National Institute for Health and Care Excellence

Final

Cardiovascular disease: risk assessment and reduction, including lipid modification

[A] Evidence review for CVD risk assessment tools: primary prevention

NICE guideline NG238 (CG181)

Evidence review underpinning recommendations 1.1.7 to 1.1.11 and 1.1.16 in the NICE guideline

May 2023

Final

Developed by National Institute for Health and Care Excellence

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1. Cardiovascular risk assessment tools in adults without established cardiovascular disease

1.1. Review question

What is the most accurate tool for determining 10-year and lifetime cardiovascular risk in adults without established cardiovascular disease?

1.1.1. Introduction

A number of risk tools, using a combination of modifiable and non-modifiable risk factors, have been developed to assess a person's risk of experiencing a cardiovascular event. Previous iterations of this guideline have assessed these for accuracy and at present recommend QRISK2 for risk assessment in those who have not experienced a cardiac event (the primary prevention population). There are annual updates of the QRISK tool adding in new clinical variables, and other tools continue to be developed with a view to improve the tools to better predict events and more accurately assess risk in different population subgroups that were either absent in previous tools derivation and validation populations, or in which the prior existing tools performed less well.

Risk tools have been developed to predict both 10 year and lifetime risk of adverse events. The previous guideline recommends that 10-year risk is calculated as there was insufficient evidence to recommend that lifetime risk assessment tools be recommended. Research into lifestyle risk assessment tools has also progressed, with new tools being developed and those existing ones being enhanced by additional clinical variables in their equations. It is also suggested that lifetime risk tools may better facilitate communication of risk to people having their cardiovascular risk assessed.

This evidence review therefore intends to update the previous review with the new evidence that has been published in both risk tools for predicting both 10-year and lifetime cardiovascular risk for primary prevention to determine whether the newer tools are superior to QRISK2.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years and over) without established CVD, including adults with chronic kidney disease, type 1 diabetes, and type 2 diabetes • Validation studies in a UK population • Derivation studies from the UK, or non-UK cohorts if the tool has subsequently been validated in a UK population.
Risk tools	**10-year risk** • QRISK 2 • QRISK 3 • SCORE 2 • SCORE 2 – OP • AHA/ASCVD risk engine • LIFE-CVD • PRIMROSE (BMI model and lipid model) • CCRISK

	• CRISK **Lifetime risk** • QRISK lifetime • AHA/ASCVD risk engine • LIFE-CVD
Patient outcomes	Overall CVD events, including: • All-cause mortality • CV mortality • Non-fatal myocardial infarction • Non-fatal stroke
Statistical outcomes	**Discrimination:** • Area under the ROC curve (c-index, c-statistic). • Classification measures at 5%, 7.5%, 10%, 15% and 20% predicted risk thresholds: sensitivity, and specificity. • D statistic **Calibration**: • Calibration plots • Predicted risk versus observed risk • Statistical tests for agreement between predicted and observed events (E.g. Hosmer-Lemeshow or Nam–D'Agostino statistics) **Reclassification / revalidation** • net classification improvement • integrated discrimination index
Study design	Cohort (external validation, internal validation)
Specific groups	Subgroups that will be investigated: • presence of type 1 diabetes • presence of CKD (eGFR <60 ml/min/1.73 m^2 and/or albuminuria)

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

When a specific risk assessment tool was validated in multiple publications using the same data source and population, only the most recent study or study with the largest applicable sample size was included if the patient registration dates overlap. Therefore, earlier reports/reports of smaller cohorts from the same database were excluded to avoid double counting.

1.2. Risk prediction evidence

Evidence was available for all risk tools included in the protocol. The predictor variables included, and the outcomes predicted in these tools are summarised in Table 2 and Table 3, respectively. Full details of the predictor variables can be found in Appendix D.1.

Table 2: Predictor variables included in CVD risk assessment tools

Risk Score	Age	Sex	Ethnicity	BMI	Total cholesterol	LDL- cholesterol	HDL- cholesterol	Non-HDL- cholesterol	Systolic blood pressure	Blood pressure medication	Diabetes	Smoking	Family history of CVD	Social deprivation	Chronic kidney disease	Rheumatoid arthritis	SBP variability	Migraine	Corticosteroids	Systemic lupus erythematosus	Erectile dysfunction	Antipsychotics	Severe mental illness	HIV/AIDS	Antidepressants	History of heavy drinking
ASCVD	X	X	X		X		X		X	X	X	X														
CRISK	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CRISK-CCI	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
LIFE-CVD	*	X		X				X	X		X	X	X													
PRIMROSE-BMI	X	X		X					X		X	X		X								X	X		X	X
PRIMROSE-lipids	X	X			X		X		X		X	X		X								X	X		X	X
QRISK2	X	X	X	X	X		X		X	X	X	X	X	X	X	X										
QRISK3	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
QRISK-lifetime	*	X	X	X	X	X	X		X	X	X	X	X	X	X	X										
SCORE2	X	X			X		X		X		X	X														
SCORE-OP	X	X			X		X		X		X	X														

**Age considered as the underlying time function of the model, not as a predictor variable*
Definitions: ASCVD; atherosclerotic cardiovascular disease score derived in US cohorts, CRISK; Competing risk model, CRISK-CCI; Competing risk model with Charlson comorbidity index, LIFE-CVD; prediction algorithm for cardiovascular disease derived from a US cohort (MESA). QRISK; prediction algorithm for cardiovascular disease derived from UK cohort, QResearch; large consolidated database derived from the anonymised health records from general practices using Egton Medical Information Systems clinical computer system in the UK, PRIMROSE; Prediction risk score for people with severe mental illnesses derived from a European cohort, SCORE; risk prediction algorithm for cardiovascular disease in Europe, SCORE-OP; risk prediction algorithm estimating incident cardiovascular event risk in older persons in four geographical risk regions

Table 3: Outcomes predicted by CVD risk assessment tools

Risk Score	Derivation cohort and region	Publication year	Myocardial infarction	Coronary heart disease death	Stroke	Stroke death	Transient ischaemic attack	Coronary revascularisation	Angina pectoris	Unstable angina
ASCVD	ARIC (Atherosclerosis Risk in Communities), CARDIA (Coronary Artery Risk Development in Young Adults), CHS (Cardiovascular Health Study), Framingham USA	2013	X	X	X	X				
CRISK	CPRD (UK Clinical Practice Research Datalink) Gold UK	2017	X	X	X	X	X		X	X
CRISK-CCI	CPRD Gold UK	2017	X	X	X	X	X		X	X
LIFE-CVD	MESA (Multi-Ethnic Study of Atherosclerosis) USA	2020	X	X	X	X				
PRIMROSE-BMI	THIN (The Health Improvement Network) UK	2015	X	X	X	X	X	X	X	X
PRIMROSE-lipids	THIN UK	2015	X	X	X	X	X	X	X	X
QRISK2	QRESEARCH UK	2009	X	X	X	X	X		X	X
QRISK3	QRESEARCH UK	2017	X	X	X	X	X		X	X
QRISK-lifetime	QRESEARCH UK	2010	X	X	X	X	X		X	X

Risk Score	Derivation cohort and region	Publication year	Myocardial infarction	Coronary heart disease death	Stroke	Stroke death	Transient ischaemic attack	Coronary revascularisation	Angina pectoris	Unstable angina
SCORE2	45 prospective cohorts Europe, Canada, USA	2021	X	X	X	X				
SCORE-OP	ARIC, CPRD, HYVET (Hypertension in the Very Elderly Trial), MESA, PROSPER (PROspective study of pravastatin in the elderly at risk), SPRINT (Systolic Blood Pressure Intervention Trial) Europe, USA	2021	X	X	X	X				

1.2.1. Included studies

A search for cohort studies assessing the validation of risk assessment tools for cardiovascular disease (CVD) events and mortality was undertaken. Only tools that have UK validation and studies of adults without established CVD were included.

Sixteen cohort studies on 11 risk tools, reported in 17 papers, were included in the review.[1-3, 5-11, 13-16, 19, 21, 23]

Evidence from these studies on the discriminative ability of the tools is summarised in the overview tables (Table 5, Table 6, and Table 7), and the clinical evidence summary (Table 8) below. Evidence on their calibration and on reclassification is summarised in sections 1.2.5 and 1.2.6, respectively.

The results of one study[6] are not included in the summary, but are available in Appendix D. They are not included in the evidence summary because this is the original derivation study for the ASCVD tool in an American population, and so is included for reference only because UK validation studies are available for this tool.

See also the study selection flow chart in Appendix A, study evidence tables in Appendix D, and forest plots and summary ROC curves in Appendix E.

1.2.2. Excluded studies

One Cochrane review[12] was identified but excluded because none of the included studies used a tool specified in the review protocol.

One study[22] from the 2014 update of CG181 was excluded, although it assessed a tool within the protocol for this update of the review, because it was based on a simulated population and did not provide any data of relevance for decision making.

See the excluded studies list in Appendix I.

1.2.3. Summary of studies included in the prognostic evidence

The included study characteristics are summarised in Table 4 below.

Table 4: Summary of studies included in the evidence review

Study (cohort)	Risk tool(s)	Population, N (Country)	Age, years (range)	Outcomes (including definitions)	No. of CVD events
From 2014 update of CG181					
Collins 2012B[3] (THIN) External validation of QRISK2	• QRISK2-2008 • QRISK2-2010 • QRISK2-2011	2,084,445 UK	30-84	Fatal or non-fatal CVD: myocardial infarction, angina, CHD, stroke, transient ischaemic attacks	93,563
Hippisley-Cox 2008[10] (QResearch) Development and validation of QRISK2 (10-year risk)	• QRISK2-2008	2,285,815 UK	35-74	Fatal or non-fatal CVD: coronary heart disease (angina and myocardial infarction), stroke, or transient ischaemic attacks.	96,709
Hippisley-Cox 2010[9] (QResearch) Development and validation of QRISK2 (lifetime risk)	• QRISK2-2010 lifetime	3,601,918 UK	30-84	Fatal or non-fatal CVD: coronary heart disease (angina and myocardial infarction), stroke, or transient ischaemic attacks.	121,623
From update search					
Anonymous 2021 (SCORE2 working group)[2] (CPRD) Development, internal and external validation	• SCORE2	677,684 (derivation) 30 plus countries (ERFC) and UK 1,133,181 (validation) 15 European countries: Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, UK, Czech Republic, Estonia, Poland, Lithuania, Russia Validation cohort: MORGAM project, BiomarCaREConsortium, EPIC-CVD, CPRD, HNR, Estonian Biobank, HAPIEE study, HUNT	40-69	Fatal or non-fatal CVD. Cause-specific mortality due to hypertensive disease, ischemic heart disease, arrhythmias, heart failure, cerebrovascular disease: atherosclerosis/abdominal aortic aneurysm, sudden death and death within 24h of symptom onset	30,121 (derivation cohort) 43,492 (validation cohort)

Study (cohort)	Risk tool(s)	Population, N (Country)	Age, years (range)	Outcomes (including definitions)	No. of CVD events
From 2014 update of CG181					
		study, DETECT study, Gutenberg Health Study		Non-fatal cardiovascular disease: non-fatal myocardial infarction, non-fatal stroke	
Anonymous 2021 (SCORE2-OP working group)[1] (CPRD) Development, internal and external validation	• SCORE2-OP • ASCVD	28,503 (derivation) Norway 338,615 (validation) USA, Europe, and UK Validation cohort: ARIC, MESA, and CPRD cohorts, and the combined study populations of the HYVET, PROSPER, and SPRINT trial	65 and older	Cause-specific mortality due to: hypertensive disease, ischemic heart disease, arrhythmias, heart failure, cerebrovascular disease, atherosclerosis/AAA, sudden death and death within 24, h of symptom onset Non-fatal cardiovascular disease: non-fatal myocardial infarction, non-fatal stroke	10,089 (derivation cohort) 33,219 (validation cohort)
Dziopa 2022[5] (CPRD) External validation	• QRISK2 • QRISK3 • ASCVD	168,871 (type 2 diabetes) UK	Range: NR Mean (SD): 59.3 (13.9)	CVD: the first occurrence of fatal or non-fatal myocardial infarction, sudden cardiac death, ischaemic heart disease, fatal or non-fatal stroke, or PAD since diagnosis of type 2 diabetes. Additional outcomes (CVD+) included all of the above plus heart failure and atrial fibrillation	38,335

Study (cohort)	Risk tool(s)	Population, N (Country)	Age, years (range)	Outcomes (including definitions)	No. of CVD events
From 2014 update of CG181					
Goff 2014[6] Development, internal and external validation	• ASCVD	24,626 USA Validation cohort: NHLBI-sponsored cohort studies, including the ARIC study Cardiovascular Health Study, CARDIA study combined with applicable data from the Framingham Original and Offspring Study cohort	40-79	CVD: nonfatal myocardial infarction, CHD death, or fatal or nonfatal stroke	2689
Hippisley-Cox 2014[8] (CPRD) External validation	• QRISK2-2014	3,271,512 UK	25–99	CVD: defined as a composite outcome of coronary heart disease, ischaemic stroke, or transient ischaemic attack	139,485
Hippisley-Cox 2017[7] (QResearch) Development and internal validation of QRISK3	• QRISK2-2017 • QRISK-3	7,889,803 (derivation) 2,671,298 (validation) UK	25-84	CVD: coronary heart disease, ischaemic stroke, or transient ischaemic attack	363,565 (derivation)
Jaspers, 2020[11] (EPIC-Norfolk) Development, internal and external validation	• LIFE-CVD	6715 (MESA derivation) 23548 (validation) Europe	45-80	CVD: fatal or non-fatal MI or stroke, resuscitated cardiac arrest, and coronary heart disease death	621 (MESA derivation)
Lindbohm 2019[14] (Whitehall II cohort) External validation	• ASCVD • Revised ASCVD	6964 UK	40-64	CVD: fatal coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal stroke	617
Lindbohm 2021[13] (Whitehall II cohort)	• ASCVD	7996 UK	40-63	CVD: nonfatal myocardial infarction,	1840

Study (cohort)	Risk tool(s)	Population, N (Country)	Age, years (range)	Outcomes (including definitions)	No. of CVD events
From 2014 update of CG181					
External validation				CHD death, or fatal or nonfatal stroke	
Livingstone 2021[15] (CPRD Gold database) External validation	• QRISK3	2,904,773 UK	25-84	CVD: coronary heart disease, ischaemic stroke, or transient ischaemic attack	95,517
Livingstone 2022[16] (CPRD Gold database) Development and internal validation of CRISK tools External validation of QRISK3	• CRISK • CRISK-CCI • QRISK3	1,936,516 (derivation) 968,257 (validation) UK	25-84	CVD: coronary heart disease, ischaemic stroke, or transient ischaemic attack	31,839
Osborn 2015[21] and 2019[19, 20] (THIN) Development and internal validation	• PRIMROSE BMI • PRIMROSE lipid	38,824 UK – adults with severe mental illness	30-90	CVD: myocardial infarction, angina pectoris, cerebrovascular accidents, or major coronary surgery	2324
Tillin 2014[23] (SABRE) External validation	• QRISK2-2012	3674 UK	40–69	CVD: myocardial infarction, coronary revascularisation, angina, transient ischaemic attack or stroke	465

See Appendix D for full evidence tables. See Appendix J for List of abbreviations used in Table 4.

