Supplementary material

SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions

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Supplementary Methods

1.1 Model derivation study population

Cohort of Norway (CONOR) is a collaboration between several population based regional health surveys in Norway carried out between 1994 and 2003. The data collection followed a standard procedure. Participants underwent a simple physical examination and a non-fasting blood sample was drawn at the screening site. Participants filled in one or more questionnaires about their health and disease, family history of disease, use of medication and lifestyle [1].

Cardiovascular endpoints were obtained through the CVDNOR project (CVDNOR) project (https://cvdnor.b.uib.no) [2,3]. The CVDNOR project is a collaboration between the University of Bergen and the previous Norwegian Knowledge Centre for the Health Services, now part of the Norwegian Institute of Public Health. CVDNOR includes information from cardiovascular-related discharge diagnosis [International Classification of Disease (ICD)-9 codes 390-459 or ICD-10 codes I00-I99)] retrieved from the electronic patient administrative systems (PAS) of all Norwegian hospitals from 1994 through 2009. The project obtained date and cause of death from the Cause of Death Registry and information about hospital stays 2008-2014 from the Norwegian Patient Registry. CONOR was linked to the endpoint registries by means of the personal identification number unique for each resident in Norway and this leads to high level of complete outcome registration of both fatal and non-fatal events [4,5].

The Regional Ethics Committee approved the baseline health surveys and follow-up record linkages. The participants have signed a written informed consent for research and linkage of health registries.

Selmer *et al.* have previously used the linked CONOR data in the development of a Norwegian cardiovascular risk model (NORRISK2) which is included in the Norwegian guidelines for prevention of cardiovascular disease [6]. Furthermore, the CONOR study has previously been used for model derivation for SCORE O.P., using only the fatal CVD endpoint [7].

1.2 External validation study populations

ARIC

This study is a cross-sectional analysis, using data from visit 6 (2016–2017) of the ARIC study, which was originally designed to investigate the natural history of atherosclerotic disease from mid- to late-life. 15,792 participants were recruited during 1987–1989 from four communities in the United States (Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD) and completed the first study visit (visit 1). The participants subsequently completed six study visits (visit 2 in 1990–1992, visit 3 in 1993–1995, visit 4 in 1996–1998, visit 5 in 2011–2013, visit 6 in 2016–2017, and visit 7 in 2018–19). Additionally, they were contacted annually (semiannually, beginning in 2012) to obtain updated information on medical history and lifestyle. For the current study, baseline data collected at visit 5 were used, including assessment for cardiovascular disease and risk factors including laboratory testing. The ARIC study was approved by the institutional review board of each participating center, and written informed consent was obtained from participants at each study visit. Further details on ARIC study design have been described elsewhere [8].

CPRD

We used data from the UK Clinical Practice Research Datalink (CPRD) that were linked to Hospital Episode Statistics (HES) inpatient data, and Office for National Statistics (ONS) mortality data. The CPRD database prospectively collects primary care records from consenting general practitioners across the UK. Approximately 7% of the UK population are represented in the database. CPRD obtained approval from a national research ethics committee for researchers to use deidentified data for observational research subject to the approval of a study protocol from the Independent Scientific Advisory Committee. Approximately 80% of CPRD practices registered in England have consented to their patients' primary care records being linked to other data sources. HES records include all National Health Service–funded inpatient hospitalizations in England since 1997, including diagnoses and procedures. ONS-linked mortality data contain the underlying cause of death, recorded on the death certificate, along with up to 15 other recorded causes of death. The data requested for this study covers the period 2006 to 2017 and participants could be enrolled in the study at any time between these years. Further details on CPRD study design have been described elsewhere [9].

HYVET

HYVET was a double blind placebo controlled trial of an antihypertensive regimen (thiazide-like diuretic, indapamide 1.5 sustained release, with the optional addition of an angiotensin converting enzyme inhibitor, perindopril 2–4 mg) in those aged 80 and over. Participants with hypertension (mean systolic BP 160–199 mm Hg and a standing systolic BP ≥140 mm Hg) were recruited between February 2001 and October 2007 from over 90 primary and secondary care centres in 13 countries and randomised to receive trial treatment or matching placebo. All required ethical approvals were obtained. Participants were seen during a 2-month placebo run-in phase, at baseline, every 3 months during the first year and every 6 months thereafter. Trial endpoints were reported as they occurred and included death, stroke, myocardial infarction, and incident or worsening heart failure. Validation of trial endpoints was carried out by a trial endpoint committee of international experts blinded to trial treatment allocation and with full access to supporting documentation, for example, death certificates, hospitalization reports etc. Median follow-up was 1.8 years, after the study was stopped preliminary at second interim analysis due to a significant reduction in all-cause mortality in the active treatment arm. Full details of the HYVET protocol have been published elsewhere [10].

MESA

MESA is a multi-ethnic, community-based, multiethnic prospective cohort study of 6,814 men and women of 4 self-identified racial/ethnic groups (non-Hispanic whites, African American, Hispanic, or Chinese American). MESA participants were recruited between 2000 and 2002 in 6 field centers: Wake Forest University in Winston-Salem, NC; Columbia University in New York, NY; The Johns Hopkins University in Baltimore, MD; University of Minnesota in Minneapolis; Northwestern University in Chicago, IL; and University of California in Los Angeles. The age range at baseline was 45 to 84 years, and participants had to be free of clinically overt atherosclerotic cardiovascular conditions to be eligible for inclusion. All study participants provided written informed consent at each examination, and study protocols were approved by site-specific Institutional Review Boards at respective MESA-participating institutions. Further details on the MESA study design have been described elsewhere [11].

PROSPER

The PROSPER trial is a large, prospective multicenter randomized clinical trial that assessed whether treatment with pravastatin diminishes the risk of major vascular events in older individuals from three countries (the Netherlands, Scotland, Ireland). Between December 1997 and May 1999, 5804 men and women aged 70–82 years were enrolled if they had pre-existing vascular disease or increased risk due to smoking, hypertension, or diabetes. Participants with the following conditions were not recruited in the PROSPER study: congestive heart failure; significant arrhythmia; cognitive impairment (Mini-Mental Score Examination score <24). Included participants were randomly assigned to either pravastatin or placebo for an average 3.5-year intervention period. The full methodology of PROSPER has been described in more detail elsewhere [12].

SPRINT

The design, eligibility, and baseline characteristics of SPRINT have been described elsewhere [13,14]. SPRINT was a randomized, controlled, open-label trial that was conducted at 102 clinical sites (organized into 5 clinical center networks) in the United States. The trial protocol was approved by the institutional review board at each participating site. Study participants were required to be at increased risk for cardiovascular disease. A person was excluded if he or she had type 2 diabetes, a history of stroke, symptomatic heart failure within the past 6 months or reduced left ventricular ejection fraction (<35%), a clinical diagnosis of or treatment for dementia, an expected survival of less than 3 years, unintentional weight loss (>10% of body weight) during the preceding 6 months, an SBP of less than 110 mm Hg following 1 minute of standing, or resided in a nursing home. Sociodemographic data were collected at baseline, whereas both clinical and laboratory data were obtained at baseline and every 3 months. Eligible participants were assigned to a systolic blood-pressure target of either less than 140 mm Hg (the standard-treatment group) or less than 120 mm Hg (the intensive-treatment group). For the current study, patients aged 65 years or older were included between November 2010 and March 2013. To investigate the effect of blood pressure lowering therapy in older persons, a subgroup of elderly aged 75 years or older was pre-specified in the study design and, as such, well-represented within the study population [14].
A committee unaware of treatment assignment adjudicated the protocol-specified clinical outcomes. The primary cardiovascular disease outcome was a composite of nonfatal myocardial infarction, acute

coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. Secondary outcomes included all-cause mortality and the composite of the SPRINT primary outcome and all-cause mortality. In August 2015, the trial was ended preliminarily after interim analysis, after a median follow-up of 3.3 years.

1.3 Model development (adapted from Hageman et al. [15])

The interlinked stages of model development, including model derivation and recalibration are summarised in **Supplementary Methods Figure 1**. An overview of the process as follows: Fine and Gray models were derived using data from CONOR (**Box 1**). Four geographical risk regions were defined according to the age-standardized country-specific cardiovascular mortality rates. For each region, annual age- and sex-specific mortality rates were then translated to 10-year mortality risk estimates, allowing for competing risk of non-CVD death (**Box 2**). In order to translate 10-year mortality to 10-year risk of fatal and non-fatal CVD, region- age- and sex-specific multiplication factors were estimated using representative registry data and cohorts from each risk region. Multiplication factors were defined as the ratio between the cumulative incidence of fatal and non-fatal CVD events and the cumulative incidence of fatal CVD (**Box 3**). Multipliers were then used to translate region, sex and age specific 10-year mortality incidence to expected 10-year risk of fatal and non-fatal CVD events (**Box 4**). Region, sex and age-specific predicted 10-year risks were then estimated using the core, un-calibrated 10-year risk models (derived in **Box 1**) with region, sex and age-specific risk factors from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC) (**Box 5**). The region and sex and age-specific predicted risks (from **Box 5**) were compared to expected risks (from **Box 4**) and rescaling factors were estimated to recalibrate the models for each region and sex (**Box 6**). Finally, the rescaling factors are applied with the original un-calibrated model to give new, recalibrated risk predictions in new individuals (**Box 7**).

The methods applied in **Boxes 1, 2, 3** and **6** warrant further explanation and are detailed as follows:

<u>Box 1: Model derivation</u>

For model derivation, sex-specific coefficients were estimated using Fine and Gray competing risk-adjusted models. Risk predictors were age, sex, current smoking, history of diabetes mellitus, systolic

blood pressure, and total and HDL cholesterol and age-interactions were added for all predictors. Continuous risk predictors were centred before analysis. There were no or minimal violations of the proportional hazards assumptions as assessed visually based on plotted Schoenfeld residuals.

Box 2: Estimation of 10-year competing risk adjusted mortality for each risk region

Estimates of CVD event incidence were based on the most recent WHO cardiovascular mortality rates, which were transformed to estimates of CVD event incidence using a multiplier approach. WHO cause-specific mortality rates are supplied by every country and coded in ICD-9 or ICD-10. Rates included mortality from all causes included in the original SCORE endpoint [16] (Supplementary Table 1). Non-CVD mortality was defined as all mortality from causes not included in the SCORE endpoint.

