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Risk prediction of cardiovascular disease in the Asia-Pacific region: the SCORE2 Asia-Pacific model

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Abstract

Background and Aims To improve upon the estimation of 10-year cardiovascular disease (CVD) event risk for individuals without prior CVD or diabetes mellitus in the Asia-Pacific region by systematic recalibration of the SCORE2 risk algorithm.

Methods The sex-specific and competing risk-adjusted SCORE2 algorithms were systematically recalibrated to reflect CVD incidence observed in four Asia-Pacific risk regions, defined according to country-level World Health Organization age- and sex-standardized CVD mortality rates. Using the same approach as applied for the original SCORE2 models, recalibration to each risk region was completed using expected CVD incidence and risk factor distributions from each region.

Results Risk region-specific CVD incidence was estimated using CVD mortality and incidence data on 8 405 574 individuals (556 421 CVD events). For external validation, data from 9 560 266 individuals without previous CVD or diabetes were analysed in 13 prospective studies from 12 countries (350 550 incident CVD events). The pooled C-index of the SCORE2 Asia-Pacific algorithms in the external validation datasets was .710 [95% confidence interval (CI) .677–.744]. Cohort-specific C-indices ranged from .605 (95% CI .597–.613) to .840 (95% CI .771–.909). Estimated CVD risk varied several-fold across Asia-Pacific risk regions. For example, the estimated 10-year CVD risk for a 50-year-old non-smoker, with a systolic blood pressure of 140 mmHg, total cholesterol of 5.5 mmol/L, and high-density lipoprotein cholesterol of 1.3 mmol/L, ranged from 7% for men in low-risk countries to 14% for men in very-high-risk countries, and from 3% for women in low-risk countries to 13% for women in very-high-risk countries.

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Conclusions The SCORE2 Asia-Pacific algorithms have been calibrated to estimate 10-year risk of CVD for apparently healthy people in Asia and Oceania, thereby enhancing the identification of individuals at higher risk of developing CVD across the Asia-Pacific region.

Structured Graphical Abstract

Key Question

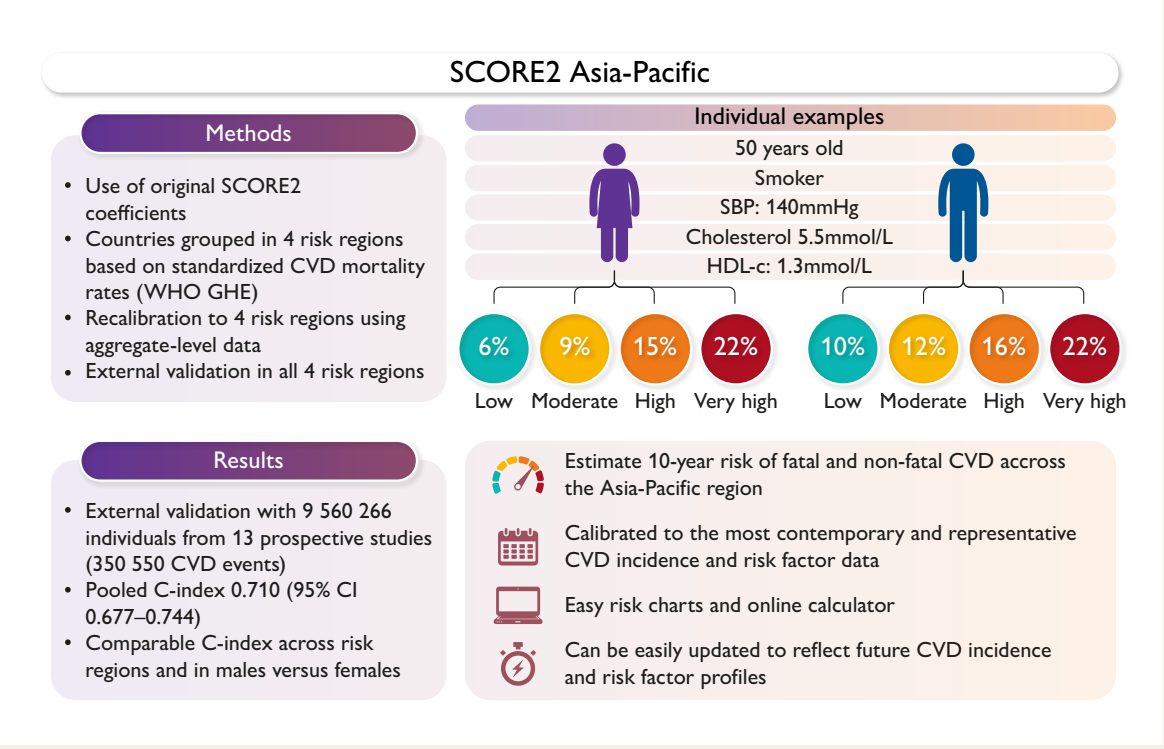
How can the estimation of 10-year cardiovascular disease (CVD) event risk for individuals without prior cardiovascular disease or diabetes be improved in the Asia-Pacific region?

Key Finding

The SCORE2 algorithms were recalibrated to reflect sex-specific and risk-adjusted CVD incidence in four Asia-Pacific regions, achieving a pooled C-index of 0.710. Risk varied significantly across regions, highlighting regional differences in CVD risk profiles.

Take Home Message

The recalibrated SCORE2 Asia-Pacific algorithms enhance the identification of individuals at high risk for CVD, enabling better-targeted prevention strategies across the Asia-Pacific region.



Example of the SCORE2 Asia-Pacific model recalibrated to all four risk regions in the Asia-Pacific region, highlighting regional differences in cardiovascular disease (CVD) risk profiles. HDL-c, high-density lipoprotein cholesterol; SBP, systolic blood pressure; WHO GHE, World Health Organization's Global Health Estimates.

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

Introduction

Cardiovascular diseases (CVDs), 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] Guidelines recommend the use of risk prediction models to enhance healthcare and population-wide prevention. These models integrate information on several CVD risk factors and typically estimate individual risk over a 10-year period. The goal is to identify people at higher risk of CVD who benefit most from preventive action. In 2021, the Systematic COronary Risk Evaluation 2 (SCORE2) was published and implemented in the 2021 European Society of Cardiology (ESC) CVD prevention guidelines.[2,3] Improvements of the SCORE2 algorithms in comparison to its predecessors include competing risk adjustment and systematic recalibration using aggregate data.

While age-adjusted CVD mortality rates are higher in many highly populated Asian countries in comparison to other parts of the world,[4] most CVD risk prediction algorithms have been developed and validated solely in Western countries.[5] Locally derived risk prediction models are not widely available and used, with a few exceptions, such as the CHINA-PAR risk model or the Japanese JALS risk score.[6,7] Risk prediction models developed in Western populations can provide useful tools for risk stratification in Asian populations, but first need recalibration (statistical adjustment) to reflect important differences in

risk factor distributions and CVD incidence patterns between Asian and Western populations. Adequate recalibration to the Asia-Pacific region's clinical practice is scarce, with the exception of the World Health Organization (WHO) risk charts and Globorisk.[8,9]

The aim of the current project is to recalibrate the SCORE2 risk algorithms, tailoring them to age- and sex-specific CVD incidence and risk factor distributions observed across the Asia-Pacific region. The recalibrated SCORE2 Asia-Pacific algorithms will provide a more accurate means of 10-year CVD risk estimation for individuals without prior CVD or diabetes mellitus in these populations.