1.2.4. Summary of prognostic evidence: discrimination

1.2.4.1. Overview of outcome data

Table 5: Summary of results: AUC (95% CI)

Tool and subgroup	AUC (95% CI) Women	Men
Hippisley-Cox 2008[10]. QRISK2-2008; QResearch database		
QRISK2-2008	0.817 (0.814–0.820)	0.792 (0.789–0.794)
Collins 2012[3]. QRISK2; THIN database		
QRISK2-2011. Age 30–84	0.835 (0.834–0.837)	0.809 (0.807–0.811)
QRISK2-2010. Age 30–84	0.835 (0.833–0.837)	0.811 (0.809–0.812)
QRISK2-2011. Age 35–74	0.802 (0.800–0.804)	0.771 (0.769–0.773)
QRISK2-2008. Age 35–74	0.800 (0.798–0.803)	0.772 (0.769–0.774)
Hippisley-Cox 2014[8]. QRISK2-2014; CPRD database		
QRISK2-2014	0.883 (0.882-0.884)	0.859 (0.858-0.861)
Tillin 2014[23]. QRISK2-2012; SABRE cohort		
QRISK2-2012 European White	0.750 (0.670-0.820)	0.700 (0.660-0.740)
QRISK2-2012 South Asian	0.750 (0.660-0.840)	0.730 (0.690-0.770)
QRISK2-2012 African Caribbean	0.650 (0.540-0.760)	0.670 (0.570-0.770)
Hippisley-Cox 2017[7]. QRISK2-2017 and QRISK3; QResearch database		
QRISK2-2017: full cohort	0.879 (0.878-0.88)	0.858 (0.856-0.859)
QRISK3 – with SBP variation: full cohort	0.880 (0.879-0.882)	0.858 (0.857-0.860)
QRISK3 – without SBP variation: full cohort	0.880 (0.878-0.881)	0.858 (0.857-0.859)
QRISK3 – without SBP variation: CKD stage 3-5	0.742 (0.720-0.764)	0.737 (0.715-0.776)
QRISK3 – without SBP variation: type 1 diabetes	0.823 (0.789-0.857)	0.804 (0.760-0.832)
QRISK3 – without SBP variation: type 2 diabetes	0.701 (0.691-0.711)	0.696 (0.687-0.704)
QRISK3 – without SBP variation: SMI	0.844 (0.837-0.851)	0.817 (0.809-0.852)
QRISK3 – without SBP variation: age <40	0.747 (0.728-0.766)	0.781 (0.771-0.792)
QRISK3 – without SBP variation: age 40-59	0.752 (0.747-0.757)	0.732 (0.728-0.736)
QRISK3 – without SBP variation: age 60+	0.692 (0.689-0.695)	0.659 (0.656-0.663)

Tool and subgroup	AUC (95% CI)	
	Women	Men
Dziopa 2022[5]. QRISK2, QRISK3 &ASCVD; CPRD database		
QRISK2: type 2 diabetes	0.664 (0.660-0.668)	
QRISK3: type 2 diabetes	0.664 (0.660-0.667)	
ASCVD: type 2 diabetes	0.668 (0.664-0.671)	
Lindbohm 2019[14] and 2021[13]. ASCVD; Whitehall II cohort		
ASCVD (original version) Age 40-64	0.71	
ASCVD (revised for Whitehall II cohort) Age 40-64	0.72	
ASCVD (original version) Age 40-75 (cohort overlaps with above)	0.699	
Livingstone 2021[15] and 2022[16]; QRISK3, CRISK and CRISK-CCI; CPRD database		
QRISK3: in full CPRD cohort	0.865 (0.861-0.868)	0.834 (0.831-0.837)
QRISK3: in full CPRD cohort; age 25-44	0.758 (0.747-0.769)	0.757 (0.749-0.764)
QRISK3: in full CPRD cohort; age 45-64	0.707 (0.702-0.713)	0.681 (0.677-0.685)
QRISK3: in full CPRD cohort; age 65-74	0.641 (0.635-0.647)	0.612 (0.606-0.617)
QRISK3: in full CPRD cohort; age 75-84	0.611 (0.605-0.616)	0.585 (0.579-0.591)
QRISK3: in CRISK validation cohort (subset of above cohort)	0.863 (0.858-0.869)	0.832 (0.827-0.836)
QRISK3: in CRISK validation cohort; age 25-44	0.765 (0.747-0.783)	0.740 (0.727-0.753)
QRISK3: in CRISK validation cohort; age 45-64	0.708 (0.698-0.717)	0.679 (0.672-0.686)
QRISK3: in CRISK validation cohort; age 65-74	0.641 (0.631-0.652)	0.606 (0.596-0.615)
QRISK3: in CRISK validation cohort; age 75-84	0.614 (0.605-0.622)	0.590 (0.580-0.601)
CRISK	0.863 (0.858-0.869)	0.833 (0.828-0.837)
CRISK; age 25-44	0.761 (0.743-0.779)	0.744 (0.731-0.757)
CRISK; age 45-64	0.710 (0.701-0.720)	0.683 (0.676-0.690)
CRISK; age 65-74	0.645 (0.634-0.655)	0.610 (0.600-0.619)
CRISK; age 75-84	0.614 (0.605-0.622)	0.594 (0.583-0.604)
CRISK-CCI	0.864 (0.859-0.869)	0.819 (0.815-0.824)

Tool and subgroup	AUC (95% CI)	
	Women	Men
CRISK-CCI; age 25-44	0.763 (0.745-0.781)	0.733 (0.720-0.746)
CRISK-CCI; age 45-64	0.713 (0.703-0.722)	0.661 (0.654-0.668)
CRISK-CCI; age 65-74	0.647 (0.637-0.658)	0.591 (0.581-0.600)
CRISK-CCI; age 75-84	0.616 (0.607-0.624)	0.570 (0.559-0.580)
Osborn 2015 [21]. PRIMROSE (internal validation); UK THIN database		
PRIMROSE-BMI	0.779 (0.749–0.810)	0.784 (0.735–0.833)
PRIMROSE-lipid	0.790 (0.755–0.824)	0.796 (0.758–0.833)
SCORE2 working group 2021[2]. SCORE2; CPRD database		
SCORE2: full cohort	0.720 (0.717-0.724)	
SCORE2: age 40-50	0.698 (0.689-0.706)	
SCORE2: age 50-59	0.653 (0.647-0.659)	
SCORE2: age 60-69	0.620 (0.614-0.625)	
SCORE2-OP working group 2021[1]. SCORE2-OP & ASCVD; CPRD database		
SCORE2-OP.	0.657 (0.655-0.662)	
ASCVD	0.663 (0.659-0.666)	
Hippisley-Cox 2010[9]. Lifetime QRISK2; QRESEARCH database		
QRISK2- lifetime (at 10 years)	0.842 (0.840–0.844)	0.828 (0.826–0.830)
Jaspers 2020[11]. LIFE-CVD; EPIC-Norfolk		
LIFE-CVD	0.76 (0.75-0.76)	

Table 6: Summary of results: D statistics

Tool and subgroup	D statistics	
	Women	Men
Hippisley-Cox 2008[10]. QRISK2-2008; QResearch database		
QRISK2-2008	1.795 (1.769–1.820)	1.615 (1.594–1.637)
Collins 2012[3]. QRISK2; THIN database		
QRISK2-2011 (aged 30–84)	1.98 (1.96–1.99)	1.73 (1.71–1.75)
QRISK2-2010 (aged 30–84)	1.97 (1.95–1.99)	1.76 (1.74–1.77)
QRISK2-2011 (aged 35–74)	1.67 (1.65–1.69)	1.44 (1.42–1.46)
QRISK2-2008 (aged 35–74)	1.66 (1.56–1.76)	1.45 (1.31–1.59)

Tool and subgroup	D statistics	
	Women	Men
Hippisley-Cox 2014[8]. QRISK2-2014; CPRD database		
QRISK2-2014	2.328 (2.313-2.343)	2.085 (2.071-2.098)
Tillin 2014[23]. QRISK2-2012; SABRE cohort		
QRISK2 - European White	1.33 (0.79 to 1.87)	1.06 (0.82 to 1.30)
QRISK2 - South Asian	1.55 (0.91 to 2.19)	1.22 (0.99 to 1.45)
QRISK2 - African Caribbean	0.74 (0 to 1.63)	0.96 (0.32 to 1.59)
Hippisley-Cox 2017[7]. QRISK2-2017 and QRISK3; QResearch database		
QRISK2-2017	2.48 (2.46 to 2.5)	2.25 (2.24 to 2.27)
QRISK3-with SBP variability	2.49 (2.47 to 2.51)	2.26 (2.25 to 2.28)
QRISK3-without SBP variability	2.48 (2.46 to 2.5)	2.26 (2.24 to 2.27)
QRISK3 – without SBP variation: CKD stage 3-5	1.32 (1.17 to 1.47)	1.28 (1.13 to 1.44)
QRISK3 – without SBP variation: type 1 diabetes	1.94 (1.66 to 2.22)	1.87 (1.64 to 2.11)
QRISK3 – without SBP variation: type 2 diabetes	1.19 (1.12 to 1.25)	1.12 (1.06 to 1.17)
QRISK3 – without SBP variation: SMI	2.16 (2.1 to 2.22)	1.94 (1.87 to 2.02)
QRISK3 – without SBP variation: age <40	1.66 (1.55 to 1.76)	1.75 (1.69 to 1.82)
QRISK3 – without SBP variation: age 40-59	1.48 (1.44 to 1.51)	1.33 (1.31 to 1.36)
QRISK3 – without SBP variation: age 60+	1.11 (1.09 to 1.13)	.903 (.883 to .922)
Livingstone 2021[15] (Royston's D) QRISK3; CPRD database		
QRISK3 (full cohort)	2.43 (2.41 to 2.45)	2.1 (2.08 to 2.12)
QRISK3 (age 25-44)	1.69 (1.63 to 1.76)	1.57 (1.52 to 1.61)
QRISK3 (age 45-64)	1.25 (1.22 to 1.28)	1.04 (1.02 to 1.07)
QRISK3 (age 65-74)	0.82 (0.77 to 0.86)	0.63 (0.59 to 0.66)
QRISK3 (age 75-84)	0.61 (0.56 to 0.66)	0.46 (0.42 to 0.51)
Osborn 2015 [21]. PRIMROSE (internal validation); UK THIN database		
PRIMROSE BMI	1.8 (1.7 to 1.9)	1.84 (1.73 to 1.96)
PRIMROSE lipid	1.87 (1.76 to 1.98)	1.92 (1.8 to 2.03)
Hippisley-Cox 2010. Lifetime QRISK2 [9]. Lifetime QRISK2; QRESEARCH database		
QRISK2 lifetime	NR	NR
Abbreviation: NR; not reported		

Table 7: Summary of results: sensitivity and specificity

Tool	Threshold	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Hippisley-Cox 2014[8]. QRISK2-2014; CPRD database			
QRISK2-2014	20.7% (top decile of predicted risk) Observed risk 31.8%	49.9	91.9
Livingstone 2022[16]. QRISK3 and CRISK-CCI; CPRD database*			
QRISK3	7.5%	Women: 75.0 Men: 79.5	Women: 81.2 Men: 71.5
	10%	Women: 68.3	Women: 85.3

Tool	Threshold	Sensitivity, % (95% CI)	Specificity, % (95% CI)
		Men: 71.3	Men: 77.9
	20%	Women: 47.0 Men: 45.1	Women: 93.1 Men: 90.9
CRISK-CCI	7.5%	Women: 73.3 Men: 77.9	Women: 82.5 Men: 72.5
	10%	Women: 65.9 Men: 69.1	Women: 69.1 Men: 79.0
	20%	Women: 41.2 Men: 37.6	Women: 94.5 Men: 92.3

**Sensitivity and specificity values have been calculated from data available in the study report and are therefore approximate. See also Appendix E.2 and E.3.*

1.2.4.2. Clinical evidence profile for C statistic data

Table 8: Clinical evidence profile: Discriminative capacity of selected CVD risk prediction tools

