Supplementary material

SCORE2-Diabetes: new calibrated models to estimate 10-year risk of cardiovascular disease in individuals with type 2 diabetes in Europe

SCORE2-Diabetes working group and the ESC Cardiovascular Risk Collaboration

Supplementary Methods

SCORE2-Diabetes derivation

SCORE2-Diabetes is an extension of the SCORE2 models for CVD risk prediction in Europe, to include additional information needed to estimate CVD risk in individuals with diabetes. The original SCORE2 models were derived using 44 studies from the Emerging Risk Factors Collaboration (ERFC) and the UK Biobank (UKB), and were recalibrated to four risk regions defined by CVD mortality rates, using risk factor averages and estimated incidence for each region. The 45 derivation cohorts included individuals with and without diabetes and the SCORE2 models included an adjustment for diabetes status

Original SCORE2 risk models

The SCORE2 risk models take the following form.

1) Uncalibrated_score2 = 1-$S_o(10)^{\exp(\text{LP\_score2})}$

Where, using the transformed variables defined in **Supplementary Methods table 1**:

LP_score2= β_1*cages + β_2*smoking + β_3*csbp + β_4*ctchol + β_5*chdl + β_6*hxdiabetes + β_7*cages*smoking + β_8* cages *csbp + β_9* cages *ctchol + β_{10}* cages *chdl + β_{11}* cages*hxdiabetes

β_{1-11} are the sex-specific log HR estimates from the original SCORE2 derivation data

$S_o(10)$ is the baseline sex-specific survival estimate from the derivation data

2) Recalibrated_score2 = 1-exp(-exp(scale1 + scale2 * ln(-ln(1 – uncalibrated_score2)))), where scale1 and scale2 are the region and sex-specific recalibration factors estimated for each of the four risk regions

Extension of SCORE2 to add new risk predictor effects specific to improving risk prediction for individuals with diabetes: The SCORE2-Diabetes model

The SCORE2-Diabetes prediction models are structured as follows:

Uncalibrated_score2_DM2 = $1 - S_o(t)^{LP_{score2}+LP_{DM}+SCORE2vars}$, where

LP_{score2} and $S_o(t)$ are exactly as defined for SCORE2

$LP_{DM} = \beta_{12}$*cagediab + β_{13}*chba1c + β_{14}*cages*chba1c + β_{15}*clnegfr + β_{16}*clnegfr*clnegfr + β_{17}*cages*clnegfr

$SCORE2vars$ = β_{18}* cages + β_{19}*Smoking + β_{20}*csbp + β_{21}*ctchol + β_{22}*chdl + β_{23}*Diabetes + β_{24}*cages*Smoking + β_{25}*cages*csbp + β_{26}*cages*ctchol + β_{27}*cages*chdl + β_{28}*cages*Diabetes

β_{12-28} are the sex-specific log SHR estimates from the new derivation data

The additional inclusion of SCORE2 variables (as well as their use in the offset term) enabled inclusion of interactions between baseline age and the new variables of interest, corrected for any residual correlation/confounding between the conventional SCORE2 variables and the additional SCORE2-Diabetes variables, and allowed the SCORE2 predictor effects to be modified for individuals with diabetes.

This process was completed separate for each sex and data source and the estimates of β_{12-28} pooled using fixed effect meta-analysis, yielding the final model for use in clinical practice.

The final SCORE2-Diabetes models and estimation process are summarized in **Supplementary Methods Table 1,** which displays the combined effects of β_{1-11} and β_{18-28} for the conventional SCORE2 risk predictors (mathematically identical to applying the two sets individually). The full set of β_{1-11} with β_{18-28} from the derivation models are provided for information in **Supplementary Methods Table 2.**

Missing Data

Missing data in all model derivation datasets, in the Swedish National Diabetes Register (SNDR) and in the Information System for Research in Primary Care (SIDIAP) were imputed using multiple chained equations with predictive mean matching with 10 imputations, including in the imputation model all risk predictors and Nelson-Aalen estimators for both the CVD, and non-cvd death, outcomes.

Estimation of regionally representative predicted risk distributions

To compare the proportion of the population at different levels of CVD risk according to the SCORE2-Diabetes algorithm in the four risk regions, predicted risk distributions were estimated by rescaling individual participant data in CPRD according to estimated relative differences in age- and sex-specific means and prevalences of risk factors values in each region, compared to the low risk region.

The region-specific risk factor means and prevalences were estimated by pooling summary data from CPRD, NDA, SNDR, SIDIAP and contributing registries from EUBIROD using a linear mixed model with fixed effects for sex, 5-year age group, risk region, interactions of sex with 5-year age group and risk region, and random effect for country.

Ratios corresponding to expected relative differences in risk factor means and prevalences in comparison to the low risk region were calculated and applied to rescale individual level data in CPRD to estimate region-specific risk distributions. This approach accounted for expected regional differences in risk factor levels, but assumed risk factor correlations were broadly similar to those observed in the CPRD dataset.

Supplementary Methods table 1: Calculation of 10-year CVD risk using SCORE2-Diabetes

1) Calculation of Linear Predictor

Risk factor (units)	Transformed Risk factor	Log SHR	
		Men	Women
SCORE2 variables			
Age (yrs)	cage = (age - 60)/5	0.5368	0.6624
Smoking (current vs. other)	smallbin	0.4774	0.6139
SBP (mm Hg)	csbp = (sbp - 120)/20	0.1322	0.1421
Diabetes (yes vs. no)	hxdiabbin	0.6457	0.8096
Total cholesterol (mmol/L)	ctchol = (tchol - 6)/1	0.1102	0.1127
HDL cholesterol (mmol/L)	chdl = (hdl - 1.3)/0.5	-0.1087	-0.1568
Smoking interaction with age	cage*smallbin	-0.0672	-0.1122
SBP interaction with age	cage*csbp	-0.0268	-0.0167
Diabetes interaction with age	cage*hxdiabbin	-0.0983	-0.1272
TCHOL interaction with age	cage*ctchol	-0.0181	-0.0200
HDL interaction with age	cage*chdl	0.0095	0.0186
SCORE2-DM2 additional variables			
Diabetes age at diagnosis (yrs)	cagediab=(agediab - 50)/5 if hxdiabbin=1, else 0.	-0.0998	-0.118
HbA1c (mmol/mol)	chba1c=(hba1c - 31)/9.34	0.0955	0.1173
Ln eGFR (ml/min/1.73m^2)	clnegfr=(lnegfr - 4.5)/0.15	-0.0591	-0.0640
Ln eGFR^2	clnegfr* clnegfr	0.0058	0.0062
HbA1c interaction with age	chba1c*cage	-0.0134	-0.0196
Ln eGFR interaction with age	clnegfr*cage	0.0115	0.0169

Linear predictor= ∑ (transformed risk factor x log SHR)

2) 10-year risk estimation (un-calibrated) = 1-basesurv $^{\exp(\text{linear predictor})}$

Men	**Women**
Uncalibrated risk = 1-0.9605 $^{\exp(\text{linear predictor})}$	Uncalibrated risk = 1-0.9776 $^{\exp(\text{linear predictor})}$

3) Calibration of risk estimate according to region specific scaling factors

Calibrated 10-year risk = 1-exp(-exp(scale1 + scale2 x ln(-ln(1-un-calibrated 10-yr risk))

Risk region	**Male**	**Female**
Low	1-exp(-exp(-0.5699+0.7476 x ln(-ln(1 un-calibrated 10-yr risk))))	1-exp(-exp(-0.7380+0.7019 x ln(-ln(1- un-calibrated 10-yr risk))))
Moderate	1-exp(-exp(-0.1565+0.8009 x ln(-ln(1- un-calibrated 10-yr risk))))	1-exp(-exp(-0.3143+0.7701 x ln(-ln(1- un-calibrated 10-yr risk))))
High	1-exp(-exp(0.3207+0.9360 x ln(-ln(1- un-calibrated 10-yr risk))))	1-exp(-exp(0.5710+0.9369 x ln(-ln(1 un-calibrated 10-yr risk))))
Very high	1-exp(-exp(0.5836+0.8294 x ln(-ln(1- un-calibrated 10-yr risk))))	1-exp(-exp(0.9412+0.8329 x ln(-ln(1- un-calibrated 10-yr risk))))

Note: final estimate should be multiplied by 100 in order to express as a percentage rather than a probability

eGFR: estimated Glomerular Filtration Rate (ml/min/1.73m^2) calculated using the CKD epi 2009 equations; HbA1c (mmol/mol): glycated haemoglobin, in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units

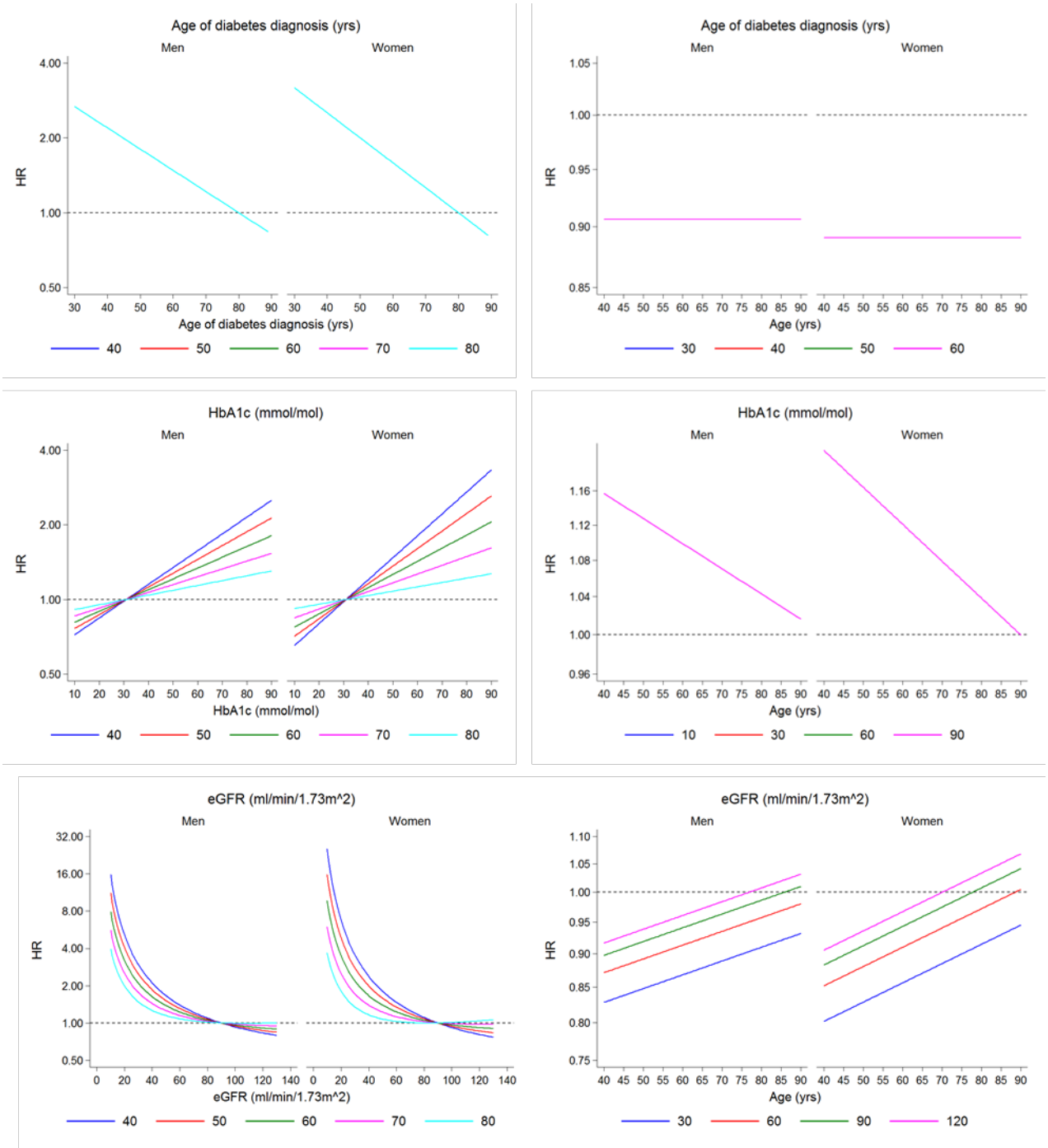
Supplementary Methods Table 2. Subdistribution Hazard ratios estimated during derivation of SCORE2-Diabetes

