

Prediction of incident heart failure in individuals without prior cardiovascular disease: the SCORE2-HF risk model

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Abstract

Background and Aims Heart failure (HF) presents a significant and growing public health challenge. The aim of this study was to develop and validate SCORE2-HF, a model for HF risk estimation in European adults aged over 40-years without previous cardiovascular disease.

Methods Using data from 25 prospective cohorts (14 countries, 611 778 individuals, 21 818 incident HF events) the sex-specific, competing risk-adjusted SCORE2-HF models were derived including age, smoking status, systolic blood pressure, antihypertensive

1 treatment, body mass-index (BMI), estimated glomerular filtration rate, and type 2 diabetes
2 mellitus (T2DM), including age at diagnosis and glycated haemoglobin. Using Europe-wide
3 statistics from the World Health Organization and linked health records from five countries
4 (>36 million individuals, 515 466 incident HF events) models were recalibrated to
5 contemporary 10-year and 30-year HF incidence in four European risk regions. SCORE2-HF
6 was validated using data from three further cohorts (three countries; 1 336 824 participants;
7 36 841 incident HF-events).

8 **Results** In the three external validation cohorts, C-indices (95% confidence interval) were
9 0.827 (0.824–0.829), 0.839 (0.827–0.850) and 0.874 (0.863–0.884). SCORE2-HF risks varied
10 importantly by individual's risk factors, and risk region. For example, in the low-risk region,
11 the average 10-year risk for 70-year-old individuals with zero versus four adverse risk
12 factors (smoking, T2DM, hypertension and BMI >30 kg/m²), was 8% versus 24% in men and
13 6% versus 20% in women. By contrast, in the very high-risk region, average SCORE2-HF risk
14 with four adverse risk factors was 59% in 70-year-old men or women.

15 **Conclusions** SCORE2-HF – a model derived, recalibrated and validated to estimate 10-year
16 and 30-year risk of incident HF across European countries – may enhance the identification
17 of individuals at higher risk of developing HF.

20 Introduction

21 Heart failure (HF) – a condition that leads to diminished quality of life, frequent
22 hospitalizations, substantial healthcare costs, and high mortality rates^{1,2} - presents a

1 significant and growing public health challenge^{3,4}. Globally, age-standardized prevalence
2 has increased over the past three decades.⁵ Age-standardized rates have increased in the
3 United Kingdom (UK) and the United States (US) in the last decade, including for individuals
4 <70 years,^{6,7} but the overall burden is significantly propelled by population ageing^{4,8}.

5 There may be unrealized opportunities to enhance HF prevention, linking it with established
6 initiatives that aim to prevent atherosclerotic cardiovascular disease (CVD)^{9–13}. For example,
7 the 2021 European Society of Cardiology (ESC) guidelines on CVD prevention, the 2023
8 Guidelines on CVD and diabetes, and the 2025 focused update of the guidelines for
9 management of dyslipidaemias, recommend personalized risk assessment using the
10 SCORE2, SCORE2-OP and SCORE2-Diabetes risk models to guide preventive
11 interventions^{4,10,13–16}. However, while these SCORE2 models estimate 10-year risk of non-
12 fatal myocardial infarction, non-fatal stroke or CVD death, they do not include non-fatal HF
13 as an outcome, highlighting opportunities for additional targeted strategies to mitigate HF
14 risk in high-risk individuals¹⁷, such as with sodium–glucose cotransporter 2 (SGLT2)
15 inhibitors that substantially reduce HF risk in high-risk adults without established CVD.^{18,19}

16 Most existing HF risk prediction models are not specifically focused on individuals without
17 prior CVD making them unsuitable for use in primary prevention strategies²⁰. Furthermore,
18 HF models that are focused on primary prevention have limitations, especially for use in the
19 European context; including lack of derivation or validation in European populations,
20 inclusion of risk predictors not routinely available in general practice, e.g. electrocardiogram
21 (ECG) variables^{12,20,21}; and/or failure to statistically adapt (“recalibrate”) models to the level
22 of HF risk in contemporary target populations^{12,20,21}.

To address these limitations, we detail the development and validation of SCORE2-HF, a new prediction model to estimate risk of incident HF among individuals aged over 40 years without previous CVD across Europe.

Methods

Study design

The SCORE2-HF project involved multiple data sources (**Figure 1**). First, to enable reliable estimation of age- and sex-specific relative risks, we derived models for the prediction of fatal and non-fatal HF outcomes using individual-participant data from the UK Biobank (UKB) cohort²² and 24 cohorts from the Emerging Risk Factors Collaboration (ERFC)²³. Second, to ensure applicability to the broader contemporary primary prevention population in different regions of Europe, we recalibrated the derived risk models using estimated age- and sex-specific incidence estimates and risk factor distributions derived from contemporary national or subnational population-representative data sources. Third, to enhance validity and generalisability, we performed external validation using individual-participant data from England's Clinical Practice Research Datalink (Gold data source, CPRD)²⁴, Norway's Trøndelag Health Study (Third survey: HUNT3)²⁵, and the Estonian Biobank (2018 wave, EstBB)²⁶. Fourth, to illustrate the variation of CVD risk across European countries, we applied the model to contemporary populations.

Data sources

For model derivation, we used individual-participant data from UKB and ERFC. UKB is a large prospective cohort study with individual-participant data on approximately 500 000

1 participants aged >40 years recruited across 23 UK based assessment centres between
2 2006 and 2010 and followed-up for cause-specific morbidity and mortality through linkages
3 to multiple health records²². The ERFC has collated and harmonised individual-participant
4 data from >100 long-term prospective cohort studies of CVD risk factors and outcomes²³.
5 Prospective studies in the ERFC were included in this analysis if they met all the following
6 criteria: were approximately population-based (i.e. did not select participants on the basis
7 of having previous disease [e.g. case-control studies]); had recorded cause-specific deaths
8 and/or non-fatal HF events for at least 1 year of follow-up; and had recorded baseline
9 information on the following risk factors necessary to derive risk prediction models: age,
10 current smoking, history of type 2 diabetes mellitus (T2DM), systolic blood pressure (SBP),
11 antihypertensive medication use, body mass index (BMI), estimated glomerular filtration
12 rate (eGFR, estimated using the 2021 Chronic Kidney Disease Epidemiology Collaboration
13 [CKD-EPI] creatinine-based equations²⁷) or creatinine (to calculate eGFR), and T2DM
14 characteristics (age at diagnosis and glycated haemoglobin [HbA1c], or glucose).

15 To match the target populations of the SCORE2, SCORE2-Diabetes and SCORE2-OP risk
16 scores, individuals from UKB and ERFC cohorts with and without T2DM and aged 40 years
17 or over were included for model derivation if they had no recorded history of CVD or HF at
18 baseline (**Supplementary Figure 1**; prior disease definitions are detailed in **Supplementary**
19 **Table 1**).

