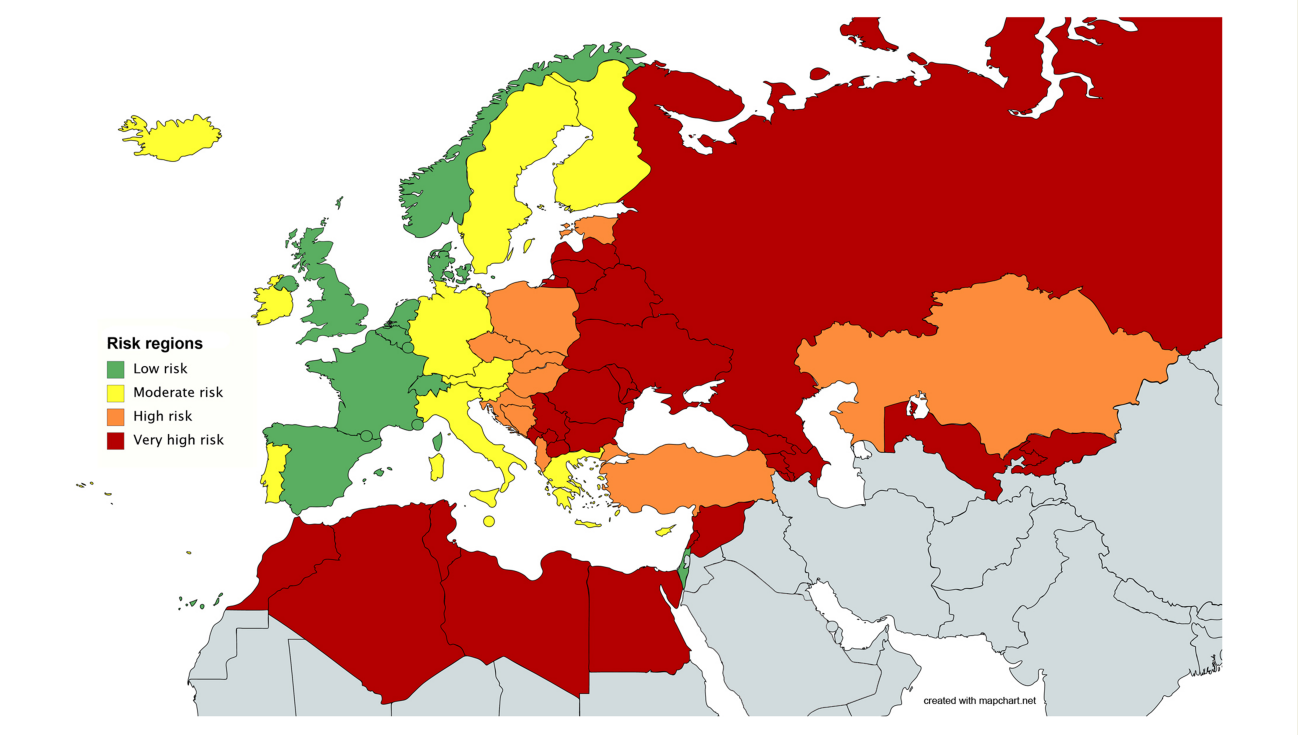


Figure 2 Risk regions based on standardised cardiovascular disease mortality rates. Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD chapters 9, I00-I99). The four groupings were: low risk (<100 CVD deaths per 100,000), moderate risk (100 to <150 CVD deaths per 100,000), high risk (150 to <300 CVD deaths per 100,000), and very high risk (≥300 CVD deaths per 100,000).