	SCORE2 variables				SCORE2-Diabetes variables		
	Main effects from SCORE2	**Age interaction terms from SCORE2**	**Adjustment to SCORE2 main effects for individuals with diabetes**	**Adjustment to SCORE2 age interaction terms for individuals with diabetes**		**Main effects**	**Age interaction terms**
Men							
Age (per 5 years)	1.47 (1.44, 1.49)	-	1.18 (1.15, 1.20)		Diabetes age at diagnosis (per 5-years)	0.90 (0.89, 0.91)	
Current smoking	1.88 (1.81, 1.95)	0.92 (0.91, 0.94)	0.88 (0.85, 0.92)	1.01 (0.99, 1.02)	HbA1c (per 9.34 mmol/mol)	1.10 (1.09, 1.11)	0.99 (0.98, 0.99)
SBP (per 20mmHg)	1.32 (1.29, 1.34)	0.98 (0.97, 0.98)	0.86 (0.85, 0.88)	1.00 (0.99, 1.01)	ln eGFR (per 0.15 ln(ml/min/1.73m^2))	0.94 (0.93, 0.96)	1.01 (1.01, 1.01)
Total cholesterol (per 1 mmol/L)	1.16 (1.15, 1.17)	0.98 (0.97, 0.98)	0.97 (0.95, 0.98)	1.01 (1.00, 1.02)	Ln eGFR^2 (quadratic term)	1.01 (1.00, 1.01)	
HDL cholesterol (per 0.5 mmol/L)	0.76 (0.74, 0.78)	1.05 (1.03, 1.06)	1.17 (1.14, 1.21)	0.97 (0.96, 0.98)			
History of diabetes mellitus	1.93 (1.82, 2.04)	0.91 (0.88, 0.94)					
Women							
Age (per 5 years)	1.62 (1.59, 1.65)	-	1.22 (1.19, 1.25)	-	Diabetes age at diagnosis (per 5-years)	0.89 (0.88, 0.90)	
Current smoking	2.25 (2.15, 2.37)	0.89 (0.86, 0.91)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	HbA1c (per 9.34 mmol/mol)	1.12 (1.11, 1.14)	0.98 (0.98, 0.98)
SBP (per 20mmHg)	1.36 (1.33, 1.39)	0.97 (0.96, 0.98)	0.84 (0.82, 0.86)	1.01 (1.00, 1.02)	ln eGFR (per 0.15 ln(ml/min/1.73m^2))	0.94 (0.92, 0.95)	1.02 (1.01, 1.02)
Total cholesterol (per 1 mmol/L)	1.10 (1.08, 1.12)	0.98 (0.97, 0.99)	1.01 (0.99, 1.03)	1.00 (1.00, 1.01)	Ln eGFR^2	1.01 (1.00, 1.01)	
HDL cholesterol (per 0.5 mmol/L)	0.76 (0.74, 0.78)	1.06 (1.04, 1.08)	1.11 (1.07, 1.15)	0.96 (0.95, 0.97)			
History of diabetes mellitus	2.35 (2.18, 2.53)	0.88 (0.84, 0.91)		-			

eGFR: estimated Glomerular Filtration Rate (ml/min/1.73m^2) calculated using the CKD epi 2009 equations; HbA1c (mmol/mol): glycated haemoglobin, in International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) units.

Age was centered at 60 years, systolic blood pressure at 120 mmHg, total cholesterol at 6 mmol/L, HDL cholesterol at 1.3 mmol/L, age at diabetes onset at 50 years HbA1c at 31 mmol/mol and eGFR 90 ml/min/1.73^2 (i.e. Ln-eGFR of 4.5). The median baseline survival at 10 years in the derivation cohorts was 0.9625 for men and 0.9795 for women. For HbA1c, 1 SD = 9.34 mmol/mol and for eGRF 1SD=0.15 ln(ml/min/1.73m^2)

Supplementary Methods Figure: Association of Diabetes-associated variables with CVD outcomes in the SCORE2-Diabetes risk models; shown by age



Graphs on the left hand side show the shape of the association between each risk predictor and CVD outcomes, with each line representing a different baseline age. Graphs on the right hand side show how each risk predictor effect changes with age, with each line representing a different level of the relevant risk predictor.

Supplementary Tables and Figures

Supplementary Table 1 Summary of data sources used in SCORE2-Diabetes development

Data source	Country	study	Median year of recruit-ment	Number of Partic-ipants	Ages Mean (SD)	Age range: min, max	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean (SD)	Total cholest-erol (mmol/L) Mean (SD)	HDL cholest-erol (mmol/L) Mean (SD)	Age of diabetes diagnosis	HbA1c (mmol/ mol) Mean (SD)	eGFR mean (SD)	Median follow-up years (IQR)	Number of CV events	Number of competin g events (non-CVD death)
CPRD	UK	CPRD	2008	72,751	64 (11)	41-90	38,599 (53)	11,423 (21)	136 (16)	4.39 (1.0)	1.24 (0.36)	58 (11)	52 (19)	76 (17)	6.0 (0.8, 11.0)	7247	5211
SCID	Scotland	-	2008	136,192	65 (11)	40-89	72,525 (53)	24,447 (18)	135.6 (16)	4.4 (1.0)	1.24 (0.40)	58 (17)	74 (20)	74 (20)	10.9 (6.8, 11.0)	34595	21062
ERFC	France	DESIR	1995	253	55 (7)	41-66	155 (61)	69(27)	144 (19)	6.1 (1.3)	1.42 (0.34)	48 (8)	49 (16)	80 (13)	5.5 (0.0 to 9.2)	8	0
ERFC	Germany	ESTHER	2001	933	63 (6)	49-75	473 (51)	151 (17)	144 (20)	5.6 (1.3)	1.23 (0.35)	56 (8)	53 (15)	83 (20)	5.0 (1.2 to 6.0)	41	11
ERFC	Germany	SHIP	1999	367	64 (10)	41-81	210 (57)	70 (19)	151 (20)	5.9 (1.2)	1.26 (0.39)	55 (10)	55 (15)	74 (16)	0.0 (0.0 to 11.5)	7	0
ERFC	Italy	BRUN	1990	28	68 (9)	52-79	13 (46)	4 (14)	165 (24)	5.6 (1.0)	1.29 (0.32)	59 (12)	56 (19)	76 (15)	12.5 (4.4 to 20.5)	10	11
ERFC	UK	BWHHS	2000	136	69 (5)	60-79	0 (0)	16 (12)	155 (25)	6.1 (1.1)	1.45 (0.37)	61 (8)	50 (16)	66 (12)	12.1 (4.3 to 13.4)	19	31
ERFC	USA	NHANES3	1990	936	64 (12)	40-89	383 (41)	179 (19)	141 (21)	5.6 (1.2)	1.21 (0.40)	55 (12)	63 (23)	66 (22)	13.1 (1.6 to 22.0)	264	400
ERFC	USA	WHS	1994	715	57 (7)	46-76	0 (0)	87 (12)	136 (13)	5.7 (1.2)	1.14 (0.36)	50 (9)	58 (21)	92 (17)	17.6 (3.7 to 20.0)	107	6
UK Biobank	UK	ZZUKBIOBANK	2009	17,149	60 (7)	40-76	10251 (60)	1808 (11)	142 (17)	4.53 (1.03)	1.21 (0.32)	53 (8)	55 (20)	90 (16)	11.4 (5.1 to 13.1)	1408	1493
TOTAL ERFC/UKB			-	20,517	60 (8)	40-89	11,485 (56)	2353 (12)	142 (17)	4.70 (1.14)	1.21 (0.33)	53 (9)	55 (20)	88 (17)	11.3 (2.8 to 13.6)	1864	1953

Supplementary Table 2: Summary of missing data in cohorts used for model derivation

			N(%) missing								
Data source	Study	Total number of participants	Ages	Sex	Smoking	Systolic BP	Total cholesterol	HDL cholesterol	Age of diabetes diagnosis	HbA1c	eGFR
SCID		136192	0 (0)	0 (0)	7653 (5.6)	6347 (4.7)	7704 (5.7)	28298 (20.8)	0 (0)	9142 (6.7)	19521 (14.3)
CPRD		72751	0 (0)	0 (0)	17936(24.7)	3413 (4.7)	4201 (5.8)	9270 (12.7)	0 (0)	5550 (7.3)	4266 (5.9)
ERFC	DESIR	253	0 (0)	0 (0)	1 (0.6)	1 (0.6)	0 (0)	8 (5.2)	39 (25.3)	0 (0)	1 (0.6)
ERFC	ESTHER	933	0 (0)	0 (0)	21 (2.3)	22 (2.4)	5 (0.6)	347 (38.2)	313 (34.4)	10 (1.1)	5 (0.6)
ERFC	SHIP	367	0 (0)	0 (0)	0 (0)	1 (0.3)	1 (0.3)	1 (0.3)	125 (34.4)	0 (0)	2 (0.6)
ERFC	BRUN	28	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ERFC	BWHHS	136	0 (0)	0 (0)	0 (0)	13 (9.6)	18 (13.2)	19 (14)	7 (5.1)	17 (12.5)	18 (13.2)
ERFC	NHANESIII	936	0 (0)	0 (0)	2 (0.2)	18 (1.9)	517 (55.3)	526 (56.3)	39 (4.2)	511 (54.7)	526 (56.3)
ERFC	WHS	715	0 (0)	0 (0)	0 (0)	28 (3.9)	9 (1.3)	9 (1.3)	37 (5.2)	2 (0.3)	9 (1.3)
UK Biobank	ZZUKBIOBANK	17149	0 (0)	0 (0)	66 (0.4)	39 (0.2)	1184 (6.9)	2545 (14.8)	263 (1.5)	1390 (8.1)	1198 (7)
Total ERFC/UKB		20517	0 (0)	0 (0)	0 (0)	122 (0.6)	1734 (8.5)	3455 (16.9)	823 (4)	1930 (9.5)	1759 (8.6)

ERFC: Emerging Risk Factors Collaboration, CPRD: Clinical Practice Research Datalink, SCID: Scottish Care Information – Diabetes