20 SCORE2-HF was recalibrated to reflect contemporary HF incidence in four risk-regions of
21 Europe using methodology described in the statistical analysis and **Supplementary**

methods. This involved the use of summary data on risk predictors obtained from the Non-Communicable Disease Risk Factor Collaboration (NCD-RisC),^{28,29} and CPRD, and estimates of first HF incidence computed using a combination of CVD mortality rates from the World Health Organization (WHO) mortality database and national or subnational electronic health records data on >36 million individuals in five European countries. The electronic health records comprised the entire populations aged over 40 years in England (2022-2024)³⁰, Denmark (2010-2019, 2021-2022)³¹, the Stockholm region of Sweden (2010-2021)³², Estonia (2015-2023)³³, and the Podlaskie region of Northeastern Poland (2014-2015)³⁴. In all data sources used for recalibration, non-fatal HF outcomes were captured using hospital admissions data with HF in any diagnostic position. Additional information from primary care records were used to exclude those with prior CVD where relevant (**Supplementary Table 1**). Further details of the five included data sources are given in **Supplementary Tables 2 and 3**, and **Supplementary Figure 2**.

Data from CPRD²⁴, HUNT³⁵, and EstBB²⁶ were used for external validation of SCORE2-HF. Full details of the data sources are given in **Supplementary Table 4**; all represent general populations and inclusion criteria were the same as for the cohorts used for model derivation (**Supplementary Figure 1**).

The primary outcome was fatal or non-fatal HF (with either preserved or reduced ejection fraction). Follow-up was until the first non-fatal HF hospitalisation, death or end of the registration period. Non-fatal, non-HF CVD events during follow-up were ignored. Deaths not due to HF (non-HF deaths) were treated as competing events. International Classification of Diseases 10th Revision (ICD-10) codes included in the outcomes are provided in

Supplementary Table 1. A 10-year time-frame for risk prediction was chosen to align with previous CVD risk estimation systems already in clinical use^{36–38}. In addition, 30-year risk estimation was incorporated to allow risk estimation over a longer time period for individuals aged 40–59 whose 10-year risk may appear low, despite adverse levels of risk predictors. Missing data were imputed, using multiple imputation with chained equations, as described in the **Supplementary Methods**.

Statistical analysis

For model derivation, sex-specific coefficients (i.e. subdistribution hazard ratios [SHRs]) were estimated using Fine and Gray competing risk-adjusted models, stratified by cohort, and where relevant, by trial arm.³⁹ The sex-specific models included the following predictors: age (years), smoking (current vs other), history of T2DM (yes/no, defined by self-report and biochemical measurements/treatments), SBP (mmHg), antihypertensive medication use (current vs other), BMI (kg/m²), and eGFR (mL/min/1.73 m², estimated using the 2021 CKD-EPI creatinine-based equations). For individuals with T2DM, age at diagnosis (years) and HbA1c (mmol/mol) were also included. The risk factors were selected a priori due to their predictive ability based on previous literature^{20,21} as well as their availability in target populations for screening/clinical use, derivation cohorts, and population statistics needed for model recalibration. The modelling approach also aligns with the SCORE2, SCORE2-OP and SCORE2-Diabetes models, which also comprise sex-specific Fine and Gray models with similar readily available risk factors. Since previous research showed that associations of these risk factors with HF decline with increasing age,⁴⁰ age interactions were included for all predictors. An interaction between SBP and

1 antihypertensive medication was also included to capture increased risk associated with
2 treatment resistant hypertension. All continuous risk factors were included in the model
3 without categorization. Quadratic terms were included for eGFR and BMI to parsimoniously
4 capture non-linear associations observed in exploratory analysis of the shape of dose-
5 response relationships using fractional polynomials. There were no (or very minimal)
6 violations of proportional hazards assumptions, as assessed by inclusion of time varying
7 coefficients.

8 Risk models were recalibrated to four risk regions using methods detailed in the
9 **Supplementary Methods**. Briefly, risk regions were defined to align with the SCORE2
10 project (low-, moderate-, high- and very high-risk regions of Europe defined by their CVD
11 mortality rates, **Supplementary Table 5**). For each risk region, expected HF risk was
12 compared to predicted SCORE2-HF risk using sex-specific linear regressions of the
13 transformed risks over 5-year age groups. The intercept and slope from the regression was
14 applied to recalibrate the models. This process was completed for recalibration of the
15 ERFC/UKB models to give both 10-year risks and 30-year risks.

16 For the 'x-axis' values in the recalibration regressions, predicted risks by region, sex and age
17 group were estimated by applying the uncalibrated SCORE2-HF risk models with sex and
18 age group-specific average risk factor values from each risk region, obtained from the
19 NCD-RisC collaboration^{28,29} (supplemented by CPRD estimates for eGFR, HbA1c and age
20 of diabetes diagnosis only).

1 For the 'y-axis' values in the recalibration regressions, expected 10-year and 30-year HF
2 risks by region, sex and age group, adjusted for competing risk of non-HF death, were
3 estimated for each risk region using a lifetable approach. The lifetable was constructed
4 from derived estimates of HF incidence and non-HF mortality, which were obtained by
5 applying multipliers, pooled from the five representative data sources (**Supplementary**
6 **Tables 2 and 3**), to the region, sex and age group-specific WHO CVD mortality and non-HF
7 mortality estimates. The multiplier's calculation formula was designed to ensure that the
8 resulting rates applied to the population with no-prior CVD or HF. In this way, absolute HF
9 risk for individual countries, was determined primarily according to the country's regional
10 CVD mortality rate and the ratio of HF incidence to CVD mortality which was consistently
11 observed across the five representative data sources. Full details of the methods used to
12 estimate and apply the multipliers are given in the **Supplementary methods**.

13 For validation we assessed discrimination using Harrell's C-index, utilizing all available
14 follow-up time and adjusting for competing risks⁴¹. For internal validation, the C-index was
15 calculated separately within each of the ERFC/UKB cohorts and pooled weighting by the
16 number of contributing events⁴², and 10-fold cross-validation was performed to check for
17 optimism. Calibration was assessed by graphical comparison of predicted and observed
18 risk (with adjustment for competing risk). The performance of SCORE2-HF was also
19 compared with that seen for the AHA-PREVENT-HF, using the published, simplified logistic
20 regression implementation of PREVENT-HF¹².

21 To compare the proportion of the population estimated to be at different levels of HF risk
22 according to the SCORE2-HF 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.

Results

Model derivation involved a total of 611 778 individuals without previous CVD from UKB and 24 ERFC cohorts (**Table 1, Supplementary Table 6**). Median (interquartile range [IQR]) age at recruitment was 58 (49–64) years among men and 58 (51–64) among women (**Table 1**), with men constituting 45% of the cohort (275,006 individuals).