For every age-group, CVD mortality rates were used which were observed at the midpoint of the projected 10-year follow-up period, so the CVD mortality rates of one 5-year age-group ahead (i.e. for prediction in the 40 to 44 year age-group the rates for 45 to 49 years were used as these are at the midpoint of the 10-year interval). WHO rates of both the fatal cardiovascular outcome and the competing outcome non-CVD mortality were converted to 1–year mortality risks (r) using the following formula:

$$r = 1 - e^{(-fatal\ rate)}$$

The 1-year risks of fatal CVD were corrected for the competing risk of non-CVD death and extrapolated to 10-year risks. This was done using life-tables with 1-year intervals, using follow-up time as a timescale [17,18]. For every interval, CVD-free survival was calculated using the following formula:

$$S_{t+1} = S_t \times (1 - r_{cvd,t} - r_{comp,t}).$$

In which S_t=probability of being alive at start of interval *t*; S_{t+1}=probability of being healthy and alive at end of interval *t*; and $r_{cvd,t}$ and $r_{comp,t}$ are the probabilities of experiencing a fatal CVD event or competing events respectively during interval *t,* given disease-free survival up to start of interval *t*; For each 1-year interval of the 10-year timeframe of interest, the cause-specific CV mortality risk was calculated using:

$$\mathrm{CVrisk}_t = \frac{r_{cvd,t}}{r_{cvd,t} + r_{comp,t}} * (S_t - S_{t+1})$$

The 10-year cumulative cause-specific risk was calculated as the sum of the 1-year cause-specific risks:

$$\mathrm{CVrisk}_{t1-10} = \sum_{1-10} CVrisk_t$$

Box 3: Estimation of Multipliers to convert mortality to incidence estimates in each risk region

To convert 10-year mortality estimates to incidence estimates, age- and sex-specific multiplication factors were defined as:

$$\frac{Cumulative\ 10\ year\ incindence\ total\ CV\ events_{without\ prior\ CVD}}{Cumulative\ 10\ year\ incindence\ fatal\ CV\ events_{entire\ population}}$$

These allowed the population level mortality statistics, which are calculated among the whole population, regardless of prior disease status, to be converted into first event incidence estimates, representative of the target primary prevention population (those without prior CVD). Multiplication factors were derived in Clinical Practice Research Datalink [9] (CPRD; n = 2,589,074) for the low risk region, the Swedish Patient Registry [19] for the moderate risk region (n = 5,252,592), the Estonian biobank [20] (n = 67,474) for the high risk region, and the HAPIEE study [21] (Lithuania + Russia, n = 16,521) for the very high risk region. In each cohort and sex, two Fine and Gray models, adjusted for baseline age and age-squared were fit: one modelling 1st CVD event as the outcome and using only individuals without prior CVD, and one with fatal CVD as the outcome and including all participants (regardless of prior disease). The relevant cumulative 10-year incidence was then estimated using each model, for each age group, and age group-specific 10-year CVD event risk was then estimated as follows:

$$\mathrm{CVDrisk}_{total,10} = \frac{Cumulative\ incindence\ fatal + nonfatal\ CV\ events_{without\ prior\ CVD}}{Cumulative\ incindence\ fatal\ CV\ events_{General\ population}} * \mathrm{CVrisk}_{t1-10}$$

Multiplication factors were assumed to be stable within each region and over time [15]. To aggregate the multipliers from the different cohorts to a single set of multipliers for the low/moderate and for the high/very high risk regions, the mean was calculated of all relevant multipliers, weighted by the size of the multiplier-derivation cohort. The region-, age- and sex-specific multipliers can be found in Supplementary Table 4. Age and sex-specific 10-year mortality CVD rates and derived incidence rates are shown for each region in Supplementary Figure 4. The age-specific and sex-specific estimated CVD event rates used for recalibration are presented by region in Supplementary Table 5.

Box 6: Relate expected to predicted risks to calculate rescaling factors for model recalibration

Recalibration of the core SCORE2-OP model was performed separately for each geographical risk region, using a previously described methodology, which is summarized in Supplementary Methods Figure 2 [15,22]. This involved the use of regional age- and sex-specific mean risk factor levels (from NCD-

RisC) and age- and sex-specific estimates of expected cumulative 10-year risk, estimated as described above. We used the core SCORE2-OP risk models to estimate 10-year predicted risk of the endpoint for each of the age groups using the mean risk factor values. Having completed this process for each age group, as shown in Figure 2 we then regressed transformed expected 10-year risk across age groups on that predicted by the core SCORE2-OP models to derive recalibration factors (the intercept and slope of the resulting regression line, Supplementary Methods Table 1). The SCORE2-OP risk models, rescaled using the recalibration factors were then used to estimate appropriate risks for each potential risk factor combination, for a new individual or for formation of the example risk charts.

A stepwise approach for how to estimate individualized 10-year CVD event risk estimations can be found in Supplementary Methods Table 2, with individual example calculations shown in Supplementary Methods Table 3.

1.4 Missing data

Because complete case analysis may lead to loss of statistical power and possible bias, values of predictors were imputed by single regression imputation with predictive mean matching for all cohort data. As the CPRD consists of care-as-usual data, missing data was much more frequent and missingness was more likely to correlate with cardiovascular disease risk. Therefore, multiple imputation was performed for the external validation in CPRD with fully conditional specification using 5 imputed datasets.

1.5 Uncertainty of risk predictions

In clinical practice, clinical decision are made based on the best available evidence. In risk prediction, this is the point estimate as estimated with the risk model. However, it is good to realize that there is uncertainty around these point estimates. To calculate confidence intervals surrounding individual predicted risks based on the uncertainty of all model coefficients, risk predictions were repeated with the lower or upper bounds of the confidence intervals of all beta coefficients **(Table 2)**. In **Supplementary Figure 8** the uncertainty around the point estimates is presented in risk charts.

1.6 Predicting treatment effects from risk factor treatment using SCORE2-OP

It has previously been shown that risk estimations can be combined with relative treatment effects from trials to calculate absolute individualized treatment effects [18].

To show the potential use of using SCORE2-OP in daily practice, we included analyses on the individual absolute benefit of blood pressure lowering and lipid lowering in older persons. To estimate the effect of blood pressure lowering on CVD, average relative treatment effects were added to SCORE2-OP, using a hazard ratio (HR) of 0.80 per 10 mmHg SBP reduction taken from a large meta-analysis for blood pressure lowering [23], and estimating the benefit from the reduction of office SBP to the target of <140mmHg for persons with hypertension at baseline (SBP >140 mmHg) from the HYVET and SPRINT trials (both blood pressure lowering trials [13,24]). For lipid lowering, an HR of 0.78 per 1 mmol/L LDL reduction was used [25], and the treatment benefit of lowering LDL cholesterol to < 2.6 mmol/L was estimated for all patients with an LDL cholesterol >2.6 mmol/L from the PROSPER trial (a lipid lowering trial [12]). For both treatment effects, it was assumed that the HR can be applied across the entire age range. Indeed, no evidence for heterogeneity of these treatment effects across different age ranges has been found [23,26,27].

First, we tested the assumption that the same relative treatment effect can be used in all individuals by making a Cox model in respectively the HYVET, SPRINT, and PROSPER study populations including a *"model linear predictor * trial allocation"* interaction term [28].

Then treatment benefit was calculated for the respective risk factor treatment by combining the hazard ratio with the individualized estimated 10-year CVD event risk (here shown for SBP reduction):

$$Risk_{with\ treatment} = 1 - (1 - risk_{original}^{\exp\left(\log(HR)\times\left(\frac{SBP\ reduction}{10}\right)\right)})$$

Treatment benefit for individual patients is defined as the absolute risk reduction (ARR) from treatment:

$$ARR = \left(risk_{original} - risk_{with\ treatment}\right) * 100$$

Histograms were constructed showing the distribution of treatment effects from blood pressure lowering in the combined study population from the HYVET and SPRINT trials (Figure 4), and from lipid lowering in the PROSPER trial (Figure 5), respectively.

Supplementary Methods Table 1: Region-specific rescaling factors

	Men		**Female**	
	Scale 1	*Scale 2*	*Scale 1*	*Scale 2*
Low risk region	-0.34	1.19	-0.52	1.01
Moderate risk region	0.01	1.25	-0.1	1.1
High risk region	0.08	1.15	0.38	1.09
Very high risk region	0.05	0.7	0.38	0.69

Rescaling factors for the SCORE2-OP model to scale predicted risks to the target population in very risk region, based recent nationally representative estimates of incident cardiovascular disease and risk factor levels.

Supplementary Methods Table 2: A stepwise approach to estimating 10-year CVD risk for an individual patient

Calculate 10-year CVD event risk	
1. Calculate individual model linear predictor (LP)	**$LP = \sum \beta_{sex\text{-}specific} * (x - x_{cen})$** Where: $\beta_{sex\text{-}specific}$ are the sex-specific coefficients (Table 2), x is the individual person value of the predictor x_{cen} is the value at which each predictor was centered: age = 73, SBP = 150; total cholesterol = 6; HDL cholesterol =1.4.
2. Calculate the original (or unrecalibrated) 10-year risk ($\theta_{original}$)	**$\theta_{original} = 1 - basesurv_{sex\text{-}specific}^{\exp(LP - meanLP_{sex\text{-}specific})}$** Where: $Basesurv_{sex\text{-}specific}$ is the sex-specific 10-year baseline survival for an average patient: for men, 0.758; for women, 0.808 meanLP is the sex-specific mean linear predictor: for men, 0.093; for women, 0.229
3. Use the age-, sex-, and region-specific rescaling factors from Supplementary Methods Table 1 to calculate the recalibrated 10-year risk for your individual patient (θ)	**$\theta = 1 - \exp(-\exp(Scale1 + Scale2 \times \ln(-\ln(1 - \theta_{original}))))$** Multiply by 100 to get your individual 10-year risk as a percentage.
Calculate 10-year risk of CVD events incl. heart failure	
Include the multiplication factor from Supplementary Table 4 in step 2, the rest of the procedure is identical	**$\theta_{original} = 1 - basesurv_{sex\text{-}specific}^{\exp(LP - meanLP_{sex\text{-}specific} - \ln(multiplier_{age,sex}))}$** Where: $Multiplier_{age,sex}$ is the age- and sex-specific multiplier

Supplementary Methods Table 3: Example calculations for the estimated CVD event risk for an individual patient using SCORE2-OP

<table>
<tr><th colspan="3">Calculation of estimated 10-year CVD event risk using SCORE2-OP</th></tr>
<tr><td>Individual risk factor levels</td><td colspan="2">Model coefficients (women)</td><td>Calculation of 10-year CVD event risk using SCORE2-OP</td></tr>
<tr><td rowspan="11">Sex = female
Age = 75
Total cholesterol = 5.5
HDL cholesterol =1.3
SBP = 140mmHg
Diabetes = No
Smoking = Yes</td><td>Age (per year)</td><td>0.0789</td><td rowspan="11">$\sum \beta(x - x_{cen})$ = 0.0789 x (75-73)
+ 0.6010 x 0
+ 0.4921 x 1
+ 0.0102 x (140-150)
+ 0.0605 x (5.5-6)
- 0.3040 x (1.3-1.4)
- 0.0107 x (75-73) x 0
- 0.0255 x (75-73) x 1
- 0.0004 x (75-73) x (140-150)
- 0.0009 x (75-73) x (5.5-6)
+ 0.0154 x (75-73) x (1.3-1.4)
= -0.5029