Supplementary Table 3 Summary of data used in SCORE2-Diabetes validation

Cohort/ data source	Country	Median year of study recruit-ment	No of Partici-pants	Ages Mean (SD)	Age range: min, max	Men n (%)	Current smoker n (%)	Systolic BP (mmhg) Mean (SD)	Total cholesterol (mmol/L) Mean (SD)	HDL cholesterol (mmol/L) Mean (SD)	Age of diabetes diagnosis median (IQR)	HbA1c (mmol/ mol) median (IQR)	eGFR (ml/min/ 1.73m^2) median (IQR)	Median follow-up years (IQR)	Number of CV events	Number of competing events (non-CVD death)
SNDR	Sweden	2008	168585	66 (11)	40-90	90321 (54)	22672 (15)	138 (17)	4.9 (1.0)	1.3 (0.4)	57 (49-65)	54 45-59)	85 (69-95)	11.4 (6.8-11.4)	34944	41379
SIDIAP	Spain	2010	21754	69 (12)	40-110	11008 (51)	3194 (15)	136 (16)	5.1 (1.0)	1.3 (0.3)	62.3 (17.3)	48 (19)	79 (27)	7.0 (5.2-7.0)	2472	3097
EUBIROD*	Malta	2015	3876	68 (11)	40-90	2102 (54)	634 (16)	142 (19)	4.6 (1.1)	1.4 (0.4)	58 (13)	52 (18)	101 (28)	4.8 (0.9)	239	291
EUBIROD*	Croatia	2015	22821	66 (10)	40-90	10651 (47)	4112 (18)	136 (15)	5.3 (1.2)	1.3 (0.3)	61 (14)	51 (16)	94 (29)	2.9 (0.3)	947	1128

*Summary statistics for EUBIROD are for the complete case dataset used in validation analysis

Missing data (imputed) by variable for SNDR were smoking: 9%, SBP:4%, total cholesterol: 16%, HDL cholesterol: 24% age of diabetes diagnosis: 7%, HbA1c: 3%, eGFR: 9%

Missing data (imputed) by variable for SIDIAP were smoking: 0%, SBP:24%, total cholesterol: 31%, HDL cholesterol: 40% age of diabetes diagnosis: 0%, HbA1c: 35%, eGFR: 33%

SNDR: Swedish National Diabetes Register (SNDR), SIDIAP: Information System for Research in Primary Care, EUBIROD: EUropean Best Information through Regional Outcome in Diabetes

Supplementary Table 4: Endpoint definitions

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

Endpoints included	*ICD10-codes*	*ICD9-codes*
Hypertensive disease	I10-16	401 – 405
Ischemic heart disease	I20-25	410 - 414
Arrhythmias, heart failure	I46-52	426 - 429
Cerebrovascular disease	I60-69	430 - 438
Atherosclerosis/aortic aneurysm	I70-73	440 - 443
Sudden death and death within 24h of symptom onset	R96.0-96.1	798.1 , 798.2
Endpoints excluded from the above endpoint:		
Myocarditis, unspecified	I51.4	426.7
Subarachnoid haemorrhage	I60	429
Subdural haemorrhage	I62	430
Cerebral aneurysm	I67.1	432.1
Cerebral arteritis	I68.2	437.3
Moyamoya	I67.5	437.4
Non-fatal cardiovascular disease*		
Non-fatal myocardial infarction	I21-I23	*410*
Non-fatal stroke	I60-69	*430-438*
Excluded from the non-fatal stroke endpoint:		
Subarachnoid hemorrhage	I60	429
Subdural hemorrhage	I62	430
Cerebral aneurysm	I67.1	432.1
Cerebral arteritis	I68.2	437.3
Moyamoya	I67.5	437.4

*An endpoint also included peripheral artery disease (I70-71) and Heart Failure (I11.0, I50) for exploratory analyses

Supplementary Table 5. Definition of history of vascular disease at baseline

Prior disease	ICD code
Coronary heart disease	I20-I25
Stroke	I60-69
TIA	G45
Peripheral artery disease	I70-71

Supplementary Table 6: Age- and sex- standardized WHO CVD mortality rates per country

Country	Age and sex standardised CVD mortality per 100 000 person years, ICD chapter 9	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
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 neighbouring countries.

Supplementary Table 7. Subdistribution hazard ratios for predictor variables in the SCORE2-Diabetes risk models when using CPRD and SCID data only

	Men		Women	
	Main effect	**Age interaction term**	**Main effect**	**Age interaction term**
SCORE2 variables				
Age (per 5 years)	1.72 (1.68, 1.77)	-	1.95 (1.90, 2.01)	-
Current smoking	1.63 (1.55, 1.71)	0.93 (0.91, 0.96)	1.86 (1.74, 1.98)	0.90 (0.87, 0.92)
Systolic blood pressure (per 20mmHg)	1.14 (1.11, 1.17)	0.97 (0.96, 0.98)	1.15 (1.12, 1.19)	0.98 (0.97, 0.99)
Total cholesterol (per 1 mmol/L)	1.12 (1.10, 1.14)	0.98 (0.97, 0.99)	1.12 (1.10, 1.15)	0.98 (0.97, 0.99)
HDL cholesterol (per 0.5 mmol/L)	0.90 (0.86, 0.93)	1.01 (0.99, 1.02)	0.85 (0.82, 0.89)	1.02 (1.00, 1.04)
History of diabetes mellitus	1.91 (1.84, 1.98)	0.91 (0.89, 0.93)	2.25 (2.15, 2.35)	0.88 (0.86, 0.90)
SCORE2-DM2 additional variables				
Diabetes age at diagnosis (per 5-years)	0.90 (0.89, 0.91)		0.89 (0.88, 0.90)	
HbA1c (mmol/mol)	1.10 (1.09, 1.11)	0.99 (0.98, 0.99)	1.13 (1.11, 1.14)	0.98 (0.98, 0.98)
Ln eGFR (ml/min/1.73m^2)	0.94 (0.93, 0.96)	1.01 (1.01, 1.02)	0.94 (0.93, 0.96)	1.02 (1.01, 1.02)
Ln eGFR^2 (quadratic term)	1.01 (1.00, 1.01)		1.01 (1.01, 1.01)	

Sex-specific subdistribution hazard ratios from Fine and Gray models predicting the risk of fatal and non-fatal CVD events as derived for SCORE2 and adapted in individuals with diabetes from CPRD and SCID to include adjustments to SCORE2 effects and SCORE2-DM2 additional variables. Age was centered at 60 years, systolic blood pressure at 120 mmHg, total cholesterol at 6 mmol/L, HDL cholesterol at 1.3 mmol/L, age at diabetes onset at 50 years HbA1c at 31 mmol/mol and eGFR 90 ml/min/1.73^2 (i.e. Ln-eGFR of 4.5). The median baseline survival at 10 years in the derivation cohorts was 0.9625 for men and 0.9795 for women.

*Values shown are the combination of original SCORE2 coefficients and additional coefficients which modify the associations for individuals with diabetes.

Supplementary Table 8. Comparison: subdistribution hazard ratios for SCORE2-Diabetes predictor variables when using the SCORE2-Diabetes CVD endpoint, versus the extended endpoint also including non-fatal heart failure and PAD

	Men			
	Main effect		Age interaction term	
	Original endpoint	Extended endpoint	Original endpoint	Extended endpoint
SCORE2 variables				
Age (per 5 years)	1.71 (1.66, 1.76)	1.73 (1.68, 1.78)	-	-
Current smoking	1.61 (1.53, 1.70)	1.58 (1.50, 1.67)	0.94 (0.91, 0.96)	0.94 (0.92, 0.97)
Systolic blood pressure (per 20mmHg)	1.14 (1.11, 1.17)	1.15 (1.12, 1.18)	0.97 (0.96, 0.99)	0.97 (0.96, 0.98)
Total cholesterol (per 1 mmol/L)	1.12 (1.10, 1.14)	1.10 (1.08, 1.13)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
HDL cholesterol (per 0.5 mmol/L)	0.90 (0.86, 0.93)	0.91 (0.87, 0.94)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
History of diabetes mellitus	1.91 (1.81, 2.01)	1.91 (1.81, 2.01)	0.91 (0.88, 0.93)	0.91 (0.88, 0.93)
SCORE2-DM2 additional variables				
Diabetes age at diagnosis (per 5-years)	0.90 (0.89, 0.92)	0.90 (0.89, 0.91)	-	-
HbA1c (mmol/mol)	1.10 (1.09, 1.11)	1.10 (1.09, 1.11)	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)
Ln eGFR (ml/min/1.73m^2)	0.94 (0.93, 0.96)	0.94 (0.92, 0.95)	1.01 (1.01, 1.01)	1.01 (1.01, 1.02)
Ln eGFR^2 (quadratic term)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	-	-
	Women			
	Main effect		Age interaction term	
	Original endpoint	Extended endpoint	Original endpoint	Extended endpoint
SCORE2 variables				
Age (per 5 years)	1.94 (1.88, 2.00)	1.95 (1.89, 2.02)	-	-
Current smoking	1.85 (1.73, 1.98)	1.80 (1.68, 1.93)	0.89 (0.87, 0.92)	0.90 (0.87, 0.92)
Systolic blood pressure (per 20mmHg)	1.15 (1.12, 1.19)	1.15 (1.11, 1.19)	0.98 (0.97, 1.00)	0.98 (0.97, 0.99)
Total cholesterol (per 1 mmol/L)	1.12 (1.09, 1.15)	1.10 (1.08, 1.13)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
HDL cholesterol (per 0.5 mmol/L)	0.85 (0.82, 0.89)	0.86 (0.82, 0.90)	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
History of diabetes mellitus	2.25 (2.11, 2.40)	2.25 (2.11, 2.40)	0.88 (0.85, 0.91)	0.88 (0.85, 0.91)
SCORE2-DM2 additional variables				
Diabetes age at diagnosis (per 5-years)	0.89 (0.88, 0.90)	0.88 (0.87, 0.89)	-	-
HbA1c (mmol/mol)	1.12 (1.11, 1.14)	1.13 (1.12, 1.14)	0.98 (0.98, 0.98)	0.98 (0.98, 0.98)
Ln eGFR (ml/min/1.73m^2)	0.94 (0.92, 0.95)	0.93 (0.91, 0.94)	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)
Ln eGFR^2 (quadratic term)	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)	-	-

Sex-specific subdistribution hazard ratios from Fine and Gray models predicting the risk of fatal and non-fatal CVD events as derived for SCORE2 and adapted in individuals with diabetes to include adjustments to SCORE2 effects and SCORE2-DM2 additional variables. Age was centered at 60 years, systolic blood pressure at 120 mmHg, total cholesterol at 6 mmol/L, HDL cholesterol at 1.3 mmol/L, age at diabetes onset at 50 years HbA1c at 31 mmol/mol and eGFR 90 ml/min/1.73^2 (i.e. Ln-eGFR of 4.5). The median baseline survival at 10 years in the derivation cohorts was 0.9625 for men and 0.9795 for women.
*Values shown are the combination of original SCORE2 coefficients and additional coefficients which modify the associations for individuals with diabetes.