Table 1 Summary of available data used in SCORE2 risk model derivation

	N (%) or mean (SD)
Total participants	677 684
Male sex	300 735 (44%)
Age (years)	57 (9)
Current smoker	101 211 (15%)
Systolic blood pressure (mmHg)	136 (19)
Diabetes mellitus	31 413 (5%)
Total cholesterol (mmol/L)	5.8 (1.1)
HDL-cholesterol (mmol/L)	1.4 (0.4)
Follow-up (years, median (5th/95th percentile))	10.7 (5.0–18.6)
Cardiovascular events	30 121
Non-cardiovascular deaths	33 809

reasonable within the derivation dataset, both overall and in region-specific and in time period-specific analyses. The C-index in the derivation dataset was 0.739 (95% CI 0.736–0.741). Results were similar in sensitivity analyses that omitted UKB, or excluded studies with information only on fatal events (Supplementary material online, *Table S8*). Similar SHRs were also found in analyses of the MORGAM/BiomarCaRE consortium (Supplementary material online, *Table S9*).

Regional sex- and age-specific multipliers for conversion of CVD mortality rates to incidence rates involved 5 256 013 men and 5 520 453 women, with 731 265 CVD events recorded during follow-up (Supplementary material online, *Table S2*). Multipliers were similar over calendar time, and across different data sources within each risk region, but decreased with age, were somewhat greater in women than men, and were lower in the high-/very high-risk regions compared with low-/moderate-risk regions (Supplementary material online, *Table S10* and *Figures S3–S5*). Age- and sex-specific mean risk factor levels used for recalibration are presented by region in Supplementary material online, *Figure S6*. Age- and sex-specific 10-year mortality CVD rates and derived incidence rates are shown for each region in Supplementary material online, *Figures S7* and *S8*. After recalibration, the SCORE2 predicted risks based on mean risk factor levels showed good agreement with the estimated CVD event incidence (Supplementary material online, *Figure S9*) and with incidence rates obtained from external national registries (Supplementary material online, *Figure S10*).

The SCORE2 charts for CVD risk estimation in four European risk regions are shown in the *Figure 3*. For practical and presentational purposes, the charts are displayed according to non-HDL-cholesterol rather than total cholesterol and HDL-cholesterol. The estimated absolute risk for a given age and combination of risk factors differed substantially across regions. For example, the estimated 10-