Methods

Study design

The SCORE2 Asia-Pacific project involved multiple data sources (*Figure 1*). First, to adapt risk prediction models to each Asian region, the model was systematically recalibrated to several Asia-Pacific risk regions, using the same methods as have been used for the original SCORE2 recalibration. These methods were based on aggregate data on contemporary age- and sex-specific incidence and risk factor distributions.[2] Second, the external performance was assessed by performing external validation in individual-participant data using independent data sources from all Asia-Pacific risk regions. Third, to validate whether the original SCORE2 coefficients are appropriate for Asia-Pacific populations, the SCORE2 coefficients were compared to those of locally derived models. Fourth, the variation of CVD risk across Asia-Pacific regions was illustrated using data from contemporary populations. Last, to illustrate the variation of CVD risk in all Asian-Pacific countries, we applied the model to simulated data based on contemporary populations and local risk factor levels.

The SCORE2 Asia-Pacific algorithms use the coefficients as derived in the original SCORE2 algorithms.[2] As described in the SCORE2 paper, these coefficients were derived using individual-participant data from the 44 cohorts included in the Emerging Risk Factor Collaboration, and the UK Biobank.[10,11] The sex-specific, competing risk-adjusted algorithms included the following predictors: age, current smoking, history of diabetes mellitus, systolic blood pressure (SBP), and total and high-density lipoprotein (HDL)-cholesterol, as well as age-interactions for all included predictors to account for declining relative associations with CVD occurrence with increasing age.[9] 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 was not possible to exclude people with diabetes from population-level mortality statistics and risk factor data used in recalibration as these were only available on aggregate-level. Coefficients of predictors have been shown to be stable over time and geographic region.[9]

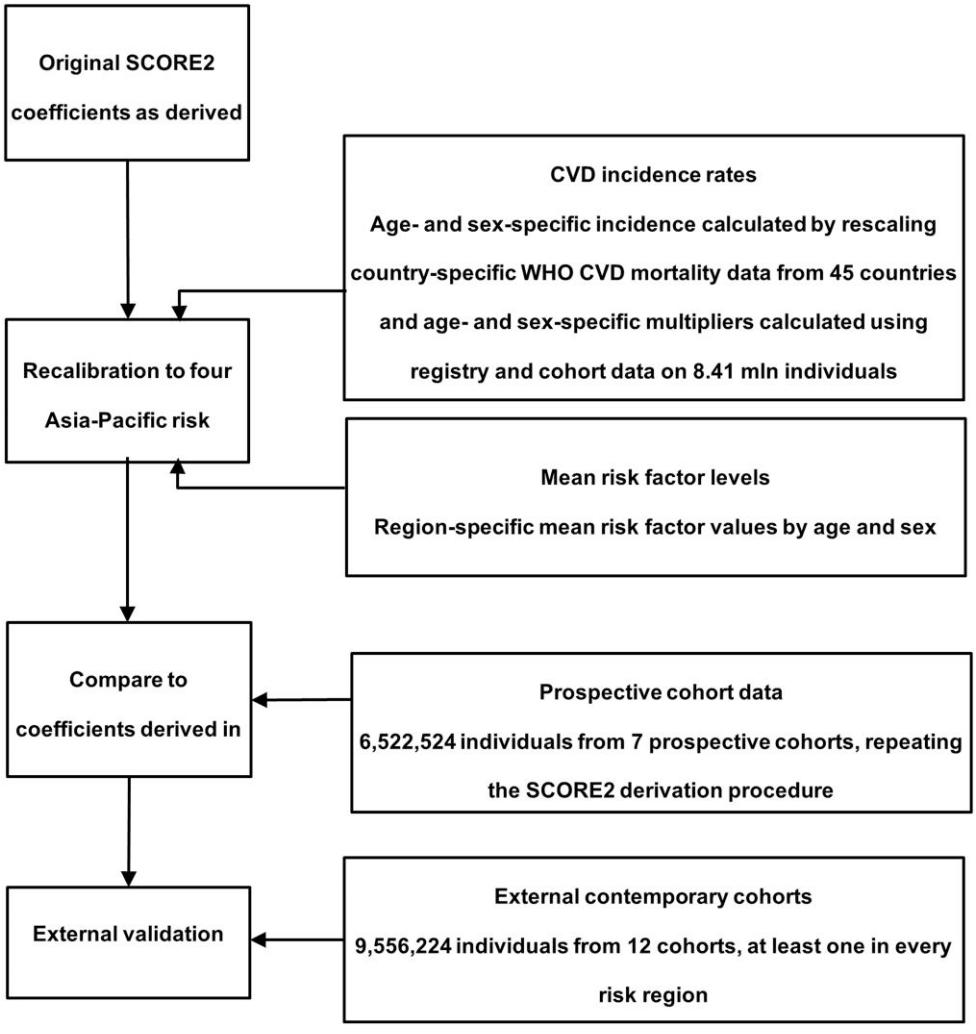


Figure 1 Study design

Data sources and procedures

For recalibration of the algorithms, we obtained country-specific CVD mortality rates reported by the WHO's Global Health Estimates (GHE) 2019,[12,13] and converted these to estimated fatal and non-fatal CVD incidence by using age- and sex-specific multipliers. Risk region-specific multipliers were obtained by combining the multipliers observed in the Singhealth dataset (Singapore), Korean National Health Insurance Service (NHIS) (South Korea)[14] the CHinese Electronic health Records Research in Yinzhou (CHERRY) study (China),[15] Brunei Healthcare Information Management System (BruHIMS) (Brunei Darussalam), and the Health Checks Ubon Ratchathani study (HCUR) (Thailand). Original SCORE2 multipliers were included in the modelling process to get more stable estimates of the multiplier's age-slopes (see Supplementary Methods).[16] Details of these data sources and methods are provided in Supplementary data online, *Table S1* and Supplementary data online, *Appendix S1*. Age-specific and sex-specific risk factor values (SBP, total and HDL cholesterol, diabetes prevalence, smoking status) were obtained from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC).[17,18] A visual representation of the underlying data and steps of the recalibration process are presented in Supplementary data online, *Figures S1–S5*.

For external validation of the algorithms, we included 12 independent data sources that did not contribute to the model derivation, although some sources contributed to multiplier derivation as part of the recalibration process as well as to the external validation. Details of the cohorts are provided in the Supplementary data online, *Appendix S1* and Supplementary data online, *Table S2*.[15,16,19–21]

In alignment with the original SCORE2 models, the target population is individuals aged 40–69 years without prior CVD or diabetes mellitus and the primary outcome estimated by the SCORE2 Asia-Pacific algorithms was defined as a composite of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke.[2] Cardiovascular disease mortality was defined as death due to coronary heart disease, heart failure, stroke, and sudden death.[22] Follow-up was until the first non-fatal myocardial infarction, non-fatal stroke, death, or end of the registration period. Deaths from non-CVD 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 data online, *Table S3*.

Statistical analysis

Details of statistical analysis and recalibration process are provided in Supplementary Methods. Risk models were recalibrated to risk regions using age- and sex-specific mean risk factor levels and CVD incidence rates.[23] All countries in the Asia-Pacific region were grouped into four risk regions according to their most recently reported WHO's GHE age- and sex-standardized overall CVD mortality rates per 100 000 population (ICD 10 chapters IX, I00–I99, *Figure 2*, Supplementary data online, *Table S4*).[12] Using the same cut-offs as the European SCORE2, 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). Incidence rates were estimated by rescaling region-specific CVD mortality rates, by applying age-, sex-, and region-specific multipliers, estimated in contemporary representative cohorts.