At a median (IQR) follow-up of 13.4 (12.3–14.2) years, a total of 21 818 first HF events were recorded (12 201 [56%] among men). SHRs are shown in **Supplementary Table 7**. The magnitude of relative associations of model predictors generally decreased with increasing age of participants (**Supplementary Figure 3**). Competing risk-adjusted associations of smoking, T2DM and antihypertensive medication use with HF were greater in magnitude for women versus men. The SCORE2-HF models showed good discrimination in the derivation data (**Figure 2**) with a C-index (95% confidence interval [CI]) of 0.754 (0.750–0.758).

For recalibration, estimation of sex- and age-specific first HF incidence rates, involved the application of multipliers from five data sources across low-, moderate- and high-risk regions (**Supplementary Table 3 and Supplementary Figure 4**). Multipliers were similar in different sources and so were pooled to give sex and age group-specific values for use across all risk regions. Multipliers were applied, within each risk region, to WHO CVD mortality statistics, to estimate first HF incidence, and to WHO non-HF mortality statistics to adjust these to be relevant to the population with no prior CVD (**Supplementary methods**). After application of

the multipliers, the estimated first HF incidence rates increased with age and risk region, and were similar in men and women (**Supplementary Figure 5**). After recalibration using the estimated recalibration factors (**Supplementary Table 8**), the SCORE2-HF predicted risks based on mean risk factor levels showed good agreement with the estimated HF event incidence (**Supplementary Figure 5**).

SCORE2-HF was externally validated using data from 1 227 276 individuals (33 946 HF events) from CPRD, 33 434 individuals (2054 HF events) from HUNT3, and 76 114 individuals (841 HF events) from EstBB, without previous CVD (**Supplementary Table 9**). SCORE2-HF showed good discrimination, with a C-index (95% CI) of 0.827 (0.825–0.829) in CPRD, 0.839 (0.827–0.850) in HUNT3 and 0.874 (0.863–0.884) in EstBB (**Figure 2**), that was similar to discrimination seen with the AHA PREVENT-HF risk score (C-index= 0.824 [0.822–0.826] in CPRD, 0.841 [0.830–0.852] in HUNT3 and 0.871 (0.860–0.882) in EstBB). C-indices were slightly higher in external validation cohorts since these had a wider age range than most cohorts used in the derivation datasets⁴² (**Supplementary Tables 6 and 9**).

Good discrimination was seen across various subgroups of the population, including those defined by sex, age and T2DM, and was comparable to PREVENT-HF in all of these subgroups (**Supplementary Figures 6-8**). Good discrimination was also seen for the 30-year SCORE2-HF models over the available follow-up period (around 10, 16 and 5 years for CPRD, HUNT3 and EstBB respectively), and this was similar to that seen with PREVENT-HF 30-year risk models (**Supplementary Figure 9**). SCORE2-HF was generally well calibrated in the contemporary and nationally representative data from CPRD, showing slight

overestimation of risk in those under the age of 70 years. Miscalibration was slightly greater for PREVENT-HF, which overestimated risk for men and women of all ages (**Supplementary Figure 10**). Likewise, SCORE2-HF showed good calibration specifically among individuals with T2DM from CPRD (**Supplementary Figure 11**).

Risk estimations varied importantly across individuals with different risk predictor values (**Figure 3**). For example, among 70-year-old men or women from the low-risk region who were non-smokers, with no history of T2DM, hypertension (defined as antihypertensive use or SBP >140 mmHg) or obesity (defined as BMI >30 kg/m²), average 10-year risk of HF was estimated to be 8% and 6%, respectively. However, for 70-year-old men or women from the low-risk region who were current smokers, with T2DM, hypertension and obesity, the average estimated 10-year risk of HF was 24% and 20%, respectively. Risk also increased substantially with risk region, with an average estimated 10-year risk for 70-year-old men or women with none of these adverse risk factors reaching 30% and 26%, respectively, in the very high-risk region (around four-fold higher compared with similar individuals in the low-risk region). Likewise, for 70-year-olds in the very high-risk region with all four adverse risk factor values, average risks were 59% for both men and women. The pattern of 30-year risks across individuals and risk regions was similar to that seen with 10-year risks (**Figure 3**). To facilitate use of SCORE2-HF during clinical encounters, a calculator to estimate individual 10-year or 30-year risk is provided in **Appendix 1**, using the process exemplified in **Supplementary Methods Table 1**.

Analysis using the individual participant risk factor distributions observed in CPRD suggested that SCORE2-HF provided further informative risk stratifications within CVD risk

categories using the SCORE2-CVD risk algorithm as recommended by the ESC guidelines (Figure 4). For example, the 2021 guidelines for CVD prevention recommend age-specific SCORE2 risk thresholds to define high-risk individuals (termed 'intermediate' risk in our analysis) in whom '*risk factor treatment should be considered*' (10-year risks of 2.5% to 7.5% for those aged 40-49, 5% to 10% for those aged 60-69, and 7.5% to 15% for those age ≥ 70). Likewise, the 2023 CVD and diabetes guidelines recommend that individuals with 10-year risk between 5% and 10% should be classified as moderate risk (defined as 'intermediate' risk for our analysis). Using these thresholds, 59%, 55%, 46% and 27% of men were defined as intermediate risk in the low-, moderate-, high- and very-high-risk regions of Europe, respectively. Of these men, 6%, 8%, 25% and 38% were estimated to have $\geq 10\%$ risk of incident HF. Likewise for the 32%, 35%, 31% and 30% of women classified at 'intermediate' CVD risk according to the guideline CVD risk thresholds, 22%, 21%, 31% and 24% would be at $>10\%$ risk of incident HF according to SCORE2-HF.

The distribution of SCORE2-HF risk estimates varied importantly across populations from different European countries (Figure 5), with over 80% of men and over 85% of women expected to be at $<10\%$ 10-year HF risk in most countries in the low-risk regions but fewer than 30% of men and fewer than 50% of women at $<10\%$ risk in the very high-risk region. As expected, HF risk estimates increased steeply with age in all risk regions (Supplementary Figure 12).

Discussion

To help empower HF prevention across European populations, we have developed, validated and illustrated SCORE2-HF, an algorithm designed to estimate the 10-year and 30-year risks of incident HF in individuals aged over 40 years, with or without T2DM, and with no prior history of CVD or HF. Designed to complement existing SCORE2 algorithms and to maximise clinical uptake, SCORE2-HF incorporates information routinely available for risk estimation in primary care settings. As SCORE2-HF has several advantages over previously developed HF risk prediction algorithms, it could enhance the identification of individuals at high HF risk across Europe who might benefit most from preventive interventions (Structured Graphical Abstract).

First, SCORE2-HF has been recalibrated to the HF risk observed in the broad target primary prevention population across four risk regions of Europe. By contrast, some previous HF models were derived in cohort studies not representative of the broader contemporary target populations in which they are intended for use. Whereas previous models have been liable to systematic mis-estimation of risk⁴³ due to their failure to account for such variations in risks by data source or geographical location, SCORE2-HF has limited such biases through systematic recalibration.