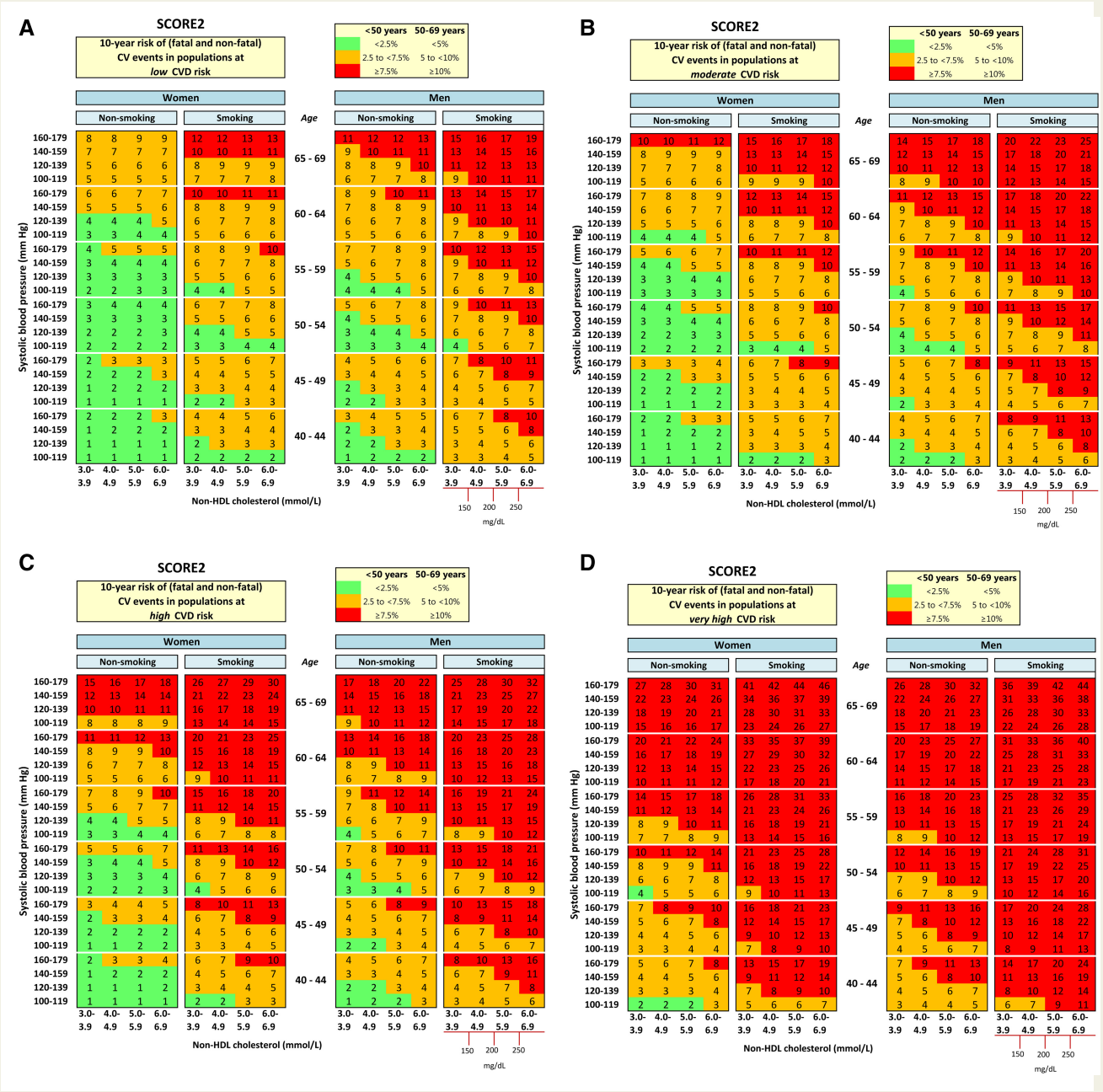


Figure 3 SCORE2 charts for estimation of CVD risk in four European risk regions.

year CVD risk for a 50-year-old male smoker and with a systolic blood pressure of 140 mmHg, total cholesterol of 5.5 mmol/L and HDL-cholesterol of 1.3 mmol/L, ranged from 5.9% in low-risk countries to 14.0% in very high-risk countries. Similarly, the 10-year risk for a 50-year-old woman with the same risk factor profile ranged from 4.2% in low-risk countries to 13.7% in very high-risk countries (Supplementary material online, *Figure S11*).

External validation of risk models involved calculation of C-indices using data from 1 133 181 individuals without previous CVD or diabetes in 25 prospective studies from 15 European countries (43 492 CVD events were observed). C-indices showed moderate-to-good discrimination in all regions (*Figure 4*), with cohort-specific values ranging from 0.67 (0.65–0.68) to 0.81 (0.76–0.86). In comparison to SCORE, SCORE2 improved overall risk discrimination (difference in C-index: 0.0100, 95% CI 0.0085, 0.0115; $P < 0.001$), particularly at younger ages (difference in C-index at ages 40–50 years: 0.0213, 95% CI 0.0162, 0.0265; $P < 0.001$), and for non-fatal CVD outcomes (difference in C-index: 0.0113, 95% CI 0.0097, 0.0130; $P < 0.001$; Supplementary material online, *Tables S11* and *S12* and *Figure S12*). Removing the contribution of total and HDL-cholesterol from SCORE2 model reduced C-index by 0.0078 (95% CI 0.0064, 0.0091), providing context for the C-index improvement of 0.01 observed in using SCORE2 rather than SCORE. To directly compare SCORE and SCORE2, we converted fatal CVD