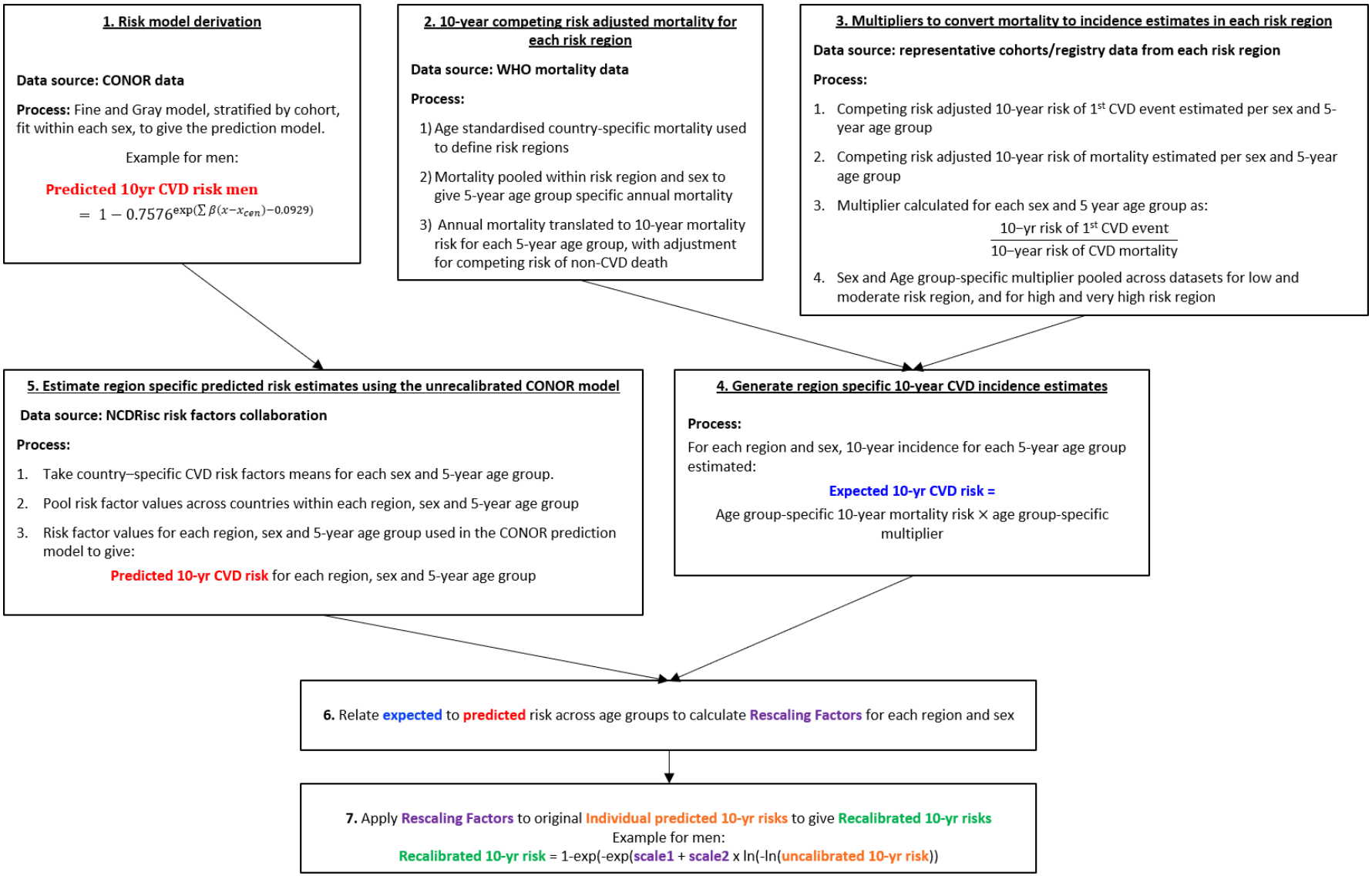
Unrecalibrated (original) risk:
10-yr risk = 1-0.8082^exp($\sum \beta (x - x_{cen}) - 0.229$)
= 1-0.8082^exp(0.5029 – 0.229)
= 0.2442 = 24.4%

Recalibrate to low risk region:
10-yr risk = 1-exp(-exp(-0.85+0.82 x ln(-ln(1- original risk))))
= 1-exp(-exp(-0.85+0.82 x ln(-ln(1- 0.2442))))
= 0.1397 = 14%</td></tr>
<tr><td>Diabetes</td><td>0.6010</td></tr>
<tr><td>Smoking</td><td>0.4921</td></tr>
<tr><td>SBP (per mmHg)</td><td>0.0102</td></tr>
<tr><td>Total cholesterol (per mmol/L)</td><td>0.0605</td></tr>
<tr><td>HDL cholesterol (per mmol/L)</td><td>-0.3040</td></tr>
<tr><td>Diabetes interaction with age</td><td>-0.0107</td></tr>
<tr><td>Smoking interaction with age</td><td>-0.0255</td></tr>
<tr><td>SBP interaction with age</td><td>-0.0004</td></tr>
<tr><td>Total cholesterol interaction with age</td><td>-0.0009</td></tr>
<tr><td>HDL cholesterol interaction with age</td><td>0.0154</td></tr>
<tr><td>Individual risk factor levels</td><td colspan="2">Model coefficients (men)</td><td>Calculation of 10-year CVD event risk using SCORE2-OP</td></tr>
<tr><td rowspan="11">Sex = male
Age = 75
Total cholesterol = 5.5
HDL cholesterol =1.3
SBP = 140mmHg
Diabetes = No
Smoking = Yes</td><td>Age (per year)</td><td>0.0634</td><td rowspan="11">$\sum \beta(x - x_{cen})$ = 0.0634 x (75-73)
+ 0.4245 x 0
+ 0.3524 x 1
+ 0.0094 x (140-150)
+ 0.0850 x (5.5-6)
- 0.3564 x (1.3-1.4)
- 0.0174 x (75-73) x 0
- 0.0247 x (75-73) x 1
- 0.0005 x (75-73) x (140-150)
+ 0.0073 x (75-73) x (5.5-6)
+ 0.0091 x (75-73) x (1.3-1.4)
= -0.3298

Unrecalibrated (original) risk:
10-yr risk = 1-0.7576^exp($\sum \beta (x - x_{cen}) - 0.0929$)
= 1-0.7576^exp(0.3298 – 0.0929)
= 0.2966 = 29.7%

Recalibrate to low risk region:
10-yr risk = 1-exp(-exp(-0.61+0.89 x ln(-ln(1- original risk))))
= 1-exp(-exp(-0.61+0.89 x ln(-ln(1- 0.2966))))
= 0.1930 = 19.3%</td></tr>
<tr><td>Diabetes</td><td>0.4245</td></tr>
<tr><td>Smoking</td><td>0.3524</td></tr>
<tr><td>SBP (per mmHg)</td><td>0.0094</td></tr>
<tr><td>Total cholesterol (per mmol/L)</td><td>0.0850</td></tr>
<tr><td>HDL cholesterol (per mmol/L)</td><td>-0.3564</td></tr>
<tr><td>Diabetes interaction with age</td><td>-0.0174</td></tr>
<tr><td>Smoking interaction with age</td><td>-0.0247</td></tr>
<tr><td>SBP interaction with age</td><td>-0.0005</td></tr>
<tr><td>Total cholesterol interaction with age</td><td>0.0073</td></tr>
<tr><td>HDL cholesterol interaction with age</td><td>0.0091</td></tr>
</table>

Supplementary Methods Figure 1: SCORE2-OP model development process



Supplementary Methods Figure 2: Methods used for recalibration of risk scores

General process:

Details/example using SCORE2-OP for men

Use population risk factor values to calculate a predicted risk for each age group in the target population using the original equation

$$\theta_{pred,agegroup} = 1 - 0.7576^{\exp(\sum \beta x - x_{cen} - 0.0929)}$$

θ = 10 year CVD risk
β = SCORE2-OP coefficients
x= age group specific mean risk factor values in the target population
x_{cen} = values at which each risk factor was centered in SCORE2-OP
0.7669 = the 10-year baseline survival
0.1111 = linear predictor at mean risk factor levels for SCORE2-OP

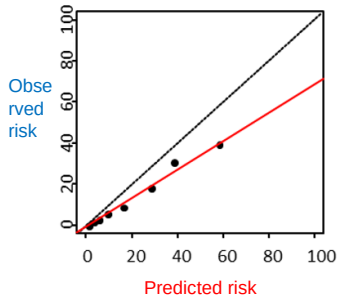
Use age group specific mortality statistics from the target population and relevant multipliers to estimate observed 10-year risk for each age group

$$\theta_{obs,agegroup}$$

Estimating using lifetable approach and application of multipliers for each age group (supplementary methods 1)

Calculate rescaling factors needed to bring predicted risks in line with observed risks for the target population

$$\ln(-\ln(1-\theta_{obs,agegroup})) = Scale1 + Scale2\ x \ln(-\ln(1-\theta_{pred,agegroup}))$$



Each point represents one age group

Fitted line

Line of equality

Regress the age-specific *observed-on-predicted* risks
(note values are first transformed)
Scale1 and Scale2 are the estimated rescaling factors)

Using rescaling factors to give a recalibrated 10-year risk estimate for each new individual/combination of risk factors

(A) Calculate original risk estimation for an individual or specific combination of risk factors:

$$\theta_{pred} = 1 - 0.7576^{\exp(\sum \beta x - x_{cen} - 0.0929)}$$

(B) Use rescaling factors to estimate the recalibrated risk:

$$\theta_{newpred} = 1 - \exp(-\exp(Scale1 + Scale2 \times \ln(-\ln(1-\theta_{pred}))))$$

β = SCORE2-OP coefficients
x are the risk factor values, either for a new individual (when using an online calculator) or for a specific entry on the risk charts

Supplementary Table 1: Endpoint definitions

1. Fatal cardiovascular disease– cause specific mortality due to any of the following:

Endpoints included	**ICD10-codes**
Hypertensive disease	I10-16
ischemic heart disease	I20-25
Arrhythmias, heart failure	I46-52
Cerebrovascular disease	I60-69
Atherosclerosis/AAA	I70-73
instantaneous death and death within 24h of symptom onset	R96.0-96.1
The following ICD codes are to be excluded from the above endpoint:	
Myocarditis, unspecified	I51.4
subarachnoid hemorrhage	I60
Subdural hemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I68.2
Moyamoya	I67.5

2. Hospitalization from cardiovascular disease

Endpoints included	**ICD10-codes**
Non-fatal myocardial infarction	I21-23
Non-fatal stroke	I60-69
Excluded from the non-fatal stroke endpoint:	
Subarachnoid hemorrhage	I60
Subdural hemorrhage	I62
Cerebral aneurysm	I67.1
Cerebral arteritis	I682
Moyamoya	I675

Supplementary Table 2: Age- and sex- standardized CVD mortality rates per country

Countries	Age- and sex-standardized CVD mortality rates (per 100,000 persons)	Year collected
Low risk region		
France	70.9	2014
Israel	76.7	2015
Spain	89.4	2015
Netherlands	89.9	2016
Switzerland	90.2	2015
Denmark	90.4	2015
Norway	90.8	2015
Luxembourg	92.9	2015
Belgium	99.2	2015
United Kingdom	99.7	2015
Moderate risk region		
Iceland	101.0	2016
Portugal	107.9	2014
Sweden	109.0	2016
Italy	110.1	2015
San Marino	-	
Ireland	111.5	2014
Cyprus	111.5	2016
Finland	128.5	2015
Austria	130.9	2016
Malta	133.3	2015
USA	131.8	2016
Greece	138.8	2015
Germany	139.0	2015
Slovenia	143.3	2015
High risk region		
Albania	184.5	2010
Czech Republic	195.0	2016
Turkey	199.5	2015
Kazakhstan	214.0	2015
Croatia	214.6	2016
Poland	223.8	2015
Estonia	234.8	2015
Slovakia	239.2	2014
Hungary	274.1	2016
Bosnia and Herzegovina	279.2	2014
Very high risk region		
Armenia	306.3	2016
Lithuania	309.0	2016
Georgia	309.6	2015
Latvia	327.2	2015
Serbia	329.1	2015
Romania	330.5	2016
Montenegro	348.4	2009
Russian Federation	368.8	2015
TFYR Macedonia	387.8	2013
Belarus	395.4	2014
Azerbaijan	416.5	2007
Bulgaria	421.2	2014
Republic of Moldova	442.2	2016
Ukraine	476.7	2015
Kyrgyzstan	476.9	2015
Uzbekistan	478.6	2014
Egypt	543.7	2015
Morocco	-	
Syria	-	
Tunisia	-	
Lebanon	-	
Algeria	-	
Libya	-	

Countries without available population or incidence data in the WHO database (indicated by -) were grouped using rates available from neighboring countries

Supplementary Table 3: Age- and sex-specific multiplication factors for fatal CVD events to total events in the different risk regions

	Low/moderate risk region		High/very high risk region	
Age group	*Men*	*Women*	*Men*	*Women*
65-70	2.6	3.2	1.6	2.5
70-75	2.1	2.5	1.4	1.9
75-80	1.6	1.9	1.3	1.5
80-85	1.3	1.5	1.1	1.4
85+	1.1	1.1	0.9	1.0

Multiplication factors for the SCORE2-OP model specific for each age group, sex and region. Multiplication factors were defined as the ratio between the cumulative incidence of fatal CVD and the cumulative incidence of CVD events. Multipliers were used to multiply observed CVD mortality rates in the agegroup stated in this table and are therefore used to recalibrate 10-year risks in one age group below.

