

Development and validation of a new algorithm for improved cardiovascular risk prediction

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SUPPLEMENTARY FIGURES AND TABLES

FIGURES

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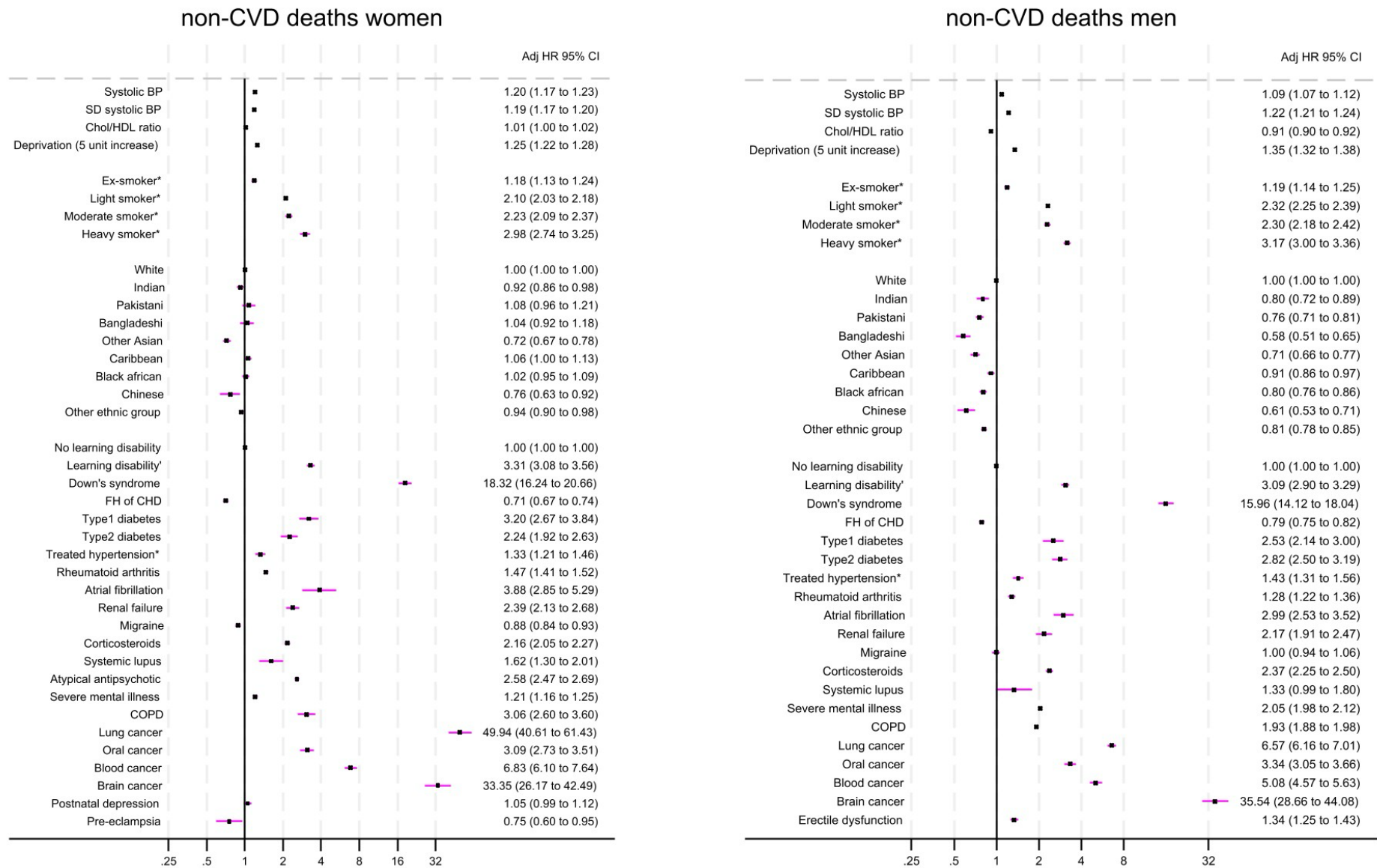
Supplementary Table 1 CVD outcome definitions for sensitivity analyses.

Supplementary Table 2 Performance of QR4, SCORE2 and ASCVD in people age 40+ using the three CVD outcome measures in men and women in the validation cohort in England.

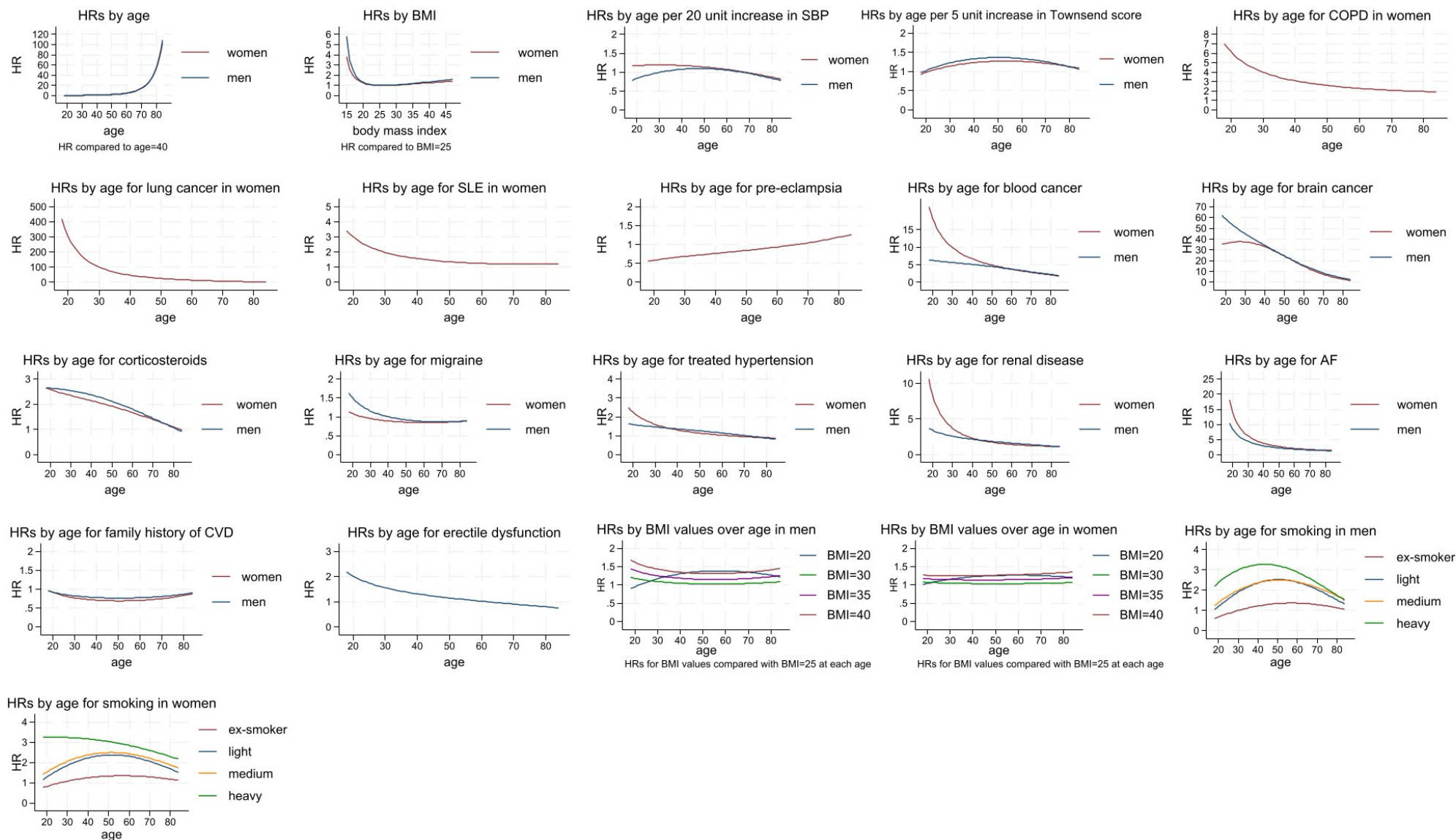
Supplementary Table 3 Characteristics of patients in the English validation cohort with a high QR4 risk score (defined as 10-year risk of CVD of 10% or greater) including characteristics of those reclassified using QR4 compared with Model A.

Supplementary Table 4: Characteristics of patients with complete vs missing data for patients aged 18-84 years in the English QResearch derivation cohort. Values are numbers (%) of patients unless indicated otherwise.