We assessed discrimination using external validation cohorts by calculating Harrell's C-index, adjusted for competing risks.[24] Comparison of SCORE2 Asia-Pacific and WHO risk charts (laboratory-based model)[9] was assessed using the respective regions for both algorithms. No direct comparison in terms of discrimination was made to the European SCORE2, as the recalibration of the model does not alter the model coefficients and has therefore little impact on the discrimination. The appropriateness of the original SCORE2 coefficients for use in the Asia-Pacific clinical practice was further validated by repeating the SCORE2 derivation process in several Asia-Pacific prospective cohort studies. The locally derived coefficients were visually compared to the original SCORE2 coefficients to identify any substantial geographical heterogeneity. This visual inspection aimed to detect clear patterns indicating potentially different predictor effects in Asian populations, which were not identified in prior risk scores, such as the WHO CVD risk charts.[9] We did not assess calibration in most of our external validation cohorts, as the incidence in the cohorts is likely not nationally representative, due to healthy participant bias or the fact that these are non-contemporary cohorts.[25] Therefore, model calibration was only assessed in cohorts deemed approximately nationally representative, which were the NHIS (South Korea), the NHG/NUHS health cluster (Singapore), the HCUR (Thailand), and BruHims (Brunei Darussalam). Calibration was assessed by plotting the predicted SCORE2 Asia-Pacific risk per 5-year age group vs. the observed cumulative CVD incidence as this best reflects our methods of recalibration. No formal statistical testing was performed on the calibration because the modified Nam–D'Agostino has no extension to the competing risk setting and because these tests are inherently power dependent. The calibration of the SCORE2 Asia-Pacific model was also compared to the calibration of the WHO CVD risk charts (laboratory-based version) using visual comparison in 5-year age groups.

To compare the proportion of the population at different levels of CVD event risk according to the SCORE2 Asia-Pacific algorithms, predicted risk distributions were simulated using age- and sex-specific risk factor value means and prevalences from NCD-RisC and risk factor correlation structures observed in NHIS cohort.

Approaches used to handle missing data are described in the Supplementary Methods. We adopted analytical approaches and reporting standards recommended by the PROBAST guidelines[26] and TRIPOD.[27] Analyses were performed with R-statistic programming (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 15.1, StataCorp, College Station, TX). The study was designed and completed by the SCORE2 Asia-Pacific Working Group in collaboration with the ESC Cardiovascular Risk Collaboration.

Results

Regional sex- and age-specific multipliers for conversion of CVD mortality rates to incidence rates including non-fatal events involved 8 405 574 individuals (556 421 CVD events, Supplementary data online, *Table S2*). Multipliers were somewhat higher in women than in men and decreased with age in a similar pattern as was seen for European multipliers.[2] Similarly, multipliers were lower in the higher risk regions compared to low/moderate-risk regions.

The SCORE2 Asia-Pacific charts for CVD risk estimation in four Asia-Pacific risk regions are presented in *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 as a result of recalibration. For example, the estimated 10-year CVD risk for a 50-year-old non-smoker, with a SBP of 140 mmHg, total cholesterol of 5.5 mmol/L, and HDL cholesterol of 1.3 mmol/L, ranged from 7% for men in low-risk countries to 14% for men in very-high-risk countries, and from 3% for women in low-risk countries to 13% for women in very-high-risk countries (see Supplementary data online, *Figure S6*). Given the same risk factor profiles, risks predicted by SCORE2 Asia-Pacific were generally higher in comparison to the original SCORE2 (see Supplementary data online, *Figure S7*).

There was no substantial geographical heterogeneity between the European SCORE2 coefficients and risk factor effects in Asian populations (see Supplementary data online, *Figure S8*). External validation of risk algorithms was completed using data from 9 560 266 individuals without previous CVD or diabetes in 13 prospective studies from 12 Asia-Pacific countries (350 550 CVD events were observed). C-indices showed moderate-to-good discrimination in all regions, with an overall pooled C-index of .710 [95% confidence interval (CI) .677–.744] (*Figure 4*).

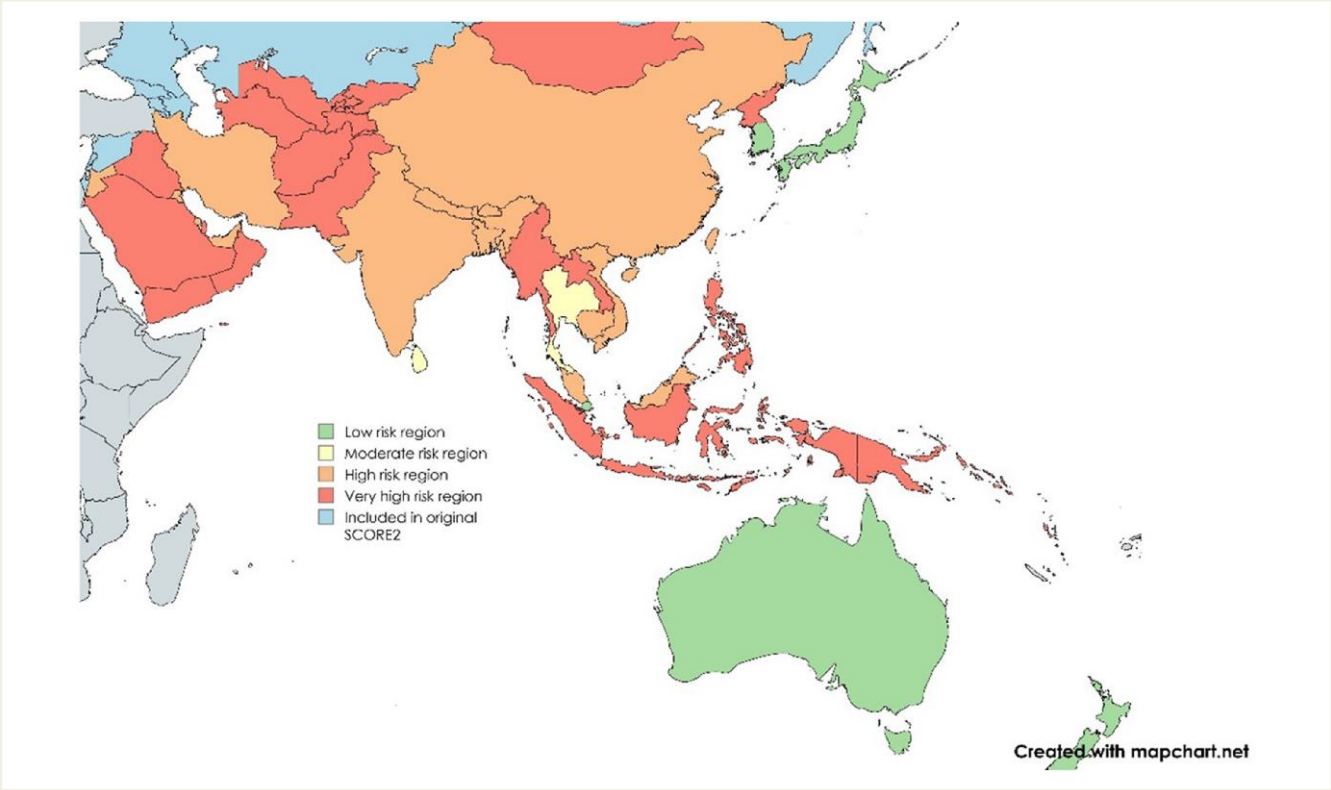


Figure 2 Risk regions based on age- and sex-standardized CVD mortality rates from the Global Health Estimates. Countries were grouped upon the most recently available age- and sex-standardized CVD mortality rates from the WHO GEH: low risk (<100 CVD deaths per 100 000), moderate risk (100 to <150 CVD deaths per 100 000), high risk (150 to <300 CVD deaths per 100 000), and very high risk (≥300 CVD deaths per 100 000). The SCORE2 Asia-Pacific writing group takes a neutral position regarding territorial claims in published maps and institutional affiliations