Supplementary Table 9. Change in discrimination: SCORE2-Diabetes vs SCORE2, SCORE2-Diabetes vs SCORE2-Diabetes without lipids, and SCORE2-Diabetes vs ADVANCE

Result for CPRD

Risk model	C-index	Difference in C-index (95% CI)
SCORE2-Diabetes	0.733 (0.727, 0.739)	reference
SCORE2-Diabetes with lipid values removed	0.730 (0.724, 0.736)	-0.0035 (-0.0046 ,-0.0025)
SCORE2	0.710 (0.704, 0.716)	-0.0228 (-0.0198, -0.0259)

Result for SNDR

Risk model	C-index	Difference in C-index (95% CI)
SCORE2-Diabetes	0.670 (0.667, 0.673)	reference
SCORE2-Diabetes with lipid values removed	0.665 (0.662, 0.668)	-0.0046 (-0.0061, -0.0031)
SCORE2	0.661 (0.658, 0.664)	-0.0088 (-0.0102, -0.0074)
ADVANCE	0.665 (0.662, 0.668)	-0.0046 (-0061, -0.0031)

Supplementary Table 10. Net reclassification when using SCORE2 diabetes versus SCORE2

A) Using the Prospective continuous NRI

Data source	Expected net appropriate reclassification of CVD events occurring before 10-years (%)	Expected net appropriate reclassification of individuals CVD event free at 10-years	Continuous NRI
SNDR	56.9 (56.0, 57.9)	-28.2 (-28.8, -27.6)	28.7 (27.7, 29.8)
CPRD	62.4 (60.0, 64.8)	-37.2 (-38.1, -36.4)	25.2 (22.4, 28.0)

B) Using the Prospective categorical NRI, with risk thresholds, 5, 10, 15, 20 and 25% CVD risk

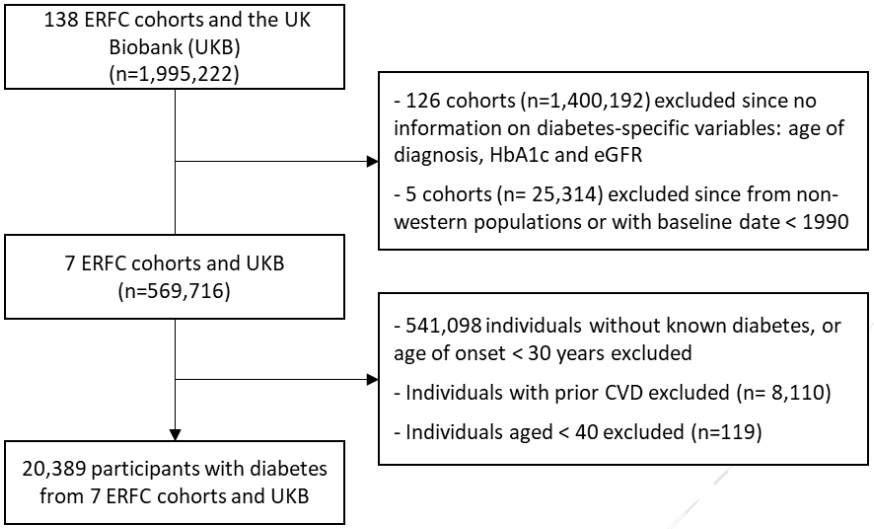
Data source	Expected net appropriate reclassification of CVD events occurring before 10-years (%)	Expected net appropriate reclassification of individuals CVD event free at 10-years (%)	Categorical NRI
SNDR	31.9 (31.2, 32.6)	-18.2 (-18.6, -17.9)	13.7 (12.9, 14.5)
CPRD	44.8 (43.0, 46.7)	-20.2 (-20.8, -19.6)	24.6 (22.5, 26.8)

CPRD: Individuals with diabetes from the Clinical Practice Research Datalink

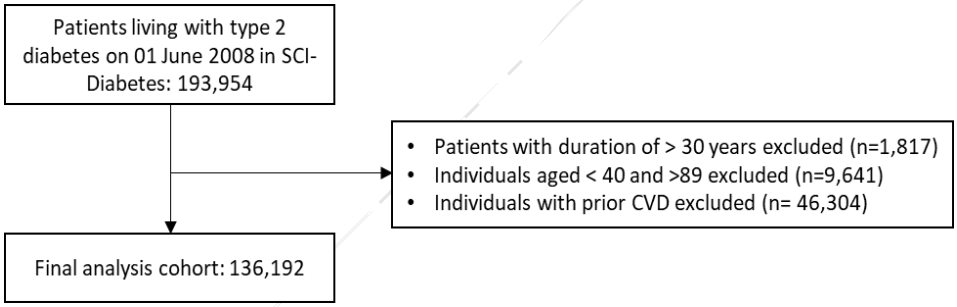
SNDR: Swedish National Diabetes Register

Supplementary Figure 1: Selection of studies and individuals for SCORE2-Diabetes model derivation

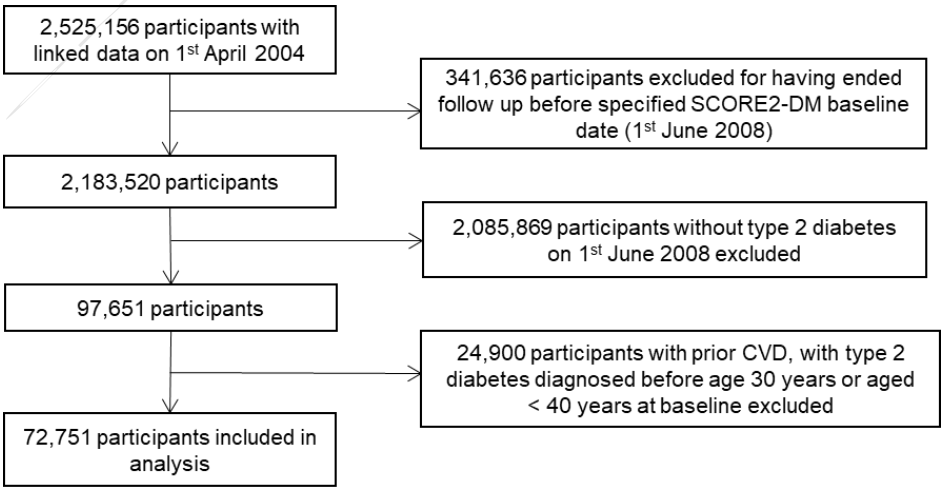
Emerging Risk Factors Collaboration/UK Biobank