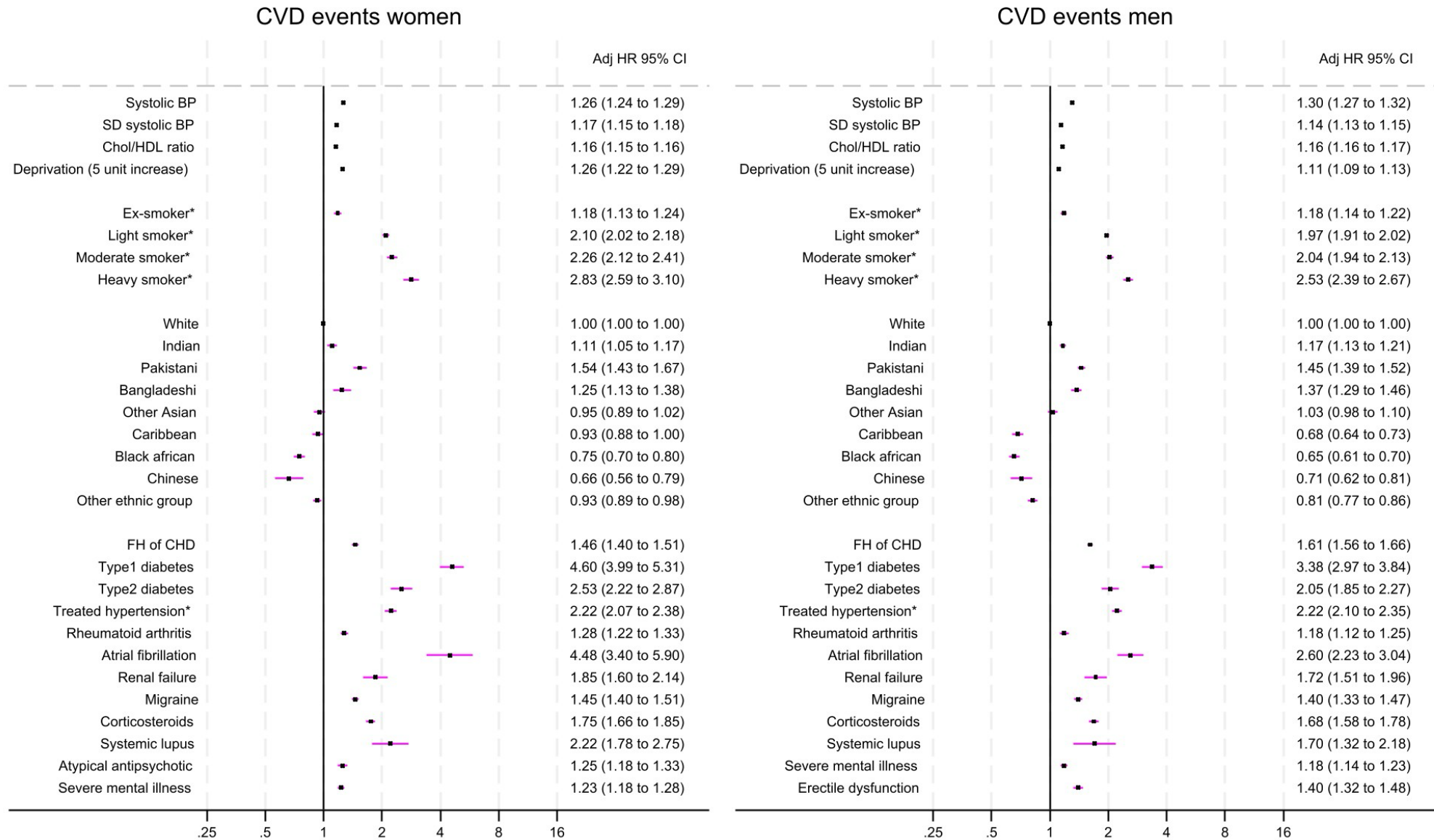
Supplementary Figure 1 Final model adjusted hazard ratios for non-CVD death. Shown are adjusted hazard ratios in 5,155,595 women and 4,820,711 men, presented at the mean age of 39 for variables with age interactions. The hazard ratios were adjusted for fractional polynomial terms for age, and BMI (see Supplementary Figure 1 which shows the relevant fractional polynomial terms. Systolic BP is per 20 unit increase.



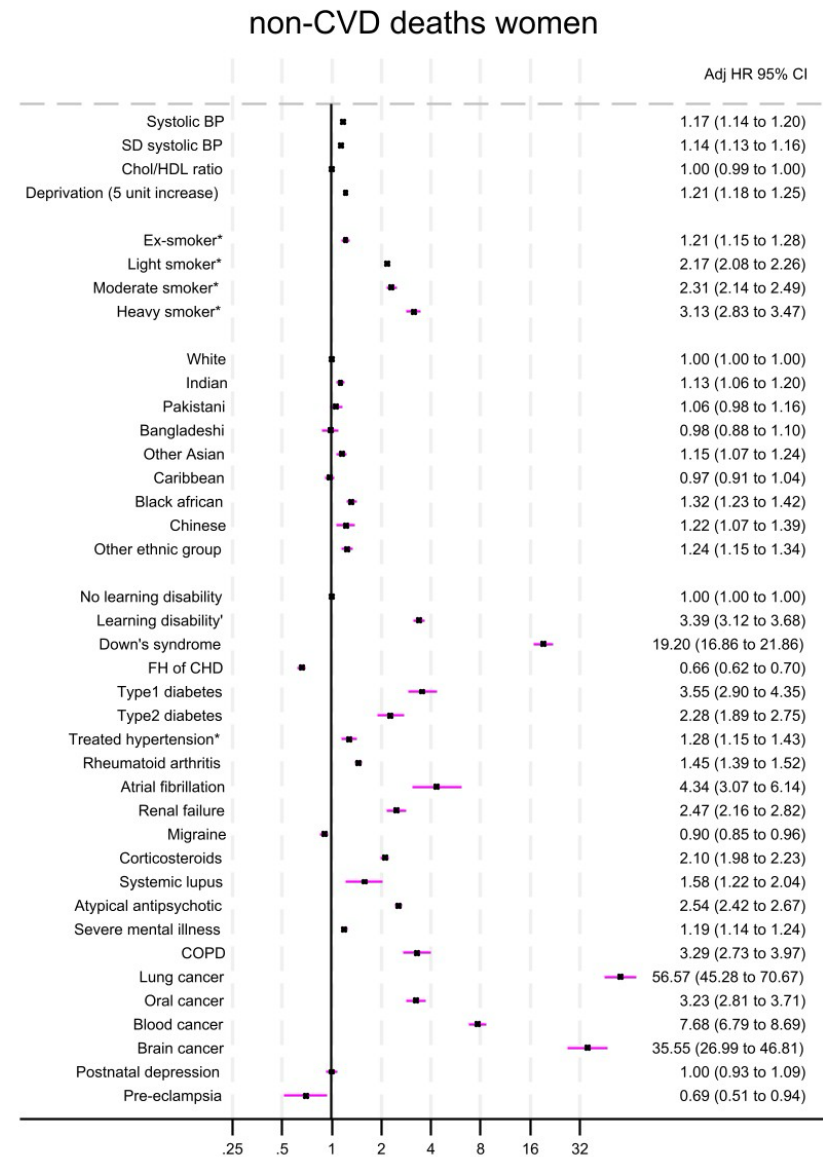
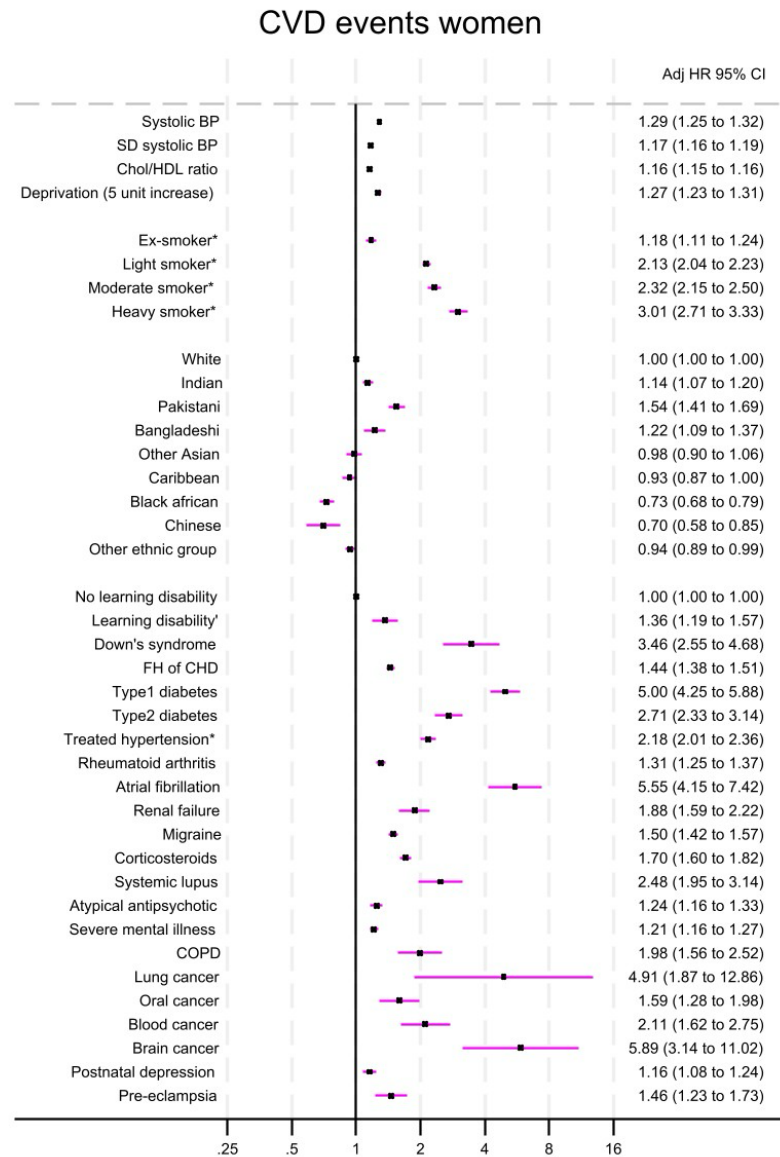
Supplementary Figure 2 Adjusted hazard ratios for non-CVD death for fractional polynomial terms for and BMI, and for age interactions