Cohort-specific C-indices ranged from .605 (95% CI .597–.613) to .840 (95% CI .771–.909). The C-index for the SCORE2 Asia-Pacific algorithms was broadly similar for men and women and in each of the four risk regions (see Supplementary data online, *Figures S9 and S10*). In comparison to the WHO CVD risk charts, SCORE2 Asia-Pacific showed comparable risk discrimination (difference in C-index: −.003, 95% CI −.034, .028) (see Supplementary data online, *Figure S11*). The calibration of the SCORE2 Asia-Pacific algorithms is shown in Supplementary data online, *Figure S12*. In NHG/NUHS from Singapore and HCUR from Thailand, the predicted risks matched the observed risks well, whereas in BruHims from Brunei Darussalam and NHIS from South Korea, predicted risks were higher than observed risks. Observed risks were best matched from the SCORE2 Asia-Pacific algorithms in the HCUR study, and in BruHims, the SCORE2 Asia-Pacific model overestimated and the WHO CVD risk charts underestimated the observed incidence. Both models had similar performance in the NHIS and NHG/NUHS studies (see Supplementary data online, *Figure S13*). Predicted risks from the SCORE2 Asia-Pacific model also generally better matched the observed incidence in comparison to the original SCORE2 model (see Supplementary data online, *Figure S14*).

When the recalibrated SCORE2 Asia-Pacific algorithms were applied to simulated data representing populations from each risk region, the proportion of individuals aged 40–69 years with an estimated risk >10% varied by region, from 38% in the low-risk region to 92% in the very-high-risk region in men and from .8% to 87%, respectively, in women, with these proportions increasing with age, as would be expected (*Figure 5*).

Discussion

In the current study, we present the SCORE2 Asia-Pacific 10-year CVD risk estimation algorithms, an adaptation of the SCORE2 algorithms to the region, sex-, and age-specific CVD incidence and risk factor characteristics of Asia-Pacific populations (*Structured Graphical Abstract*). The SCORE2 algorithms are the recommended CVD prediction model in the 2021 European guidelines on CVD prevention in clinical practice. By extending the SCORE2 algorithms to the Asia-Pacific population, we enhance the identification of individuals at higher risk of developing CVD across the Asia-Pacific region.

Several country-specific cardiovascular prediction models are being used in several Asia-Pacific countries, such as the China-PAR model or the Japanese JALS risk score.[6,7] In addition, the WHO CVD risk charts were recalibrated to several Asia-Pacific regions, which were mostly selected based on geographical location rather than expected CVD incidence as was used for SCORE2 Asia-Pacific. The WHO CVD risk charts consisted of a separate stroke and coronary heart disease endpoint, recalibrated separately, whereas the SCORE2 Asia-Pacific model had a simpler design using a single composite outcome. A direct comparison to the WHO CVD risk charts showed similar discriminatory performance of the SCORE2 Asia-Pacific algorithms, reflecting the largely similar derivation data and predictors and indicating that separate recalibration of the endpoints does not make a substantial difference to discrimination. Neither of the models had separate predictors for different stroke aetiologies. Future models could explore whether accounting for differences in stroke aetiology may improve prediction accuracy.

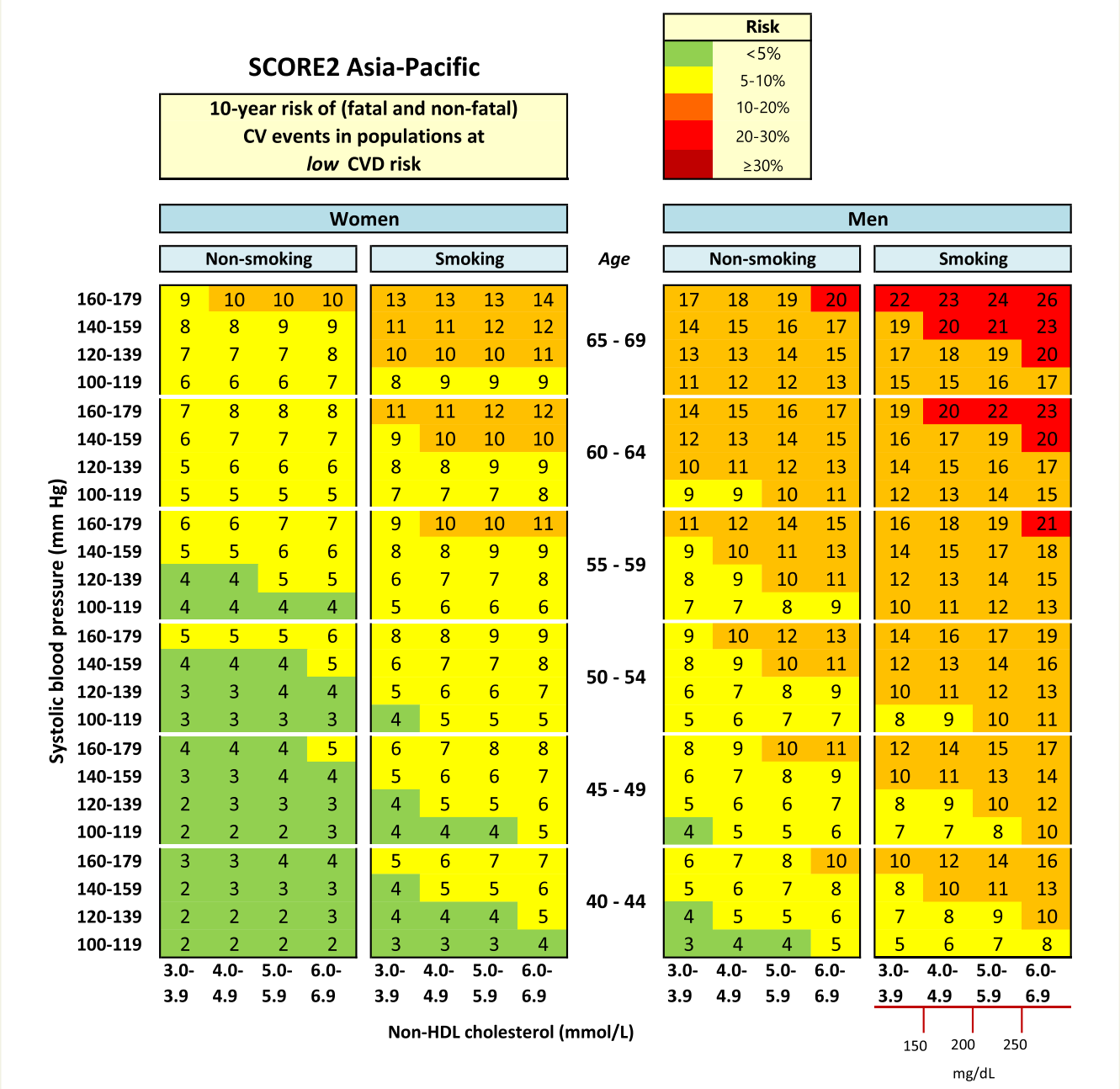


Figure 3 SCORE2 Asia-Pacific risk charts for the prediction of 10-year risk in four Asia-Pacific risk regions