Second, the recalibration approach used in SCORE2-HF has been designed so that models can be readily updated to reflect future HF incidences and risk factor profiles of any target population of apparently healthy individuals who need risk assessment. Importantly, the

model's updating approach is pragmatic, cost-effective and scalable, requiring only contemporary aggregate-level data concerning the target population.

Third, as this approach to recalibration involves the same methods and European risk region definitions as used in other models recommended by the ESC (e.g., SCORE2, SCORE2-OP and SCORE2-Diabetes), it means that CVD and HF risk estimation could be readily synergised across Europe, empowering their concurrent primary prevention. Furthermore, compared to risk predictors used in SCORE2 risk estimation, SCORE2-HF additionally requires only eGFR, BMI and antihypertensive medication use allowing for easy simultaneous risk estimation. We have provided an excel calculator for estimation of SCORE-HF risk 10-year and 30-year risks (**Appendix 1**) and further online calculators/apps will be made available to facilitate risk estimation with both the SCORE2/SCORE2-OP/SCORE2-Diabetes models and SCORE2-HF.

Fourth, we have also demonstrated that SCORE2-HF provides both distinct and complementary information to the SCORE2 models, giving a more complete picture of the total CVD risk faced by individuals. For example, the 2021 ESC guidelines on CVD prevention recommend that individuals identified by SCORE2 to be in the age-specific 'high-risk' category should *consider* medical intervention (primarily to lower lipids and/or blood pressure) in a shared decision-making process. In a representative population, we have shown a broad range of SCORE2-HF risk estimates among individuals in this subgroup which could be used to inform such decisions. Likewise, for individuals with T2DM and no prior CVD, the decision to initiate glucose-lowering medication (e.g. SGLT2 inhibitors) is currently influenced by SCORE2-Diabetes estimates,⁴⁴ but could also take

1 into account SCORE2-HF estimates. SCORE2-HF was designed to estimate HF risk in the primary
2 prevention context, thereby completing the suite of SCORE2 models for CVD prevention in the general
3 population. Other risk prediction tools provide HF risk estimation in the secondary prevention context,
4 including SMART2-HF (**Please add reference EURHEARTJ-D-25-03903R1**) for individuals with existing
5 CVD, LIFE-Preserved (**Please add reference EURHEARTJ-D-25-03902R1**) and LIFE-HF⁴⁵ for individuals
6 with a history of HF.

7 Fifth, SCORE2-HF involves a facility to estimate 30-year HF risk in individuals aged under
8 60 years, enabling estimation of longer-term risk in younger individuals with substantial risk
9 factor burden, whose 10-year risk may, nonetheless, appear modest.

10 Sixth, we have shown that SCORE2-HF performs well in external validation, with good
11 discrimination and calibration. Discrimination was similar to that seen with the AHA-
12 PREVENT-HF risk models, but the systematic recalibration of SCORE2-HF ensured it
13 performed better in terms of calibration in the Low-risk region and is also likely to be better
14 calibrated to moderate-, high- and very high-risk countries.

15 Finally, our project has illustrated the expected risk classification of individuals using
16 SCORE2-HF, using data estimated from all European countries, showing that the
17 proportions of individuals in specific risk categories differ substantially across countries.
18 This diversity highlights why policymakers and practitioners need tailored tools like
19 SCORE2-HF to help make more appropriate and locally informed decisions about the
20 allocation of prevention resources.

21 The potential limitations of this effort merit consideration. We derived the risk prediction
22 models in predominantly low-risk cohorts from 15 countries (with 78% of contributing

1 individuals from the UK). Ideally, however, the derivation of risk models would have
2 involved large nationally representative cohorts across all four European risk regions.
3 Unfortunately, availability of such data across Europe is limited. Indeed, even the European
4 cohorts included may not be nationally representative, reflecting a baseline from past
5 decades and self-selected participants such as healthy volunteers.⁴⁶ However, while
6 healthy volunteer bias can lead to low estimates of absolute risk, relative risks are generally
7 unaffected.⁴⁷ Our approach therefore makes the assumption that the relative risks
8 obtained in the derivation dataset are transferable across different populations, and this is
9 evidenced by good discrimination of the score in external validation across three countries.
10 Furthermore, to avoid systematically inaccurate absolute risk estimation due to the biases
11 of cohort studies, we recalibrated models using nationally representative HF incidence
12 rates. Currently SCORE2-HF has been recalibrated using WHO CVD mortality data from all
13 European risk regions, adapted to represent HF incidence in those with no prior CVD, using
14 relationships observed between CVD mortality and HF incidence in five large national or
15 sub-national data sources. In the future, should reliable data on first event HF incidence
16 become available by region-, country- or within-country region, they can be used to refine
17 the recalibration of SCORE2-HF.

18 To quantify HF rates in the data sources used for recalibration, non-fatal incident HF was
19 ascertained from hospital admission data and therefore may not capture chronic HF diagnoses
20 managed only in outpatient settings. Furthermore, underdiagnosis of HF has been previously
21 observed in both primary and secondary care settings^{48,49}. However, our use of hospital
22 admissions records with HF in any diagnostic position (rather than primary position only) is

likely to recover some HF diagnoses made (or missed) earlier in outpatient settings. While identification of individual HF cases using any versus primary position has been shown to have slightly lower positive predictive value, the aggregate level incidence by sex and age group used in SCORE2-HF recalibration may be better captured using this approach⁴². Likewise, while the diagnostic validity of the first HF diagnosis appearing on a death certificate may be questionable⁵⁰, this category accounted for less than 1% of observed HF incidence used for recalibration. HF incidence was therefore captured as accurately and consistently as possible given current data availability across Europe, and the recalibration approach outlined can be applied in the future, should more reliable data on HF incidence become available in nationally representative European primary care populations. None of these concerns are relevant for the estimation of the SHRs for SCORE2-HF individual predictors, since model derivation was based predominantly on individual participant cohort data with validated endpoints. Further splitting of incidence rates by HF type was not possible; SCORE2-HF estimates the risk of any HF type, without discrimination between preserved or reduced left ventricular ejection fraction.

It should be noted that SCORE2-HF estimates HF risk regardless of other CVD events that may occur in the interim; this is aligned with previous risk scores⁵¹ and ensures relevance of estimates for assignment of interventions that focus on HF prevention. However, given that some HF events will occur subsequent to another CVD event (this occurred in 8% of the HF events observed in our CPRD validation dataset), simple summation of SCORE2 CVD and HF risk estimates to give total CVD risk is not advisable and may result in slightly inflated estimates of overall CVD risk.