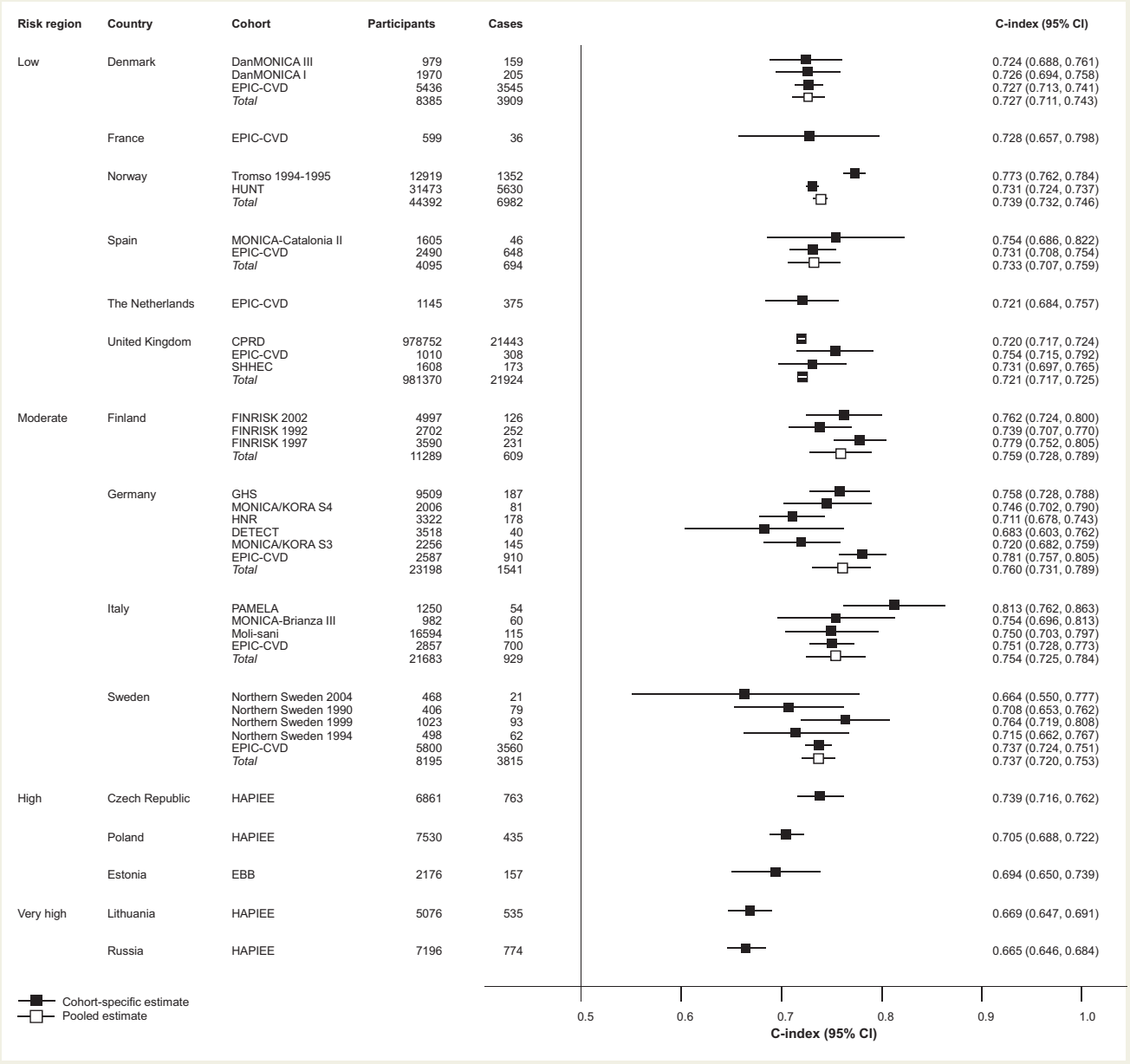


Figure 4 C-index upon assessing ability of the SCORE2 model to discriminate cardiovascular disease in external validation cohorts.

risk estimated using SCORE to fatal and non-fatal CVD risk using the approach recommended by the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias (i.e. to multiply estimates by 3 in men and by 4 in women), showing SCORE2 outperformed SCORE by avoiding over-estimation of risk (Supplementary material online, *Figure S13*) and by appropriately classifying as high-risk individuals with higher observed lifetime CVD risk (Supplementary material online, *Figure S14*).