Risk tool	No of studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Area Under Curve: Individual study effects [point estimate (95% CI)]	Confidence
QRISK2-2008 (internal and external validation)	2	Women: 1441890 Men: 1392787	No serious risk of bias[a]	Serious inconsistency[b]	No serious indirectness	No serious imprecision[c]	Women 30-84: 0.817 (0.814–0.820) Men 30-84: 0.792 (0.789–0.794) Women aged 35–74: 0.800 (0.798–0.803) Men aged 35–74: 0.772 (0.769–0.774)	MODERATE
QRISK2-2010	1	Women: 1066127 Men: 1018318	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women aged 30-84: 0.835 (0.833–0.837) Men aged 30-84: 0.811 (0.809–0.812)	HIGH
QRISK2-2011	1	Women: 1066127 Men: 1018318	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women aged 30-84: 0.835 (0.834–0.837) Men aged 30-84: 0.809 (0.807–0.811)	HIGH
QRISK2-2012	1	European White Women: 444 South Asian Women: 241 African Caribbean Women: 247 African Caribbean Men: 307	Serious risk of bias[a,d]	No serious inconsistency	No serious indirectness	serious imprecision[c]	European white women: 0.750 (0.670-0.820) South Asian women: 0.750 (0.660-0.840) African Caribbean women: 0.650 (0.540-0.760) European white men: 0.700 (0.660-0.740) South Asian men: 0.730 (0.690-0.770) African Caribbean men: 0.670 (0.570-0.770)	LOW
		European White Men: 1359 South Asian Men: 1076	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	serious imprecision[c]	European white men: 0.700 (0.660-0.740) South Asian men: 0.730 (0.690-0.770)	MODERATE
QRISK2-2014	1	Women: 1682709 Men: 1588803	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.883 (0.882-0.884) Men: 0.859 (0.858-0.861)	HIGH
QRISK2-2017	1	Women: 1360457 Men: 1310841	Serious risk of bias[a,e]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.879 (0.878-0.88) Men: 0.858 (0.856-0.859)	MODERATE

Risk tool	No of studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Area Under Curve: Individual study effects [point estimate (95% CI)]	Confidence
QRISK2-year not specified	1	168871	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Type 2 diabetes: 0.664 (0.660-0.668)	HIGH
QRISK3-year not specified	1	168871	No serious risk of bias[a]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Type 2 diabetes: 0.664 (0.660-0.667)	HIGH
QRISK3-2017 internal and external validation (with SBP variability)	2	Women: 2845054 Men: 2731017	No serious risk of bias[a]	serious inconsistency[b]	No serious indirectness	No serious imprecision[c]	Women: 0.880 (0.879-0.882) 0.865 (0.861-0.868) Men: 0.858 (0.857-0.860) 0.834 (0.831-0.837)	MODERATE
QRISK3- 2017 internal validation (without SBP variability)	1	Women: 1360457 Men: 1310841	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.880 (0.878-0.881) Men: 0.858 (0.857-0.859)	MODERATE
QRISK3-2017 (Type 1 diabetes subgroup)	1	Women: 3351 Men: 3932	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.823 (0.789-0.857) Men: 0.804 (0.760-0.832)	MODERATE
QRISK3-2017 (CKD stage 3-5 subgroup)	1	Women: 6949 Men: 4232	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.742 (0.720-0.764) Men: 0.737 (0.715-0.776)	MODERATE
ASCVD	4	Type 2 diabetes: 168871 Age≥65: 319390 Age 40-64: 6964 Age 40-75: 7996	Serious risk of bias[a,g]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Type 2 diabetes: 0.668 (0.664-0.671) Age≥65: 0.663 (0.659-0.666) Age 40-64: 0.71 Age 40-75: 0.72	MODERATE
ASCVD revised for Whitehall II cohort	1	6964	Serious risk of bias[a,h]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Age 40-75: 0.699	MODERATE
CRISK internal validation	1	Women: 494865 Men: 473392	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.863 (0.858-0.869) Men: 0.833 (0.828-0.837)	MODERATE
CRISK-CCI internal validation	1	Women: 494865 Men: 473392	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.864 (0.859-0.869) Men: 0.819 (0.815-0.824)	MODERATE

Risk tool	No of studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Area Under Curve: Individual study effects [point estimate (95% CI)]	Confidence
PRIMROSE-BMI internal validation	1	Women: 2041 Men: 1842	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.779 (0.749–0.810) Men: 0.784 (0.735–0.833)	MODERATE
PRIMROSE-lipid internal validation	1	Women: 2041 Men: 1842	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.790 (0.755–0.824) Men: 0.796 (0.758–0.833)	MODERATE
SCORE2	1	927079	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[c]	0.720 (0.717–0.724)	HIGH
SCORE2-OP	1	319390	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[c]	0.657 (0.655–0.662)	HIGH
QRISK lifetime internal validation (assessed over 10 years)	1	Women: 645012 Men: 622147	Serious risk of bias[a,f]	No serious inconsistency	No serious indirectness	No serious imprecision[c]	Women: 0.842 (0.840–0.844) Men: 0.828 (0.826–0.830)	MODERATE
LIFE-CVD	1	23548	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision[c]	0.760 (0.750–0.760)	HIGH

GRADE was conducted with emphasis on area under the curve, as this was the primary measure for decision making
a) Risk of bias was assessed using the PROBAST checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Risk of bias was serious for some risk tools because of low event rate, insufficient reporting of outcomes, lack of calibration data, or having internal validation only.
b) If no pooling were possible, inconsistency was assessed by inspection of the degree of overlap of confidence intervals between studies: if one of more CIs did not overlap then a rating of serious inconsistency was given. Reasons for heterogeneity between studies may include geographical/cultural/ethnic differences.
c) The judgement of precision was based on the spread of confidence interval across two clinical thresholds: C statistics of 0.5 and 0.7. The threshold of 0.5 marked the boundary between no predictive value better than chance and a predictive value better than chance. The threshold of 0.7 marked the boundary above which the committee might consider recommendations. If the 95% CIs crossed one of these thresholds a rating of serious imprecision was given and if they crossed both of these thresholds a rating of very serious imprecision as given.
d) Event rate <100 in each subgroup
e) Same data source as internal validation cohort
f) Internal validation only
g) Insufficient reporting (point estimate only) in 2/4 and no calibration data in 1/4 studies
h) Insufficient reporting (point estimate only)

1.2.5. Summary of prognostic evidence: calibration

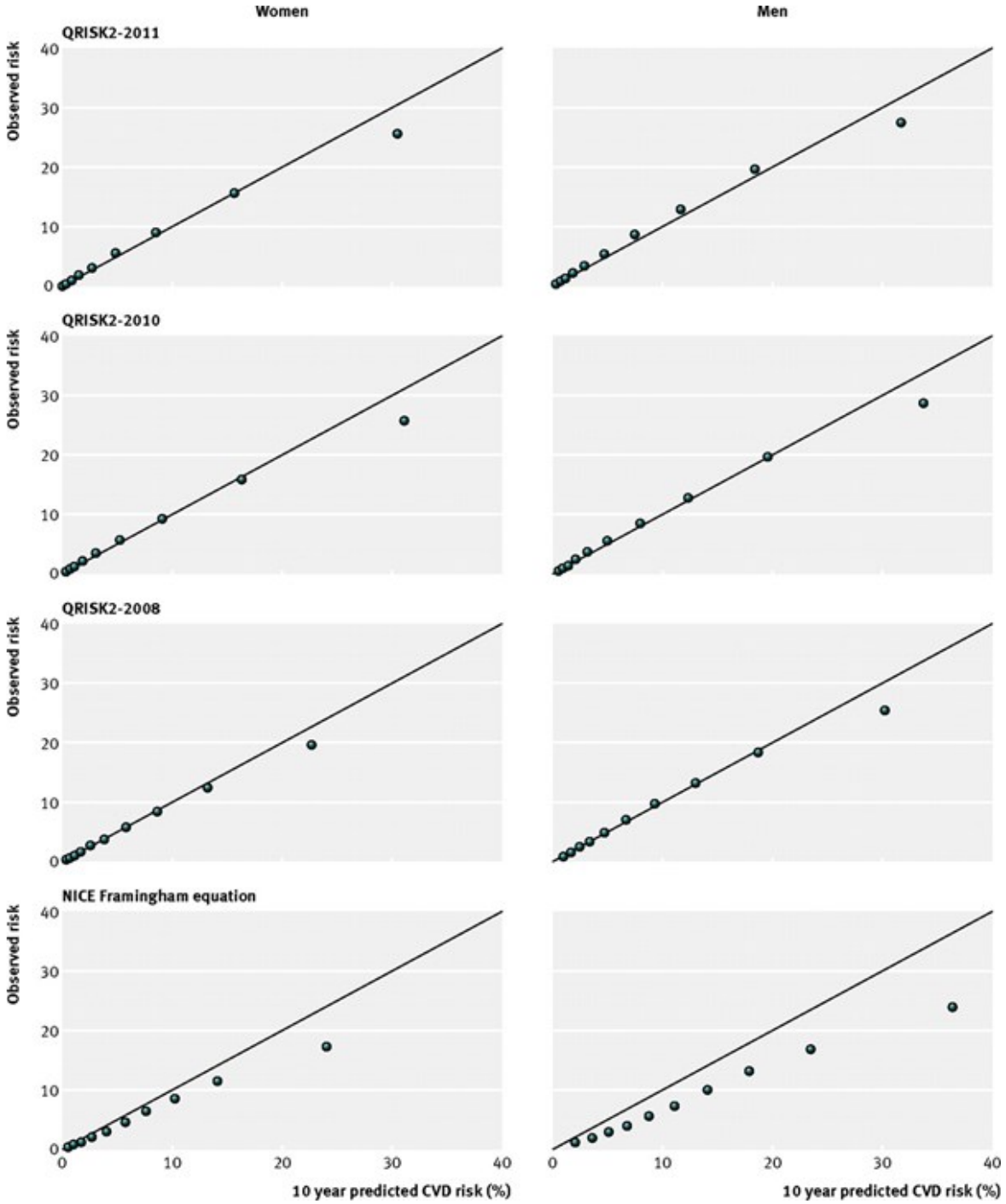
No calibration statistics matching the protocol were reported in the included studies, so GRADE assessment was not possible. However, available calibration curves and ratios of predicted to observed are provided below.

1.2.5.1. Calibration curves and predicted:observed events

QRISK2-2011, QRISK2-2010 and QRISK2-2008

Figure 1 shows the calibration plots for the 3 versions of QRISK2 and the NICE version of the Framingham equation. All 3 versions of the QRISK2 prediction models show good calibration in all 10^{ths} of risk, with the exception of the highest 10th of risk in both men and women (calibration slope, range 0.92–0.95).

Figure 1: Calibration curves: observed versus predicted 10-year risk of CVD (from Collins 2012)



Source: from Collins 2012 [3]
BMJ 2010;340:c2442
doi:10.1136/bmj.c2442
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QRISK2-2012

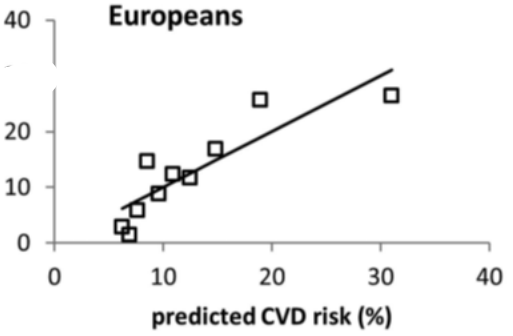
Figure 2, Figure 3 and Table 9 show the ratio of predicted to observed events for QRISK2-2012 (Tillin 2014[23]). This shows under-prediction for all ethnic groups in men, and in European white and South Asian groups in women, as well as large overprediction in African Caribbean women.

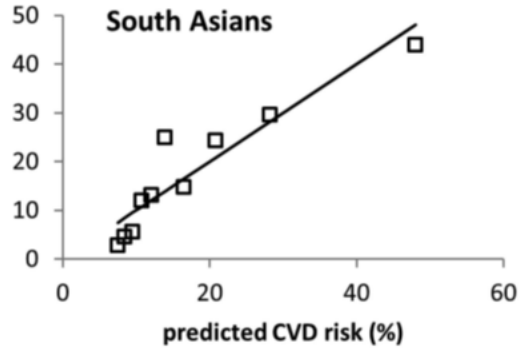
QRISK2 showed a closer relationship with observed risk in African Caribbean men, but a marked under-prediction of observed risk in South Asian women.