1 There could be some individuals who contributed data to more than one of the UK studies
2 analysed (UKB, CPRD, NHS England-wide EHR). However, given that data from these
3 sources was collected over different time periods (median baseline was 2009 for UKB,
4 2006 for CPRD, and 2022 for NHS England) using distinct protocols/methods, any precise
5 data overlap is presumed minor and unlikely to bias our validation in CPRD. Some
6 individuals in our model derivation cohorts may have initiated preventative treatment (e.g.
7 statins) during follow-up and accounting for this could improve model calibration and
8 discrimination. However, previous analyses have suggested that inclusion of information on
9 statin initiation during follow-up provides only limited clinical and public health benefit.⁵²

10 Data on type of antihypertensive medication use, family history, ethnicity, socio-economic
11 status, physical activity, smoking duration and/or former smoking, atrial fibrillation or
12 breathing disorders (e.g. asthma and chronic obstructive pulmonary disease), were either
13 not consistently available, or not uniformly defined, across the data sources used for
14 model derivation and recalibration. Hence, interpretation of SCORE2-HF estimates may
15 require clinical judgement for individuals in whom these factors are relevant. Furthermore,
16 while SCORE2-HF captures HF risk associated with kidney function through inclusion of
17 eGFR, additional assessment of albuminuria may add complementary information for
18 understanding individual kidney disease and HF risk^{44,53,54}. Likewise, several cardiac
19 biomarkers not included in SCORE2-HF have been demonstrated to improve accuracy of
20 risk estimates for HF and may warrant measurement in those found to be at intermediate
21 risk⁵⁵⁻⁵⁷.

In conclusion, we have developed, recalibrated and validated SCORE2-HF, a HF risk score tailored to the levels of HF risk in the primary prevention population in four European risk regions, and aligned with the SCORE2 models. SCORE2-HF estimations rely on routinely available risk predictors and should enhance efforts to prevent CVD and HF development in Europe.

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Acknowledgements

Data from the Clinical Practice Research Datalink (CPRD) were obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (protocol 162RMn2). CPRD uses data provided by patients and collected by the NHS as part of their care and support. The Trøndelag Health Study (HUNT) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

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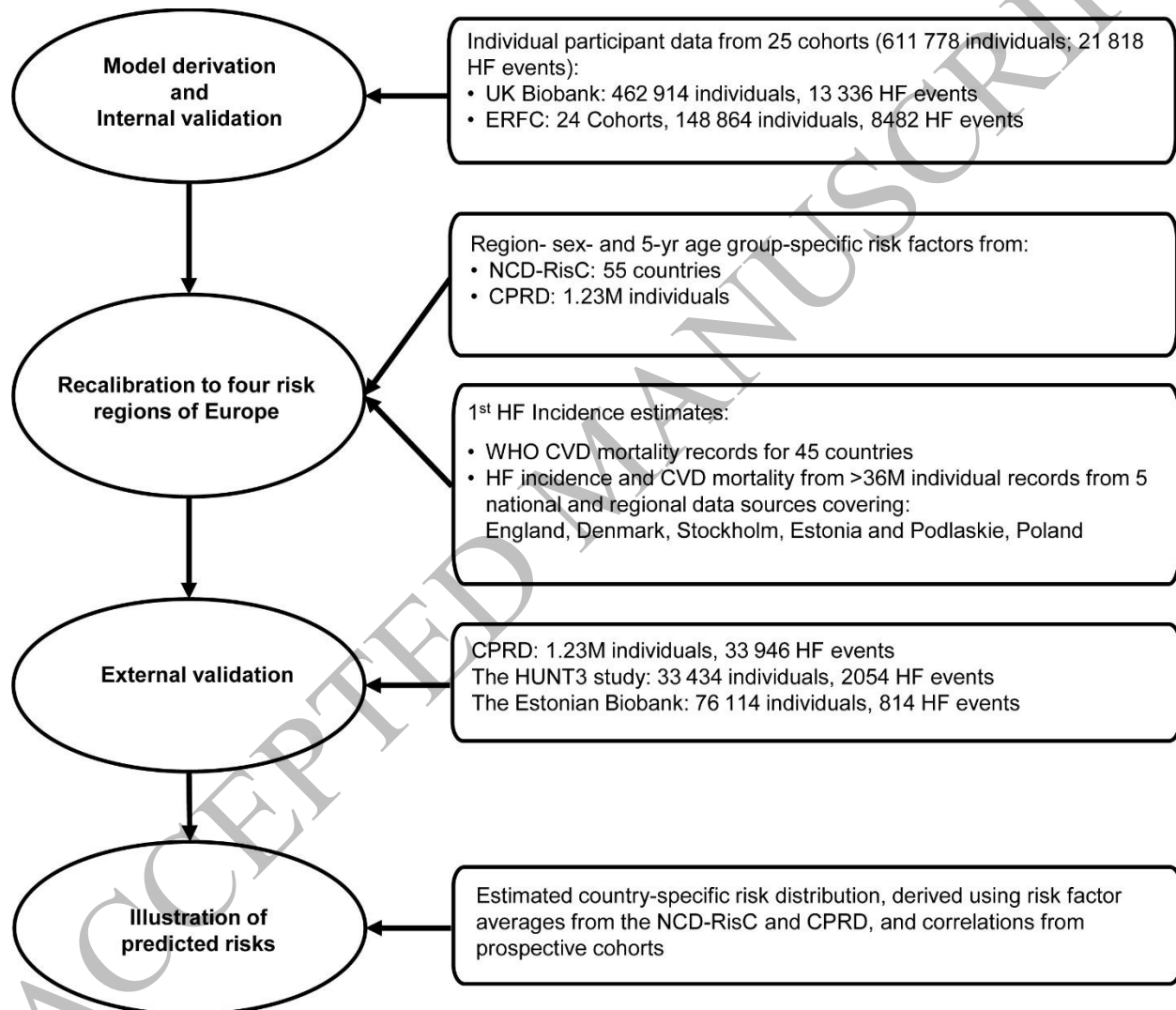
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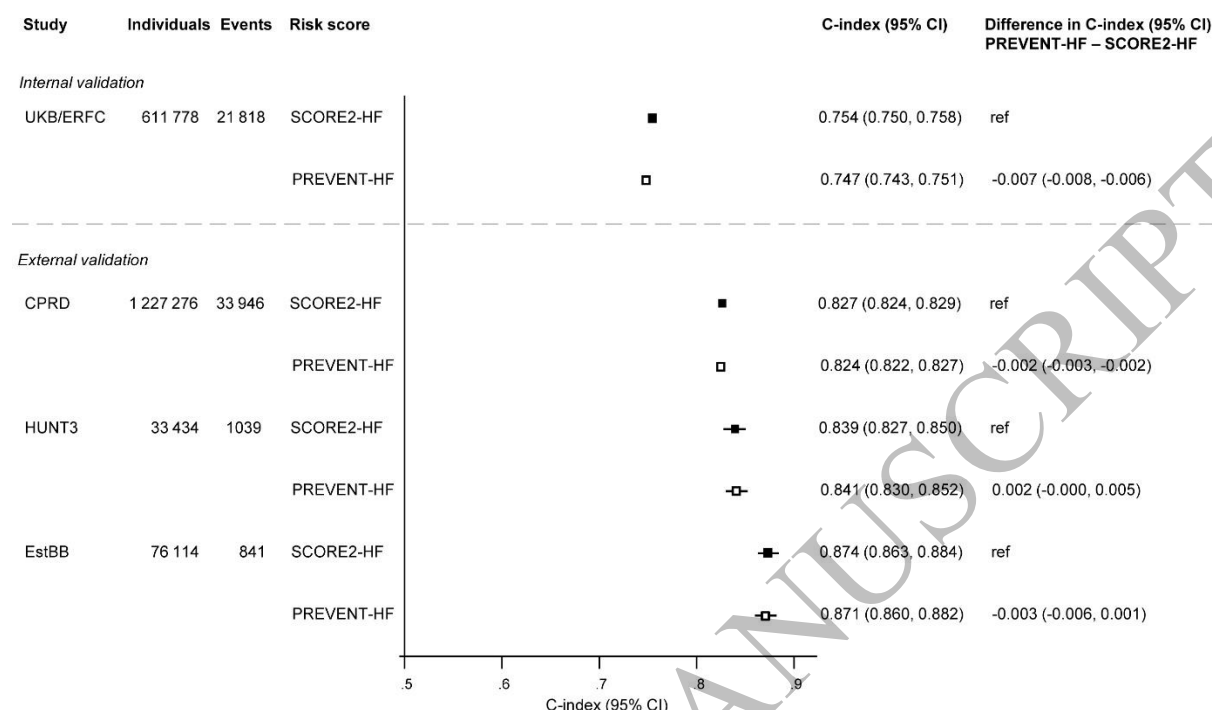
Figure Legends