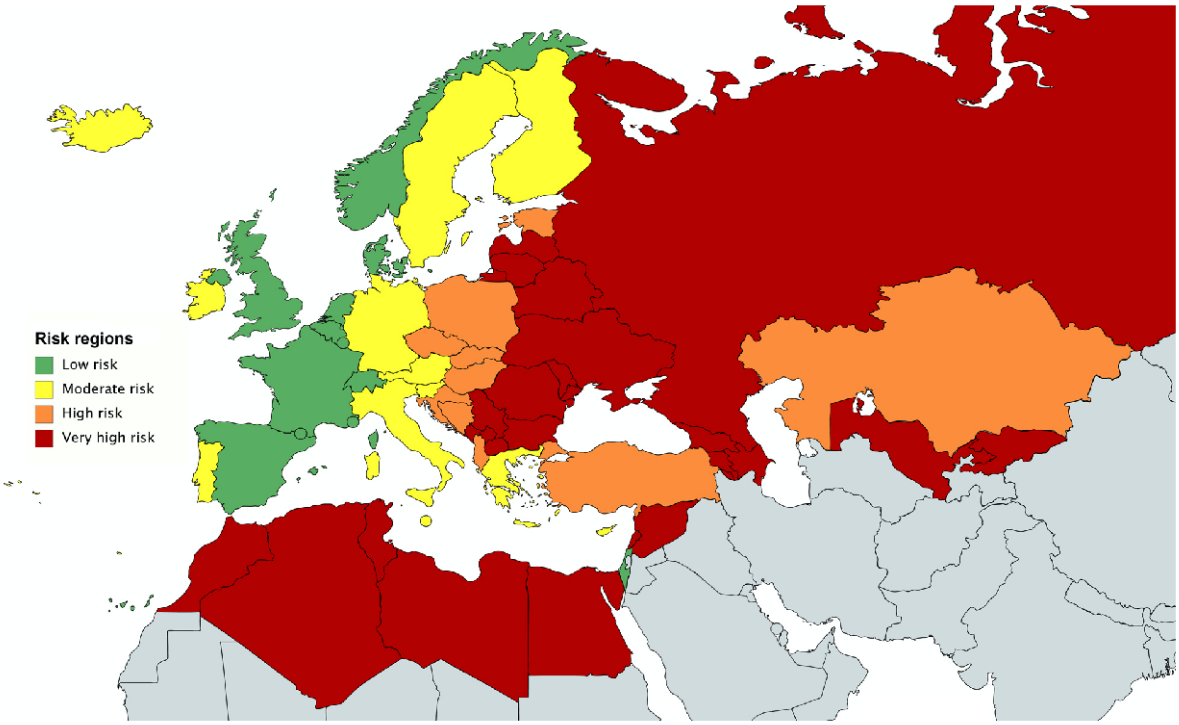
Scottish Care Information- Diabetes



Clinical Practice Research Datalink

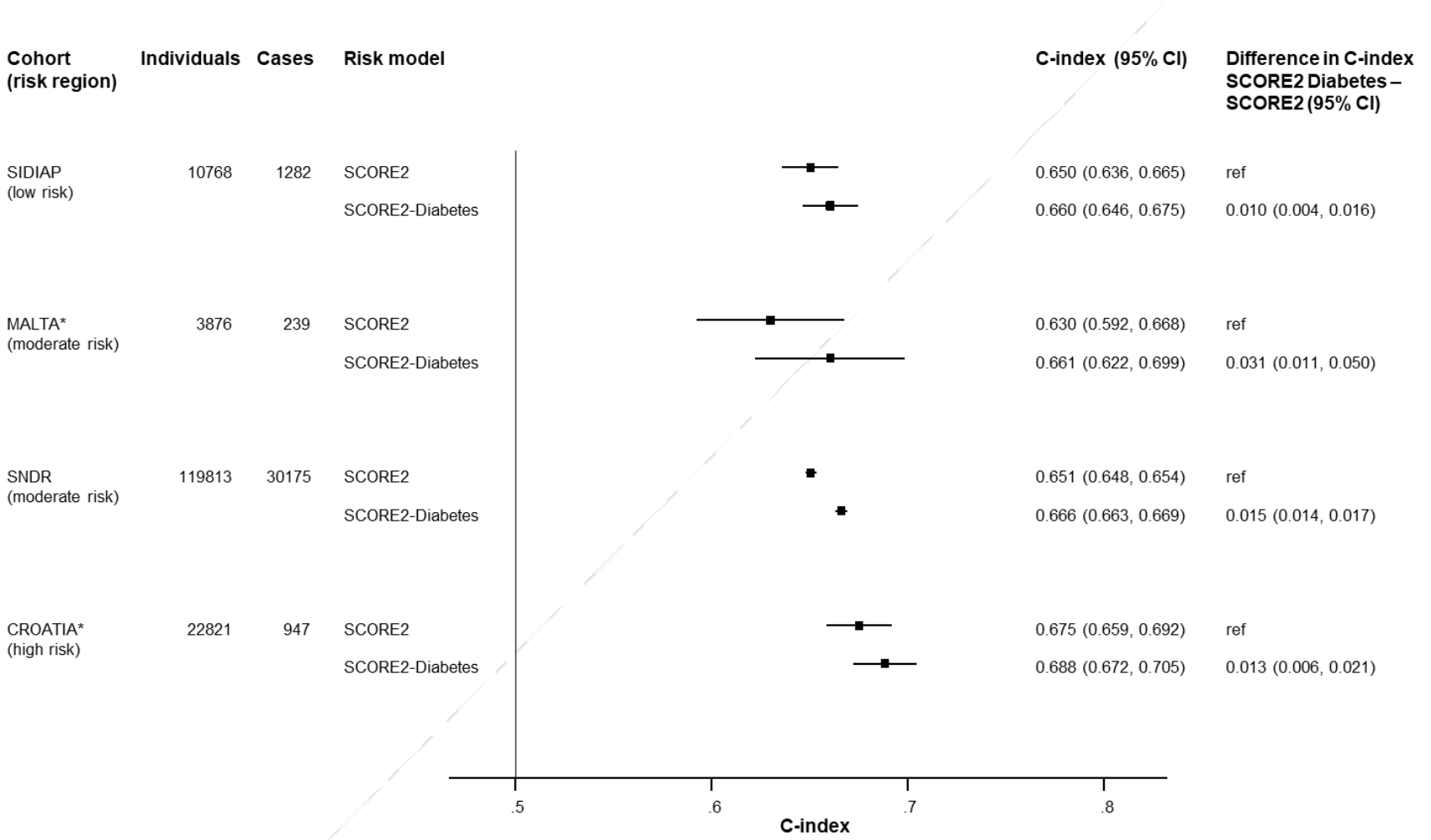


Supplementary Figure 2: risk regions for SCORE2-Diabetes application



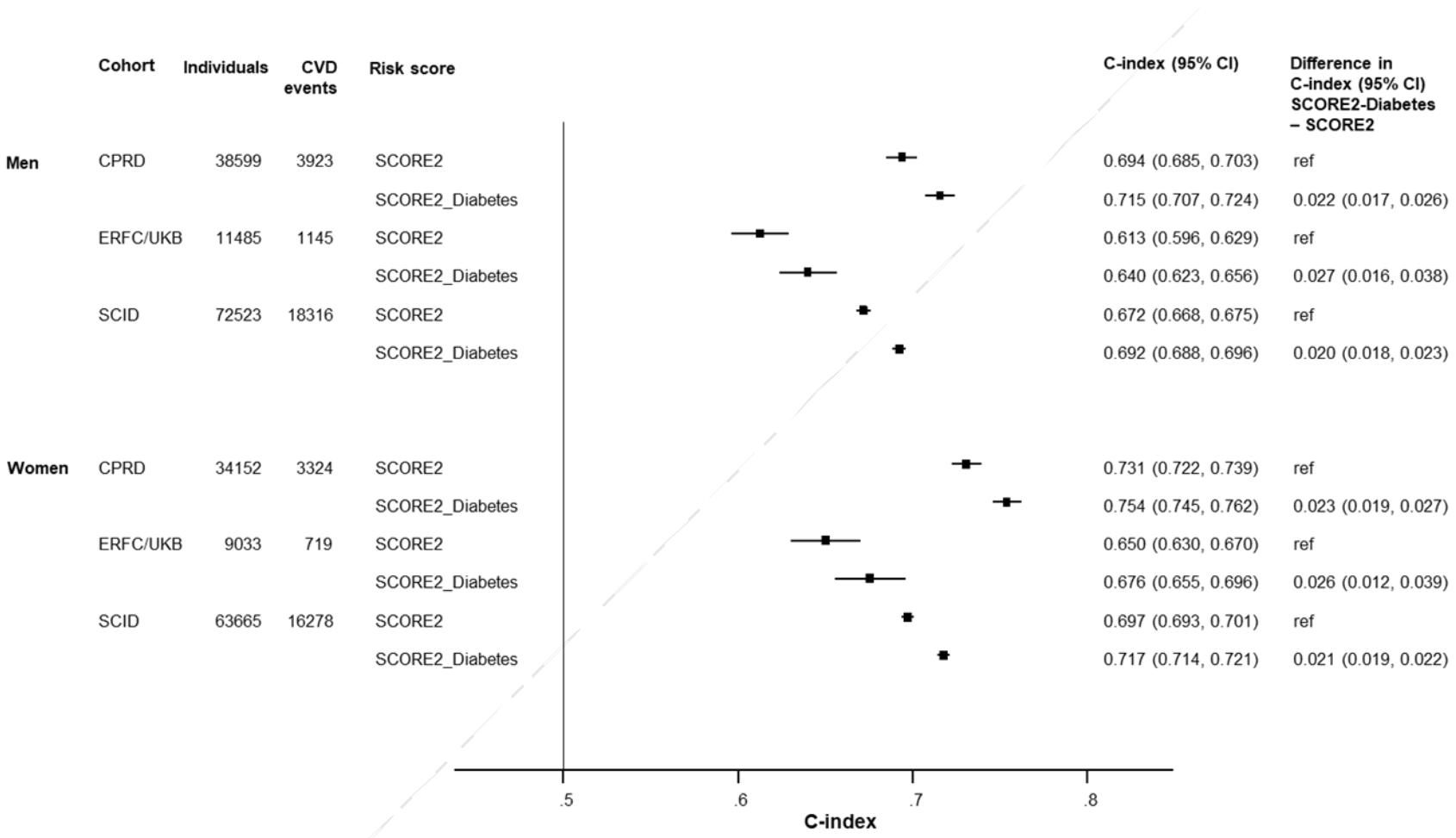
Countries were grouped into four risk regions according to their most recently reported WHO age- and sex-standardized overall CVD mortality rates per 100,000 population (ICD chapters 9, I00-I99). The four groupings were: low risk (<100 CVD deaths per 100,000), moderate risk (100 to <150 CVD deaths per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

Supplementary Figure 3. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from external data sources using complete case datasets



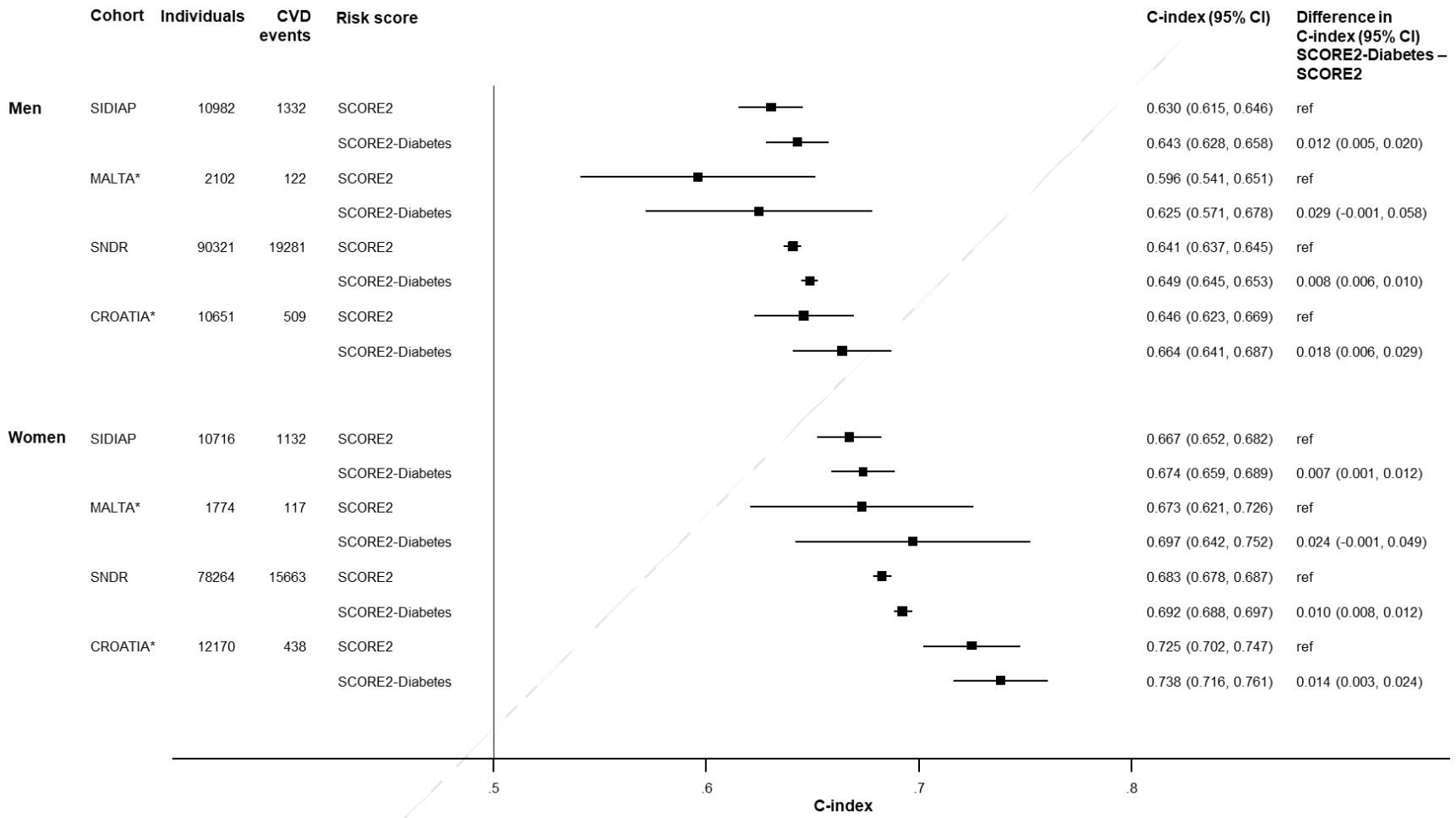
*Data source from EUBIROD (EUropean Best Information through Regional Outcome in Diabetes)
SIDIAP: Information System for Research in Primary Care; SNDR: Swedish National Diabetes Register (SNDR)

Supplementary Figure 4. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from derivation datasets, by sex