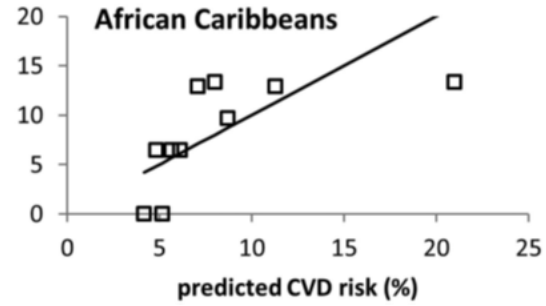
Table 9: QRISK2-2012 predicted : observed events

Tillin 2014	Men	Women
QRISK2 - European White	0.78 (0.72 to 0.85)	0.73 (0.65 to 0.80)
QRISK2 - South Asian	0.71 (0.64 to 0.78)	0.52 (0.34 to 0.72)
QRISK2 - African Caribbean	0.95 (0.80 to 1.00)	1.22 (1.04 to 1.84)

Figure 2: Calibration curves for QRISK2: observed versus predicted 10-year risk of CVD in men

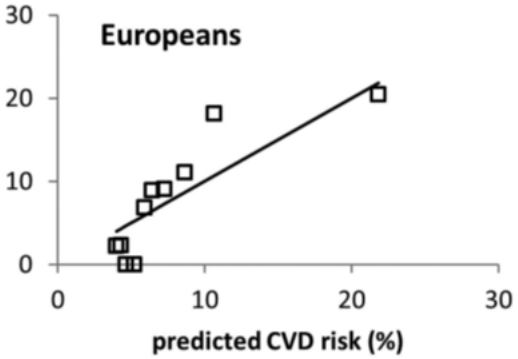


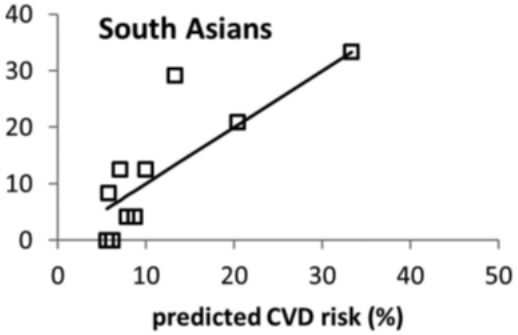


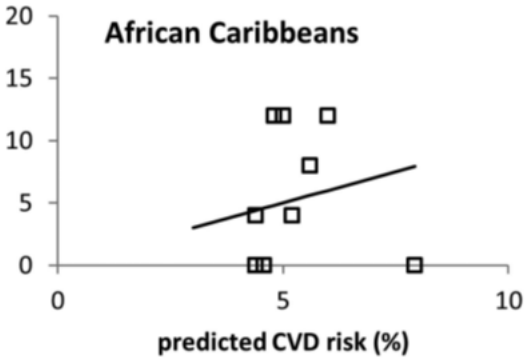


Source: Tillin 2014 [23]

Figure 3: Calibration curves for QRISK2: observed versus predicted 10-year risk of CVD in women







Source: Tillin 2014 [23]

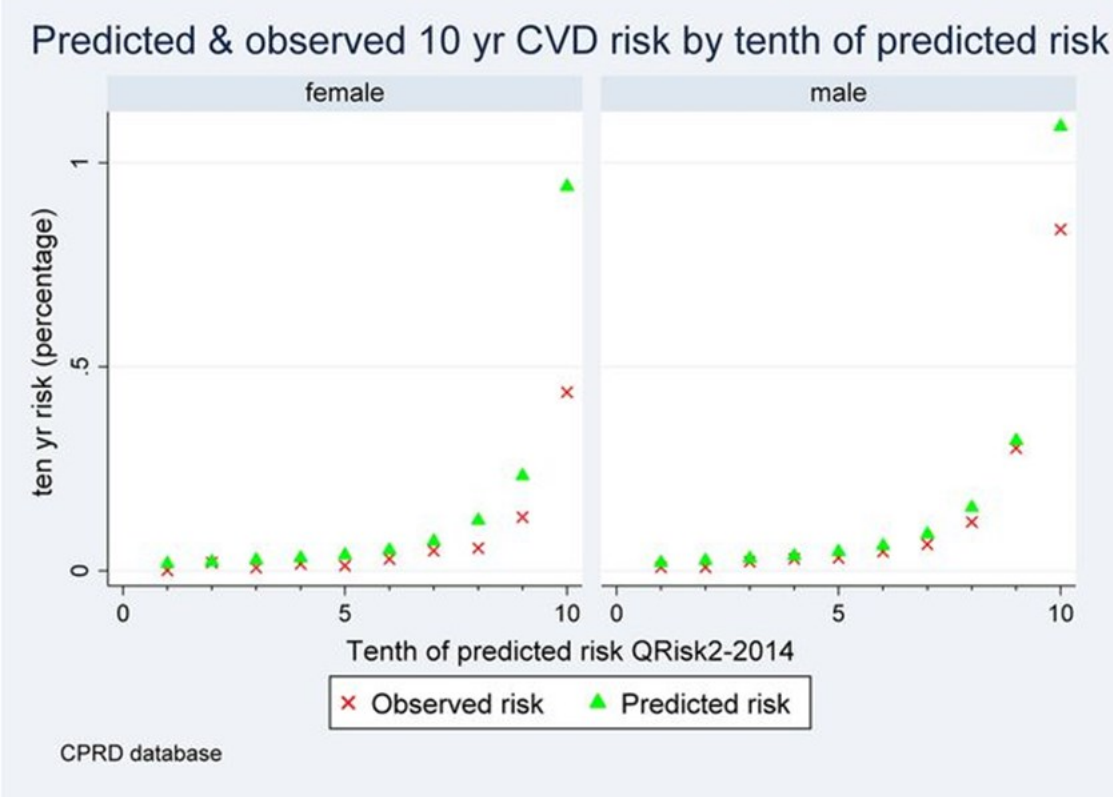
Reproduced from *Ethnicity and prediction of cardiovascular disease: performance of QRISK2 and Framingham scores in a U.K. tri-ethnic prospective cohort study (SABRE--Southall And Brent REvisited)* T Tillin et al, Heart 2014 Jan;100(1):60-7, Open Access article.

QRISK2-2014

Figure 4 shows the calibration plots for QRISK2-2014, comparing the mean predicted risks and observed risks for each score across each 10th of predicted risk. The QRISK2-2014

prediction model shows good calibration in all 10^{ths} of risk, except for the highest 10th of risk in both men and women.

Figure 4: Calibration curves: observed versus predicted 10-year risk of CVD (from Hippisley-Cox 2014)



Source: Hippisley-Cox 2014 [8]

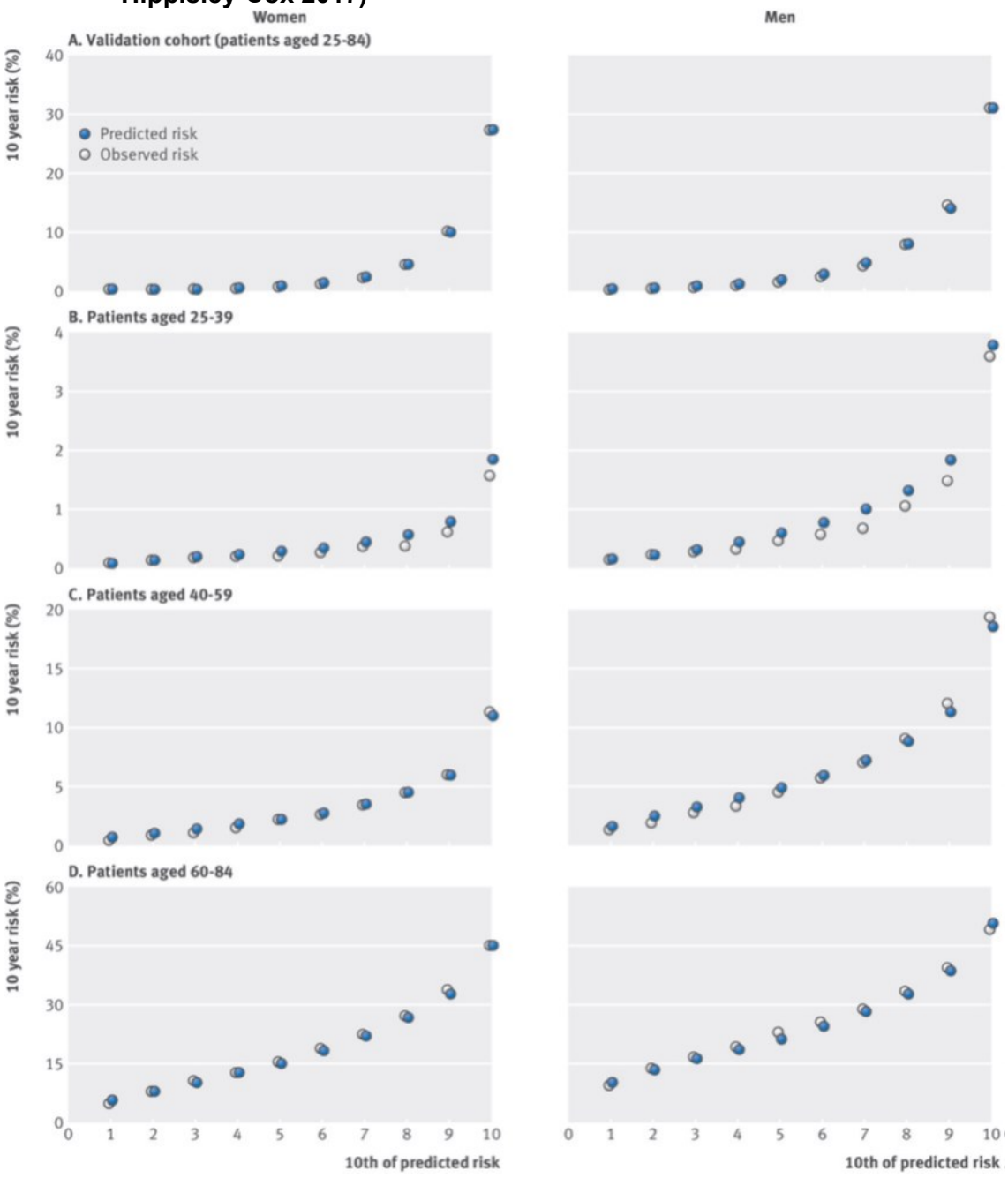
Reproduced from *The performance of seven QPrediction risk scores in an independent external sample of patients from general practice: a validation study*, Julia Hippisley-Cox, Carol Coupland, Peter Brindle, vol 4, copyright 2014, with permission from BMJ Publishing Group Ltd.

QRISK3-2017

Figure 5 shows the calibration plots for QRISK3-2017, comparing the mean predicted risks and observed risks for each score across each 10th of predicted risk (Hippisley-Cox 2017[7]). In women, the mean 10 year predicted risk was 4.7% and the observed 10 year risk was 5.8% (95% CI: 5.8% to 5.9%). In men, the mean 10 year predicted risk was 6.4% and the observed 10 year risk was 7.5% (95% CI: 7.5% to 7.6%).

QRISK3-2017 shows good calibration in all 10^{ths} of risk across all age groups, except for those aged 25-39 where mean predicted risks were slightly higher than observed risks.

Figure 5: Calibration curves: observed versus predicted 10-year risk of CVD (from Hippisley-Cox 2017)



Source: Hippisley-Cox 2017 [7]

Reproduced from *Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study*, Julia Hippisley-Cox, Carol Coupland, Peter Brindle, BMJ 2017;357:j2099, Open Access article.

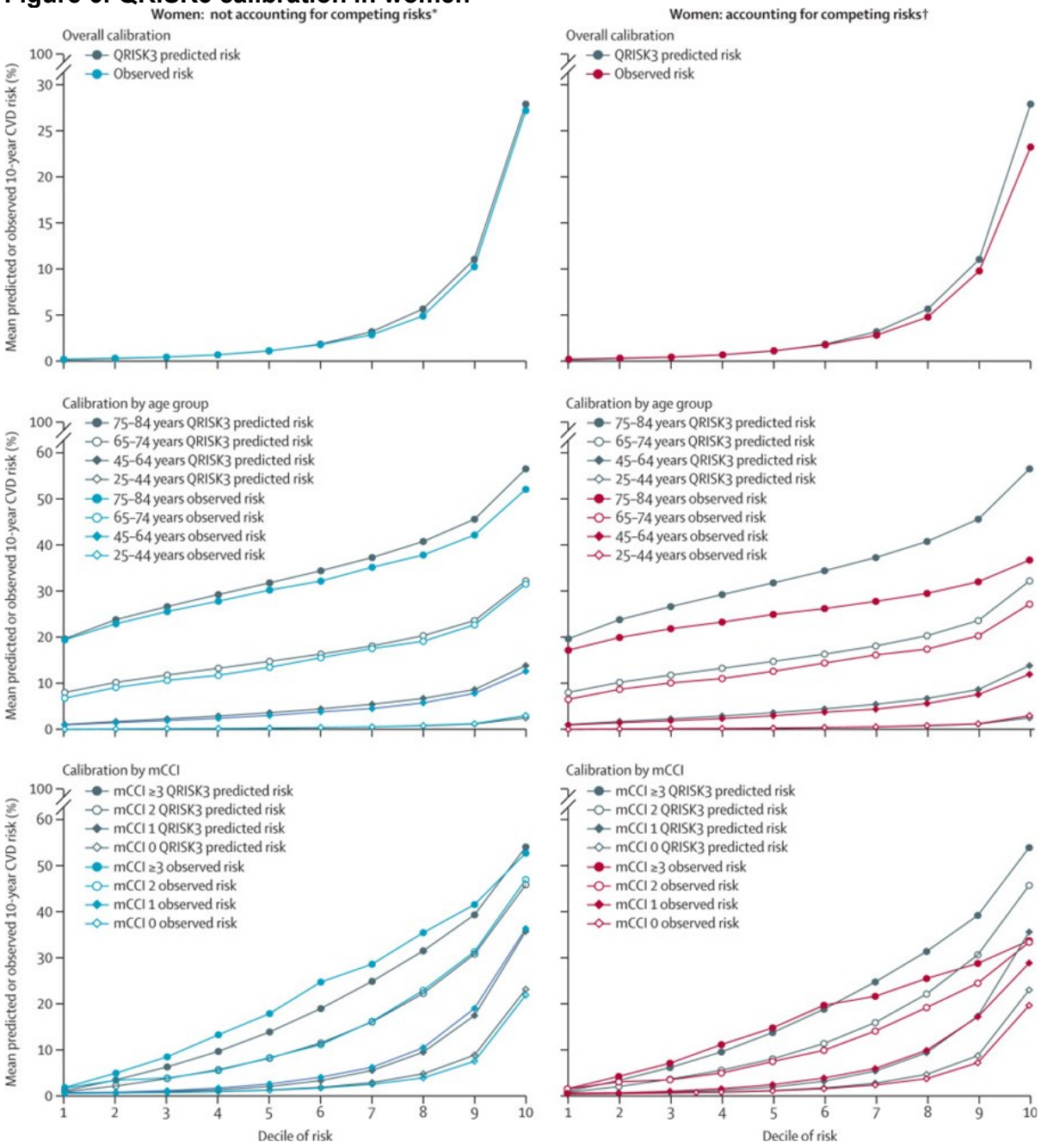
QRISK3 external validation

Figure 6 and Figure 7 show the calibration plots for QRISK3 in women and men, respectively (Livingstone 2021[15]).