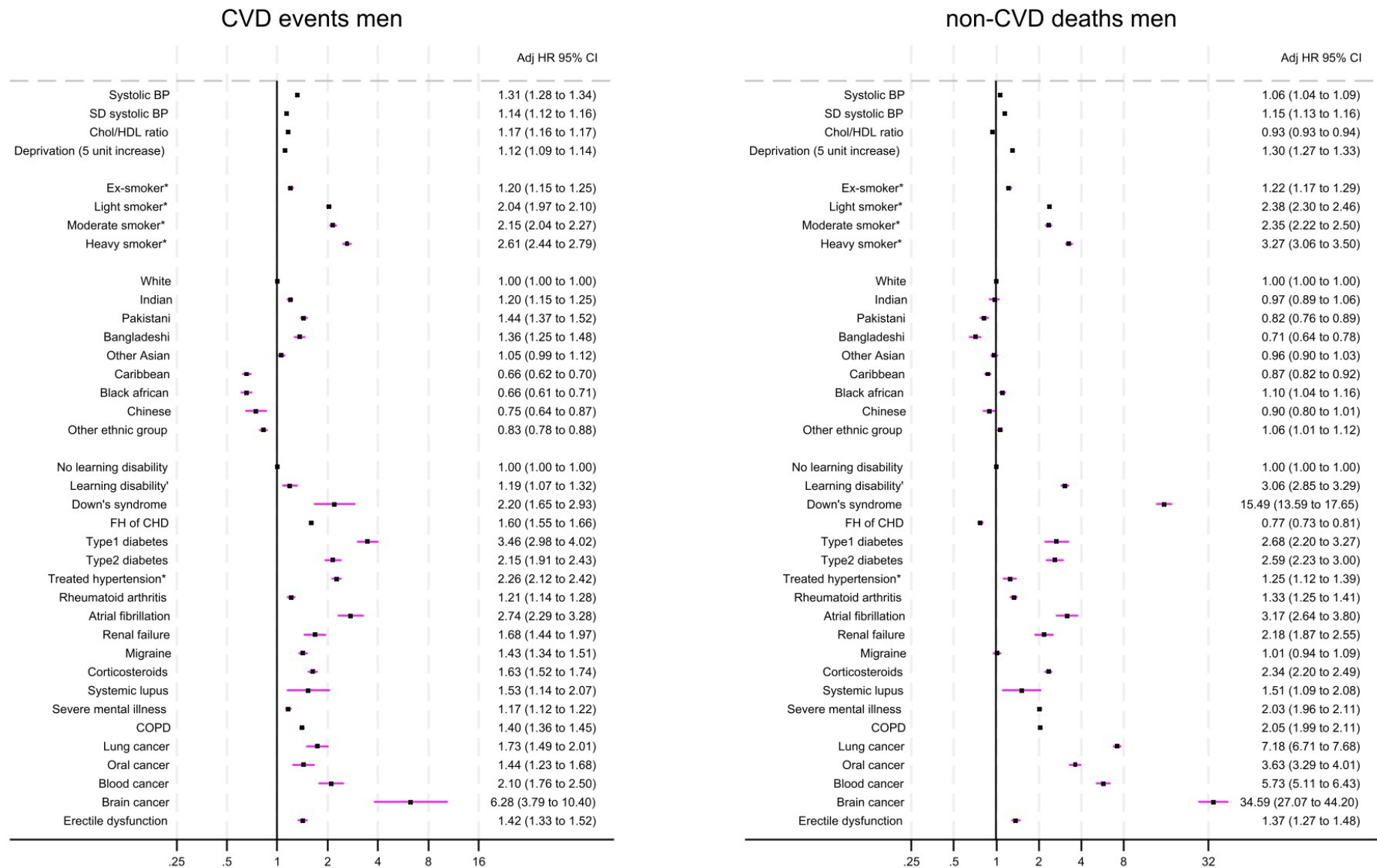
Supplementary Figure 3 Adjusted mean hazard ratios (95% confidence intervals) for Model A in 4,820,711 men and 5,155,595 women. Model A included original QRISK3 parameters without competing risks.



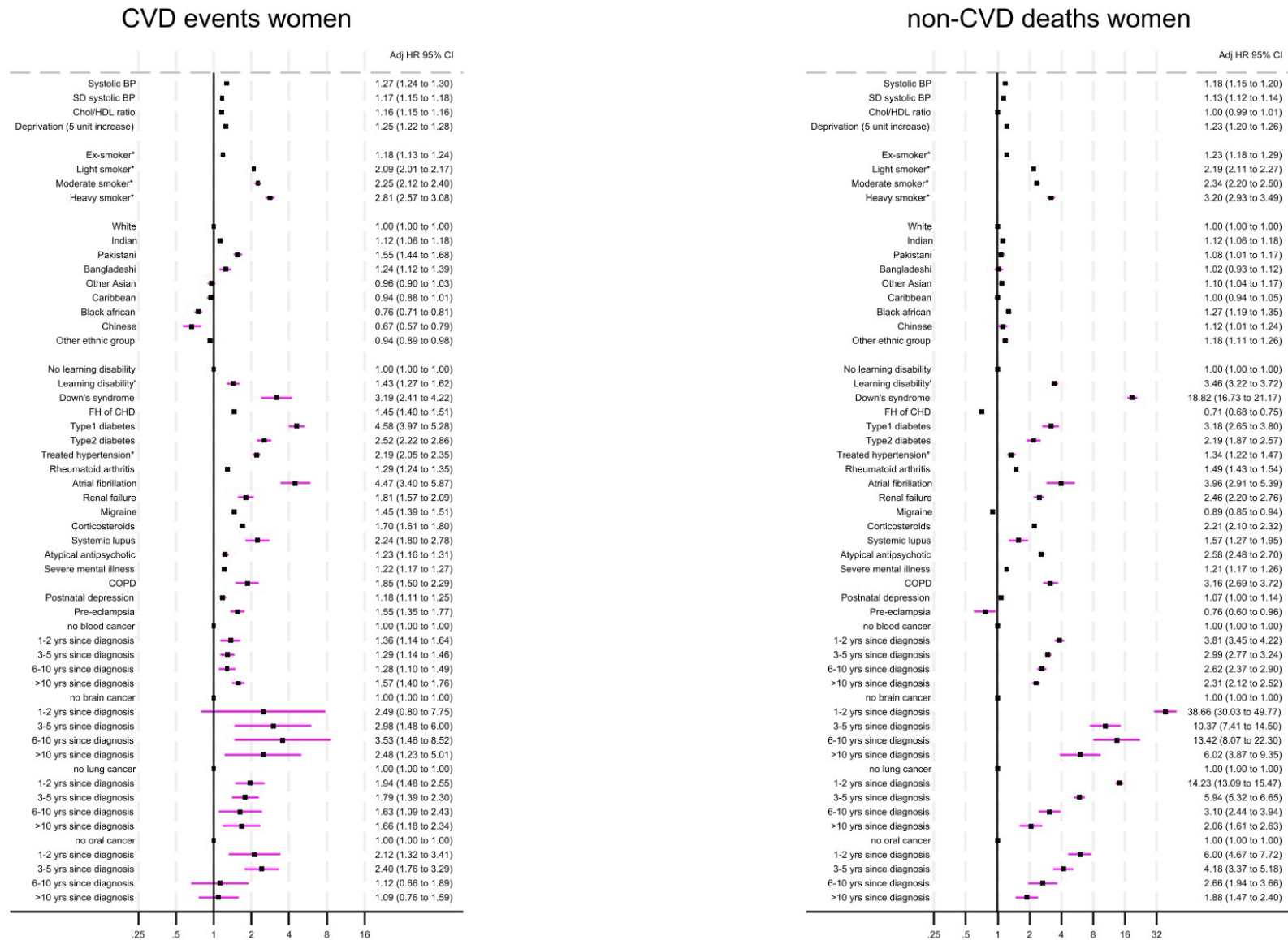
Supplementary Figure 4 Adjusted mean hazard ratios (95% confidence intervals) for Model B in 5,155,595 women. Model B had follow-up time censored on 29.02.2020, immediately prior to the COVID-19 pandemic.