In terms of calibration, the SCORE2 Asia-Pacific and WHO CVD risk charts had similar performance in two external validation data sources, whereas the SCORE2 Asia-Pacific model showed better calibration in the HCUR data. In the BruHims data, the SCORE2 Asia-Pacific model overestimated the predicted risks, whereas the WHO CVD risk charts underestimated the risks. A limitation of this data source is the follow-up duration of 7 years. Because people get older, risks are highest in the last part of the 10-year duration. Validation at 7 years may therefore have contributed to overestimation of CVD risks of the SCORE2 Asia-Pacific model. Another limitation in this dataset was the high number of missing data, which could be one explanation of diminished risk factors associations and low discrimination of both models. However, it is unclear in which direction this might affect model calibration.

The clinical performance of risk prediction models depends importantly on the differing ability to predict the correct level risk in the target population (i.e. extent of 'calibration').[23] Previous studies validating the European SCORE2 model in the Asia-Pacific region found that it overestimated risk in a Korean population and variably under- or overestimated risk in subgroups of Malaysian individuals.[28,29] Therefore, we ensured that the SCORE2 Asia-Pacific algorithms are now also well-calibrated in Asia-Pacific populations by adapting the SCORE2 algorithms to contemporary Asia-Pacific CVD incidence rates. With this, the SCORE2 Asia-Pacific model is the first model available that has been recalibrated to several regions that were grouped according to age standardized CVD mortality rates. On top of this, the SCORE2 Asia-Pacific has several other advantages in comparison to existing alternatives.

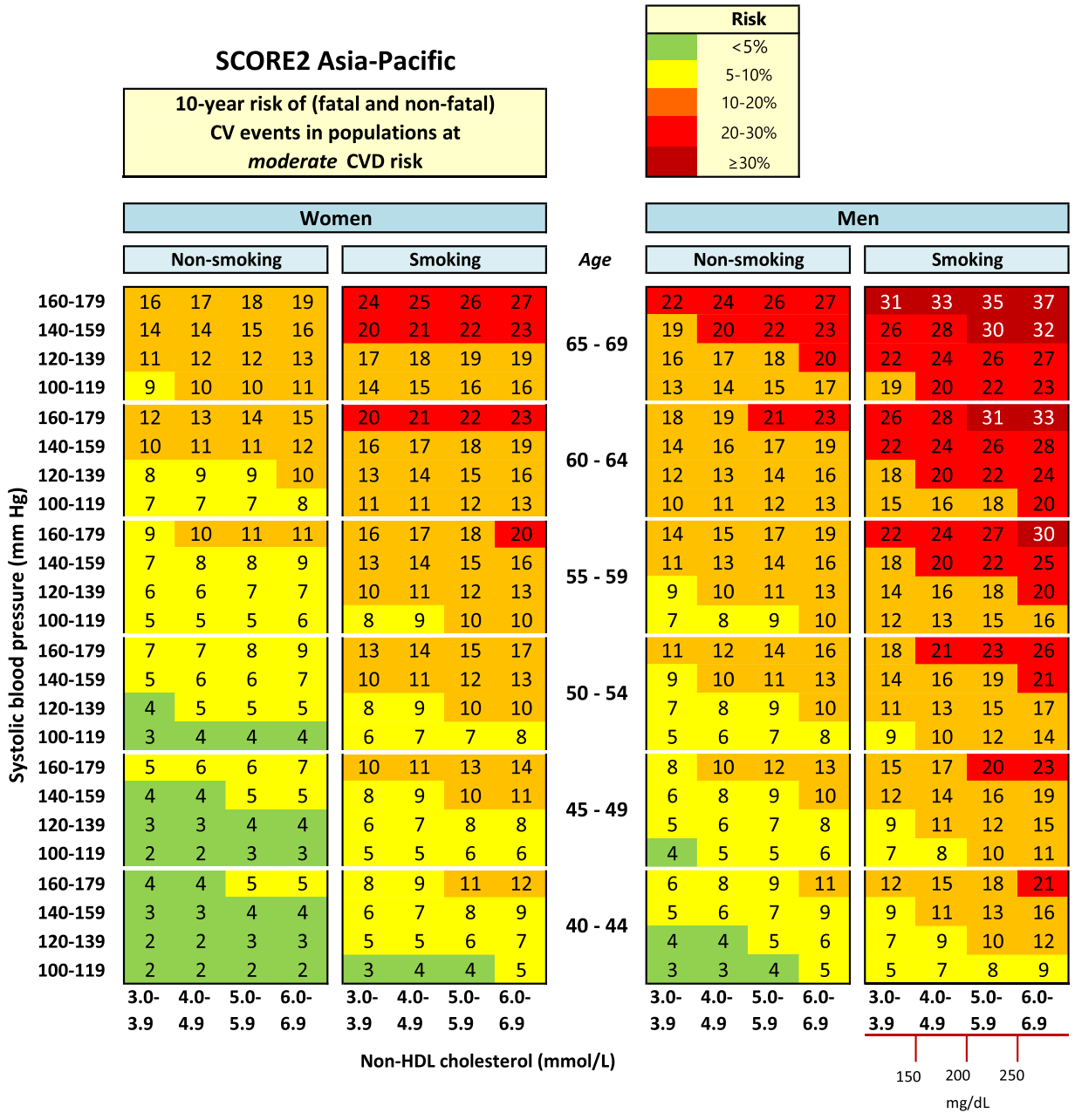


Figure 3 Continued

First, the SCORE2 Asia-Pacific model accounts for the impact of competing risks by non-CVD outcomes whereas most national Asia-Pacific risk scores as well as the WHO CVD risk charts did not do so. This statistical adjustment prevents overestimation of CVD risk and overestimation of the benefit of treatment in populations where the risk of competing non-CVD deaths is high.[24,30] For example, this adjustment should predominantly benefit treatment decisions in older individuals, and those from high- or very-high-risk regions.[30]

Second, SCORE2 Asia-Pacific has been systematically recalibrated to the Asia-Pacific clinical practice, using the most contemporary, powerful, and representative CVD rates available. The recalibration methods have previously been effectively applied within Europe and have now been repeated to adapt the model for Asia-Pacific populations, which ensures that the SCORE2 Asia-Pacific predicted risks are in line with the alarmingly high and rapidly changing CVD incidence.[1] Even though the same cut-offs in age- and sex-standardized CVD mortality rates were used to define the risk regions, SCORE2 predictions differed considerably between the respective risk regions in both continents. This further verifies that risk models may need to be adapted to the local situation, even if average levels of risk are similar as in places a model is currently recalibrated to.