When we applied recalibrated SCORE2 models to simulated data representing populations from each risk region, the proportion of individuals aged 40–69 years with an estimated risk greater than 10% varied by region, from 3.4% in the low-risk region to 51% in the very high-risk region in men and from 0.1% to 32%, respectively, in women, with these proportions increasing with age, as would be expected (*Figure 5* and Supplementary material online, *Figure S15*).

Discussion

We have developed SCORE2, an updated algorithm tailored to European populations to predict 10-year risk of first-onset CVD (*Graphical Abstract*). By updating SCORE in several aspects, the use of SCORE2 will enhance the identification of individuals at higher risk of developing CVD across Europe.

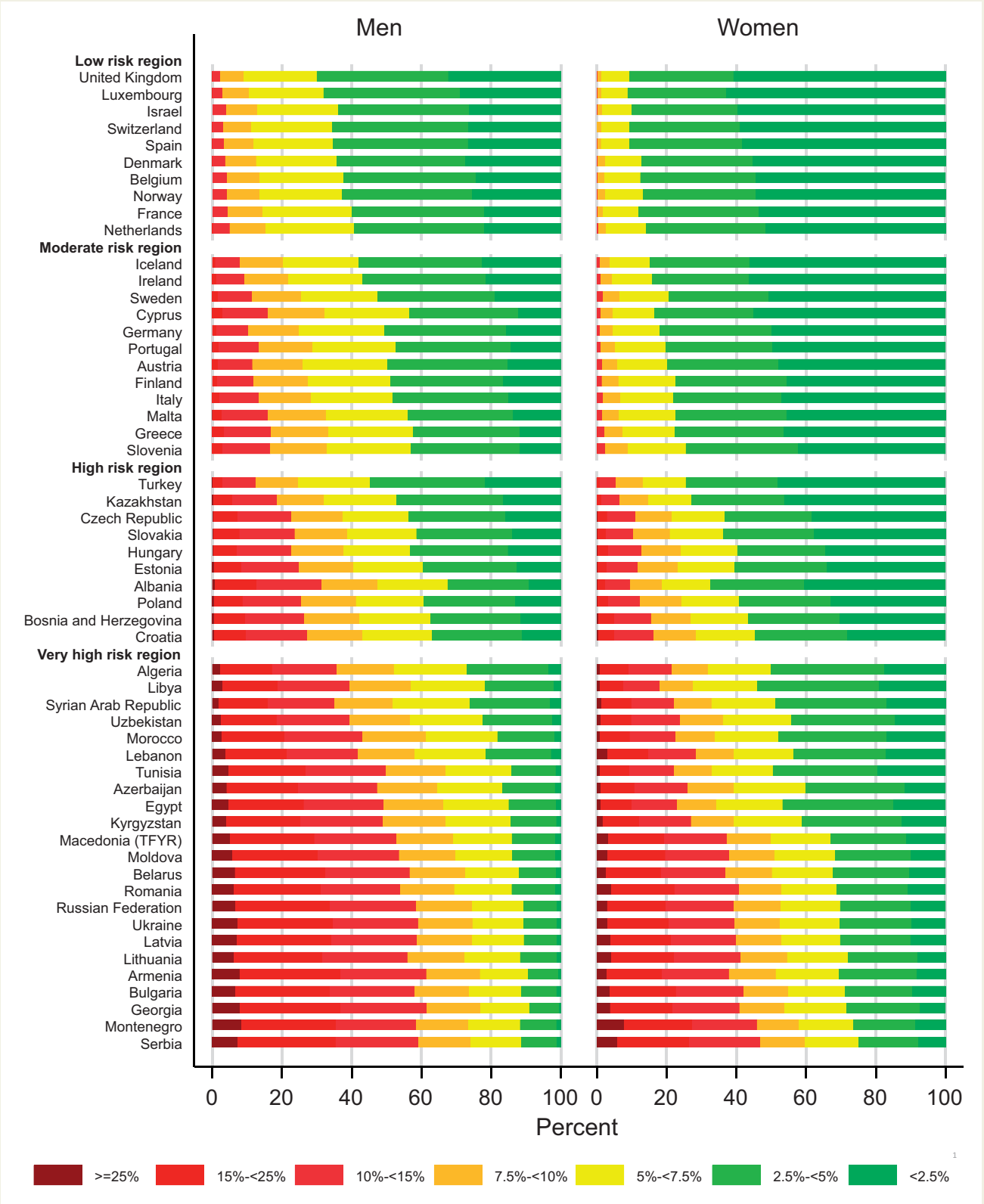


Figure 5 Distribution of 10-year cardiovascular disease risk according to recalibrated SCORE2 models across European countries. The proportion of individuals expected in each risk category was estimated to reflect the age-group and sex-specific risk factor values and specific population structure of each country (Supplementary material online, *Methods 1.3*).

First, SCORE2 provides risk estimates for the combined outcome of fatal and non-fatal CVD events, in contrast with SCORE's use of CVD mortality only. Furthermore, SCORE2 has been systematically recalibrated, using the most contemporary and representative CVD rates available, whereas the original SCORE model was based on data collected before 1986. Although it would have been possible to recalibrate SCORE to contemporary CVD mortality rates, CVD mortality-only risk models underestimate total risk, particularly when the case-fatality rates are lower (as in younger individuals). Our results suggest that SCORE2 better estimates the total burden of CVD, particularly among younger individuals, as well as showing better risk discrimination, than SCORE.