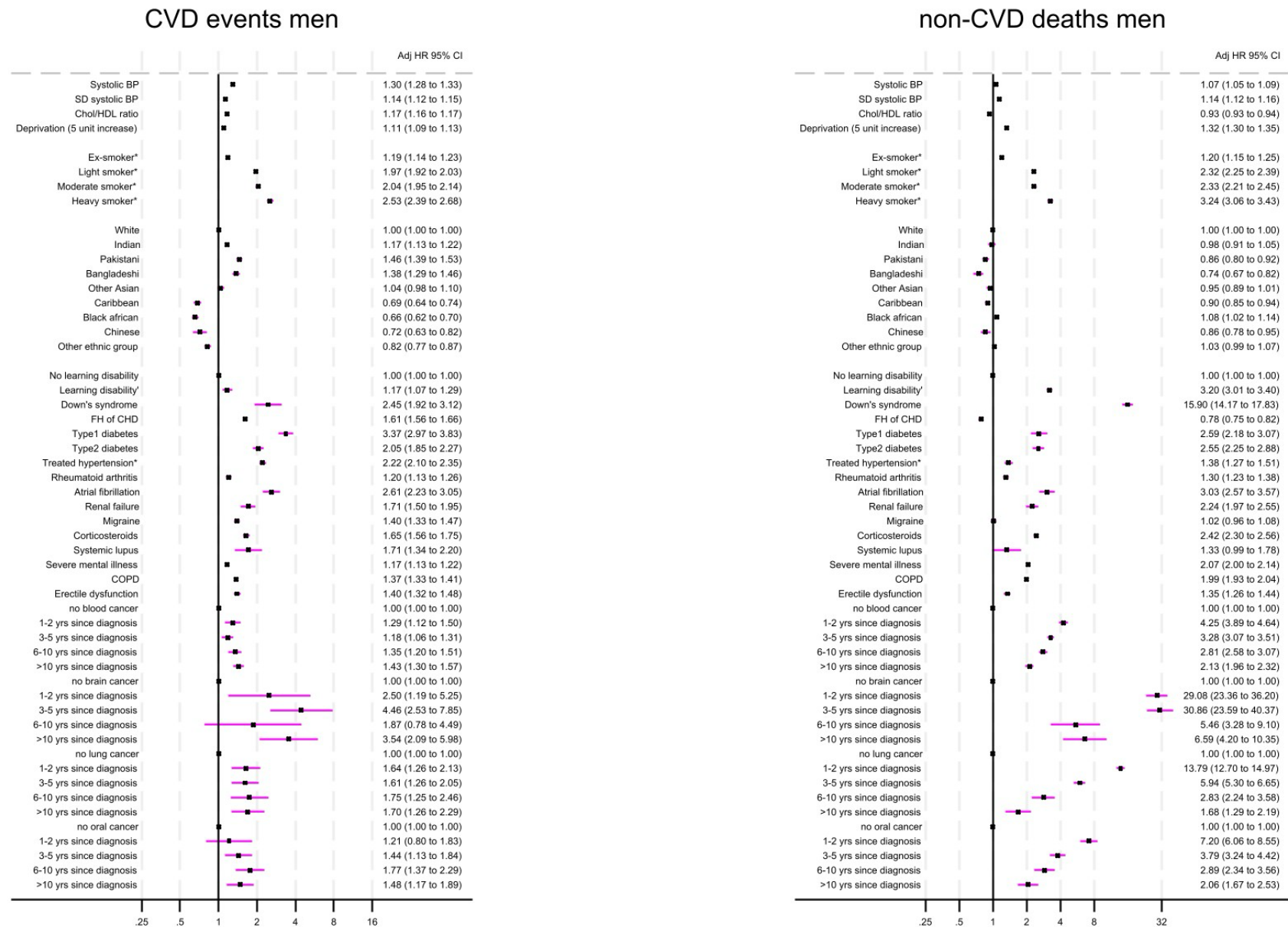
Supplementary Figure 5 Adjusted mean hazard ratios (95% confidence intervals) for Model B in 4,820,711 men. Model B had follow-up time censored on 29.02.2020, immediately prior to the COVID-19 pandemic.



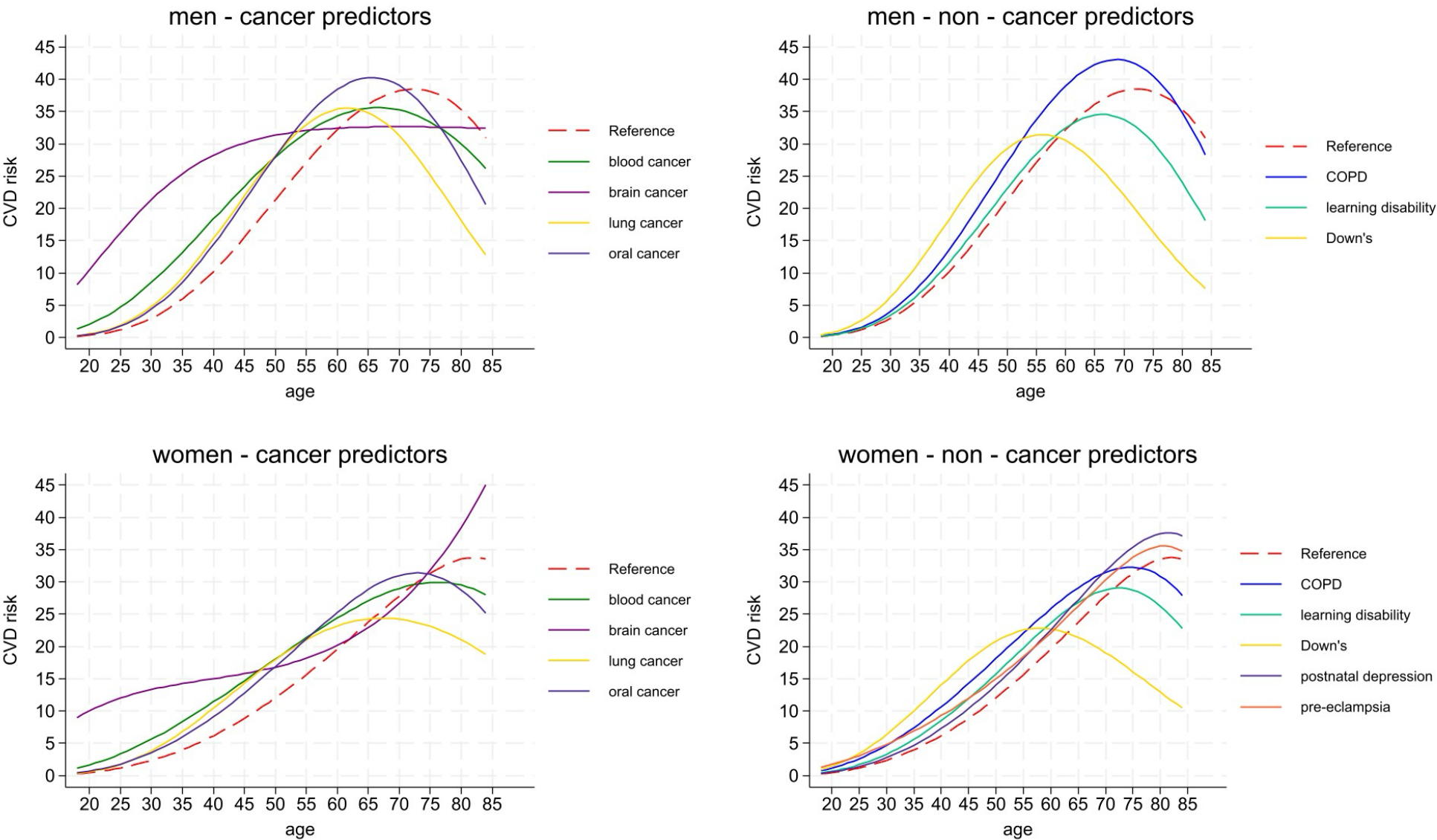
Supplementary Figure 6 Adjusted mean hazard ratios (95% confidence intervals) for Model C in 5,155,595 women. Model C includes time since diagnosis for cancer.