Supplementary Table 4: Age- and sex-specific multiplication factors in CONOR for the primary endpoint to secondary endpoint CVD events plus HF

Age group	**65**	**70**	**75**	**80**	**85+**
Men	1.10	1.15	1.19	1.20	1.17
Women	1.14	1.20	1.22	1.22	1.20

Supplementary Table 5: Regional risk factor levels and incidence rates used for recalibration

Agegroup	Region	Sex	Systolic blood pressure (mmHg)	Smoking (%)	Total cholesterol (mmol/L)	HDL-cholesterol (mmol/L)	Diabetes mellitus (%)	Expected 10-year cumulative incidence (%)
65	Low	Men	140	19.5	4.9	1.3	16.8	8.7
70	Low	Men	141	17.2	4.8	1.3	17.3	12.3
75	Low	Men	143	16.5	4.7	1.3	17.1	17.1
85	Low	Men	144	15.8	4.4	1.3	15.3	24.8
65	Low	Women	136	15.2	5.4	1.7	11.3	5
70	Low	Women	139	13.4	5.3	1.7	12.6	8.6
75	Low	Women	141	12.3	5.2	1.6	13.6	14.1
85	Low	Women	145	10.9	5.3	1.6	15.6	25.8
65	Moderate	Men	140	18.6	5.1	1.3	18.5	11.6
70	Moderate	Men	142	15.9	5	1.3	18.7	16.2
75	Moderate	Men	143	14	4.9	1.3	18.3	22.1
85	Moderate	Men	142	11.5	4.7	1.3	16.3	34.2
60	Moderate	Women	136	12.2	5.6	1.6	13.6	6.3
65	Moderate	Women	138	10	5.5	1.6	14.8	10.8
70	Moderate	Women	141	8.8	5.4	1.6	15.6	18
75	Moderate	Women	141	7.6	5.4	1.6	17.7	35.3
85	Moderate	Women	148	28	5.1	1.3	20.6	16.9
65	High	Men	150	24.6	5	1.3	20.6	22.5
70	High	Men	150	22.3	4.9	1.3	19.7	30.1
75	High	Men	149	20.1	4.7	1.3	17.3	38.7
85	High	Men	144	12.4	5.5	1.5	17.6	11.8
65	High	Women	147	10.3	5.4	1.5	18.2	19
70	High	Women	149	9.1	5.3	1.5	18.2	35.7
75	High	Women	150	7.8	5.5	1.5	19.4	49.8
85	High	Women	149	39.9	5.2	1.3	19.8	29.1
65	Very high	Men	151	36.2	5.1	1.3	19.9	38.3
70	Very high	Men	152	32.7	5	1.3	19.2	43.6
75	Very high	Men	151	30.5	4.8	1.3	16.7	46.3
85	Very high	Men	147	4.2	5.5	1.5	19	24.3
65	Very high	Women	148	3.6	5.4	1.4	19.2	38.1
70	Very high	Women	150	3.4	5.3	1.4	19	50.6
75	Very high	Women	151	2.9	5.4	1.4	19.9	58.2
85	Very high	Women	140	19.5	4.9	1.3	16.8	8.7

Supplementary Table 6: Comparison between SCORE2-OP and ASCVD risk engine in terms of discrimination (Harrell's C-statistic [95% confidence interval])

	ASCVD	**SCORE2-OP**
ARIC	0.644 (0.618-0.669)	0.668 (0.643-0.693)
CPRD	0.663 (0.659-0.666)	0.657 (0.655-0.662)
MESA	0.645 (0.621-0.668)	0.654 (0.631-0.678)
Pooled trial populations	0.612 (0.593-0.630)	0.632 (0.613-0.651)

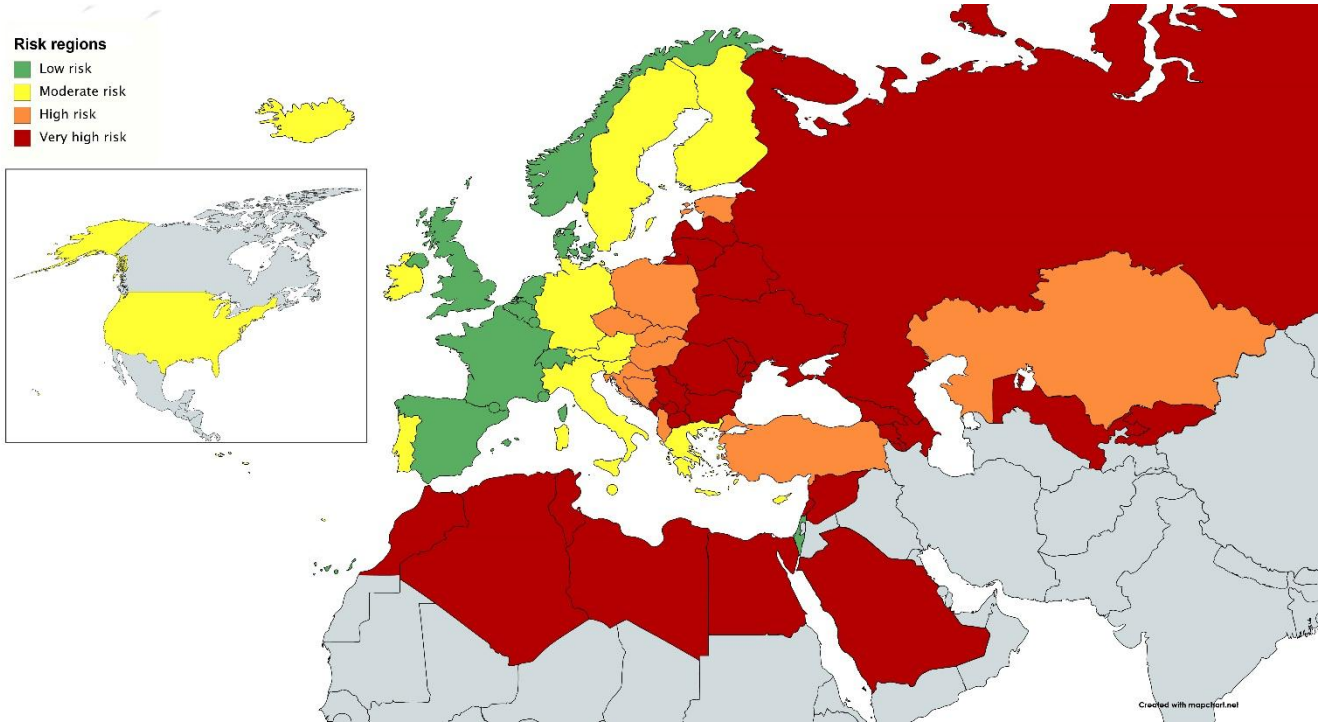
Supplementary Table 7: Comparison of the area under the curve of the Model Harrell's C-statistic, the 1-year time-dependent ROC and the time-dependent ROC at longer follow-up in the external validation cohorts

	Harrell's C-statistic	**1-year time-dependent ROC**	**Time-dependent ROC****
ARIC	0.668 (0.643-0.693)	0.711 (0.646-0.777)	0.683 (0.655-0.710) at 5 years follow-up
CPRD*	0.657 (0.655-0.662)	0.679 (0.669, 0.688)	0.646 (0.642-0.650) at 10 years follow-up
MESA	0.654 (0.631-0.678)	0.701 (0.626-0.794)	0.692 (0.663-0.721) at 10 years follow-up
Pooled trial populations	0.632 (0.613-0.651)	0.639 (0.657-0.670)	0.677 (0.657-0.698) at 3 years follow-up

***** Due to computational reasons, the time-dependent ROC was calculated using an unweighted rather than the weighted approach used in the other study populations. In this approach, patients censored without an event *before* 10 years follow-up were not included. This can lead to an underestimation of the actual area under the curve of the time-dependent ROC.

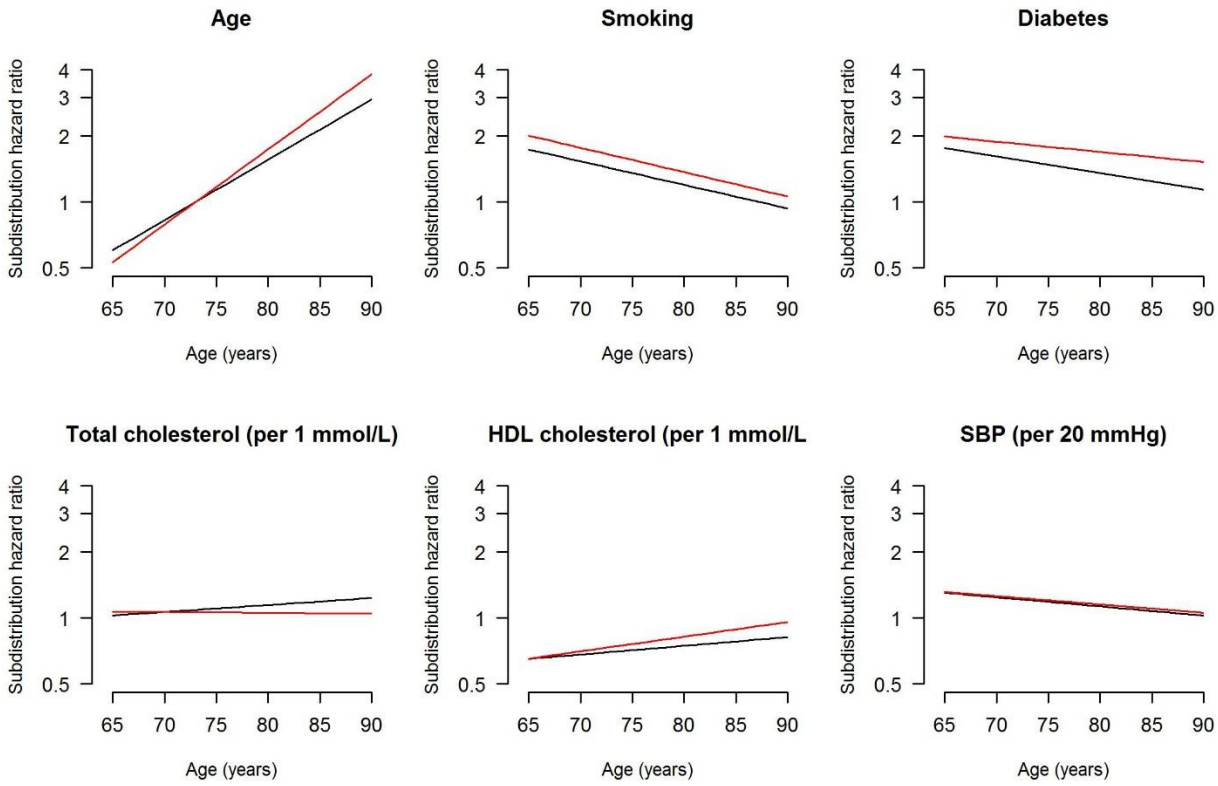
** Years of follow-up depending on the maximum number of years of follow-up available per study population that could give a reliable estimate of model performance, with a maximum of 10 years

Supplementary Figure 1: The distribution of countries in risk regions based on the age-standardized CVD mortality rates