Third, because the recalibration approach is based on registry data, the SCORE2 Asia-Pacific algorithms can be readily updated to reflect future CVD incidence and risk factor profiles of any target population of apparently healthy individuals to be screened.[2,23] This means that if descriptive age- and sex-specific epidemiological data

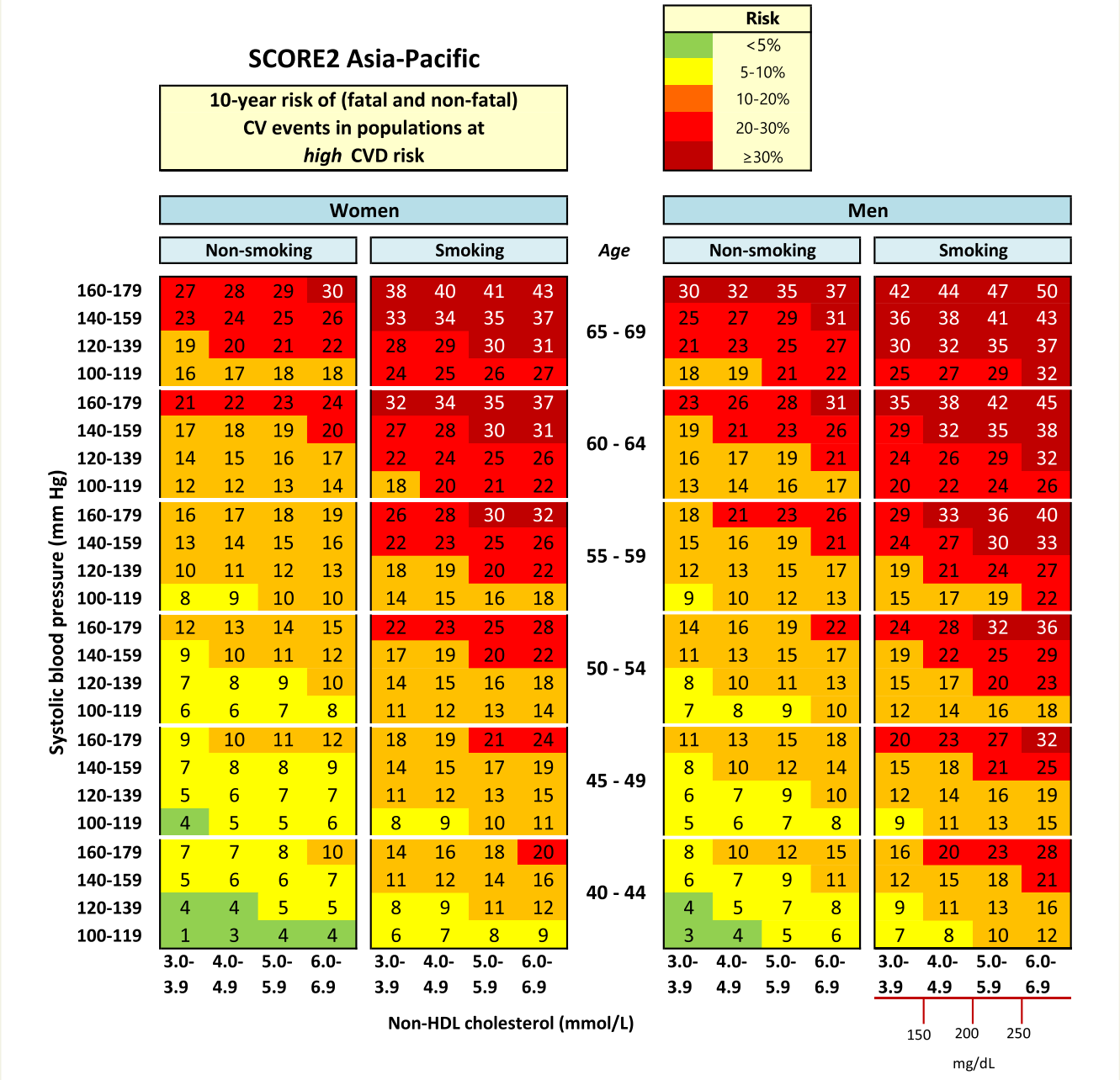


Figure 3 Continued

are available from individual countries, they can be readily incorporated to revise models at a country-level. The calibration results of the SCORE2-Asia model in the low-risk region illustrate that within-region differences still exist after the region-specific recalibration, implying that further improvement can be obtained from country-specific recalibration. Especially for large countries with substantial within-country variation, a country-level approach would still not capture the complete geographical variation of incident CVD.[31] The current recalibration approach would be suitable to recalibrate the model to within-country areas, even up to the neighbourhood level. This requires, however, high-quality data on CVD risk factors and incidence for the intended regions to ensure adequate calibration of risk algorithms.

Similar to the European SCORE2, SCORE2 Asia-Pacific can be used in a simplified form via the two-dimensional risk charts as provided in *Figure 3*. However, to accommodate more accurate predictions that do not require rounding to broad categories of CVD risk factors, the SCORE2 Asia-Pacific algorithms will be integrated into online calculators, such as the ESC CVD risk prediction app or the CE-marked U-Prevent medical device, available from www.U-Prevent.com. Because of the time required for implementation into a CE-marked medical device, the SCORE2 Asia-Pacific algorithms are integrated in an R-shiny app for scientific purposes only (i.e. not for clinical use) from https://hagemanshj.shinyapps.io/SCORE2ASIAPACIFIC/.

The SCORE2 Asia-Pacific risk charts have been provided with different colours matching categories of predicted 10-year CVD event risk.