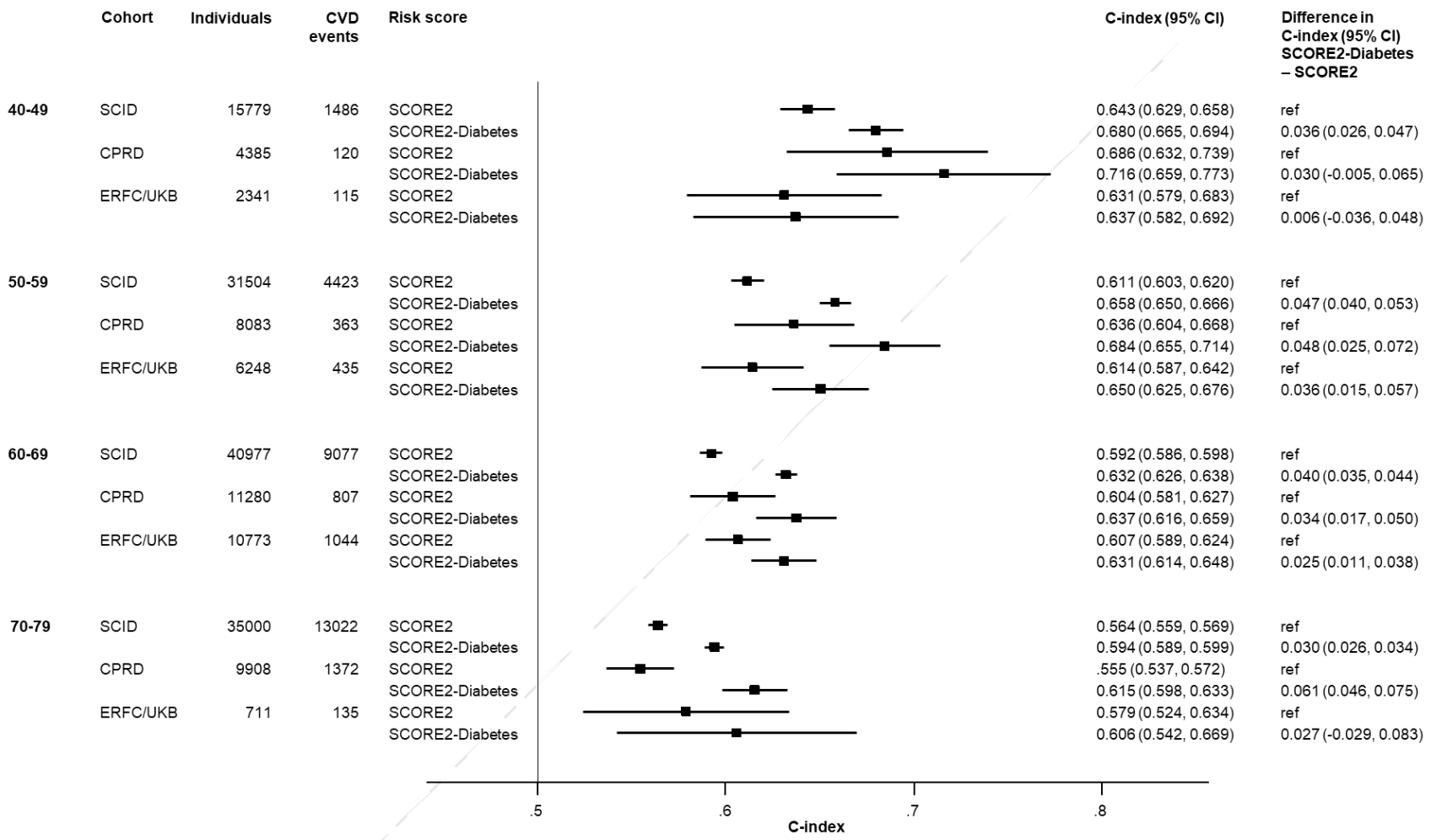
CPRD: Clinical Practice Research Datalink, ERFC: Emerging Risk Factors Collaboration, UKB: UK Biobank, SCID: Scottish Care Information- Diabetes

Supplementary Figure 5. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from external validation datasets, by sex



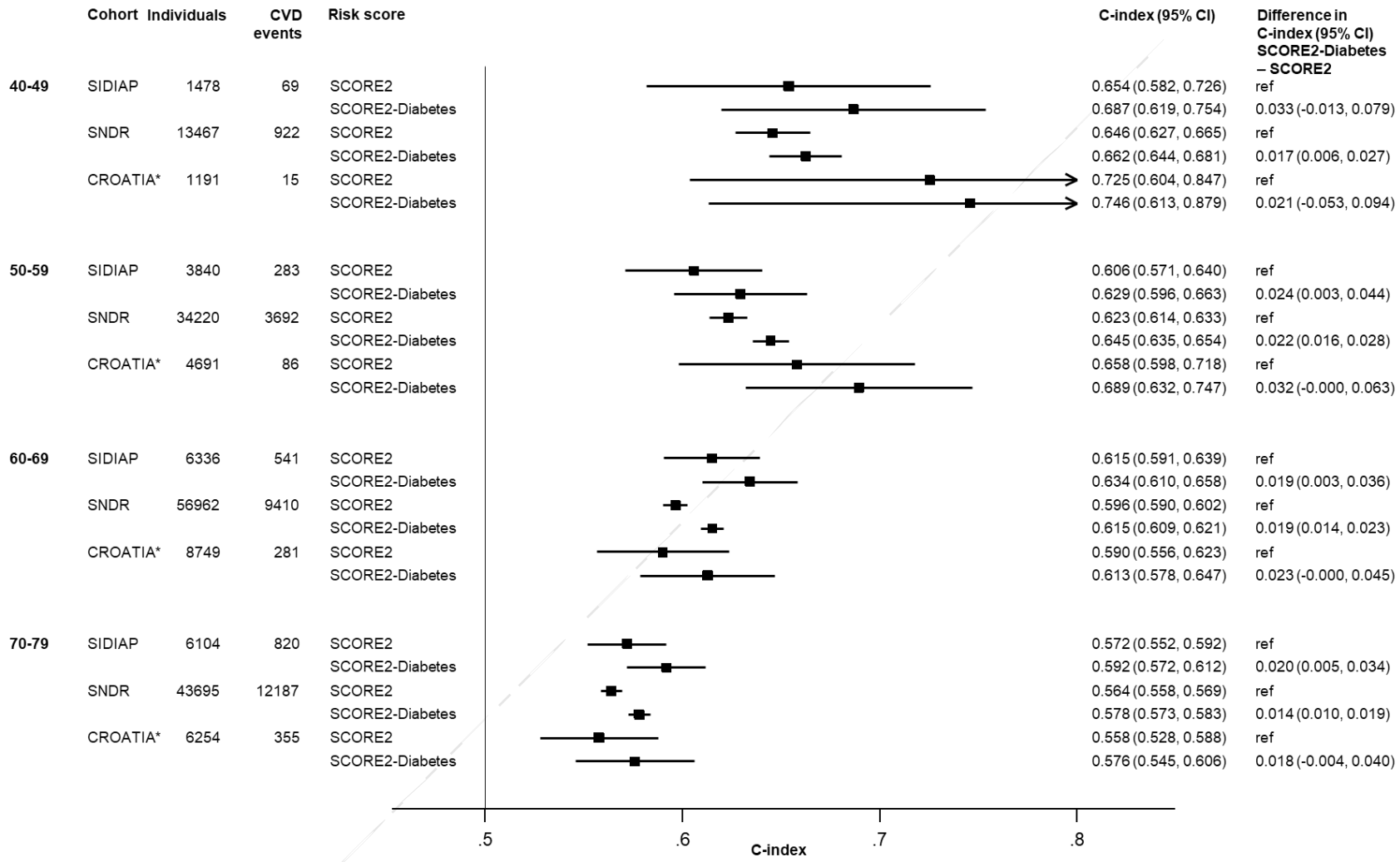
*Complete case data source from EUBIROD (EUropean Best Information through Regional Outcome in Diabetes, MALTA represents the moderate and CROATIA the high risk region).
SIDIAP: Information System for Research in Primary Care (low risk region); SNDR: Swedish National Diabetes Register (moderate risk region)

Supplementary Figure 6. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from derivation datasets, by age-group



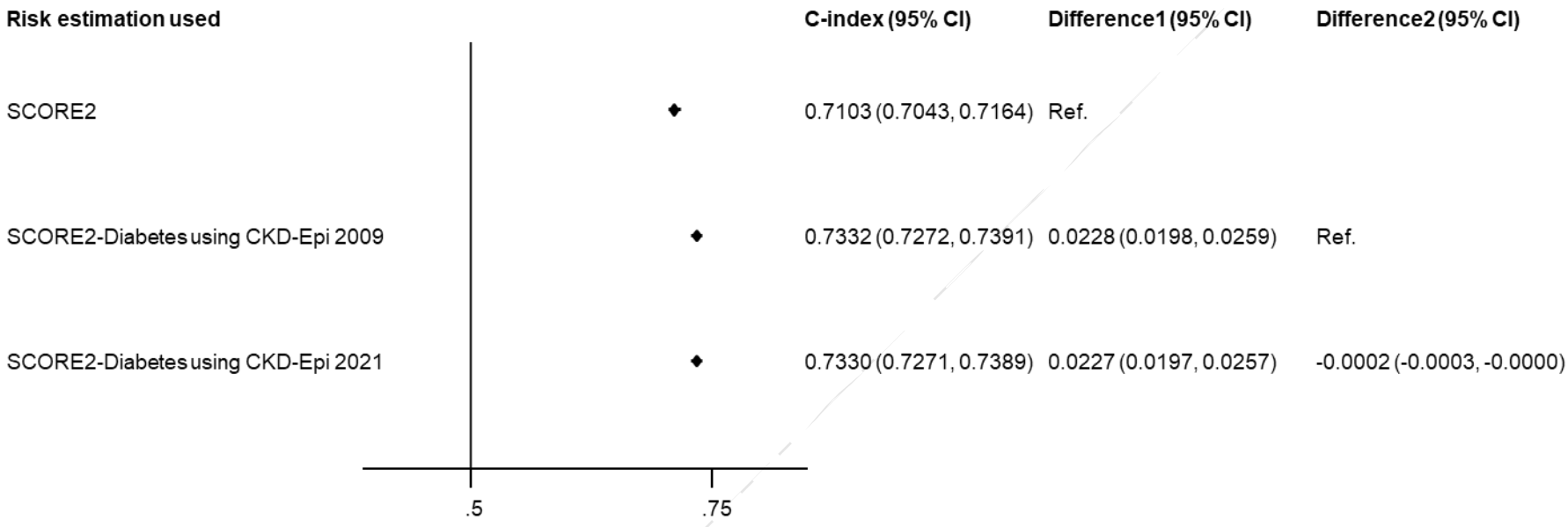
CPRD: Clinical Practice Research Datalink, ERFC: Emerging Risk Factors Collaboration, UKB: UK Biobank, SCID: Scottish Care Information- Diabetes

Supplementary Figure 7. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes from external validation datasets, by age-group