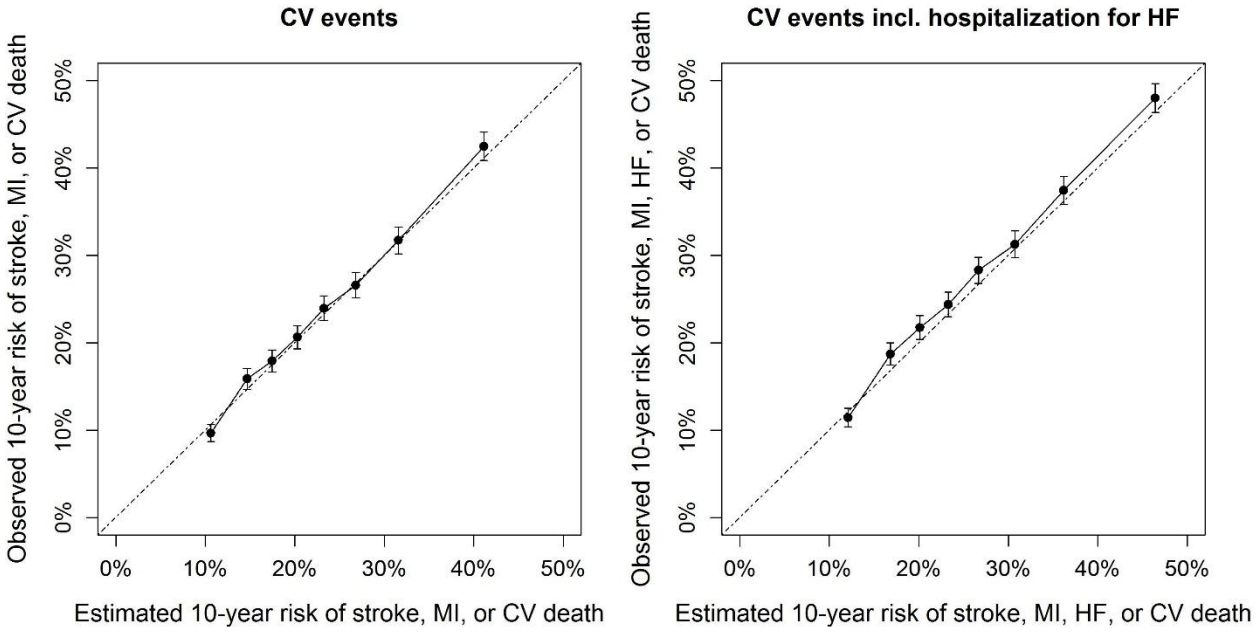


Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD chapters 9, I00-I99). The four groupings were: low risk (<100 CVD deaths per 100,000), moderate risk (100 to <150 CVD deaths per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

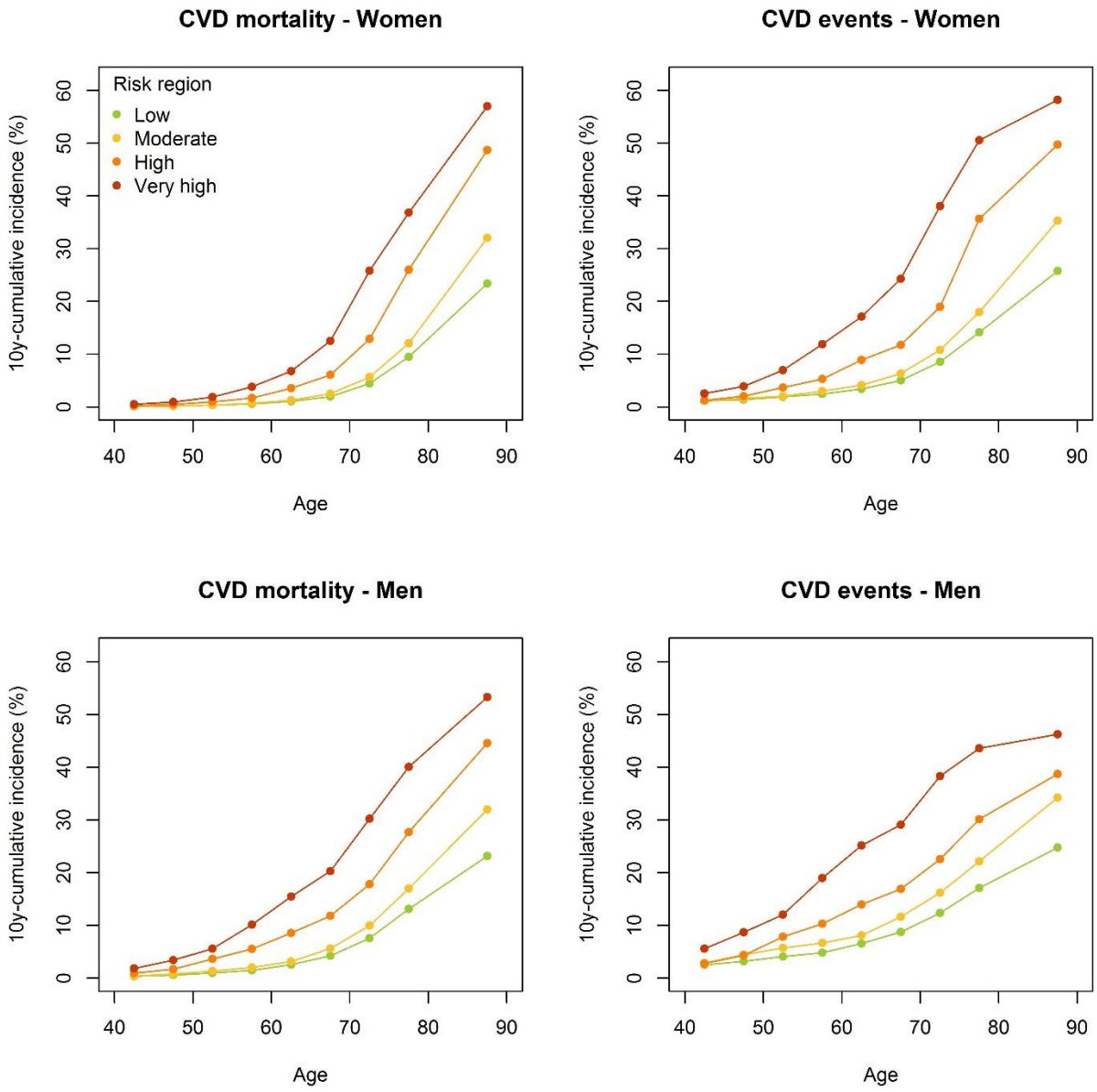
Supplementary Figure 2: The relative effect of risk factors at different ages (black=male; red=female)



Supplementary Figure 3: Calibration plots of observed versus estimated risks in deciles of risk in the CONOR study population (internal validation) for (left) CVD event risk, and (right) CVD event risk including hospitalization for heart failure

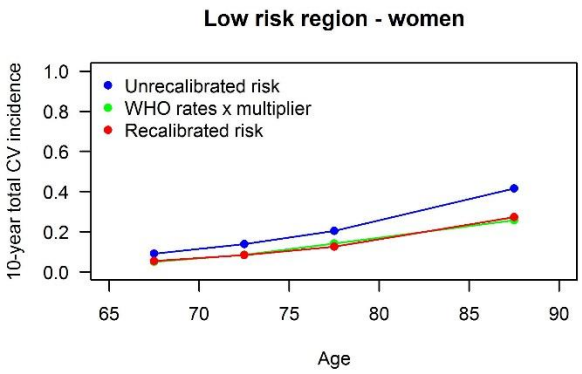


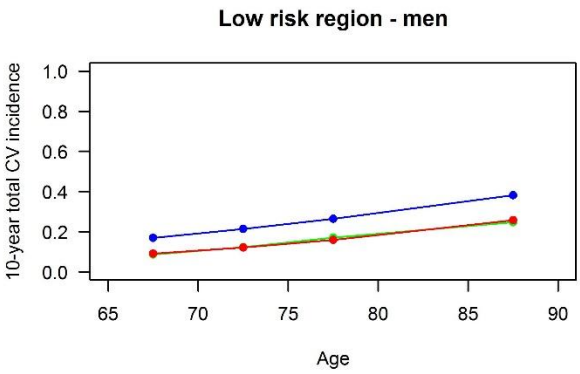
Supplementary Figure 4: Cardiovascular mortality and incidence in all risk regions in the entire middle-aged and older population.

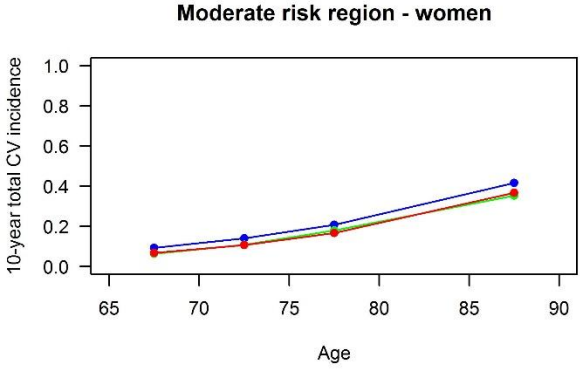


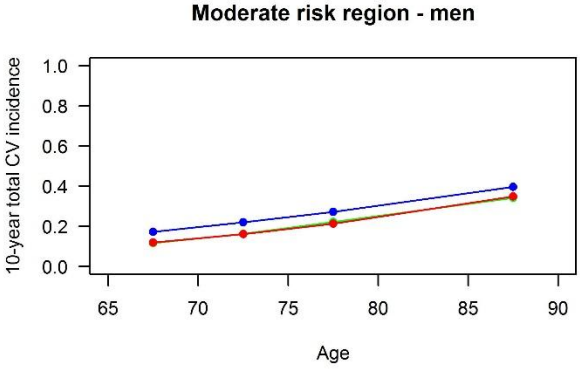
Regional age- and sex-specific CVD mortality rates (left) in the general population; regional age- and sex-specific CVD event rates in the primary prevention setting.

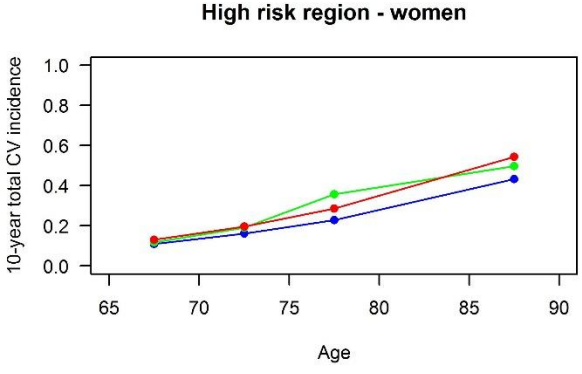
Supplementary Figure 5: Estimated CVD incidence rates and predicted risks

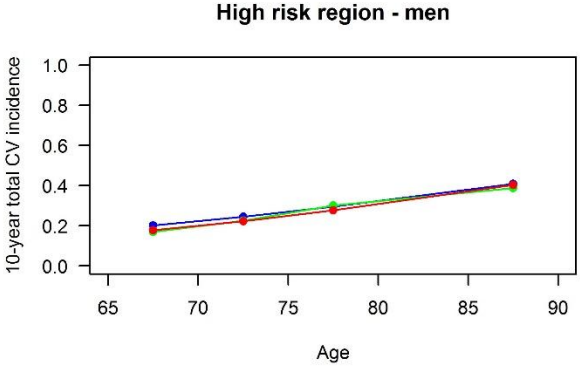

Low risk region - women
Unrecalibrated risk
WHO rates x multiplier
Recalibrated risk
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age

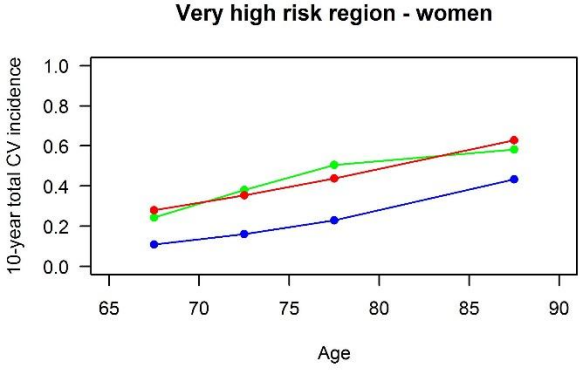

Low risk region - men
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age

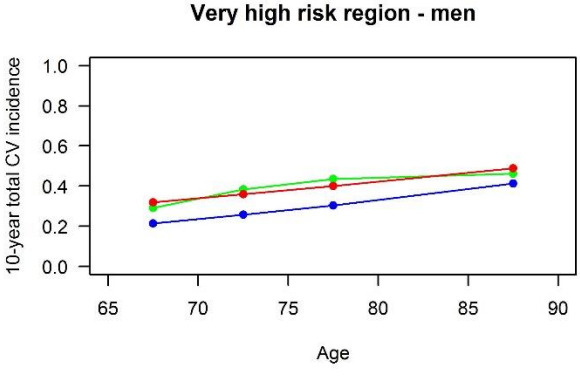

Moderate risk region - women
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age