In women, when not considering competing mortality risks, calibration was excellent for the whole cohort, and also excellent for those aged 25–44 years. However, QRISK3 over-predicted CVD risk in older age groups. When competing mortality risks were accounted for (Figure 6), there was over-prediction of risk at higher levels of predicted CVD risk in all women. The same pattern of increasing over-prediction with increasing age was observed, but in greater magnitude, and calibration was poor in older age groups.

In men, when not considering competing mortality risks, calibration was excellent, although with somewhat greater over-prediction at higher levels of predicted CVD risk than in women (Figure 7). Calibration was excellent for men aged 25–44 years, but QRISK3 progressively over-predicted CVD risk with increasing age. When competing mortality risks were accounted for, QRISK3 over-predicted risk at higher levels of predicted CVD risk in all men. Calibration was poor, with large over-prediction in older age groups.

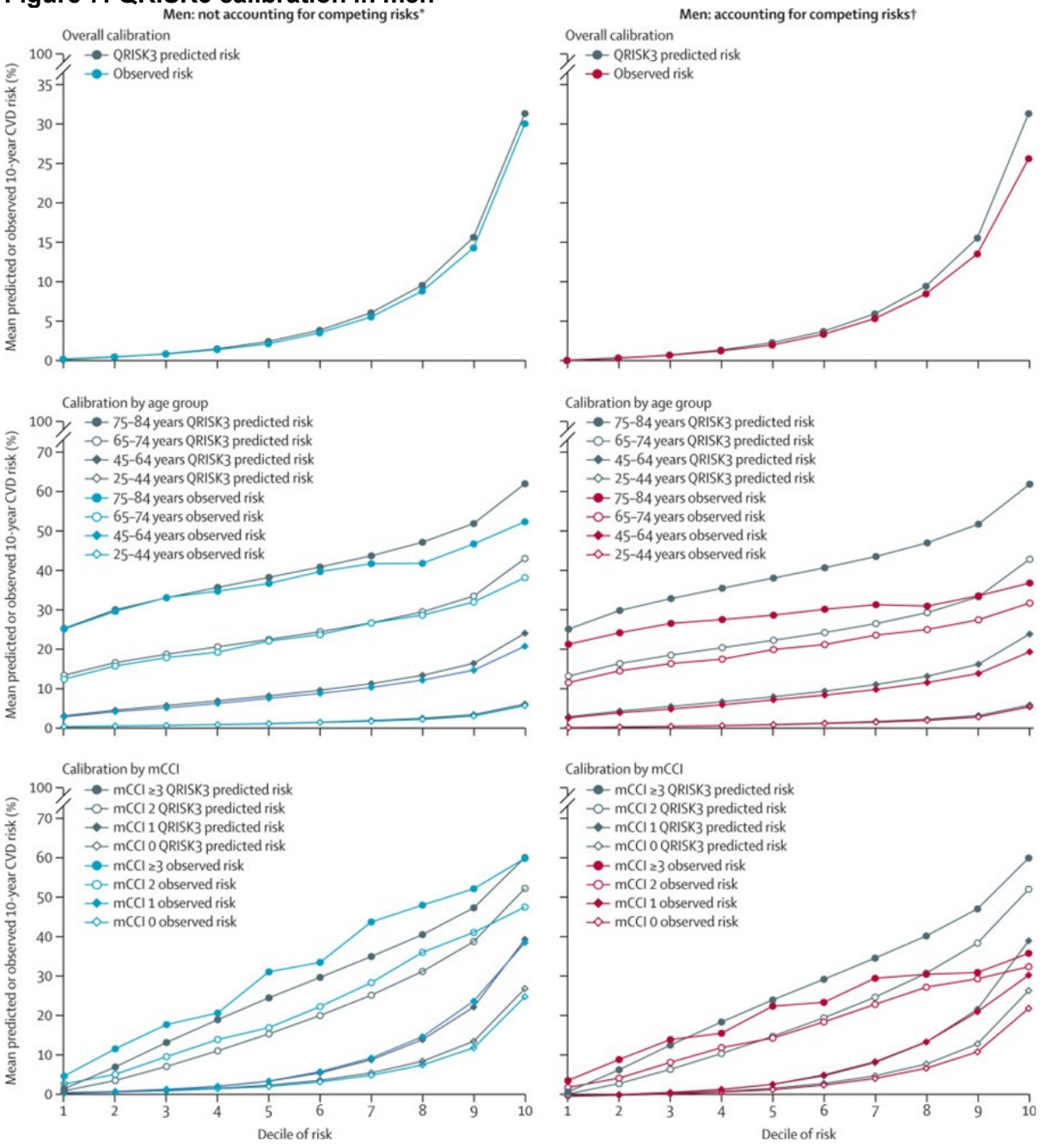
Figure 6: QRISK3 calibration in women



Source: Livingstone 2021[15]

Reproduced from *Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study*, S Livingstone et al, The Lancet VOLUME 2, ISSUE 6, E352-E361, Open Access article.

Figure 7: QRISK3 calibration in men



Source: Livingstone 2021 [15]

Reproduced from *Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study*, S Livingstone et al, The Lancet VOLUME 2, ISSUE 6, E352-E361, Open Access article.

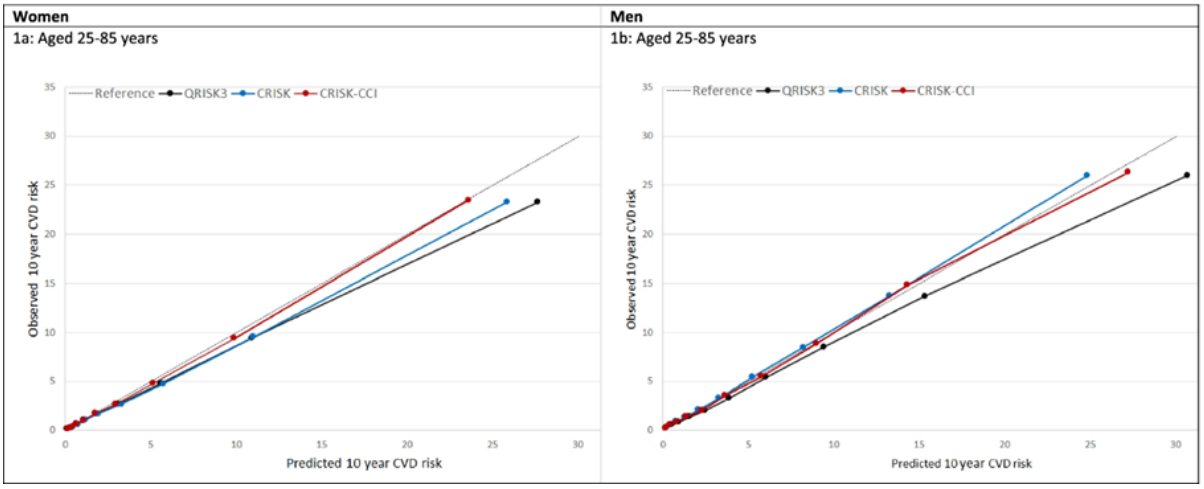
CRISK, CRISK-CCI and QRISK3

Figure 8 shows the calibration plots for QRISK3, CRISK and CRISK-CCI from Livingstone 2022[16]. Figure 9 shows the calibration stratified by age groups.

In women overall, there was some overprediction with CRISK at higher levels of predicted risk, but CRISK was better calibrated than QRISK3, whilst calibration with CRISK-CCI was excellent. In younger women, there was some underprediction with CRISK and CRISK-CCI that was similar to QRISK3. In older women, CRISK modestly over-predicted CVD risk, particularly at higher levels of predicted risk but was still better calibrated than QRISK3 whilst calibration with CRISK-CCI was excellent.

In men overall, calibration using CRISK-CCI was better than CRISK which showed some underprediction, whilst QRISK3 overpredicted CVD risk. In younger men, there was some underprediction with CRISK and QRISK3, but calibration with CRISK-CCI was excellent. In older men at lower levels of predicted risk, calibration with CRISK and CRISK-CCI was good, whilst there was overprediction with QRISK3. However, all models overpredicted risk at higher levels of predicted risk.

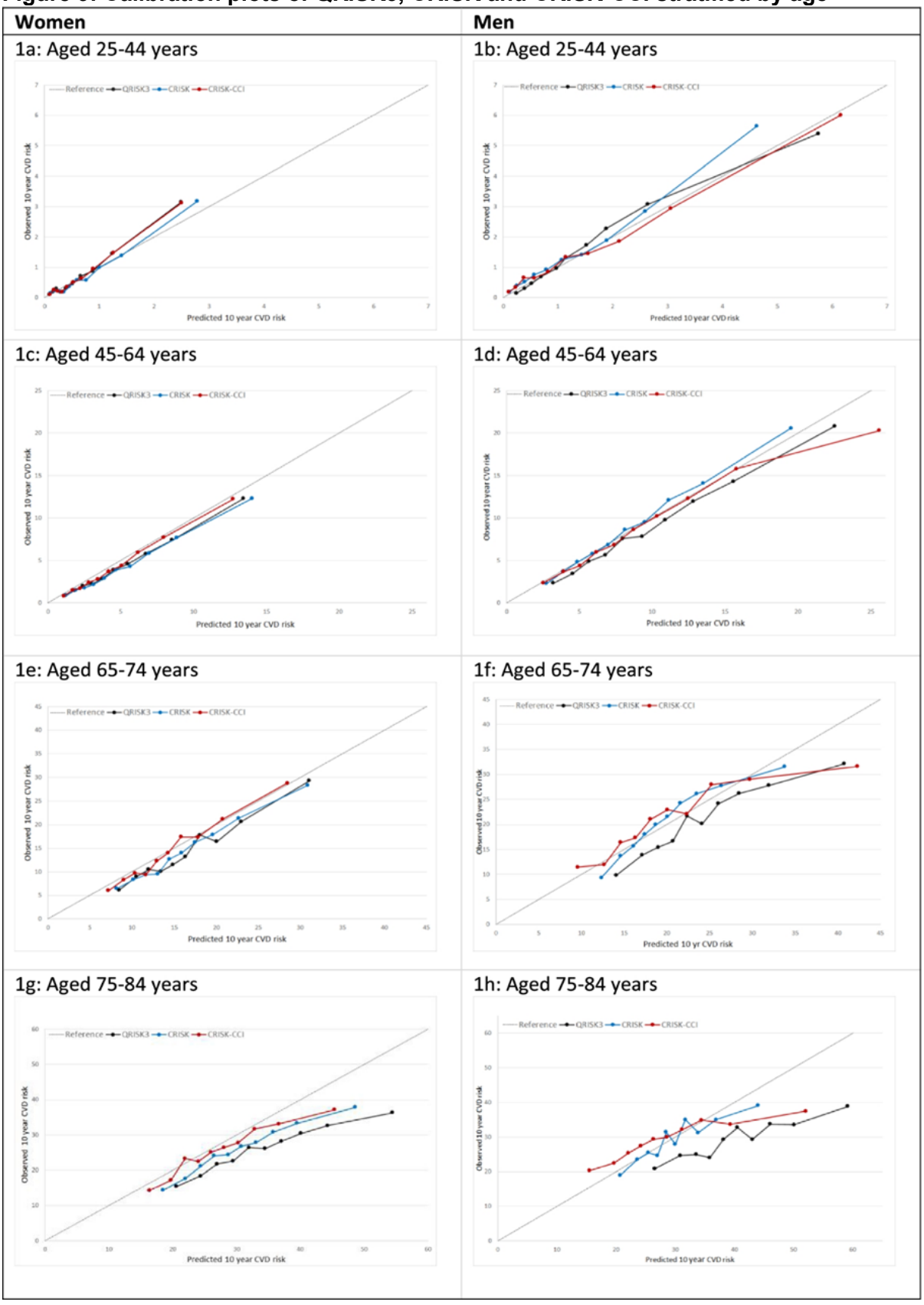
Figure 8: Calibration plot of QRISK3, CRISK and CRISK-CCI



Source: Livingstone 2022[16]

Reproduced from *Predictive performance of a competing risk cardiovascular prediction tool CRISK compared to QRISK3 in older people and those with comorbidity: population cohort study*, S Livingstone et al, BMC Medicine volume 20, Article number: 152 (2022), unadapted, Open Access article.

Figure 9: Calibration plots of QRISK3, CRISK and CRISK-CCI stratified by age



Source: Livingstone 2022[16]

Reproduced from *Predictive performance of a competing risk cardiovascular prediction tool CRISK compared to QRISK3 in older people and those with comorbidity: population cohort study*, S Livingstone et al, BMC Medicine volume 20, Article number: 152 (2022), unadapted, Open Access article.

PRIMROSE-lipid and -BMI tools

Figure 10 shows the calibration plots from the PRIMROSE tools (Osborn 2015[21]). In men, the PRIMROSE models showed over-prediction in those with 7.5-20% predicted risk and underprediction of risk in the highest risk group. In women, the PRIMROSE models were well calibrated, except for some underprediction of risk in the highest risk group for PRIMROSE-BMI.