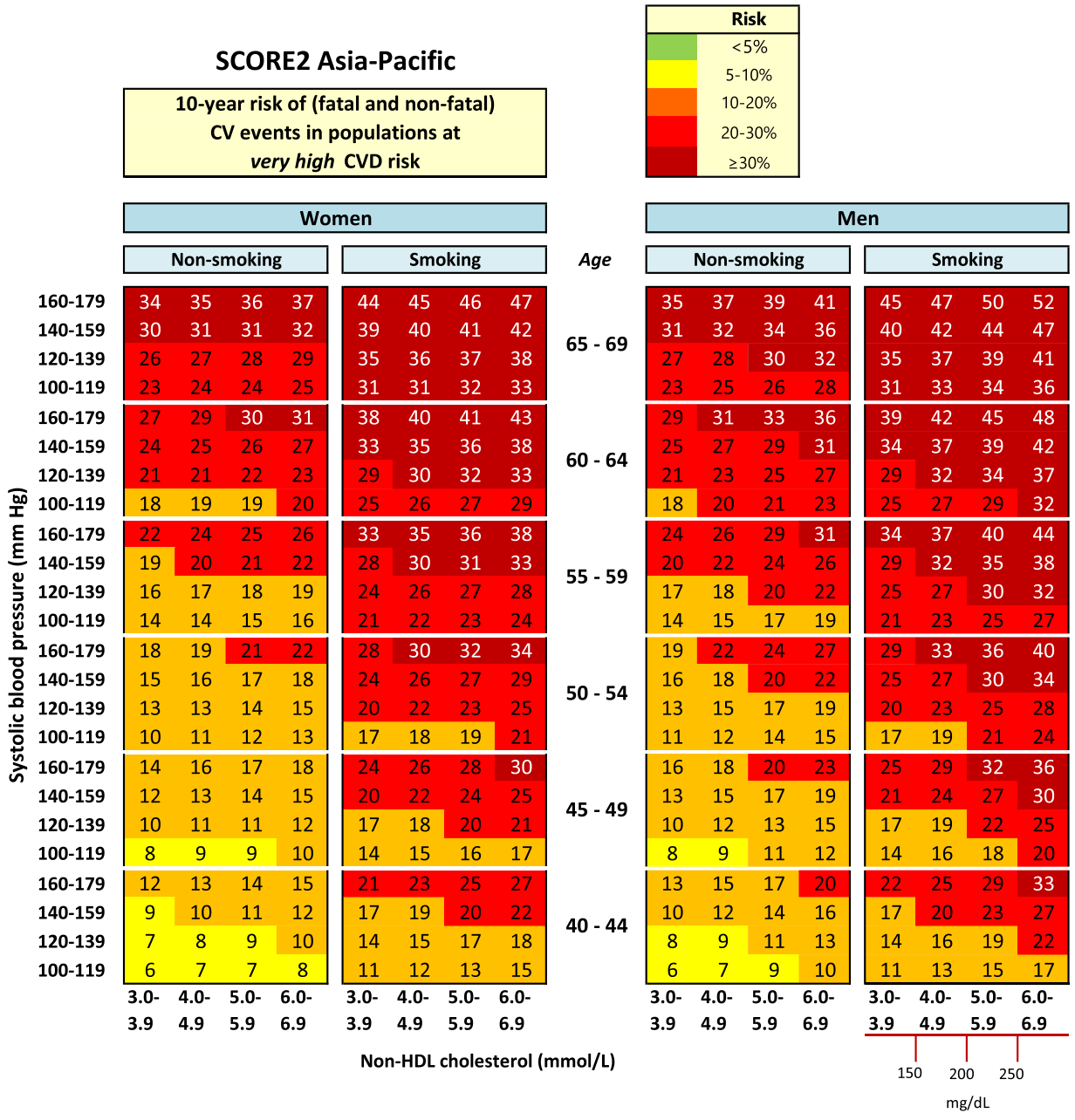


Figure 3 Continued

Specific colours on the charts do not necessarily reflect 'treatment thresholds', in which individuals with higher risks would automatically qualify for treatment. This is because such thresholds can be highly dependent on the local CVD burden, CVD prevention guidelines, and socio-economic circumstances. To aid national and regional guideline makers, we have illustrated the performance of the SCORE2 Asia-Pacific algorithms with data estimated from all Asia-Pacific countries, showing the expected proportions of individuals in specific risk categories across countries. These analyses and SCORE2 Asia-Pacific risk charts may help to determine suitable risk thresholds, which can be age-specific such as the European charts, or be independent of age. Apart from such risk thresholds, treatment decisions will likely also depend on other factors, such as preferences of the patient and physician, the risk of side effects, and other comorbidities or personal factors that may play a role.

On top of these points, strengths of the SCORE2 Asia-Pacific model include the use of very powerful, contemporary datasets and the use of proven recalibration methods based on nationally representative aggregate data. However the potential limitations of the SCORE2 Asia-Pacific algorithms need to be considered. The original SCORE2 algorithms were derived using data from mostly European regions and populations. Ideally, the derivation of risk models would have involved large nationally representative, prospective cohorts also from Asia-Pacific countries. However, analyses from the current study have shown that

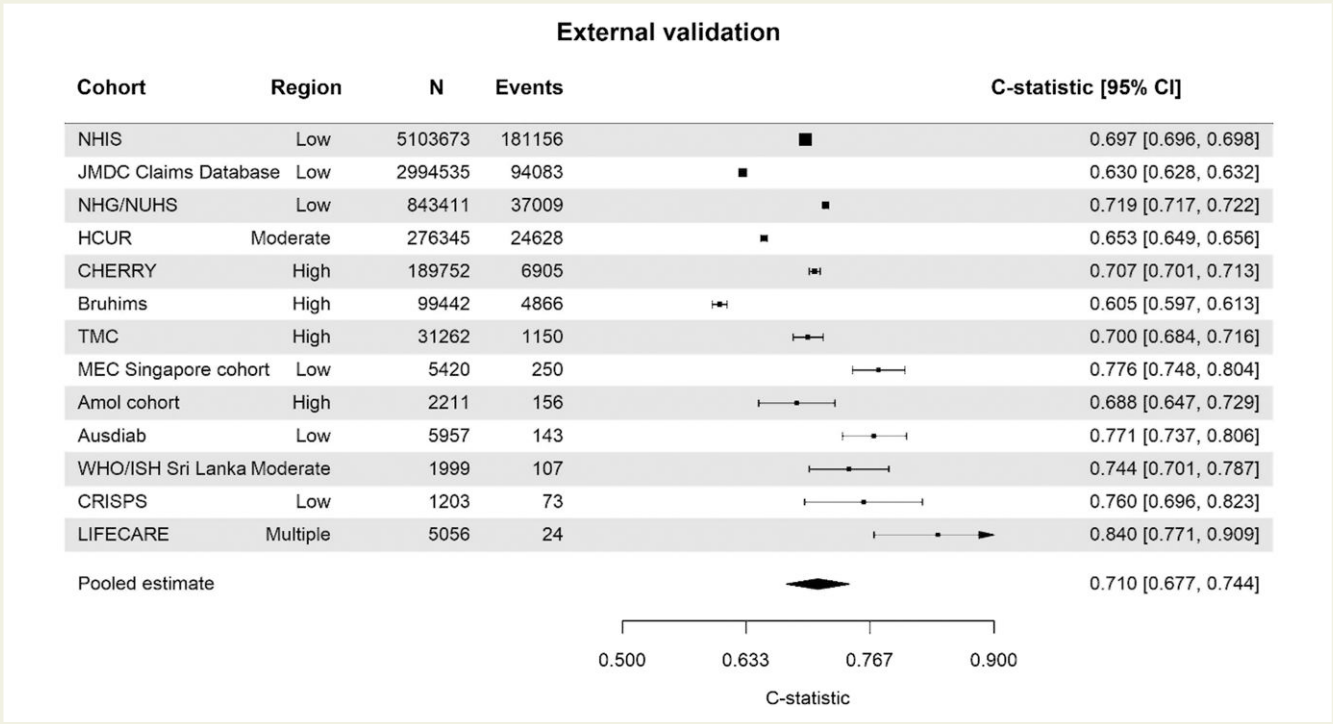


Figure 4 C-index upon assessing the ability of the SCORE2 Asia-Pacific algorithms to discriminate CVD in external validation cohorts

the coefficients from the European SCORE2 algorithms apply well to Asia-Pacific populations. The SCORE2 Asia-Pacific algorithms showed adequate discrimination in all external validation cohorts, similar to the validation of the European SCORE2 algorithms in Europe. This was further verified by refitting the SCORE2 models in several external validation cohorts, showing very similar subdistribution hazard ratios between Asia-Pacific and European data. These findings align with the WHO CVD risk charts, in which no evidence of geographical heterogeneity in the model coefficients was observed either.[9]

Another limitation of the study is that several of the external validation data sources were also used for derivation of the multipliers, as part of the recalibration procedure. This approach was chosen because powerful, approximately nationally representative data sources with both fatal and non-fatal events are scarce, whereas those are necessary for both the multiplier derivation as for external validation. As the quality of the recalibration procedure directly improves predicted risks in clinical practice, this was prioritized over keeping the processes completely separate. In addition, the recalibration process does not affect model discrimination, ensuring discrimination can be evaluated unbiased.[22] Because the recalibration procedure involves all multipliers from different data sources as well as CVD mortality rates and risk factor from all Asian-Pacific countries, the effect of multipliers from a single dataset on the final predicted risks (and therefore calibration) is also rather limited.