Moderate risk region - men
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age

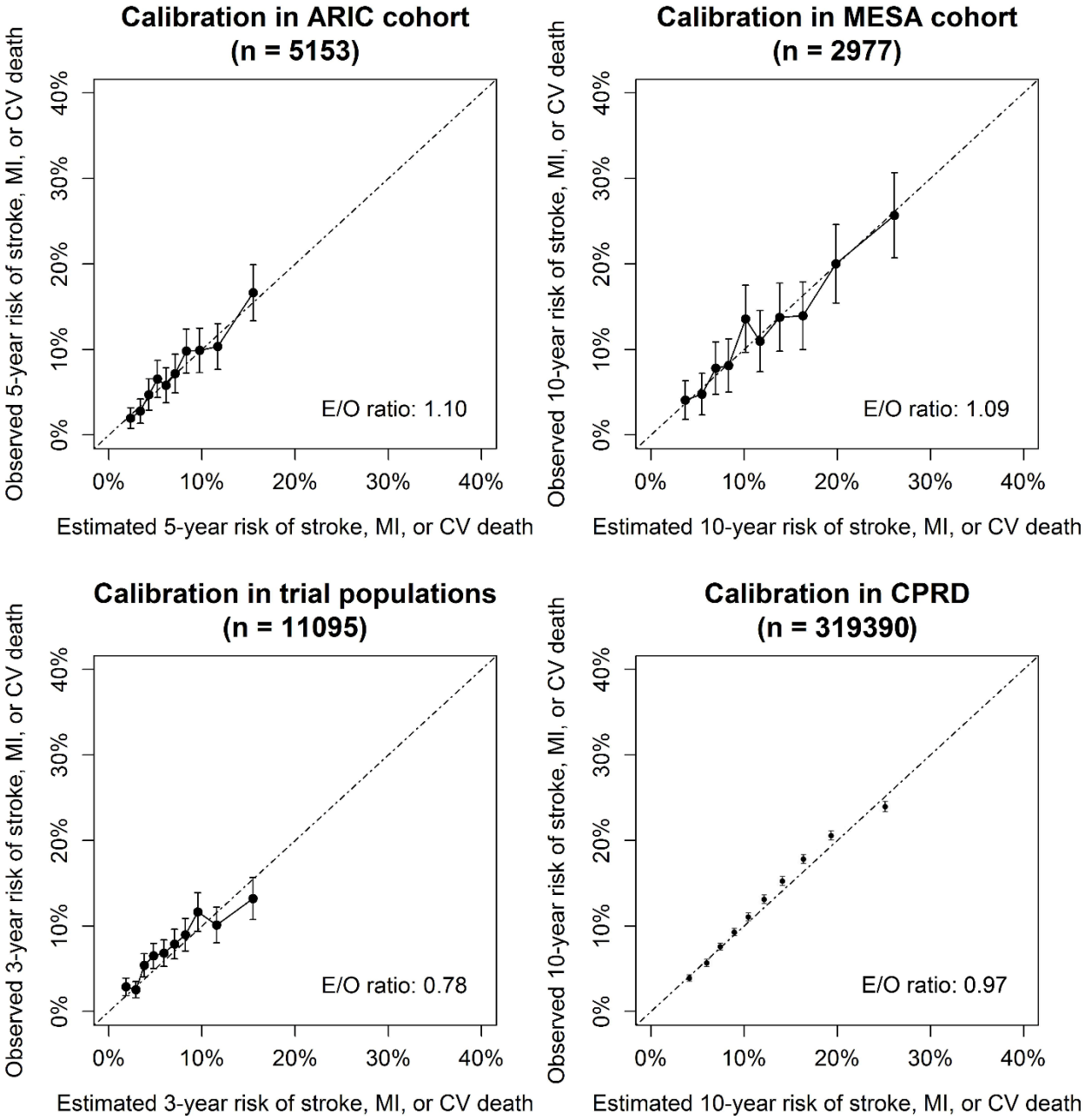

High risk region - women
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age


High risk region - men
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age


Very high risk region - women
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age

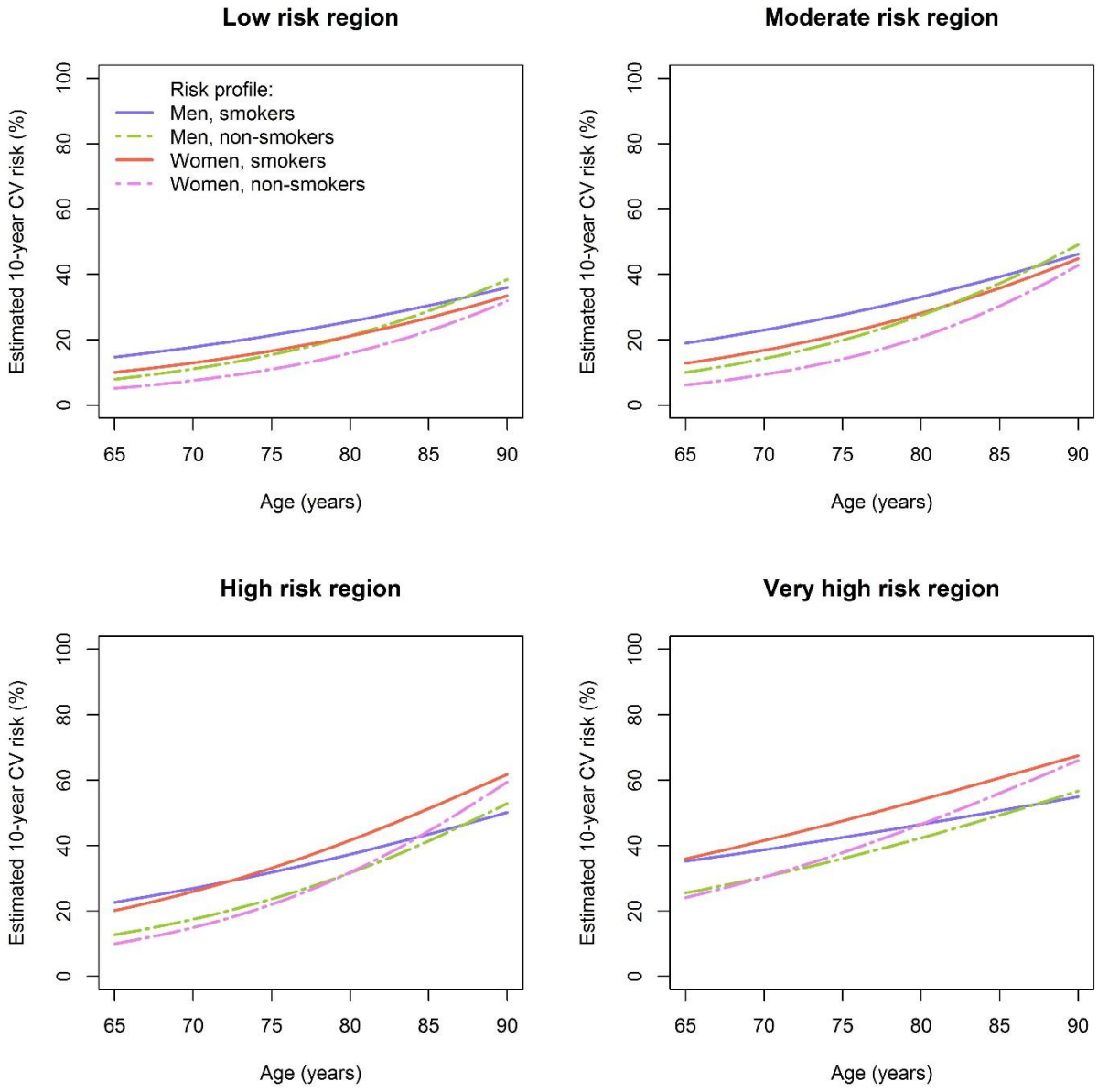

Very high risk region - men
10-year total CV incidence
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age

Supplementary Figure 6: Calibration plots of observed versus estimated (O/E) risks with O/E ratios within deciles of the external validation study populations. Risks were estimated for 3, 5, or 10 year time periods depending on available follow-up per study.



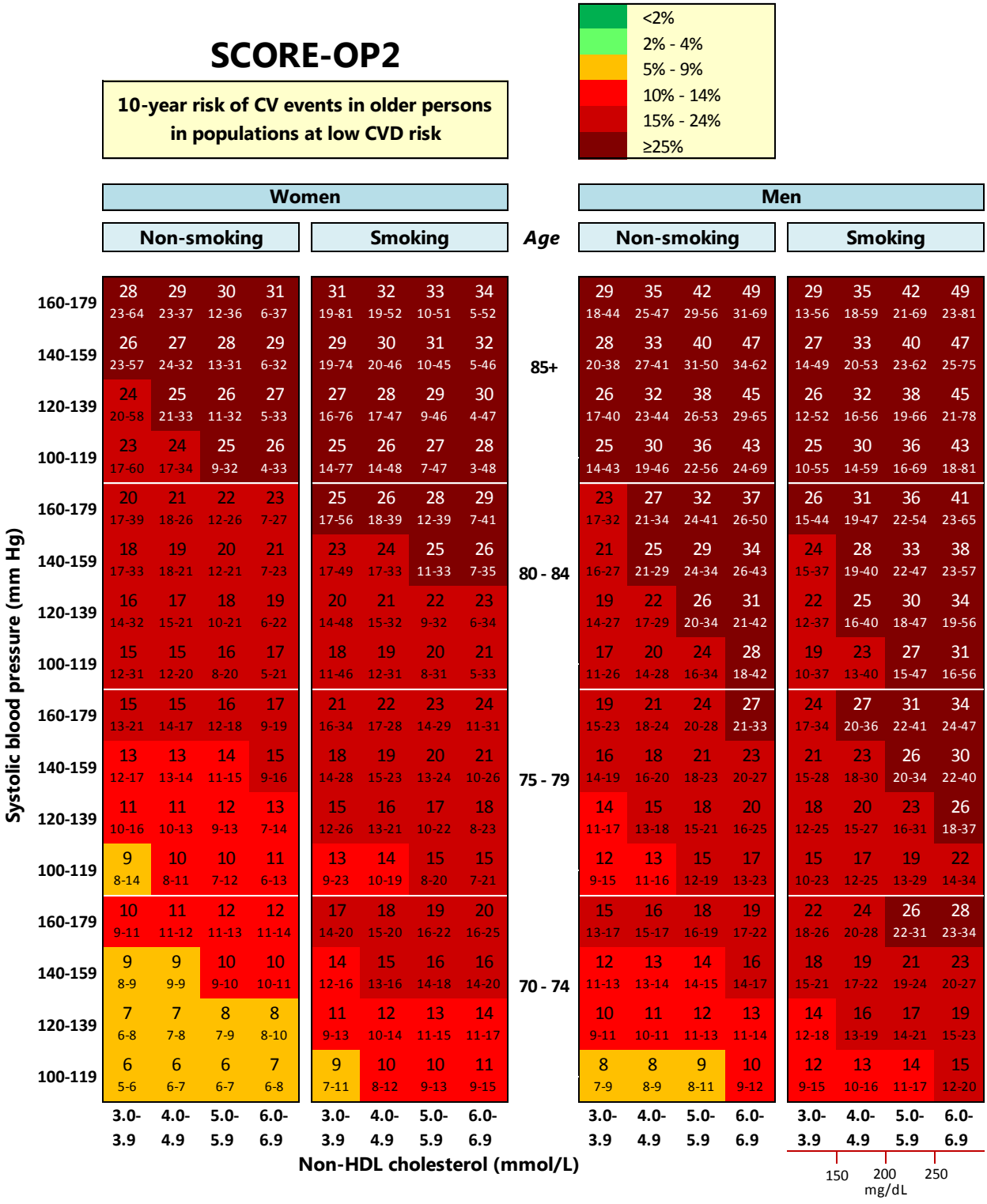
The estimated risks were recalibrated per study using the study-specific O/E ratio. The O/E ratio reflects the difference in baseline risk between the study population and risk region from which the study population comes, which may be affected due to participant selection and timeliness of the data.