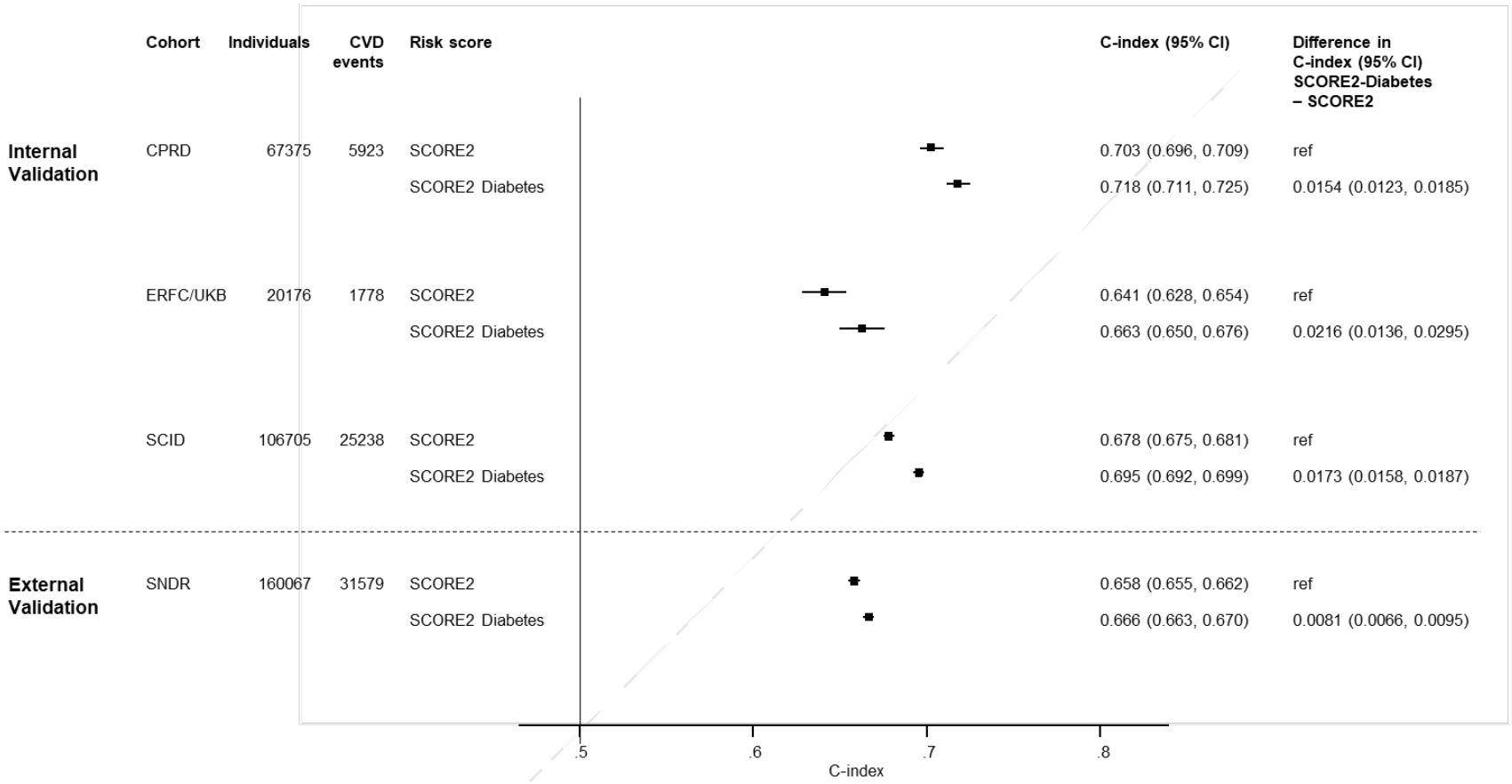


* Complete case data source from EUBIROD (EUropean Best Information through Regional Outcome in Diabetes, CROATIA represents the high risk region).
SIDIAP: Information System for Research in Primary Care (low risk region); SNDR: Swedish National Diabetes Register (moderate risk region)

Supplementary Figure 8: C-index for SCORE2-Diabetes, when using alternative eGFR CKD-Epi calculations

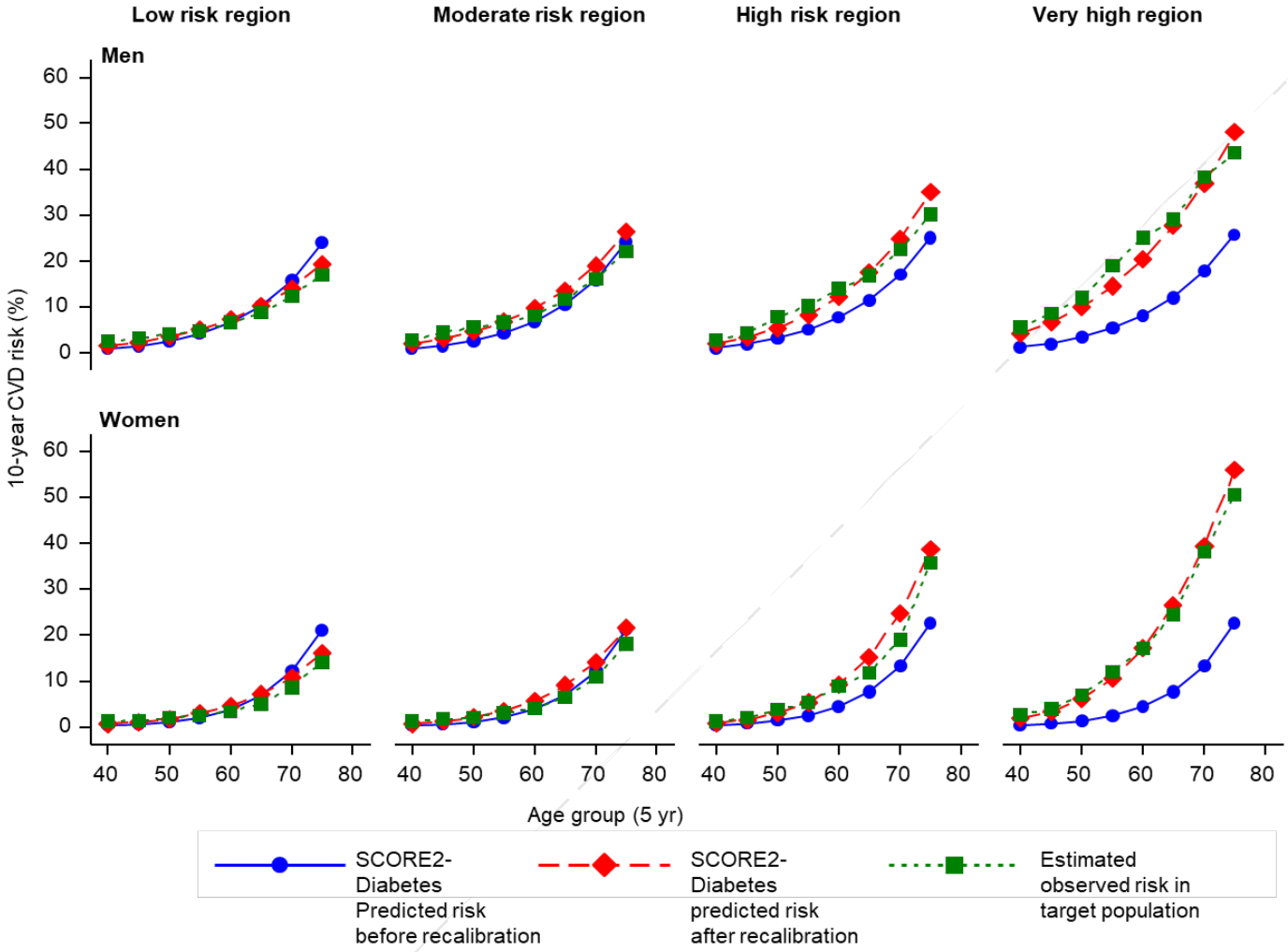


Supplementary Figure 9. C-index for SCORE2-Diabetes, and comparison to SCORE2 in individuals with diabetes and eGFR > 45 ml/min/ 1.73m^2



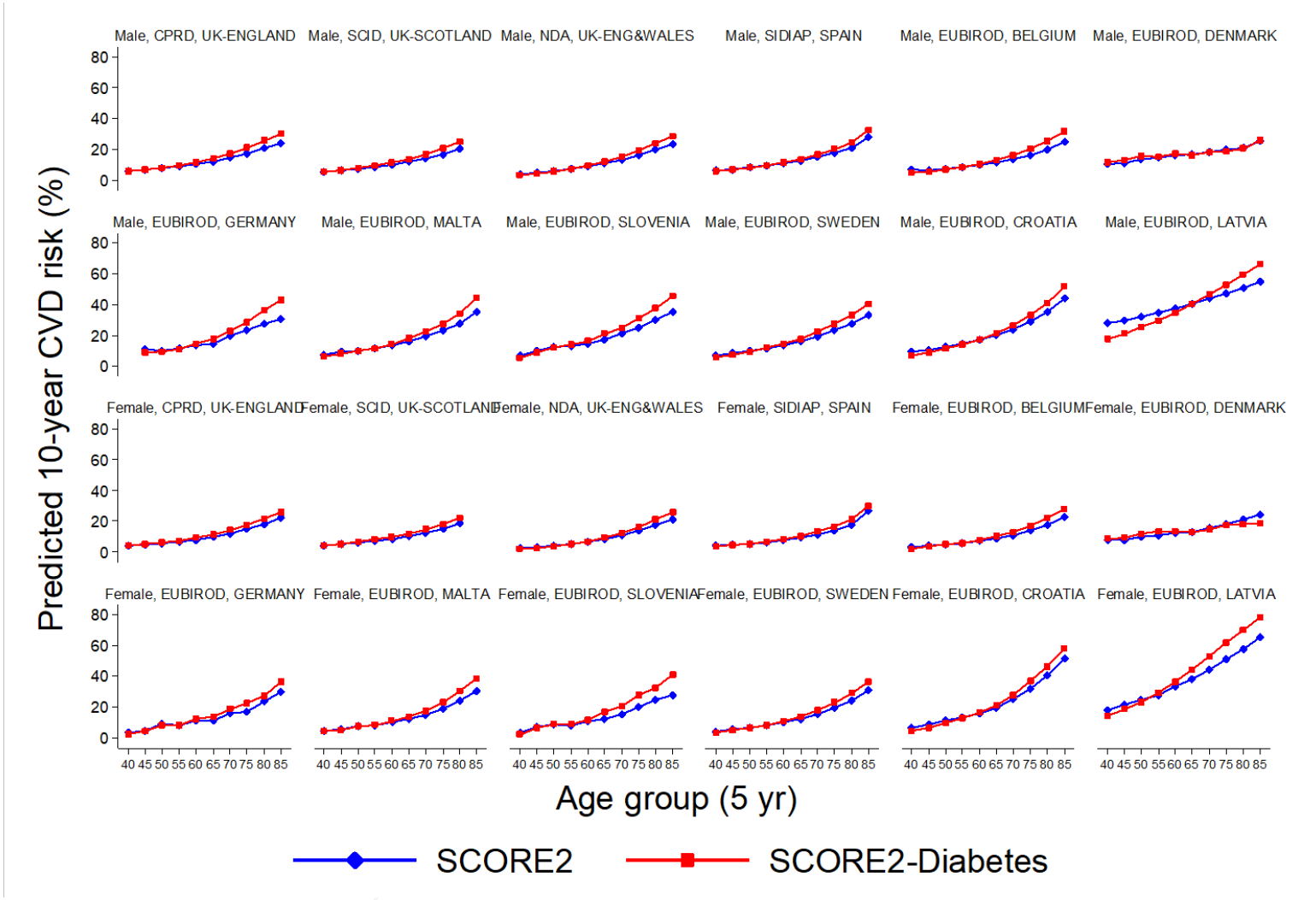
CPRD: Clinical Practice Research Datalink, ERFC: Emerging Risk Factors Collaboration, UKB: UK Biobank, SNDR: Swedish National Diabetes Register, SCID: Scottish Care Information- Diabetes

Supplementary Figure 10. SCORE2-Diabetes predicted risks and expected risks by risk region, before and after recalibration