Second, SCORE2 accounts for the impact of competing risks by non-CVD deaths whereas SCORE did not do so. This statistical adjustment prevents over-estimation of CVD risk and over-estimation of the benefit of treatment in populations where the risk of competing non-CVD deaths is high. For example, this adjustment should predominantly benefit treatment decisions in older individuals, and those from high- or very high-risk regions.

Third, the recalibration of SCORE2 to four distinct European regions defined by varying CVD risk levels improves on the two-level regional stratification provided by SCORE.[5] Furthermore, as the recalibration used for SCORE2 avoids reliance on sparse cohort or country-level data, it provides recalibrated calculators tailored to sex-specific CVD rates and risk factor levels of each region. Because the recalibration approach we used is based on registry data, the model can be readily updated to reflect future disease CVD incidence and risk factor profiles of any target population of apparently healthy individuals to be screened.[28,29] This means that if descriptive age- and sex-specific epidemiological data are available from individual European countries (or within-country regions), they can be readily incorporated to revise models at a country level.[4]

Fourth, the derivation, calibration, validation, and illustration of SCORE2 have been underpinned by exceptionally powerful, extensive, and complementary datasets of contemporary relevance to European populations. These features enhance the accuracy, generalizability, and validity of the approach. In particular, SCORE2 was developed using data on a total of more than 12.5 million individuals from dozens of countries.

Fifth, our project illustrated the performance of SCORE2 with data estimated from all European countries, showing that the proportions of individuals in specific risk categories seem to differ across countries. This diversity highlights why policymakers and practitioners need tailored tools like SCORE2 to help make more appropriate and locally informed decisions about the allocation of prevention resources.