Supplementary Figure 7: SCORE2-OP predicted risks for given risk factors in all European regions

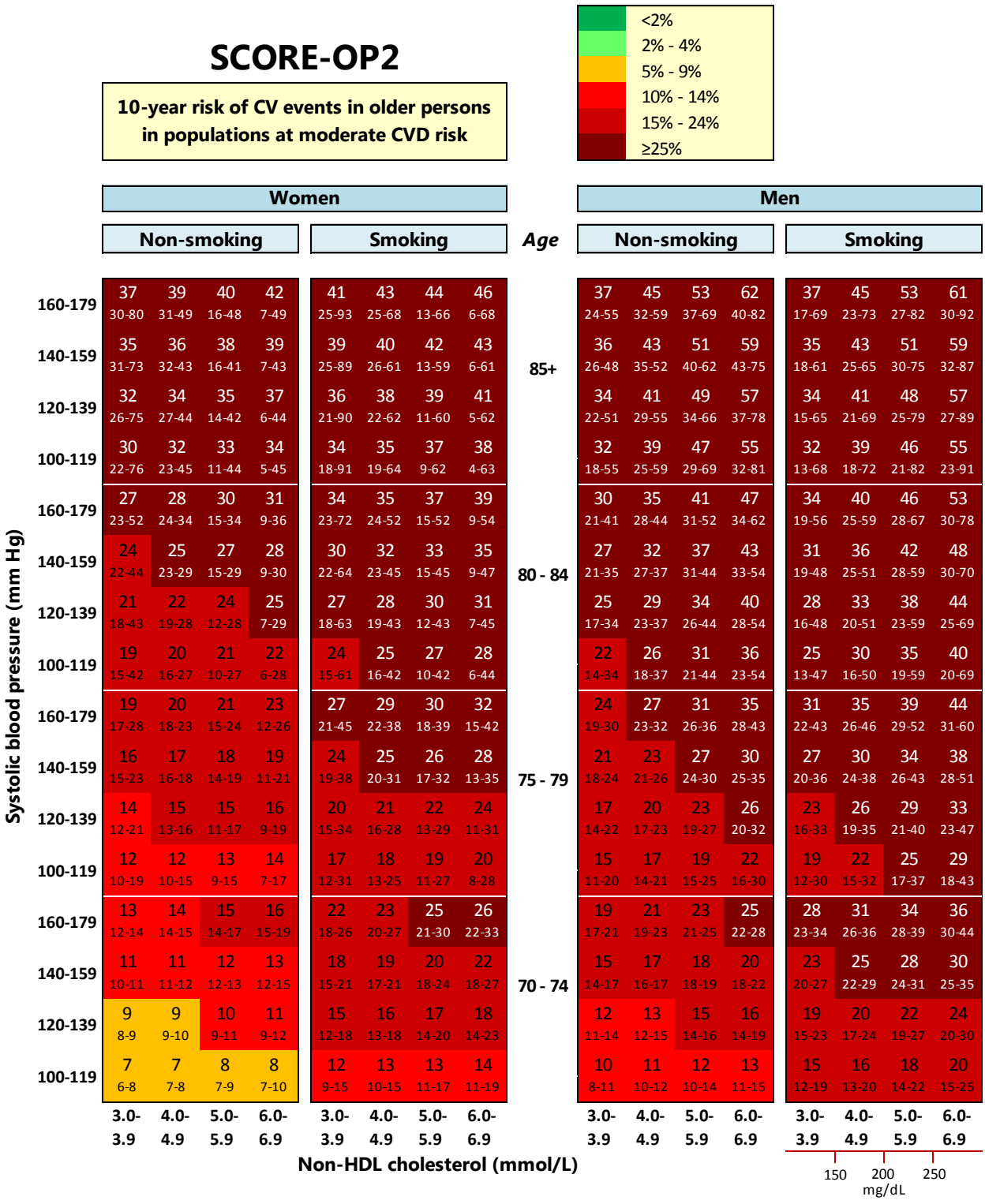


Predicted risks in all European regions for different risk profiles. Predictions for individuals with a non-HDL cholesterol of 4.5 mmol/l, and systolic blood pressure of 150mmHg, assuming no diabetes mellitus.

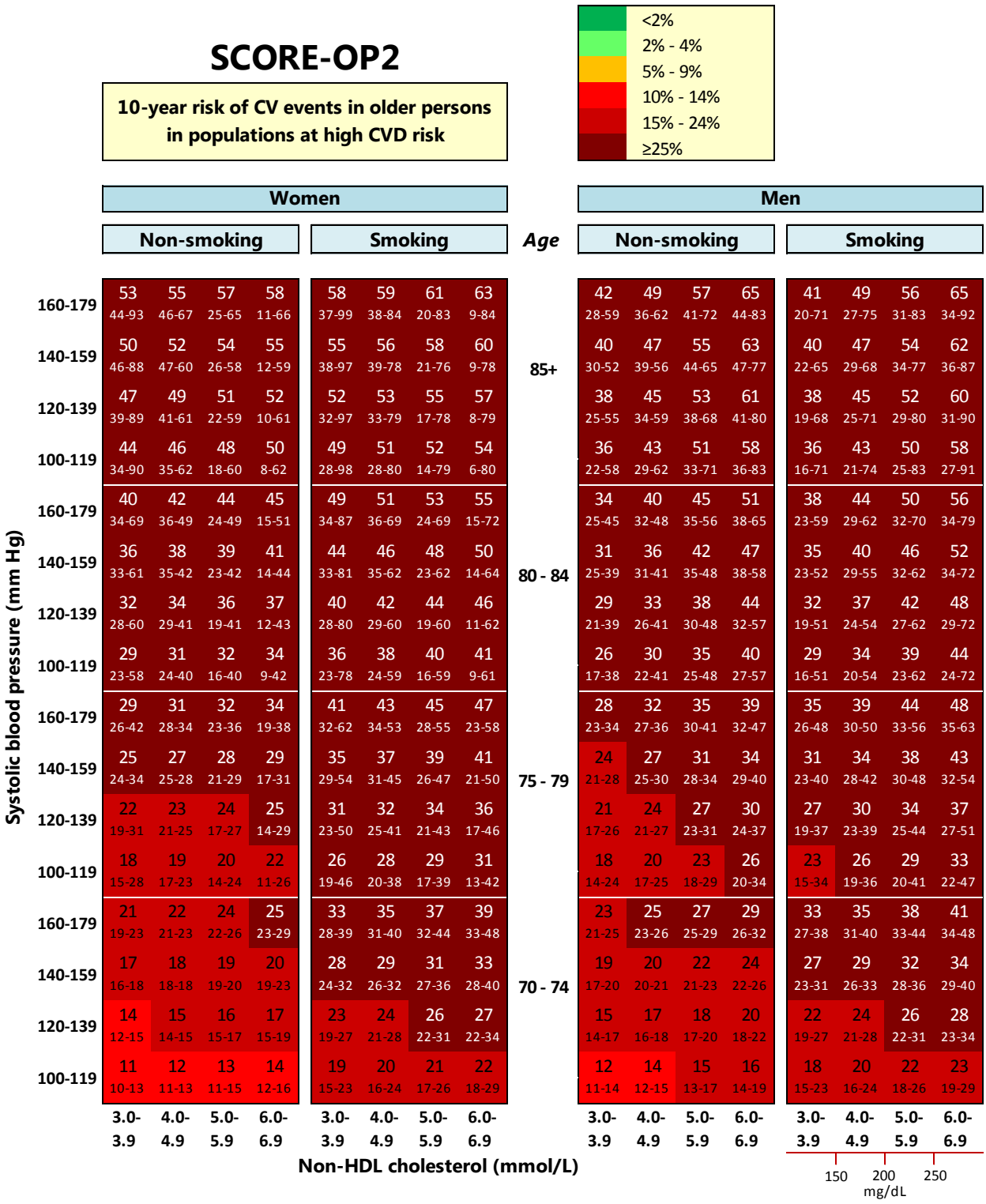
Supplementary Figure 8: Risk charts of 10-year risk in all four risk regions with uncertainty bounds based on the 95% CI of the risk model parameters



(sFig 8 cont.)

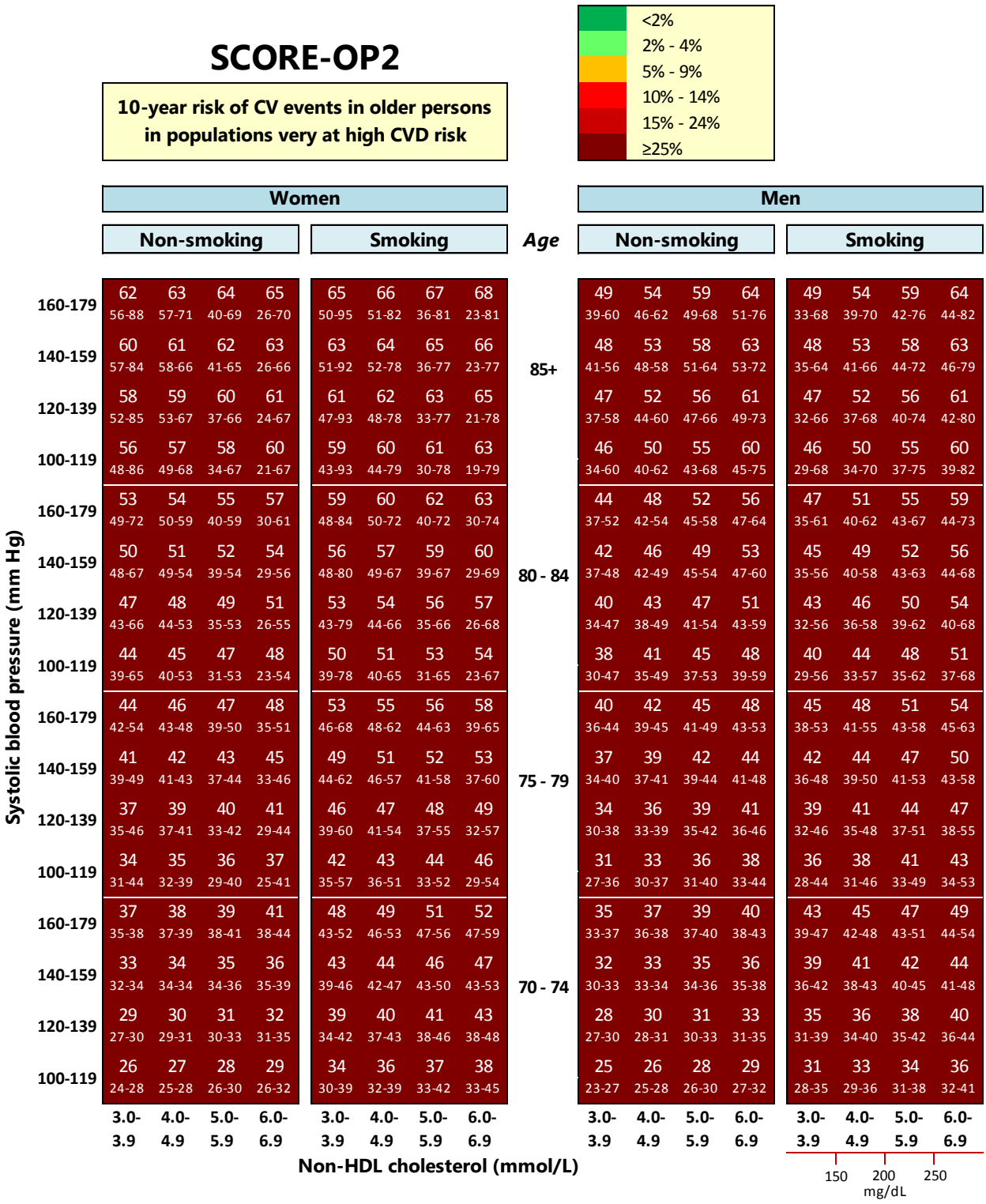

SCORE-OP2
10-year risk of CV events in older persons in populations at moderate CVD risk
<2%
2% - 4%
5% - 9%
10% - 14%
15% - 24%
≥25%
Women
Men
Non-smoking
Smoking
Non-smoking
Smoking
Age
Systolic blood pressure (mm Hg)
160-179
140-159
120-139
100-119
85+
80 - 84
75 - 79
70 - 74
3.0-3.9
4.0-4.9
5.0-5.9
6.0-6.9
Non-HDL cholesterol (mmol/L)
150
200
250
mg/dL

(sFig 8 cont.)