Figure 1: Flow diagram describing model development process and data sources



ERFC = Emerging Risk Factors Collaboration, NCD-RisC= NCD-Risc Risk Factors Collaboration. CPDR= Clinical Practice Research Datalink; WHO= World Health Organization, HUNT3 = Survey 3 of the Trøndelag Health Study

Figure 2: C-index results from internal and external validation



CPDR= Clinical Practice Research Datalink; HUNT3 = Survey 3 of the Trøndelag Health Study; EstBB = Estonian Biobank; UKB = UK Biobank; ERFC = Emerging Risk Factors Collaboration. For internal validation, 10-fold cross validation revealed minimal optimism in discrimination (optimism in C-index = 0.0003 (95% CI = 0.0002, 0.0003); **Supplementary Methods**)

Figure 3: Average SCORE2-HF risk estimates for individuals with 0, 1, 2, 3 or 4 adverse heart failure risk factors, by risk region, sex and age group

Adverse risk factors are: smoking, type 2 diabetes, hypertension (defined as taking antihypertensive medication or systolic blood pressure ≥ 140 mmHg) or body mass index ≥ 30 kg/m²

Each line illustrates the average predicted risk among sex- and age group-specific individuals who have been categorized according to the given definitions of adverse risk factors. However, individual risk estimates within each category depend on the full continuous range of systolic blood pressure, body mass index, estimated glomerular filtration rate and glycated haemoglobin. Individual-specific risks can be estimated using the calculator provided in Appendix and similar electronic calculators or apps, all of which utilise the full range of continuous risk factors. CI, confidence interval, HF, heart failure.