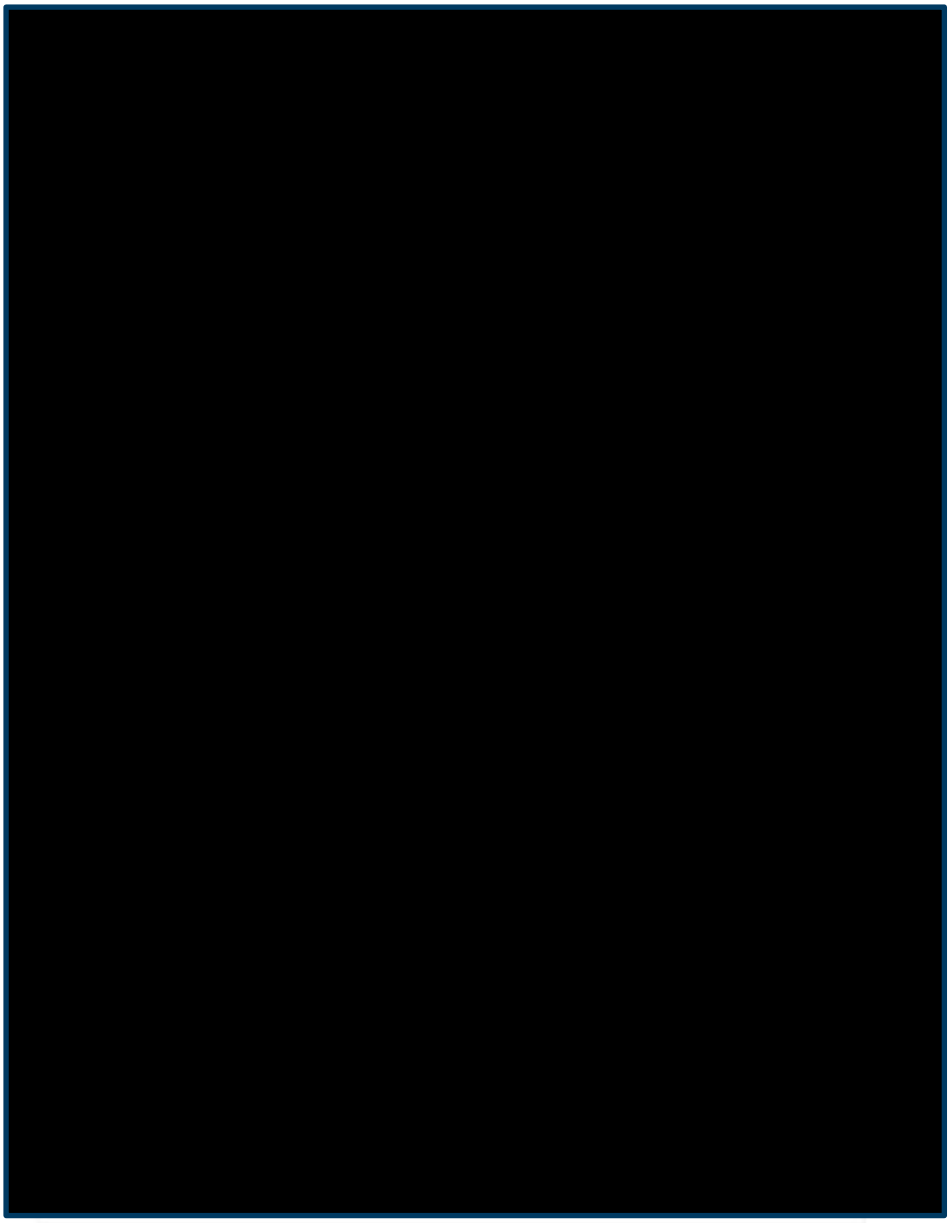
Among those estimated to be at high-risk (risk score >20%), the following proportions were observed to have developed CVD:

- PRIMROSE BMI 531/2989 (17.8%)
- PRIMROSE lipid 570/2991 (19.1%)

Among those estimated to be at low risk (risk score <20%) the following proportions were observed to have developed CVD:

- PRIMROSE BMI 641/17 418 (3.7%)
- PRIMROSE lipid 602/17 416 (3.5%)

Figure 10: Calibration plots for PRIMROSE tools



Source: Osborn 2015[21]

This figure reproduced from *Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program,* DPJ Osborn et al, JAMA Psychiatry 2015 Feb;72(2):143-51, has been redacted pending copyright approval from JAMA Psychiatry.

SCORE2

Figure 11 shows the ratio of predicted to observed events for SCORE2[2]. This shows over-prediction in younger age groups and under-prediction in older age groups, particularly in men.

Figure 11: Calibration of SCORE2 in CPRD data by age groups (SCORE2 working group 2021)

Source: SCORE2 working group 2021[2]

This figure reproduced from *SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe*, SCORE2 working group and ESC Cardiovascular risk collaboration, European Heart Journal, Volume 42, Issue 25, 1 July 2021, Pages 2439–2454, adapted (cropped to show only SCORE2 fatal + non-fatal risk), has been redacted pending copyright approval from Oxford University Press.

SCORE2-OP

Figure 12 shows the ratio of predicted to observed events for SCORE2-OP[1]. This shows good calibration, with a slight underprediction at 10-20% predicted risk and a slight overprediction at >20% predicted risk.

Figure 12: Calibration plot of observed versus estimated (O/E) risk within deciles of the CPRD cohort

Source: SCORE2-OP working group 2021[1]

This figure reproduced from *SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions*, SCORE2-OP working group and ESC Cardiovascular risk collaboration, European Heart Journal, Volume 42, Issue 25, 1 July 2021, Pages 2455–2467, has been redacted pending copyright approval from Oxford University Press.

QRISK lifetime

Table 10 shows the ratio of predicted to observed events for QRISK lifetime (Hippisley-Cox 2010[9]). This shows minor under-prediction in those at low predicted risk but good calibration in the highest 10th of risk.

Table 10: Predicted and observed lifetime risk of cardiovascular disease by 10th of predicted lifetime risk in the validation cohort of 1,267,159 patients

Model decile	Mean lifetime risk (%)		Ratio of predicted to observed
	Predicted	Observed	
Women:			
1	18.5	22.4	0.83
2	21.3	25.9	0.82
3	22.9	27.3	0.84
4	24.4	28.5	0.86
5	26.0	29.4	0.88
6	27.8	31.9	0.87
7	30.2	34.8	0.87
8	33.7	36.8	0.92
9	39.5	41.3	0.96
10	51.9	50.8	1.02
Men:			
1	22.5	25	0.90
2	27.2	32.1	0.85
3	29.8	34.9	0.85
4	32.0	37.3	0.86
5	34.2	39.3	0.87
6	36.6	42.1	0.87
7	39.5	44.9	0.88
8	43.5	47.5	0.92
9	49.9	51	0.98
10	64.4	63.7	1.01

Reproduced from *Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database*, Julia Hippisley-Cox, Carol Coupland, John Robson, Peter Brindle, BMJ 2010 Dec 9;341:c6624, with permission from BMJ Publishing Group Ltd.

LIFE-CVD

Figure 13 shows the calibration plot for the LIFE-CVD model (Jaspers 2020 [11]). This shows some over prediction at lower risk and under prediction at higher predicted risk levels.

Figure 13: External calibration of predicted vs. observed 10-year risk using the LIFE-CVD model

Source: Jaspers 2020[11]

This figure reproduced from *Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people*, NEM Jaspers et al, European Heart Journal 2020 Mar 14;41(11):1190-1199, has been redacted pending copyright approval from Oxford University Press.

1.2.6. Summary of prognostic evidence: reclassification

No reclassification statistics were reported in the included studies. Therefore, a narrative summary of the available information is provided below where both the proportion reclassified and the observed risk in this subset of patients are reported.

1.2.6.1. QRISK3 vs QRISK2 (Hippisley-Cox 2017 [7])

There were 458,263 (17.2%) people classified as high risk (risk ≥10% over 10 years) with QRISK2-2017; 458 869 (17.2%) using QRISK3 without SBP variance, and 458 868 (17.2%) using QRISK3 with SBP variance.

Of the 458,263 people classified as high risk on QRISK2-2017, 10,948 (2.4%) would be reclassified as low risk using QRISK3 without SBP variance. The 10-year observed risk among these reclassified patients was 10.3% (95% CI: 9.6% to 11.1%). Conversely, of the 2,213,035 classified as low risk using QRISK2-2017, 11,554 (0.5%) would be reclassified as high risk using QRISK3 without SBP variance. The 10-year observed risk among these reclassified patients was 12.2% (95% CI: 11.4% to 13.1%).

Of the 458,869 patients with a 10-year predicted risk score of 10% or more using QRISK3 without SBP variance, 9,102 (2.0%) would be reclassified as low risk using QRISK3 with SBP variance. The 10-year observed risk among these reclassified individuals was 9.6% (95% CI: 8.9% to 10.5%). Conversely, of the 2,213,429 with a 10-year predicted risk score of less than 10% using QRISK3 without SBP variance, 9,101 (2.4%) would be reclassified as high risk using QRISK3 with SBP variance. The 10-year observed risk among these reclassified patients was 10.7% (95% CI: 9.9% to 11.6%).

1.2.7. Economic evidence

1.2.7.1. Included studies

One health economic study with a relevant comparison was included in this review.[24] This is summarised in the health economic evidence profile below (Table 11) and the health economic evidence table in Appendix G.

1.2.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

1.2.8. Summary of included economic evidence

Table 11: Health economic evidence profile: risk assessment tools

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Zomer 2017[24] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Patient-level simulation model • Cost-utility analysis (QALYs) • Population: people with SMI and no CVD • Comparators[(c)]: 1. General population lipid algorithm 2. General population BMI algorithm 3. SMI-specific lipid algorithm 4. SMI-specific BMI algorithm • Time horizon: 10 years	2-1: £11 3-1: £5 4-1: -£7 [(d)]	2-1: -0.002 3-1: -0.001 4-1: 0.002	SMI-specific BMI algorithm is dominant (lower costs and higher QALYs than all other options)	Probability cost effective (£20K/30K threshold): 1. ~22%/~22% 2. ~17%/~17% 3. ~13%/~13% 4. ~43%/~43% In some deterministic sensitivity analyses the general population lipid algorithm became the most cost-effective option (when statin compliance was reduced to 50%, when utility in the SMI population was reduced, and in some of the scenarios when costs were doubled).

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; SMI = serious mental illness.

(a) Doesn't include comparison to general population algorithms used in current practice (general population algorithms were UK adjusted Framingham equations which don't meet the update review protocol [QRISK2 recommended in the 2014 CG181 update over Framingham-based assessments]). 2012/13 cost year and some based on resource use before 2007 may not reflect current NHS context. Cost of blood test excluded for BMI-based algorithms but would be required in patients starting statin therapy so can monitor impact of treatment.

(b) The PRIMROSE SMI-specific risk tool has not been externally validated (see clinical review). Time horizon of 10 years may not fully reflect the impact on costs and QALYs.

(c) General population algorithms were UK adjusted Framingham (D'Agostino 2008) – not included in update review protocol; SMI-specific algorithms were PRIMROSE. For all groups, people assessed as >10% 10-year CV risk receive and statin treatment (20mg atorvastatin). People already on statin therapy (in THIN) remained on treatment irrespective of risk level. A 'No risk assessment' group without additional statin treatment was also estimated but is not presented here as did not meet the protocol.

(d) 2012/13 costs. Cost components incorporated: risk assessment (GP time and blood tests); statins; CVD event costs (first and subsequent years).

1.2.9. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2.10. Evidence statements

1.2.10.1. Economic

- One cost-utility analysis found that risk assessment using an SMI-specific BMI algorithm (PRIMROSE) was the dominant strategy (lowest cost and highest QALYs) in people with serious mental illness compared to an SMI-specific lipid algorithm (PRIMROSE) and a UK-adjusted Framingham general population BMI or lipid algorithm. This analysis was assessed as partially applicable with potentially serious limitations.

1.2.11. The committee's discussion and interpretation of the evidence

1.2.11.1. The outcomes that matter most

The committee agreed that the clinical outcomes that the tools of relevance to this review should predict were CVD events, in particular cardiovascular mortality, non-fatal MI and stroke. The accuracy of prediction tools to estimate the risk of CVD events at 10-year or lifetime thresholds was measured using the following metrics:

Discrimination

- Area under the ROC curve (c-index, c-statistic).
- Classification measures at 5%, 7.5%, 10%, 15% and 20% predicted risk thresholds: sensitivity, and specificity.
- D statistic

Calibration:

- Calibration plots
- Predicted risk versus observed risk
- Statistical tests for agreement between predicted and observed events (e.g., Hosmer-Lemeshow or Nam–D'Agostino statistics)

Reclassification / revalidation:

- net classification improvement
- integrated discrimination index

The committee agreed that a good risk tool should accurately predict the true CVD risk (either 10-year or lifetime risk), that is it needs to be well calibrated; over- or under- prediction would lead to over- or under- treatment, which could result in harm. Discrimination is important to correctly classify individuals into risk groups to inform decisions on pharmacological treatment. Clinically relevant re-classification decisions are also important to compare the utility of the tools.

The committee noted that very little evidence was available for the sensitivity and specificity of the tools at specific thresholds and that no reclassification statistics were reported.

1.2.11.2. The quality of the evidence

The quality of the evidence ranged from low to high, with the majority being of moderate quality. Downgrading of the evidence was mainly due to risk of bias; some tools having internal validation only, cohorts having less than 100 events and studies not reporting calibration data. For some tools with both internal and external validation there was inconsistency in the findings between the cohorts. It was noted that some of the studies included softer end points that may be more difficult to define in their models (for example TIA or angina), or outcomes subject to practice variation (e.g., revascularisation). However, it

was agreed that this should not be considered as a reason for downgrading the quality of the evidence as the model development criteria in these studies appeared sufficiently robust to predict the primary outcomes of interest.

Data sources

The committee discussed the differences in the validation databases used in the different UK studies and whether they could be considered as distinct cohorts. It was noted that these are all UK primary care data, but that they are drawn from distinct sets of GP practices, and so can be considered different cohorts while still being representative of the UK primary care population.

1.2.11.3. Benefits and harms

Discrimination

QRISK2 and QRISK3 showed similar ability to classify individuals into risk groups based on AUC data. CRISK and CRISK-CCI tools also showed similar discrimination but did not have any external validation data. These tools all have a higher discriminative capacity in women than in men. Other tools included in the review were inferior in terms of this assessment metric.

Calibration

QRISK2 and QRISK3 were demonstrated to be generally well calibrated but showed some overprediction in the highest risk groups. Calibration of QRISK3 was also less accurate when accounting for competing mortality risk. CRISK, and especially CRISK-CCI, were better calibrated than QRISK3, but all 3 models overpredicted risk at higher levels of predicted risk in those aged 75-84 years. The committee noted that although overprediction could result in unnecessary treatment and anxiety, underprediction would have worse consequences in this context as the tools are used to identify those people who will be offered statins. This means people who would benefit from statins due to their high risk of CVD events may not be identified.