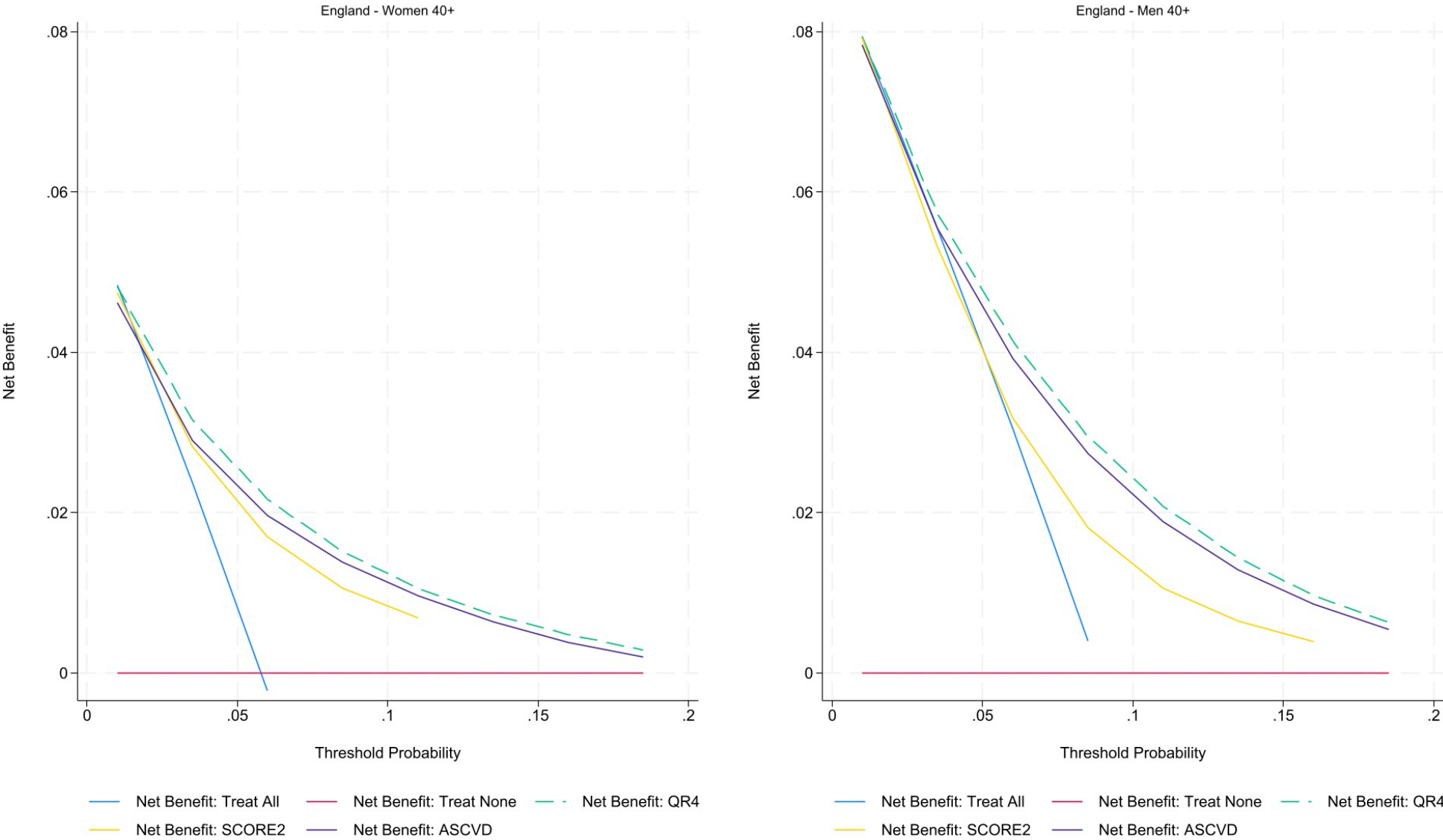
Supplementary Figure 7 Adjusted mean hazard ratios (95% confidence intervals) for Model C. Model C includes time since diagnosis for cancer for 4,820,711 men.