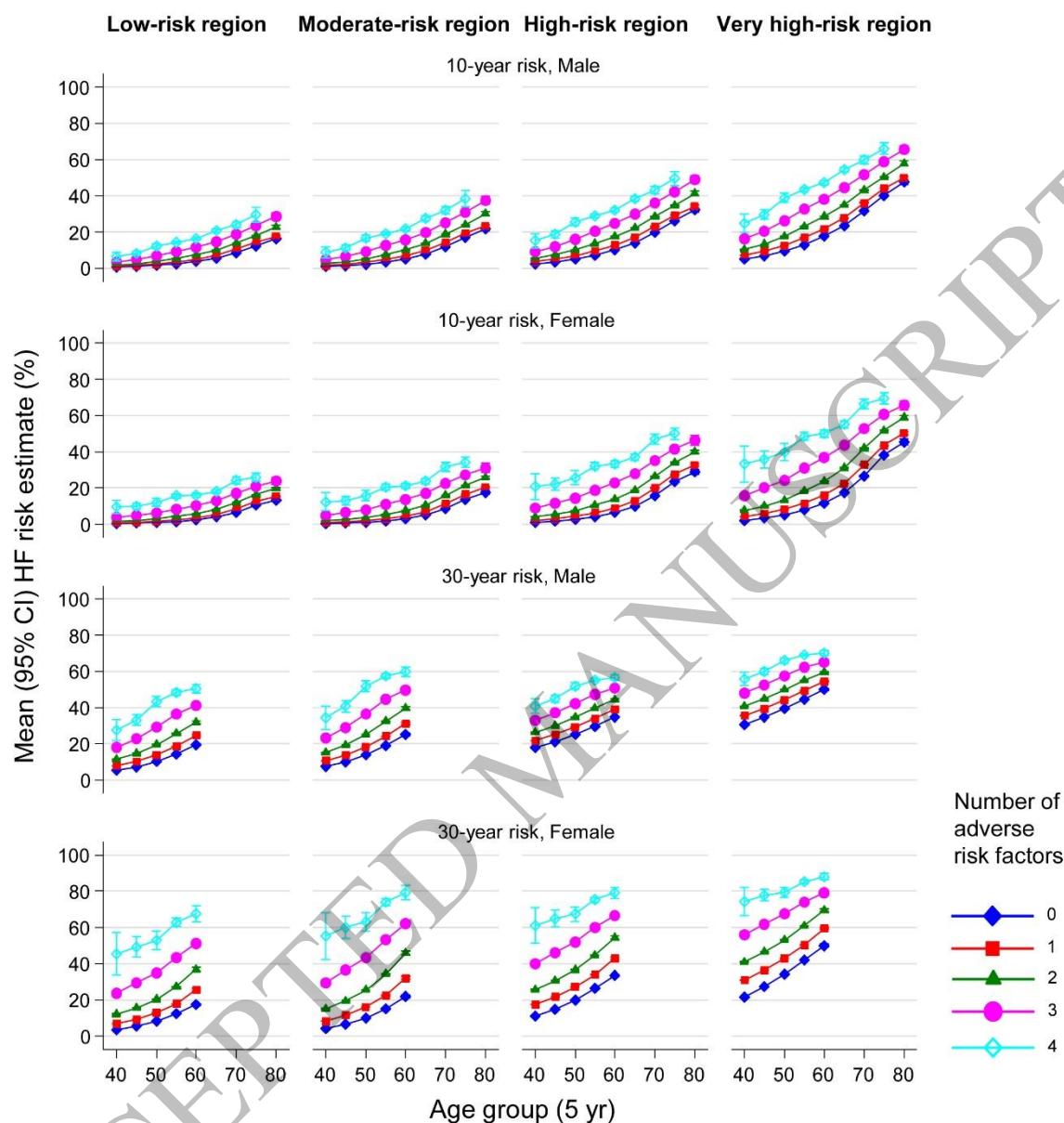


Figure 4: Comparison of risk classification with SCORE2 and SCORE2-HF

SCORE2-CVD risk groups are determined according to ESC guidelines on cardiovascular disease (CVD) prevention (2021) and CVD and diabetes (2023). In the 2021 guidelines, the ‘intermediate risk group’ is defined as at high-risk and includes those aged 40 to 49 years at 2.5 to <7.5% 10-year CVD risk, aged 50 to 69 at 5 to <10% risk and those aged 70 years or over at 7.5 to <15% risk. According to the guideline, this high-risk group identifies individuals in whom ‘risk factor treatment should be considered’ and the very high-risk group those in whom ‘risk factor treatment is generally recommended’. In the 2023 guidelines on CVD and diabetes, the ‘intermediate’ risk group is defined as ‘moderate risk’ and includes individuals with diabetes, with 10-year risk of 5 to <10%. Predicted risk distributions are based on the observed risk factor distributions in individuals from the CPRD.

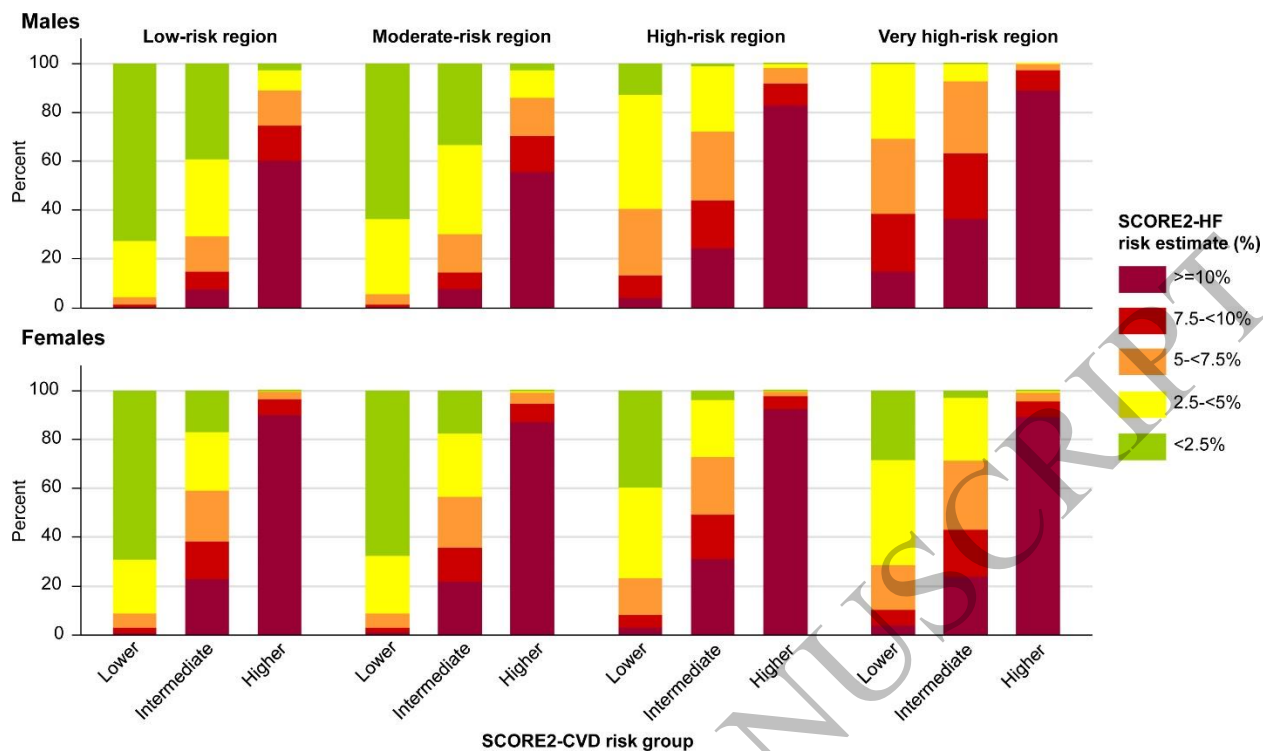
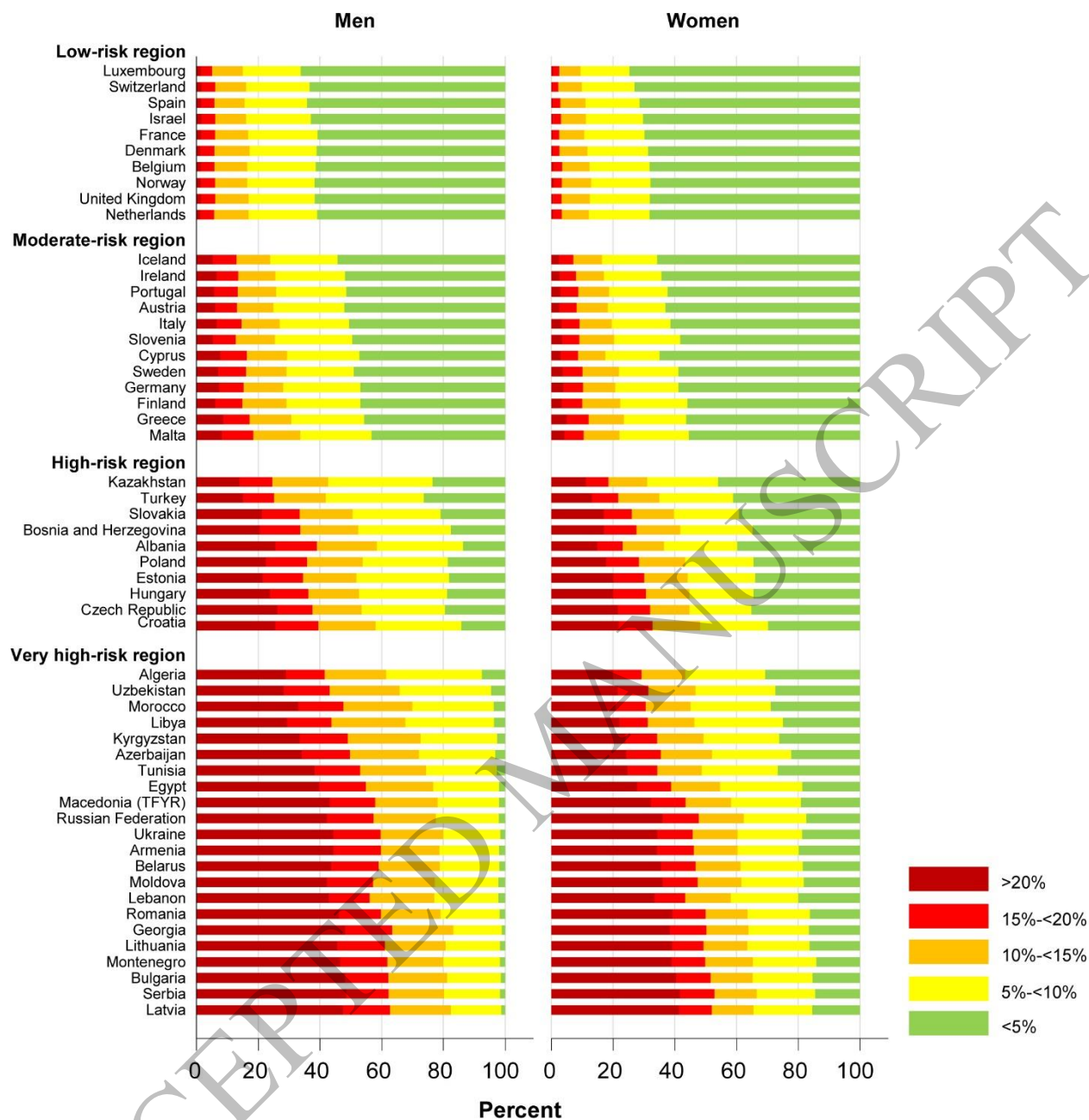