The QRISK2 and 3 and CRISK and CRISK-CCI tools were agreed to be good tools for ranking people from likely highest to lowest risk based on their calibration performance. This was agreed to be useful from a population health perspective because a tool is needed to help triage people. However, it was also noted that most CVD events occur among people who are not perceived to be at high risk because this is often the largest group; therefore, the greatest impact on population health will be based on what threshold is chosen to define those at high risk and, in turn, who should be offered statins. It was noted that whatever threshold is chosen it is likely that events will still be missed.

Given the poorer discriminative ability of other tools considered in the review, their calibration data was considered of less value for decision making and did not inform the committee discussions. However, it was noted that PRIMROSE and LIFE-CVD showed under-prediction in the highest risk groups, which significantly limits their utility. SCORE2 also showed under-prediction in older age groups and SCORE2-OP showed slight under-prediction at 10-20% predicted risk.

The evidence demonstrated that QRISK3, CRISK and CRISK-CCI over-predict in people aged over 75 and that their discriminative ability reduces with increasing age, even when accounting for competing mortality risk. However, the committee did not consider this a problem in terms of the use of the tool for determining when to offer treatment in clinical practice, as people aged over 75 would already have a greater than 10% risk. The need to assess risk was therefore agreed as important both to inform treatment threshold, but also to inform discussions with a person about risk. Calibration and discrimination data for different age subgroups were not available for QRISK2.

Reclassification

Limited data were available for reclassification, and no reclassification statistics were reported. However, data showed that QRISK3 correctly reclassified to high risk 0.5% of those who were low risk on QRISK2. The committee discussed that this reflects the benefit of QRISK3 for correctly assessing risk in people for whom the clinical variables added since QRISK2 apply. There was also evidence that a higher proportion of those with observed CVD events were correctly classified as high risk with QRISK3 than with CRISK-CCI.

Lifetime risk tools

The committee queried the value of studies assessing lifetime risk tools over a 10-year period. It was agreed this evidence was very limited in terms of how it could be used to inform accuracy of the tool over a lifetime. However, the committee discussed the potential utility of lifetime risk estimates in younger people, who may not cross the threshold for being considered high risk based on 10-year estimates. In this group, the use of lifetime risk estimates could help inform discussions about CVD risk and the importance of lifestyle modification at an earlier age. They highlighted that these tools may underestimate the effects of treatment however, as they assume the cholesterol levels entered are the value someone has always had, rather than using RCT data to estimate the impact medicines may have on reducing cholesterol. They agreed that while they should not be used for that purpose, this was not needed explicitly in the recommendation as this was worded so as not to imply this was where they could help conversations and that did not override their benefit in aiding discussions about risk. They therefore agreed to include a recommendation in the guideline within the section on communication about risk, giving the example of QRISK-lifetime of one such tool that could be used. Although this tool performed best from the limited evidence of lifetime risk tools, it was agreed the recommendation should not be restricted to that tool as newer evidence may emerge and so this was just provided as an example.

Summary

The committee agreed that all of the tools have limitations. They tend to be quite well calibrated, but less accurate in terms of discrimination therefore none are very good screening tests for predicting those who will and will not get disease, but they can be useful in splitting into low, medium and high risk, or ordering likelihood of events occurring. The committee discussed that one use of risk assessment tools for CVD is to help decide on suitability for treatment (See evidence review C for further discussion on this topic). The committee agreed that using an appropriate risk assessment tool should not replace clinical judgement and that risk score interpretation should be individualised.

The committee agreed that overall the evidence suggests that QRISK3 performs better than QRISK2, although the difference in performance was marginal. The evidence that QRISK3 appropriately reclassified 0.5% of those low risk on QRISK2 to the high-risk category was agreed to be important and reflects the added accuracy of this version of the tool for classifying people with conditions not included in the QRISK2 algorithm, such as severe mental illness and systemic lupus erythematosus. The committee raised concerns that QRISK3 would take longer to complete in practice as QRISK2 is embedded in clinical systems and so pulls the necessary data from medical records. Any additional time taken to complete such a tool would lead to a risk that it wouldn’t be fully completed, particularly when considering the current context is people working in very busy clinics when healthcare professionals are already very limited by time. The committee were aware that QRISK3 had been incorporated into the NHS health check and that discussions were ongoing at the time of development of the guideline regarding the continuation of inclusion within clinical systems. The committee however agreed the best risk assessment tool should still be recommended within the guideline as the implementation in systems would apply to all tools. It was agreed that the best tool should be recommended, but recognised that it may be necessary to use QRISK2 until QRISK3 is available in clinical systems. However, this should

not be the case for people who use corticosteroids or atypical antipsychotics or have a diagnosis of systemic lupus erythematosus, migraine, severe mental illness, or erectile dysfunction because QRISK2 may underestimate their 10-year CVD risk because, unlike QRISK3, it does not include these variables. In these cases, where QRISK2 is still the version within the care providers electronic system, the web version of QRISK3 should be used. It was acknowledged that QRISK3 is now the standard version of this tool and that the annual remodelling of the algorithm to the latest version of the QResearch database will be applied to QRISK3. Therefore, earlier versions of QRISK, including QRISK2, may not be subject to this annual remodelling and their performance may decay. This was agreed to be another reason in support of recommending QRISK3.

It was agreed that an important aspect of the use of any tool is the conversation that is had about risk between the healthcare professional and the person, and how risk is communicated.

Subgroups

Overall, it was agreed that QRISK3 appears to perform reasonably well in terms of discrimination for subgroups with comorbidities including people with CKD, type 1 diabetes and severe mental illnesses, although not so well for people with type 2 diabetes. However, it was further noted that all of this evidence was from internal validation studies only and performance was not as good as it was in the whole population cohort. Furthermore, the models considered perform relatively poorly in terms of discrimination for people with type 2 diabetes. The committee noted that this could be due to some variables associated with type 2 diabetes that would affect CVD risk not being captured in the risk tool, including the length of time someone has had diabetes, their blood sugar control and the therapies that they receive, some of which reduce CVD risk. Additionally, as the CVD event rate is already high in this population risk discrimination is more difficult.

No calibration data were available for any of these subgroups and the AUC statistic was lower than that for the overall cohort in all subgroups.

The previous update of this guideline also considered evidence for UKPDS (a type 2 diabetes specific risk calculator). They noted that the UKPDS is based on a historical cohort and had not been updated. At that time, the former committee noted that QRISK2 included diabetes as a risk factor and the development cohort included more than 40,000 people with prevalent type 2 diabetes compared to 4540 newly diagnosed type 2 diabetes patients in the UKPDS derivation cohort and the accuracy results overall were better than UKPDS (although there was no direct head-to-head comparison). They discussed that there was some suggestion that people with diabetes were of equivalent risk to a secondary prevention population, but on balance the committee consensus was that although incidence of CVD events was increased in people with type 2 diabetes, it was not quite as high as a secondary prevention and so use of a risk tool was still of value. They therefore agreed it was appropriate to recommend QRISK3 for people with type 2 diabetes despite the fact that there had not been external validation of QRISK3 in a type 2 diabetes population. The committee's opinion was that it is still difficult to persuade some people to try statin treatment, even when they know they have diabetes, and so continued use of a risk tool could help the communication of risk and improve uptake of statins, even knowing it performs less well in this group. The committee agreed that was an important factor and that a risk tool should continue to be recommended for people with type 2 diabetes, although raised that communication of risk may be better informed, in their opinion, by lifetime risk tools. In line with the previous update of this guidance, QRISK is still the best tool for this population and QRISK3 should replace QRISK2 as it is the current version of this tool.

The committee discussed whether it was appropriate to recommend the use of a risk tool for people with either chronic kidney disease (CKD) or type 1 diabetes, in whom risk tools have not previously been recommended. Although type 1 diabetes was included within QRISK3 and there was internal validation data available, the committee noted that people with type 1

diabetes are at very high risk of CVD events. As discussed in the previous version of this guideline, features of the metabolic syndrome are highly relevant to the occurrence of CVD events in type 1 diabetes and these risk factors will be recognised by specialists in diabetes who will treat people accordingly. Like QRISK2, QRISK3 only includes a tick box for type 1 diabetes, which does not include factors considered clinically important such as length of time the person has had diabetes or urine albumin. As evidence in this population is still limited the committee agreed that a recommendation not to use a risk tool in this group should be retained.

They acknowledged that QRISK3 has expanded the definition of CKD to include stage 3, and that there is now internal validation data which shows reasonable discriminative power for both population subgroups, although no calibration data were available. However, the committee agreed people with CKD are often at high CVD risk, including those with stage 1 or 2 CKD which is not captured in QRISK3 and in whom risk can actually be higher than in many people with stage 3 without albuminuria. Therefore, they considered that QRISK3 is likely to significantly underestimate CVD risk, especially those with CKD stage 1 or 2. They also noted that the AUC for this group was lower than the general population sample and was only available from an internal validation cohort. Therefore, the committee agreed that a recommendation not to use a risk tool in people with CKD should be retained. They noted that people with albuminuria (A2 or A3) or with eGFR <60 ml/min/1.73m^2 with or without albuminuria should be considered at greater risk of CVD and CVD risk modification should be considered within this group.

As QRISK3 includes consideration of more population subgroups than QRISK2, the committee agreed that these factors could be removed from the 2014 recommendation highlighting where risk tools may underestimate 10-year risk. They acknowledged that the evidence for the performance of the tool in these subgroups had not been validated in separate groups of people to those analysed for its development, nor was calibration data available for these subgroups. However, they agreed that the tool should still be recommended in these groups as the risk tool is used to determine a threshold for treatment and therefore use of QRISK3 for someone with in these subgroups could impact treatment decisions. Based on their clinical experience, the committee agreed that it remained important to highlight that risk tools may still underestimate CVD risk in certain groups of people that are not adequately reflected in the tool. These included autoimmune disorders and other systemic inflammatory disorders as although systemic lupus erythematosus and rheumatoid arthritis are included in QRISK3, this does not adequately reflect the other related conditions that are associated with an increased risk of CVD and that this should still be noted. Furthermore, it was noted that the definition of severe mental illness used in the cohort to derive and validate QRISK3 differed from that in many electronic record systems. The cohort included a large proportion with moderate to severe depression, who are not consistently defined as having severe mental illness. The committee were aware that people with severe mental illness defined as schizophrenia, bipolar disorder and other psychoses are known to be at higher risk of CVD than people with moderate to severe depression. While risk may be increased in this group compared to the general population, the likely impact of including a large proportion in the cohort is that risk may be still slightly underestimated in people with severe mental illness. The committee also noted there was the potential for risk to be overestimated in people with moderate to severe depression. However, they noted this was not evidenced and as recommendations reinforce the importance of shared decision making in CVD risk management, the impact of minimal risk of overestimation was low. The committee agreed that the QRISK3 tool did provide the best estimate of risk for people with severe mental illness, but noted it was important to retain the recommendation that risk tools may underestimate risk in people with severe mental illness. The committee agreed that clinical judgement should inform interpretation of the risk score, based on the individual's circumstances.

1.2.11.4. Cost effectiveness and resource use

One cost-effectiveness analysis was included that compared severe mental illness (SMI)-specific risk assessment using the PRIMROSE algorithm to a general population risk assessment tool in a population with SMI and without established CVD. This analysis found risk assessment using the PRIMROSE BMI algorithm was the most cost-effective option however the general population comparator was based on a UK adapted Framingham equation that was excluded from the guideline update clinical review protocol as QRISK2 was concluded as better for risk assessment in the 2014 CG181 update. In addition, QRISK3 includes fields related to SMI and so should reflect risk in people with SMI better than the general population algorithm used in this analysis. This limited the conclusions that could be drawn from this analysis. It was also noted that the PRIMROSE risk tool had not been externally validated and the clinical review did not provide evidence that this tool would perform better than QRISK3 (although no direct comparison was available).

No other cost-effectiveness analyses were identified. The committee discussed whether the different risk tools would require different resource use and so have different costs to use. The tools included in the clinical review were considered to require similar information. It was noted that QRISK3 has additional fields to complete over QRISK2 (which is currently recommended): whether the individual has a diagnosis of migraine, systemic lupus erythematosus, severe mental illness or erectile dysfunction, whether they have a prescription for corticosteroids or atypical antipsychotics, and a measure of systolic blood pressure variability. It was noted that this information can mostly be elicited quickly by asking the patient or from patient records and it was not considered likely to require additional or longer appointment times if QRISK3 was integrated into clinical systems in the same way as QRISK2 currently is, however the committee noted this is currently under discussion by the relevant parties. The committee noted that the measure of blood pressure variability may not be completed unless it was calculated within IT systems automatically but much of the clinical validation data was for QRISK3 without this field completed and the tool would still calculate risk if this was omitted.

QRISK3 is available as a web tool but the committee highlighted that QRISK2 has to-date usually been integrated into clinical IT systems and that using QRISK3 would be more time consuming to complete if it was not similarly integrated. It was noted that in August 2021 Public Health England issued guidance about using QRISK3 in NHS health checks (responsibility for the NHS Health Check programme has now transferred to the Office for Health Improvement and Disparities). This guidance includes information about integration of QRISK3 and noted that at the time of publication QRISK3 was already incorporated into one system. Also, since QRISK3 is now the standard version of QRISK provided in ClinRisk Ltd software development kits, as software updates are deployed it will become the current version by default over time. The committee were aware that there was some uncertainty about future provision of risk tools in clinical systems but that a statement had been made by EMIS in Pulse Today stating that they are working to offer the QIRSK2 calculator beyond April. Although no information was available about QRISK3, the committee agreed that if integrated into systems, use of QRISK3 was not considered likely to require additional resources over QRISK2.