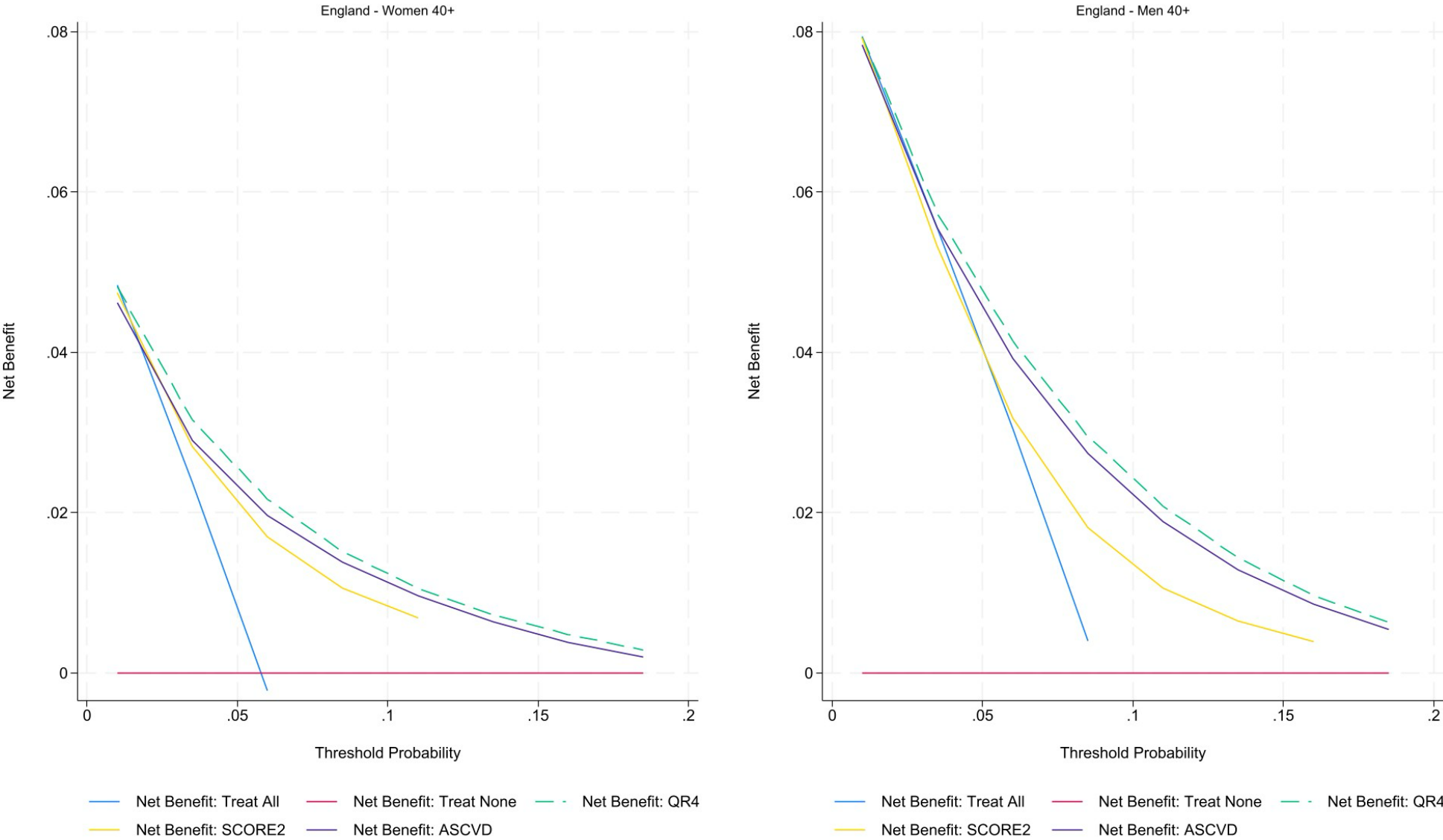
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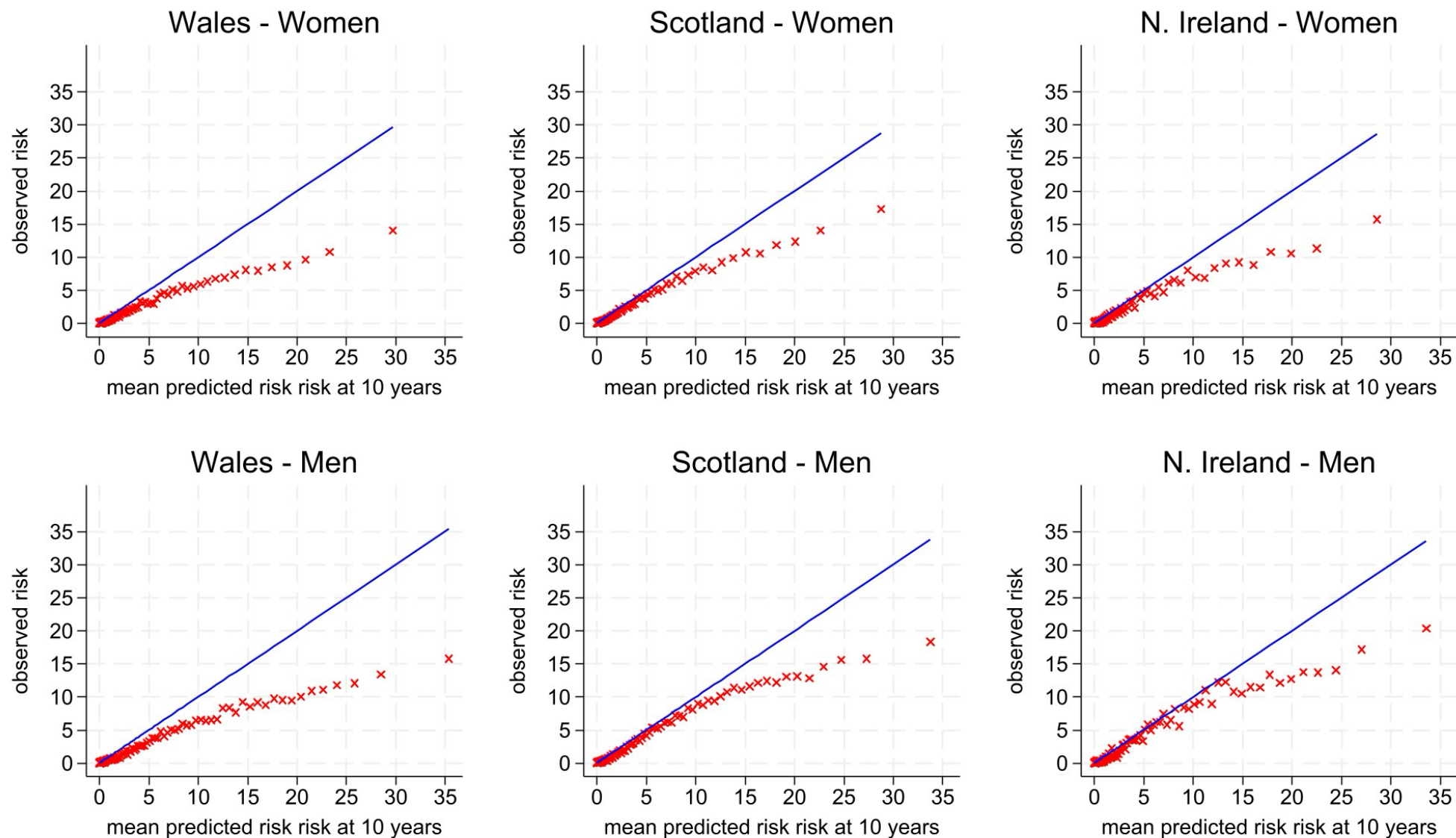
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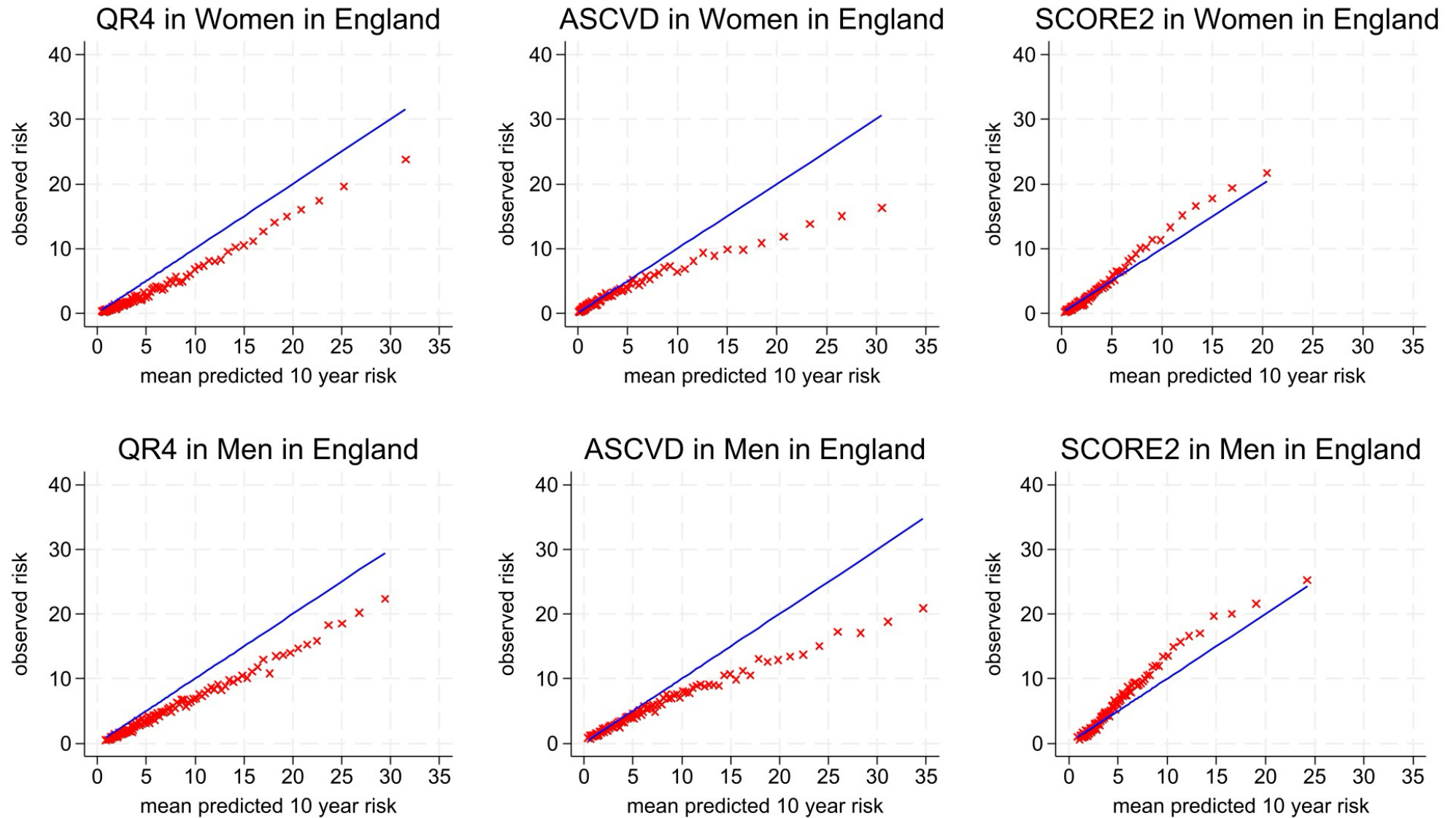
Supplementary Figure 10 Decision curves for QR4, ASCVD and SCORE2 in people aged 40+ in the England validation cohort using the third CVD outcome.