Systolic blood pressure (mm Hg)	Age	Women Non-smoking 3.0-3.9	Women Non-smoking 4.0-4.9	Women Non-smoking 5.0-5.9	Women Non-smoking 6.0-6.9	Women Smoking 3.0-3.9	Women Smoking 4.0-4.9	Women Smoking 5.0-5.9	Women Smoking 6.0-6.9	Men Non-smoking 3.0-3.9	Men Non-smoking 4.0-4.9	Men Non-smoking 5.0-5.9	Men Non-smoking 6.0-6.9	Men Smoking 3.0-3.9	Men Smoking 4.0-4.9	Men Smoking 5.0-5.9	Men Smoking 6.0-6.9
160-179	85+	53 (44-93)	55 (46-67)	57 (25-65)	58 (11-66)	58 (37-99)	59 (38-84)	61 (20-83)	63 (9-84)	42 (28-59)	49 (36-62)	57 (41-72)	65 (44-83)	41 (20-71)	49 (27-75)	56 (31-83)	65 (34-92)
140-159	85+	50 (46-88)	52 (47-60)	54 (26-58)	55 (12-59)	55 (38-97)	56 (39-78)	58 (21-76)	60 (9-78)	40 (30-52)	47 (39-56)	55 (44-65)	63 (47-77)	40 (22-65)	47 (29-68)	54 (34-77)	62 (36-87)
120-139	85+	47 (39-89)	49 (41-61)	51 (22-59)	52 (10-61)	52 (32-97)	53 (33-79)	55 (17-78)	57 (8-79)	38 (25-55)	45 (34-59)	53 (38-68)	61 (41-80)	38 (19-68)	45 (25-71)	52 (29-80)	60 (31-90)
100-119	85+	44 (34-90)	46 (35-62)	48 (18-60)	50 (8-62)	49 (28-98)	51 (28-80)	52 (14-79)	54 (6-80)	36 (22-58)	43 (29-62)	51 (33-71)	58 (36-83)	36 (16-71)	43 (21-74)	50 (25-83)	58 (27-91)
160-179	80 - 84	40 (34-69)	42 (36-49)	44 (24-49)	45 (15-51)	49 (34-87)	51 (36-69)	53 (24-69)	55 (15-72)	34 (25-45)	40 (32-48)	45 (35-56)	51 (38-65)	38 (23-59)	44 (29-62)	50 (32-70)	56 (34-79)
140-159	80 - 84	36 (33-61)	38 (35-42)	39 (23-42)	41 (14-44)	44 (33-81)	46 (35-62)	48 (23-62)	50 (14-64)	31 (25-39)	36 (31-41)	42 (35-48)	47 (38-58)	35 (23-52)	40 (29-55)	46 (32-62)	52 (34-72)
120-139	80 - 84	32 (28-60)	34 (29-41)	36 (19-41)	37 (12-43)	40 (28-80)	42 (29-60)	44 (19-60)	46 (11-62)	29 (21-39)	33 (26-41)	38 (30-48)	44 (32-57)	32 (19-51)	37 (24-54)	42 (27-62)	48 (29-72)
100-119	80 - 84	29 (23-58)	31 (24-40)	32 (16-40)	34 (9-42)	36 (23-78)	38 (24-59)	40 (16-59)	41 (9-61)	26 (17-38)	30 (22-41)	35 (25-48)	40 (27-57)	29 (16-51)	34 (20-54)	39 (23-62)	44 (24-72)
160-179	75 - 79	29 (26-42)	31 (28-34)	32 (23-36)	34 (19-38)	41 (32-62)	43 (34-53)	45 (28-55)	47 (23-58)	28 (23-34)	32 (27-36)	35 (30-41)	39 (32-47)	35 (26-48)	39 (30-50)	44 (33-56)	48 (35-63)
140-159	75 - 79	25 (24-34)	27 (25-28)	28 (21-29)	29 (17-31)	35 (29-54)	37 (31-45)	39 (26-47)	41 (21-50)	24 (21-28)	27 (25-30)	31 (28-34)	34 (29-40)	31 (23-40)	34 (28-42)	38 (30-48)	43 (32-54)
120-139	75 - 79	22 (19-31)	23 (21-25)	24 (17-27)	25 (14-29)	31 (23-50)	32 (25-41)	34 (21-43)	36 (17-46)	21 (17-26)	24 (21-27)	27 (23-31)	30 (24-37)	27 (19-37)	30 (23-39)	34 (25-44)	37 (27-51)
100-119	75 - 79	18 (15-28)	19 (17-23)	20 (14-24)	22 (11-26)	26 (19-46)	28 (20-38)	29 (17-39)	31 (13-42)	18 (14-24)	20 (17-25)	23 (18-29)	26 (20-34)	23 (15-34)	26 (19-36)	29 (20-41)	33 (22-47)
160-179	70 - 74	21 (19-23)	22 (21-23)	24 (22-26)	25 (23-29)	33 (28-39)	35 (31-40)	37 (32-44)	39 (33-48)	23 (21-25)	25 (23-26)	27 (25-29)	29 (26-32)	33 (27-38)	35 (31-40)	38 (33-44)	41 (34-48)
140-159	70 - 74	17 (16-18)	18 (18-18)	19 (19-20)	20 (19-23)	28 (24-32)	29 (26-32)	31 (27-36)	33 (28-40)	19 (17-20)	20 (20-21)	22 (21-23)	24 (22-26)	27 (23-31)	29 (26-33)	32 (28-36)	34 (29-40)
120-139	70 - 74	14 (12-15)	15 (14-15)	16 (15-17)	17 (15-19)	23 (19-27)	24 (21-28)	26 (22-31)	27 (22-34)	15 (14-17)	17 (16-18)	18 (17-20)	20 (18-22)	22 (19-27)	24 (21-28)	26 (22-31)	28 (23-34)
100-119	70 - 74	11 (10-13)	12 (11-13)	13 (11-15)	14 (12-16)	19 (15-23)	20 (16-24)	21 (17-26)	22 (18-29)	12 (11-14)	14 (12-15)	15 (13-17)	16 (14-19)	18 (15-23)	20 (16-24)	22 (18-26)	23 (19-29)

(sFig 8 cont.)


SCORE-OP2
10-year risk of CV events in older persons in populations very at high CVD risk
<2%
2% - 4%
5% - 9%
10% - 14%
15% - 24%
≥25%
Women
Men
Non-smoking
Smoking
Age
Non-smoking
Smoking
Systolic blood pressure (mm Hg)
160-179
140-159
120-139
100-119
85+
80 - 84
75 - 79
70 - 74
62 56-88 63 57-71 64 40-69 65 26-70 65 50-95 66 51-82 67 36-81 68 23-81 49 39-60 54 46-62 59 49-68 64 51-76 49 33-68 54 39-70 59 42-76 64 44-82
60 57-84 61 58-66 62 41-65 63 26-66 63 51-92 64 52-78 65 36-77 66 23-77 48 41-56 53 48-58 58 51-64 63 53-72 48 35-64 53 41-66 58 44-72 63 46-79
58 52-85 59 53-67 60 37-66 61 24-67 61 47-93 62 48-78 63 33-77 65 21-78 47 37-58 52 44-60 56 47-66 61 49-73 47 32-66 52 37-68 56 40-74 61 42-80
56 48-86 57 49-68 58 34-67 60 21-67 59 43-93 60 44-79 61 30-78 63 19-79 46 34-60 50 40-62 55 43-68 60 45-75 46 29-68 50 34-70 55 37-75 60 39-82
53 49-72 54 50-59 55 40-59 57 30-61 59 48-84 60 50-72 62 40-72 63 30-74 44 37-52 48 42-54 52 45-58 56 47-64 47 35-61 51 40-62 55 43-67 59 44-73
50 48-67 51 49-54 52 39-54 54 29-56 56 48-80 57 49-67 59 39-67 60 29-69 42 37-48 46 42-49 49 45-54 53 47-60 45 35-56 49 40-58 52 43-63 56 44-68
47 43-66 48 44-53 49 35-53 51 26-55 53 43-79 54 44-66 56 35-66 57 26-68 40 34-47 43 38-49 47 41-54 51 43-59 43 32-56 46 36-58 50 39-62 54 40-68
44 39-65 45 40-53 47 31-53 48 23-54 50 39-78 51 40-65 53 31-65 54 23-67 38 30-47 41 35-49 45 37-53 48 39-59 40 29-56 44 33-57 48 35-62 51 37-68
44 42-54 46 43-48 47 39-50 48 35-51 53 46-68 55 48-62 56 44-63 58 39-65 40 36-44 42 39-45 45 41-49 48 43-53 45 38-53 48 41-55 51 43-58 54 45-63
41 39-49 42 41-43 43 37-44 45 33-46 49 44-62 51 46-57 52 41-58 53 37-60 37 34-40 39 37-41 42 39-44 44 41-48 42 36-48 44 39-50 47 41-53 50 43-58
37 35-46 39 37-41 40 33-42 41 29-44 46 39-60 47 41-54 48 37-55 49 32-57 34 30-38 36 33-39 39 35-42 41 36-46 39 32-46 41 35-48 44 37-51 47 38-55
34 31-44 35 32-39 36 29-40 37 25-41 42 35-57 43 36-51 44 33-52 46 29-54 31 27-36 33 30-37 36 31-40 38 33-44 36 28-44 38 31-46 41 33-49 43 34-53
37 35-38 38 37-39 39 38-41 41 38-44 48 43-52 49 46-53 51 47-56 52 47-59 35 33-37 37 36-38 39 37-40 40 38-43 43 39-47 45 42-48 47 43-51 49 44-54
33 32-34 34 34-34 35 34-36 36 35-39 43 39-46 44 42-47 46 43-50 47 43-53 32 30-33 33 33-34 35 34-36 36 35-38 39 36-42 41 38-43 42 40-45 44 41-48
29 27-30 30 29-31 31 30-33 32 31-35 39 34-42 40 37-43 41 38-46 43 38-48 28 27-30 30 28-31 31 30-33 33 31-35 35 31-39 36 34-40 38 35-42 40 36-44
26 24-28 27 25-28 28 26-30 29 26-32 34 30-39 36 32-39 37 33-42 38 33-45 25 23-27 26 25-28 28 26-30 29 27-32 31 28-35 33 29-36 34 31-38 36 32-41
3.0-3.9
4.0-4.9
5.0-5.9
6.0-6.9
Non-HDL cholesterol (mmol/L)
150
200
250
mg/dL

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