The potential limitations of this effort merit consideration. We derived risk prediction models from 45 cohorts, mostly in European regions and populations at low- or moderate-risk CVD risk. Ideally, however, the derivation of risk models for use in high and very high-risk countries would have involved large nationally representative, prospective cohorts in these countries, coupled with prolonged follow-up and validation of fatal and non-fatal CVD endpoints. Unfortunately, such data do not yet generally exist. Indeed, even in low- and moderate-risk regions, the cohorts involved may not be nationally representative, reflecting past periods of time or self-selected participants such as healthy volunteers.[35] While healthy volunteer bias can lead to low estimates of absolute risk, relative risks are generally unaffected.[36] Furthermore, our approach makes the assumption that the relative risks obtained in the derivation dataset are transferable across different populations, as evidenced by broadly similar relative risk and good discrimination in external validation populations in all regions. We then recalibrated models using nationally representative incidence rates from all regions, an important step not commonly considered by other CVD risk scores, avoiding the limitations of mis-calibration provided by potentially non-representative incidence rates in cohort studies.[6,8,9]

Data on medication use, family history, socio-economic status, nutrition, physical activity, renal function, or ethnicity were not available in cohorts and registries used for model derivation and recalibration. Hence, interpretation of SCORE2 estimates may require clinical judgement, especially for individuals in whom these factors may be relevant (e.g. those taking lipid or blood pressure-lowering treatments,[37] with a family history of CVD,[38] with chronic kidney disease,[39] or in at-risk socio-economic and ethnic groups[38]). In addition, some individuals in our model derivation cohorts may have initiated preventative treatment (e.g. statin) during follow-up and accounting for this could improve model calibration and discrimination. However, previous analyses have suggested that inclusion of information on statin-initiation during follow-up provides only limited clinical and public health benefit.[40] We did not compare the performance of SCORE2 models with other risk equations already developed for use in specific high-income countries because these equations contain variables often not available in European datasets used for derivation and recalibration. However, previous analyses have suggested that only minor differences exist in risk discrimination among guideline-recommended risk prediction models. In contrast, the clinical performance of risk prediction models depends importantly on differing ability to predict the correct level risk in the target population (i.e. extent of 'calibration').[30] We, therefore, ensured SCORE2 was well-calibrated to current absolute risk levels for each European region by adapting the model to contemporary CVD incidence rates. We did not assess calibration of SCORE2 in our external validation cohorts other than the large nationally representative dataset from the CPRD, because these cohorts do not necessarily reflect contemporary absolute risk levels across European regions. We did not include diabetes as a risk predictor in SCORE2 as individuals with diabetes are generally considered at high risk of CVD (and, therefore, automatically eligible for statin medications and other preventive interventions), and specific risk scores already exist for this population.[41,42] For individuals over the age of 70, a separate risk score, SCORE2-OP, has been derived and published in parallel with the SCORE2 initiative using similar methods.[29] The SCORE2-OP risk estimation can be used as a continuum to the SCORE2 estimates. However, some small differences may be expected when estimating risks in individuals around the age of 70 years.

To recalibrate SCORE2 to the target European populations, we used CVD mortality rates provided by the WHO, rescaled to estimate CVD event incidence rates, based on multipliers derived from representative cohort studies or national registries from three of the four risk regions we defined in Europe. For the very high-risk region, we did not have suitable data for deriving the multipliers, and

therefore applied the same multipliers as for the high-risk region. Our approach assumes that CVD mortality rates provided by WHO are representative of each country, and that multipliers are valid across countries within the same region, an assumption that is difficult to test due to the lack of available incidence data in particular in the high- and very high-risk regions. However, we observed that multipliers were similar across available studies from the same region and over calendar time, suggesting that they are stable despite differences in CVD event rates. Furthermore, estimated CVD rates agreed well with national incidence rates from available independent external registries. Our risk models might have underestimated CVD risk because data used to estimate multipliers were likely to include some people already on CVD prevention therapies (e.g. statins or antihypertensive medication), but available data were insufficient to evaluate this possibility. As we have not evaluated SCORE2 in non-European populations, its value in such settings is not entirely known. Finally, further studies should assess the value of longer-term risk prediction (especially in younger individuals),[40] understand barriers to implementations,[43] and define the role of using CVD risk prediction models in primary CVD prevention.[44,45]

In summary, SCORE2, a new algorithm derived, calibrated, and validated to predict 10-year risk of first-onset CVD in European populations, enhances the identification of individuals at higher risk of developing CVD across Europe.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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*The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Appendix

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