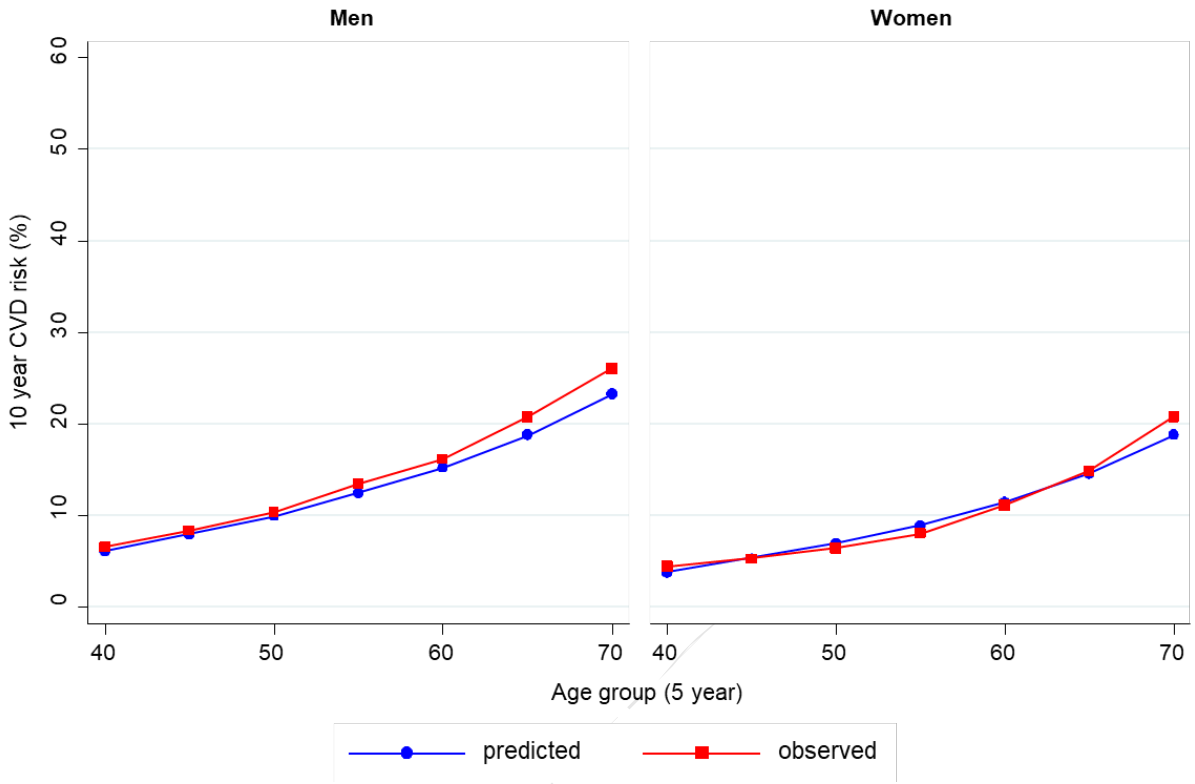
Estimated sex and age specific risk is in the whole population based on WHO mortality converted to total competing risk adjusted 10-year CVD incidence, using multipliers derived in representative data from each risk region, as used in the recalibration of SCORE2. Predicted risk is based on sex and age specific conventional risk factor means from NCD_Risc as used in the recalibration of SCORE2 and Diabetes related variable means from CPRD, applied proportionately according to the proportion with diabetes in each age group.

Supplementary Figure 11: Agreement in average age group specific risks estimated with SCORE2 and SCORE2-Diabetes in individuals with diabetes

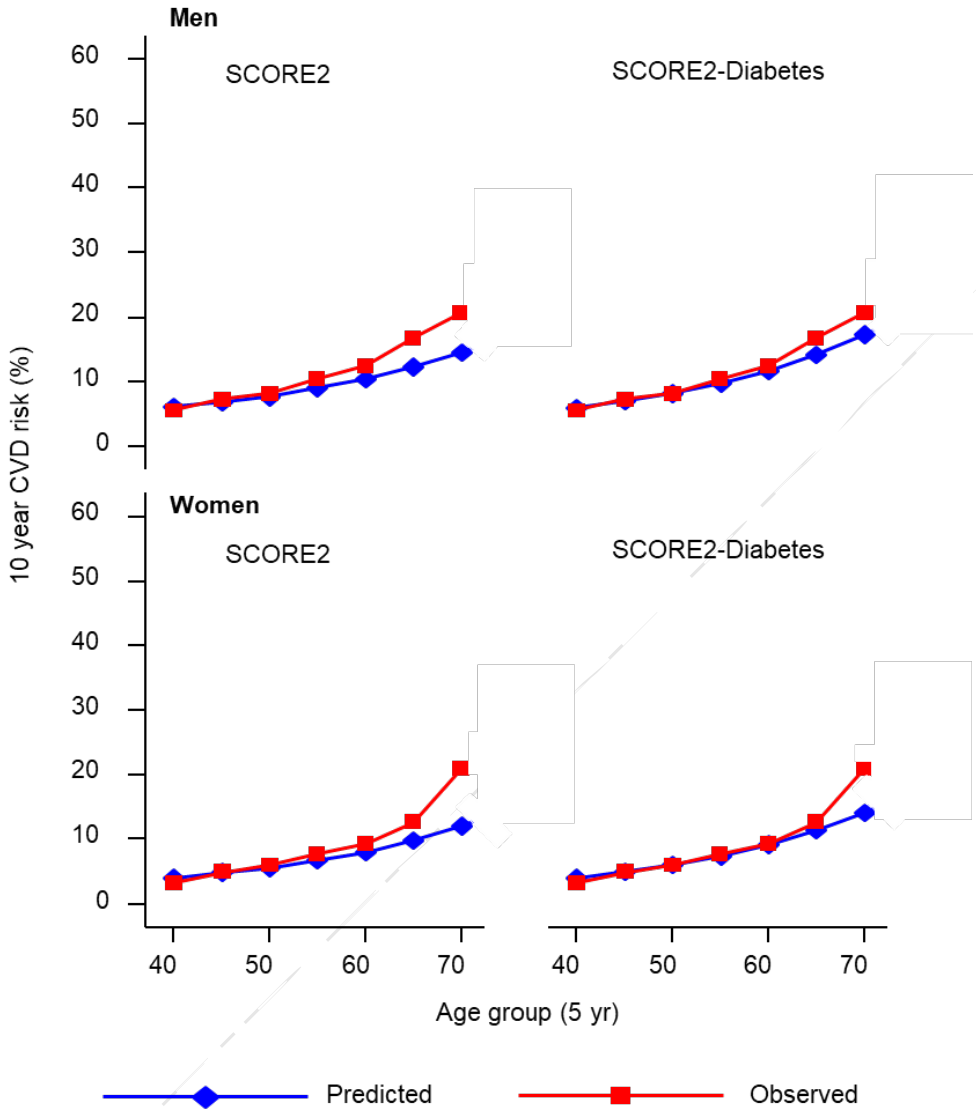


CPRD: Clinical Practice Research Datalink, NDA: National Diabetes Audit, SNDR: Swedish National Diabetes Register, SIDIAP: Information System for Research in Primary Care; SNDR: Swedish National Diabetes Register (SNDR), SCID: Scottish Care Information- Diabetes; EUBIROD (EUropean Best Information through Regional Outcome in Diabetes)

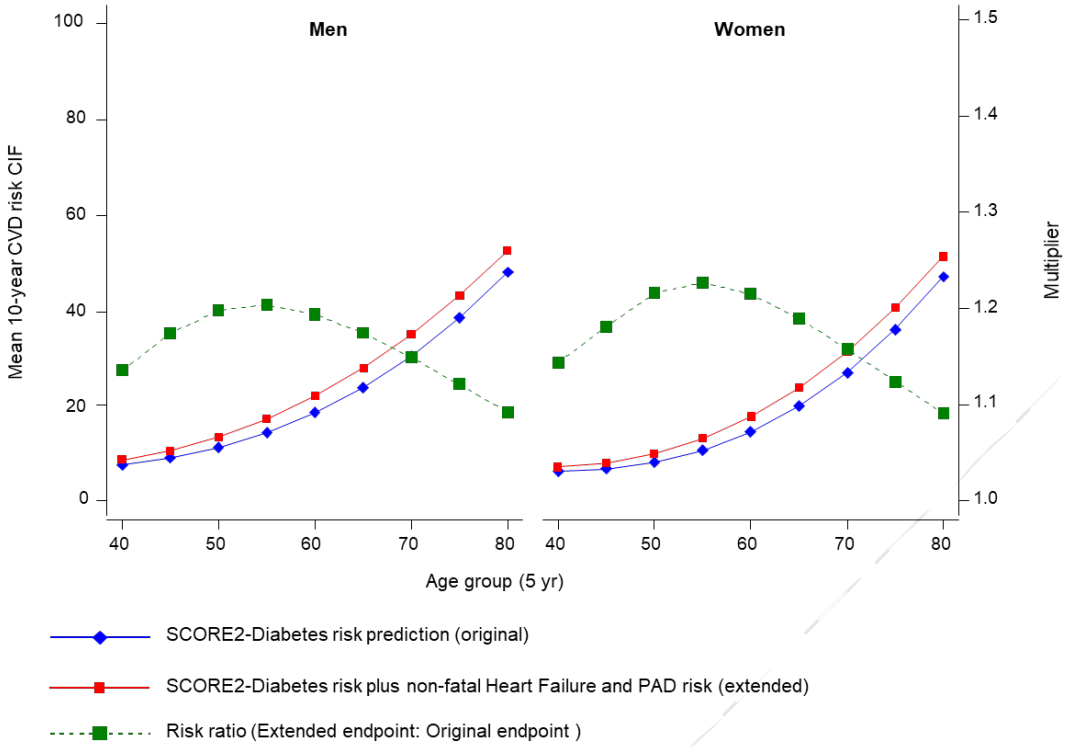
Supplementary Figure 12: Calibration of SCORE2-Diabetes using individual participant data from the Swedish National Diabetes Registry



Supplementary Figure 13: Calibration of SCORE2-Diabetes and SCORE2 using individual participant data from individuals with diabetes from the CPRD



Supplementary Figure 14 Risk of CVD accounting for non-fatal Heart failure and PAD



Age group	Multiplication factor to convert SCORE2-Diabetes risk to include additional risk of non-fatal Heart Failure and PAD	
	Men	Women
40-45	1.14	1.14
45-50	1.17	1.18
50-55	1.20	1.22
55-60	1.20	1.23
60-65	1.19	1.21
65-70	1.17	1.19
70-75	1.15	1.16
75-80	1.12	1.12

Note: While these multipliers can be applied to SCORE2-Diabetes risk of non-fatal MI, Stroke or any CVD death predictions to get a rough estimate of the additional risk posed by non-fatal Heart failure and Peripheral Artery Disease, their accuracy cannot be guaranteed. They have been calculated using data from the Low risk region only, and have not been externally validated in any region of Europe. Similarity in higher risk regions is currently unknown.

Supplementary study-specific information

Scottish Care Information – Diabetes (SCID): The use of pseudonymised data for people with diabetes in Scotland for research during this study period was approved by the Scotland A multi-centre research ethics committee reference: 11-AL-0225) and the Public Benefit and Privacy panel (reference 1617-0147)

Data from the SIDIAP database used in the current study was approved by the Ethics Committee of the IDIAP Jordi Gol i Gurina Foundation (code P17/087).