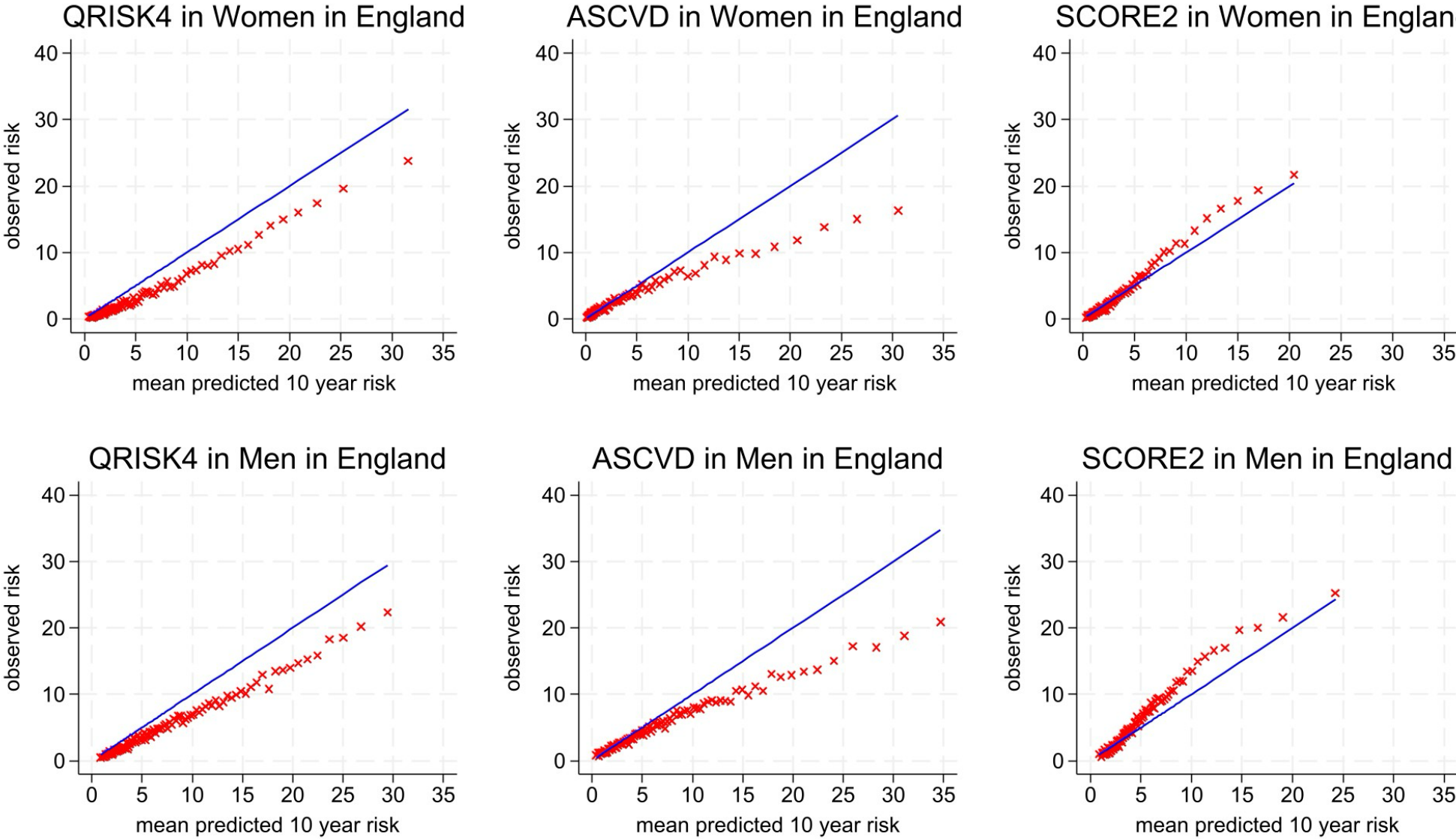
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Supplementary Figure 13 Predicted and observed 10-year CVD risks for QR4, ASCVD and SCORE2 in the validation cohort in England, using the third CVD outcome definition



Supplementary Table 1 CVD outcome definitions for QR4 model development and the definitions aligned to SCORE2 and ASCVD.

QR4	Fatal or non-fatal cardiovascular disease		<i>ICD10-codes</i>
	<i>End points included</i>	Ischemic heart disease	I20-25
		Cerebrovascular disease	I60-69
		Transient ischaemic attack	G45
	<i>Endpoints excluded</i>	Subarachnoid haemorrhage	I60
		Subdural haemorrhage	I62
		Cerebral aneurysm	I67.1
		Cerebral arteritis	I68.2
		Moyamoya	I67.5
ASCVD	Fatal cardiovascular disease		
	<i>Endpoints included</i>	Ischemic heart disease	I20-25
		Cerebrovascular disease	I60-69
	<i>Endpoints excluded</i>	Subarachnoid haemorrhage	I60
		Subdural haemorrhage	I62
		Cerebral aneurysm	I67.1
		Cerebral arteritis	I68.2
		Moyamoya	I67.5
	Non-fatal cardiovascular disease		
	<i>Endpoints included</i>	Non-fatal myocardial infarction	I21-I23
		Non-fatal stroke	I60-69
	<i>Endpoints excluded</i>	Subarachnoid haemorrhage	I60
		Subdural haemorrhage	I62
		Cerebral aneurysm	I67.1
		Cerebral arteritis	I68.2
		Moyamoya	I67.5
SCORE2	Fatal cardiovascular disease		
	<i>Endpoints included</i>	Hypertensive disease	I10-16
		Ischemic heart disease	I20-25
		Arrhythmias, heart failure	I46-52
		Cerebrovascular disease	I60-69
		Atherosclerosis/AAA	I70-73
		Sudden death and death within 24h of symptom onset	R96.0-96.1
	<i>Endpoints excluded</i>	Myocarditis, unspecified	I51.4
		Subarachnoid haemorrhage	I60
		Subdural haemorrhage	I62
		Cerebral aneurysm	I67.1
		Cerebral arteritis	I68.2
		Moyamoya	I67.5
	Non-fatal cardiovascular disease		
	<i>Endpoints included</i>	Non-fatal myocardial infarction	I21-I23
		Non-fatal stroke	I60-69
	<i>Endpoints excluded</i>	Subarachnoid haemorrhage	I60
		Subdural haemorrhage	I62
		Cerebral aneurysm	I67.1
		Cerebral arteritis	I68.2
		Moyamoya	I67.5

Supplementary Table 2 Performance of QR4, SCORE2 and ASCVD in 3,246,602 people age 40+ using three different CVD outcome definitions in the England validation cohort.

	Women	Women	Women	Men	Men	Men
	QR4	ASCVD	SCORE2	QR4	ASCVD	SCORE2
	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)
Outcome 1						
C statistic	.781 (.778 to .784)	.767 (.764 to .770)	.767 (.764 to .770)	.741 (.739 to .744)	.727 (.725 to .730)	.728 (.725 to .730)
Slope	.870 (.863 to .878)	.869 (.860 to .878)	.733 (.727 to .739)	.898 (.891 to .905)	.900 (.893 to .907)	.720 (.715 to .725)
Intercept	-.130 (-.137 to -.122)	-.131 (-.140 to -.122)	-.267 (-.273 to -.261)	-.102 (-.109 to -.0946)	-.100 (-.107 to -.0926)	-.280 (-.285 to -.275)
Outcome 2						
C statistic	.790 (.787 to .794)	.777 (.773 to .781)	.778 (.774 to .781)	.742 (.739 to .745)	.729 (.726 to .732)	.730 (.727 to .733)
Slope	1.16 (1.15 to 1.17)	1.39 (1.37 to 1.40)	.936 (.929 to .943)	1.16 (1.16 to 1.17)	1.22 (1.21 to 1.23)	.891 (.885 to .896)
Intercept	.162 (.152 to .172)	.386 (.368 to .403)	-.0642 (-.0712 to -.0573)	.164 (.156 to .173)	.223 (.213 to .233)	-.109 (-.115 to -.104)
Outcome 3						
C statistic	.793 (.790 to .797)	.780 (.776 to .783)	.780 (.777 to .784)	.744 (.741 to .747)	.731 (.728 to .735)	.732 (.729 to .735)
Slope	1.03 (1.02 to 1.04)	1.12 (1.11 to 1.13)	.846 (.840 to .851)	1.07 (1.06 to 1.08)	1.11 (1.10 to 1.11)	.831 (.826 to .836)
Intercept	.0304 (.0224 to .0384)	.117 (.105 to .128)	-.154 (-.160 to -.149)	.0692 (.0618 to .0767)	.106 (.0974 to .114)	-.169 (-.174 to -.164)

Supplementary Table 3. Characteristics of 3,246,602 patients in the English validation cohort with a high QR4 risk score (defined as 10-year risk of CVD of 10% or greater) including characteristics of those reclassified using QR4 compared with Model A.