Figure 5: Estimated risk distributions using SCORE2-HF in individual countries across Europe

Predicted risk distributions were simulated using age- and sex-specific risk factor value means and prevalences from NCD-RisC and correlation structures observed in cohorts from the Emerging Risk Factors Collaboration.



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Table 1: Summary of data used for derivation of the sex-specific SCORE2-HF models

	Men N = 275 006 (45%)	Women N = 336 772 (55%)
Predictors included in the risk model		
Age (years)	58 [49–64]	58 [51.0–64]
Systolic blood pressure (mmHg)	140 (18)	136 (20)
Body mass index (kg/m ²)	27.5 (4.2)	27.1 (5.3)
eGFR (mL/min/1.73 m ²)	95 [83–103]	94.6 [80–102]
Current hypertensive medication use	61 229 (23)	68 903 (21)
Current smoking	48 481 (18)	38 481 (11)
History of type 2 diabetes	21 657 (8)	19 140 (6)
Predictors used only in those with diabetes		
HbA1c (mmol/mol)	51 [41–64]	52 [42–66]
Age of diabetes diagnosis (years)	54 [46–60]	55 [46–61]
Incident events and follow-up		
Heart failure	12 201 (4)	9617 (3)
Non-heart failure mortality	23 821 (9)	21 170 (6)
Follow-up (years)	13.4 [12.3–14.2]	13.4 [12.4–14.2]

Data are presented as median [interquartile range], *n* (%), or mean (standard deviation).

eGFR, estimated glomerular filtration rate (estimated using the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine-based equations); HbA1c, glycated haemoglobin.

Key Question

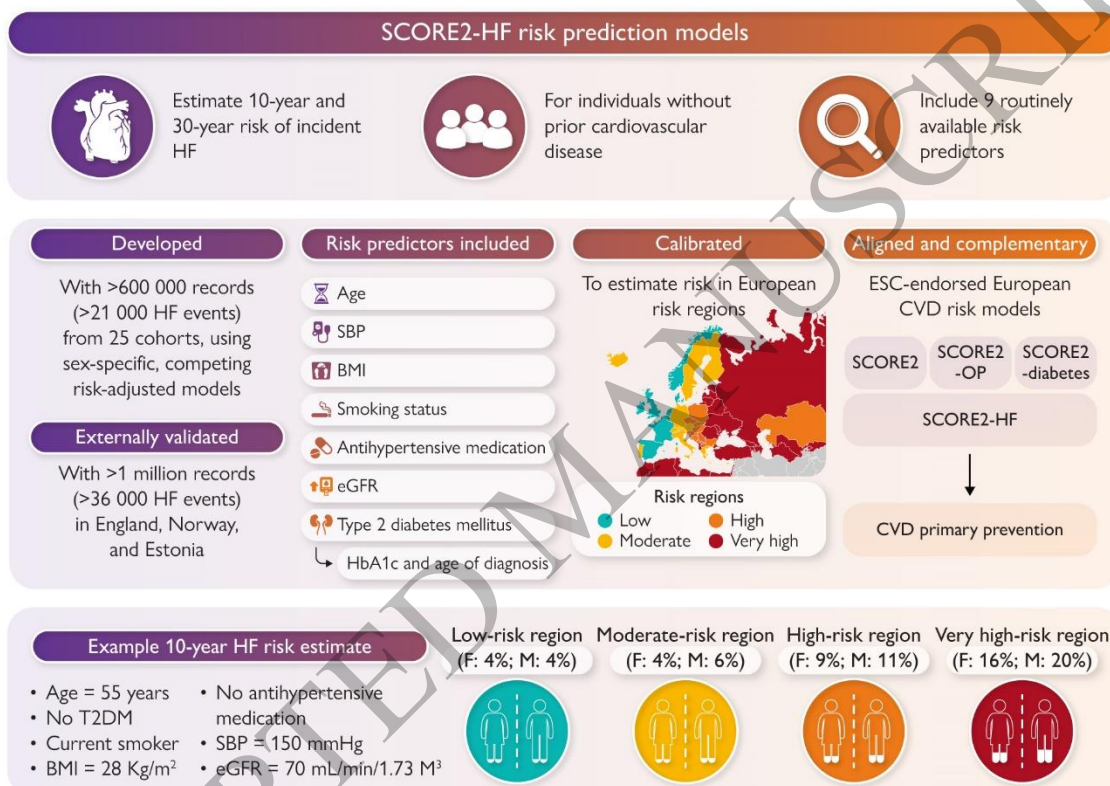
Can a primary prevention-focused prediction model estimate incident heart failure (HF) risk in European regions with different HF prevalences?

Key Finding

SCORE2-HF was developed to estimate sex-specific 10-year and 30-year risks of HF in four risk-regions of Europe. It showed excellent validation and provided distinct, complementary information to the 10-year cardiovascular disease risk estimates from the SCORE2, SCORE2-OP and SCORE2-Diabetes models.

Take Home Message

SCORE2-HF may improve the identification of individuals at higher risk of developing HF, and enhance efforts to prevent HF in Europe.



BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus
Kaptoge S, et al. *European Heart Journal*.

1
2 Structured Graphical Abstract