In the current study, the SCORE2 Asia-Pacific algorithms were validated in 12 Asian-Pacific countries. In the low- and moderate-risk regions, we were able to access multiple high-quality data sources that provided a more comprehensive view of the population. These data sources were from different geographical areas within these regions, allowing us to demonstrate the model's discrimination and calibration. However, in several countries, especially in high- and very-high-risk regions, suitable high-quality longitudinal data for external validation were not available. This limitation also extends to the recalibration, as the current approach relies on high-quality age-specific CVD mortality data to accurately adapt the SCORE2 model to the Asian-Pacific region. Similar to the external validation data, these data for recalibration were often of lower quality in high- and very-high-risk countries.

Moreover, while high-quality data were available for external validation in some countries, these datasets were not always nationally representative. This limitation is particularly significant in larger, more diverse countries where the need for further external validation remains essential to ensure the model's applicability across various subpopulations. For all countries, however, CVD mortality and risk factor data were used in the recalibration process. Should high-quality data become available in these countries, this may contribute to the ongoing validation efforts of SCORE2 Asia-Pacific and other CVD prediction algorithms, ensuring ongoing accuracy and applicability.

Data on medication use, family history, socio-economic status, nutrition, physical activity, renal function, or ethnicity were not included in the original SCORE2 algorithms as these were unavailable in cohorts and registries.[2] 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, with a family history of CVD,[32] with chronic kidney disease,[33] or in at-risk socio-economic and ethnic groups).[32,34] For individuals with several of these risk factors, solutions have been developed to accurately incorporate these additional risk factors on top of existing prediction models.[33,35]

In conclusion, the SCORE2 Asia-Pacific algorithms have been adapted to different Asia-Pacific risk regions for prediction 10-year CVD risk for individuals without DM or CVD. The SCORE2 coefficients are the foundation of the algorithms, which have now been shown to apply well to Asian-Pacific populations. As the SCORE2

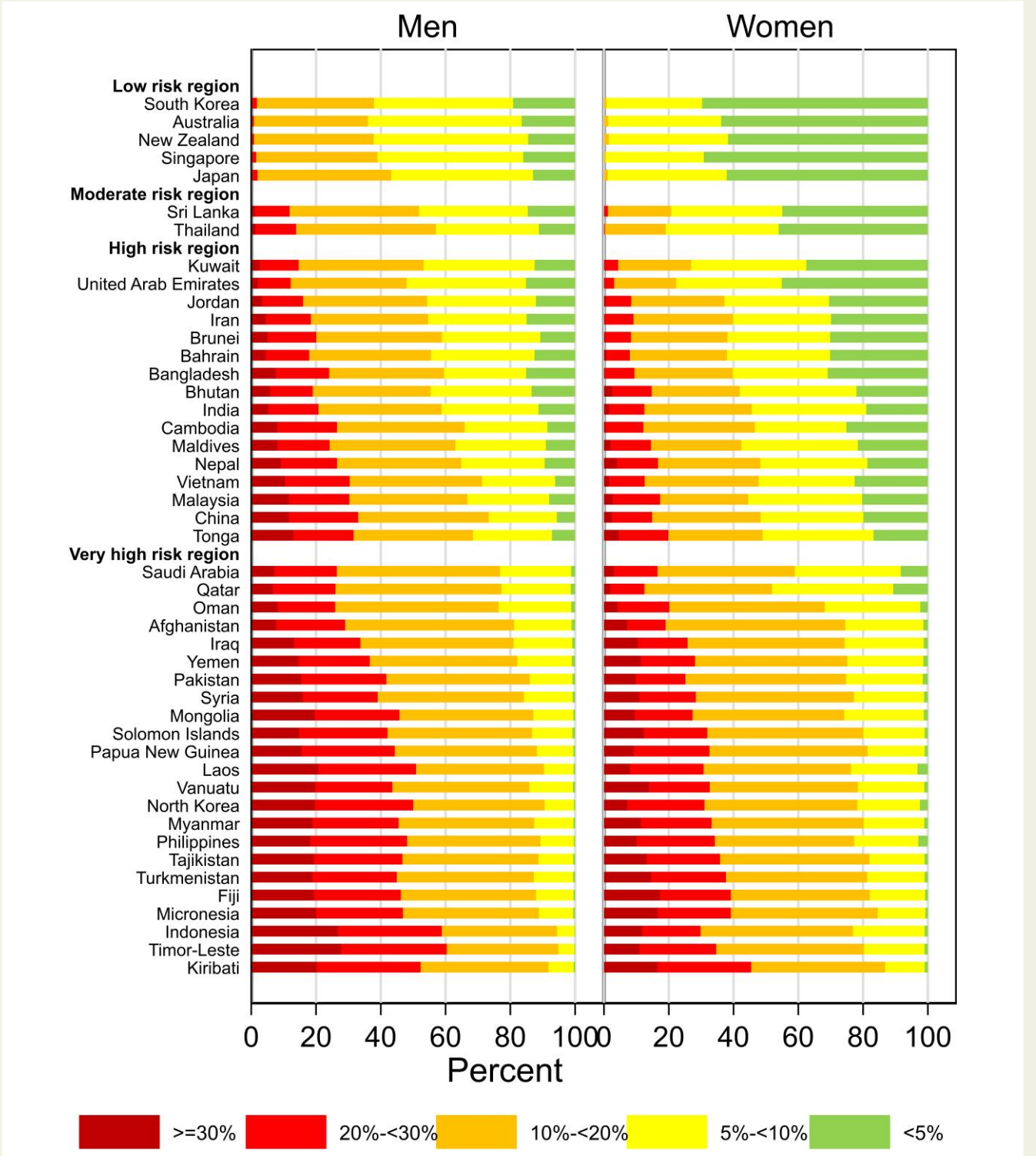


Figure 5 Distribution of 10-year CVD risk according to recalibrated SCORE2 models across Asia-Pacific countries. The proportion of individuals expected in each risk category was estimated to reflect the age-group and sex-specific risk factor values and specific population structure of each country (see Supplementary Methods S1.3)

Asia-Pacific algorithms, they are adapted to reflect risk factor levels and CVD incidences across the Asian-Pacific region. SCORE2 Asia-Pacific is part of a family of high-quality prediction algorithms using contemporary data and methodology and provide an accurate tool for identification of individuals at high CVD risk in the Asia-Pacific region. With the recalibration approach used, the model can be readily updated to further refine predictions to even smaller geographical regions and to adapt to changing CVD incidences.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

The authors included in the SCORE2 Asia-Pacific writing group have nothing to disclose relevant to the current project.

Data Availability

Data used for the current study are available upon reasonable request and approval of the individual cohorts or collaborative groups.

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Ethical Approval

Relevant ethical approval and participant consent were already obtained in all studies that contributed data to this work (see Supplementary Material).

Pre-registered Clinical Trial Number

None supplied.

Appendix

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