	<i>Total population (col %)</i>	<i>Patients with a high QR4 score (Col %)</i>	<i>Patients with high Model A but low QR4 (Col %)</i>	<i>Patients with low Model A score but high QR4 (Col %)</i>	<i>row% for patients with a high QR4</i>
Total number	3,246,602	309,768	12791	4068	9.5
Men	1564545 (48.2)	198064 (63.9)	5961 (46.6)	1790 (44.0)	12.7
Mean age (SD)	38.9 (14.9)	66.7 (9.8)	61.2 (8.1)	56.8 (7.9)	n/a
White	2309239 (71.1)	269023 (86.8)	10951 (85.6)	3529 (86.8)	11.6
Indian	153153 (4.7)	8830 (2.9)	147 (1.1)	105 (2.6)	5.8
Pakistani	81802 (2.5)	5608 (1.8)	117 (0.9)	68 (1.7)	6.9
Bangladeshi	69121 (2.1)	3066 (1.0)	41 (0.3)	75 (1.8)	4.4
Other Asian	108631 (3.3)	5049 (1.6)	147 (1.1)	72 (1.8)	4.6
Caribbean	56976 (1.8)	5148 (1.7)	453 (3.5)	58 (1.4)	9.0
Black African	152375 (4.7)	4334 (1.4)	399 (3.1)	48 (1.2)	2.8
Chinese	76795 (2.4)	961 (0.3)	61 (0.5)	8 (0.2)	1.3
Other	238510 (7.3)	7749 (2.5)	475 (3.7)	105 (2.6)	3.2
Learning disability	10962 (0.3)	1187 (0.4)	46 (0.4)	180 (4.4)	10.8
Down's syndrome	1507 (0.0)	160 (0.1)	12 (0.1)	119 (2.9)	10.6
Type 1 diabetes	9274 (0.3)	897 (0.3)	44 (0.3)	20 (0.5)	9.7
Type 2 diabetes	27881 (0.9)	15946 (5.1)	475 (3.7)	91 (2.2)	57.2
Treated hypertension	141393 (4.4)	83310 (26.9)	2084 (16.3)	567 (13.9)	58.9
Rheumatoid arthritis	18181 (0.6)	6876 (2.2)	269 (2.1)	64 (1.6)	37.8
Atrial fibrillation	14592 (0.4)	11923 (3.8)	72 (0.6)	23 (0.6)	81.7
Renal failure (CKD3-5)	28149 (0.9)	18799 (6.1)	408 (3.2)	110 (2.7)	66.8
Migraine	204739 (6.3)	19818 (6.4)	672 (5.3)	435 (10.7)	9.7
Corticosteroids	83031 (2.6)	31294 (10.1)	2046 (16.0)	888 (21.8)	37.7
SLE	2616 (0.1)	720 (0.2)	21 (0.2)	10 (0.2)	27.5
Atypical antipsychotics	26101 (0.8)	5202 (1.7)	403 (3.2)	111 (2.7)	19.9
Severe mental illness	60840 (1.9)	11281 (3.6)	732 (5.7)	241 (5.9)	18.5
Erectile dysfunction	63722 (2.0)	29218 (9.4)	468 (3.7)	178 (4.4)	45.9
COPD	26156 (0.8)	20668 (6.7)	143 (1.1)	2120 (52.1)	79.0
Lung cancer	1353 (0.0)	900 (0.3)	151 (1.2)	153 (3.8)	66.5
Blood cancer	10039 (0.3)	4373 (1.4)	34 (0.3)	712 (17.5)	43.6
Brain cancer	370 (0.0)	138 (0.0)	6 (0.0)	67 (1.6)	37.3
Oral cancer	1220 (0.0)	716 (0.2)	12 (0.1)	157 (3.9)	58.7
Postnatal depression	29763 (0.9)	941 (0.3)	0 (0.0)	225 (5.5)	3.2
Pre-eclampsia	6735 (0.2)	721 (0.2)	0 (0.0)	136 (3.3)	10.7

Supplementary Table 4: Characteristics of patients with complete vs missing data for patients aged 18-84 years in the English QResearch derivation cohort. Values are numbers (%) of patients unless indicated otherwise. Complete data is defined as values recorded for all of ethnicity, cholesterol/HDL ratio, BMI, smoking, systolic blood pressure. Diagnoses are assumed to be not present if not recorded.

	<i>not complete data</i>	<i>complete data</i>
total patients	8223690	1752616
men	4035820 (49.1)	784891 (44.8)
mean age(SD)	36.8 (14.3)	49.4 (14.0)
mean Townsend score (SD)	0.8 (3.2)	0.5 (3.2)
BMI recorded	5997020 (72.9)	1752616 (100.0)
Chol/HDL ratio recorded	1075677 (13.1)	1752616 (100.0)
SBP recorded	6247094 (76.0)	1752616 (100.0)
mean BMI (SD)	25.1 (5.0)	27.3 (5.5)
mean chol/HDL (SD)	3.8 (1.2)	3.8 (1.2)
mean SBP (SD)	122.6 (15.2)	127.1 (15.5)
Ethnicity recorded	4433551 (53.9)	1752616 (100.0)
White	3106755 (37.8)	1284387 (73.3)
Indian	213781 (2.6)	87633 (5.0)
Pakistani	127703 (1.6)	58326 (3.3)
Bangladeshi	84312 (1.0)	31370 (1.8)
Other Asian	162334 (2.0)	56221 (3.2)
Caribbean	66717 (0.8)	36861 (2.1)
Black African	199902 (2.4)	85424 (4.9)
Chinese	133855 (1.6)	14924 (0.9)
Other	338192 (4.1)	97470 (5.6)
Smoking status recorded	7673710 (93.3)	1752616 (100.0)
non smoker	4700431 (57.2)	1063711 (60.7)
Ex-smoker	1218807 (14.8)	381554 (21.8)
light smoker	1355030 (16.5)	234086 (13.4)
moderate smoker	279321 (3.4)	47897 (2.7)
heavy smoker	120121 (1.5)	25368 (1.4)
Learning disability	25487 (0.3)	9176 (0.5)
Down's syndrome	3599 (0.0)	1218 (0.1)
Type 1 diabetes	13236 (0.2)	15043 (0.9)
Type 2 diabetes	32771 (0.4)	54993 (3.1)
Treated hypertension	201191 (2.4)	232912 (13.3)
Rheumatoid arthritis	36767 (0.4)	20991 (1.2)
Atrial fibrillation	28100 (0.3)	18085 (1.0)
Renal failure (CKD3-5)	49425 (0.6)	38727 (2.2)
Migraine	484195 (5.9)	149991 (8.6)
Corticosteroids	173306 (2.1)	82901 (4.7)
SLE	5180 (0.1)	2687 (0.2)
Atypical antipsychotics	51286 (0.6)	28600 (1.6)
Severe mental illness	133819 (1.6)	62937 (3.6)
Erectile dysfunction	117648 (1.4)	80655 (4.6)
COPD	47863 (0.6)	32128 (1.8)
Lung cancer	2941 (0.0)	1481 (0.1)

Blood cancer	21890 (0.3)	9119 (0.5)
Brain cancer	958 (0.0)	287 (0.0)
Oral cancer	2564 (0.0)	1300 (0.1)
Postnatal depression	76100 (0.9)	20363 (1.2)
Pre-eclampsia	14479 (0.2)	5754 (0.3)