Assuming risk tools continue to be integrated in clinical systems and that significant differences in resource use are not expected related to carrying out risk assessment, whatever risk tool is used, the cost effectiveness of using a risk assessment tool will therefore be related to its effectiveness in correctly predicting risk. The committee discussed what influence risk assessment will have on the treatment and outcomes in the rest of the treatment pathway. It was noted that risk assessment is currently used to determine who starts statin treatment. It is also used when considering starting other treatments including blood pressure lowering medication for people with stage 1 hypertension and type 2 diabetes treatment. The committee also highlighted that if individuals have a better understanding of

their CVD risk and its implications this could also improve their willingness to start treatment, adhere to treatment and make lifestyle modifications.

Theoretically, the consequence of inaccurate risk assessment could be that a group of people incorrectly calculated as being above the selected risk threshold are prescribed medication but do not get sufficient benefit to justify their use; and/or a group of people incorrectly calculated as being below the selected risk threshold are not prescribed medication and health benefits and cost savings of avoiding future health events are missed. It was noted that statins were shown to be cost-effective even at low risk levels. Therefore, overestimation of risk by a tool will be less of an issue than underestimation or mis-classification from a statins cost-effectiveness perspective. Overestimation will lead to more people being treated and lower absolute benefit in the additional people treated but is likely to still be cost effective. For other treatments not looked at in this guideline however this may not always be the case.

The clinical review found that although QRISK3 performed better than QRISK2, the tools' performance did not vary substantially overall and so changing to QRISK3 may not have a large impact to costs or outcomes on a population level. However, it was noted that for people in the specific population groups that have been added to QRISK3 it will increase their risk estimate and so may change their risk category which could affect the treatments they are offered and therefore the health benefits they receive.

The committee discussed that calculating lifetime risk is likely to require healthcare professionals to enter data into an online calculator as it is not currently incorporated into clinical IT systems. This would take some additional time however it is not clear whether this would result in longer consultations or not. In addition, it would not be done for everyone. If integrated into clinical systems time impact would be minimal. Lifetime risk calculation is likely to be useful in younger people who do not meet conventional criteria for being high risk but who do have risk factors for cardiovascular disease that could confer a high lifetime risk. Lifetime risk estimates could also be useful in some people for whom additional information about cardiovascular risk is deemed helpful to fully inform the patient and encourage them to make lifestyle changes or start or adhere to risk reducing treatments. Given this, any additional time costs were considered likely to improve management of cardiovascular risk and so reduce clinical events.

1.2.11.5. Other factors the committee took into account

It was noted that QRISK3 is only validated for use in people aged 25-84 inclusive. The committee therefore agreed it was important to retain the 2014 recommendation highlighting that people aged 85 years or older should be considered at high risk due to age alone. There are no risk tools validated in people aged under 25, and as the majority of people of this age group would not be high risk, the committee agreed no separate recommendation was required.

The committee were aware that hormone therapies used for gender reassignment may impact a person's risk of CVD. They were aware however that the NHS Health Check best practice guidance states that gender should be recorded as reported by the individual. If the individual discloses gender reassignment, they should be provided with CVD risk calculations based on both genders and advised to discuss with their GP which calculation is most appropriate for them as an individual. They agreed that healthcare professionals should follow this guidance when undertaking formal risk assessments.

The committee discussed other equalities issues that were highlighted when starting development of the update. They noted that the factors included in QRISK3 do address consideration of many relevant factors, for example severe mental illness (as mentioned above), ethnicity and socio-economic status. They also agreed that when full formal CVD risk assessments were first introduced some factors were not consistently recorded in people's medical records, however this was no longer a particular issue, and so they agreed

recommendations to highlight these as risk factors for CVD, or areas in which risk might be underestimated, were no longer required in the guideline.

The committee discussed how sudden death was captured in the databases used. Some committee members raised that in the past where sudden death was listed as the cause of death on a death certificate, it was listed as MI in medical records, leading to an innate bias. The committee were unsure if this was still true. They queried whether the databases used in the development of these models included sudden death in cardiovascular mortality. It was noted that the committee's knowledge of these databases was that if the sudden death was 30 days within an MI, then this was listed within cardiovascular mortality (due to MI). The committee considered this was appropriate.

It was noted when a cut off for a tool is selected (for example, using a 10% risk on QRISK2) it corresponds to a particular point on the area under the curve, and therefore a particular sensitivity and specificity. The committee discussed that it would be useful to know the detection rate at the threshold that was being considered as that in which statin treatment should be offered to a person. This data was not reported in the included papers, but it was possible to calculate this for QRISK3 from an external validation cohort. The committee noted that the sensitivity improved as the high risk threshold was lowered from 10% to 7.5%, but at the expense of an increased false positive rate. They noted it was important to be aware of the trade-off between these metrics when considering whether it was appropriate to lower the threshold for treatment.

The committee discussed whether cardiovascular risk assessment was needed at all and whether risk assessment could be stopped if all people over a certain age were offered statins given that they were found to be cost effective for most people between 40 and 80 years of age and they considered that age was the largest single determinant of risk. However, age alone had not been considered as part of the review, and although it may be possible to determine at what age everyone was over a defined high-risk threshold for a particular tool, there were concerns that this would be detrimental to a person's understanding of their individualised CVD risk and the importance of risk factor modification. It was noted that statins are not the only primary prevention treatment where initiation is influenced by CV-risk. In addition, it was agreed that it was important to be able to assess level of risk to aid discussions about lifestyle changes and treatment initiation because people at higher risk were likely to be more motivated to make changes or start treatment and would also receive the largest benefit of doing so. The committee were aware of reports indicating that the uptake of statins in those at greater than 10% risk is currently less than 50%. They raised concerns that without a risk assessment or good communication about risk in absolute terms on an individual level, this could be even lower. Furthermore, it was noted that there could be an equalities consideration regarding engagement with lipid-lowering strategies. In the committee's experience, people with lower levels of education and from lower socio-economic groups may be less likely to take statins, even when they are at high risk. Not informing people of their risk score as a motivator of change, would likely negatively impact this as they may be even less likely to engage in lifestyle modification or consider treatment if they are unaware of their risk. This was not evidenced by recent audit data that the committee were aware of, but the committee agreed it was nevertheless important to be aware of with a view to not negatively impacting this. A further equalities consideration was the ability to reach people who are not registered with a GP, who are likely to also overlap with the above group. The committee agreed this is a particular challenge in reducing health inequalities, as NICE guidelines apply where NHS care is commissioned or delivered, they agreed that this should equally be considered by outreach services that may also include people not registered with GPs in order to try to help all people have a better understanding of CVD risk. Therefore, they agreed it is beneficial to recommend that a risk assessment tool is used to inform a threshold for treatment to enable effective communication of risk and avoid reinforcing health inequalities.

Overall, it was agreed, risk assessment as a starting point for risk management is beneficial irrespective of the treatment initiation threshold for statins (the treatment initiation threshold is discussed in the statins evidence report C).

The committee also noted that healthcare professionals may be familiar with the JBS3 tool for assessing lifetime risk. They discussed that this tool was based using the QRISK-Lifetime algorithm and therefore it was not included separately within the review. QRISK-Lifetime was provided as an example of a lifetime risk calculator in the new recommendation for communicating risk, but the recommendation was not restricted to QRISK-Lifetime.

1.2.12. Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.7 to 1.1.11 and 1.1.16.

1.2.13. References

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Appendices

Appendix A Review protocols

A.1 Review protocol for CVD risk assessment tools: primary prevention

ID	Field	Content
0.	PROSPERO registration number	CRD42022349147
1.	Review title	Risk assessment tools for predicting the risk of cardiovascular disease (CVD) events in adults without established CVD.
2.	Review question	What is the most accurate tool for determining 10-year and lifetime cardiovascular risk in adults without established cardiovascular disease?
3.	Objective	The aim is to update the review from the 2014 version of CG181 to determine whether there is now a more accurate tool that should replace QRISK2 and whether lifetime risk tools provide accurate estimates.
4.	Searches	Key paper: Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017; 357:j2099 (REF ID:89) The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • Date limitations – none

ID	Field	Content
		• English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Risk assessment for primary prevention of cardiovascular disease
6.	Population	Inclusion: • Adults (18 years and over) without established CVD, including adults with chronic kidney disease, type 1 diabetes, and type 2 diabetes • Validation studies in a UK population • Derivation studies from UK or non-UK cohorts if the tool has subsequently been validated in a UK population. Non-UK studies will be downgraded for indirectness. • Studies in mixed populations with and without established CVD will be included if at least 80% were without CVD. Studies in mixed populations including the UK and other countries will be included if at least 80% of the sample are from the UK, or if subgroup data are available for the UK cohort. Exclusion: • Adults with established cardiovascular disease

ID	Field	Content
		• Children aged < 18 years of age • Non-UK cohorts for validation studies • People with familial hypercholesterolaemia. • People with familial clotting disorders that increase cardiovascular risk. • People with other monogenic disorders that increase cardiovascular risk. • People at high risk of CVD or abnormalities of lipid metabolism because of endocrine or other secondary disease processes other than diabetes. • People receiving renal replacement therapy.
7.	Tools (risk assessment/prediction tools)	CVD risk assessment tools validated in England and/or Wales: • 10-year risk • QRISK 2 • QRISK 3 • SCORE 2 • SCORE 2 – OP • AHA/ASCVD risk engine • LIFE-CVD • PRIMROSE (BMI model and lipid model) • CCRISK • CRISK • Lifetime risk • QRISK lifetime • AHA/ASCVD risk engine • LIFE-CVD • 10-year and lifetime risk tools are separate strata and not to be compared head-to-head.
8.	Target condition	Overall CVD events, including: • All-cause mortality • CV mortality

ID	Field	Content
		• Non-fatal myocardial infarction • Non-fatal stroke
9.	Types of study to be included	Inclusion: • Internal or external validation studies (prospective or retrospective cohort studies or systematic review of these). • External validation studies (tested on a different study sample to the derivation sample) are preferred, although internal derivation studies (where the validation sample are different, but still drawn from the identical population to the derivation sample) will also be included. • Published NMAs and IPDs will be considered for inclusion. • Exclusion: • Case-control studies • Cross-sectional studies
10.	Other exclusion criteria	Non-English language studies.
11.	Context	The process of atherosclerosis that leads to CVD is difficult to diagnose easily, prior to the occurrence of significant clinical events such as CVD-related death, myocardial infarction or stroke. Epidemiological studies, such as the Framingham cohort studies in the USA, have identified a large number of CVD risk factors which can be divided into the principal non-modifiable CVD risk factors, such as age and gender, and modifiable risk factors, including smoking, blood pressure, presence of diabetes and ratio of total cholesterol to HDL cholesterol. The significance of these principal risk factors has been confirmed in worldwide epidemiological cohort studies, including in the UK. The cohort studies can be used to devise risk tools that calculate the percentage risk of a CVD event prospectively over a defined period of time, for example a decade. The 2014 version of NICE CG181 recommends (1.1.8) using the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. Since this guideline was published, QRISK has been updated to its third version, QRISK3, and evidence has emerged on the use of lifetime risk measures in addition to 10-year risk.

ID	Field	Content
		This review will aim to update the current evidence review and potentially change current recommendations. For example, the inclusion of additional clinical variables in QRISK3 has potential value to identify those at most risk of heart disease and stroke, beyond QRISK2, and may perform better for people with type 1 diabetes, chronic kidney disease, and severe mental illness.
12.	Primary outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Accuracy of estimation of CVD events as 10-year or lifetime risk measured as follows: Discrimination: • Area under the ROC curve (c-index, c-statistic). • Classification measures at 5%, 7.5%, 10%, 15% and 20% predicted risk thresholds: sensitivity, and specificity. • D statistic • Calibration: • Calibration plots • Predicted risk versus observed risk • Statistical tests for agreement between predicted and observed events (E.g. Hosmer-Lemeshow or Nam–D'Agostino statistics) • Reclassification / revalidation • net classification improvement • integrated discrimination index
13.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

ID	Field	Content
		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments • Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the PROBAST checklist as described in Developing NICE guidelines: the manual.
15.	Strategy for data synthesis	Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG181. Analyses with and without accounting for competing risks will be included. Discrimination, calibration, and re-classification data will be reported separately. If appropriate, C statistic and net reclassification index data will be meta-analysed (if at least 3 studies reporting data at the same threshold) in RevMan. Summary outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Sensitivity and specificity data will be meta-analysed using a Bayesian approach (using WinBugs software) if 3 or more data points are found.

ID	Field	Content	
		Heterogeneity between the studies in effect measures will be assessed using visual inspection of the sensitivity/specificity or net reclassification index RevMan 5 plots, or summary area under the curve (AUC) plots. If data are pooled, an I^2 of 50-74% will be deemed serious inconsistency and an I^2 of 75% or above very serious inconsistency. If meta-analysis is not possible, data will be presented and quality assessed as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
16.	Analysis of sub-groups (do the tools work differently in these groups)	Subgroups that will be investigated: presence of type 1 diabetes presence of CKD (eGFR <60 ml/min/1.73 m2 and/or albuminuria)	
17.	Type and method of review	☐	Intervention
		☐	Diagnostic
		☒	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	21.03.2022	

ID	Field	Content		
21.	Anticipated completion date	19.04.2023		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☑
		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
23.	Named contact	5a. Named contact NICE Guideline Development Team NGC 5b Named contact e-mail CVDupdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
24.	Review team members	From the NICE Guideline Development Team NGC: • Serena Carville, Guideline lead • Eleanor Samarasekera, Senior systematic reviewer • Maheen Qureshi, Systematic reviewer • Kate Lovibond, Health economist • Lina Gulhane, Information specialist		
25.	Funding sources/sponsor	This systematic review is being completed by NICE Guideline Development Team NGC.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must		

ID	Field	Content	
		declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10178	
28.	Other registration details	NA	
29.	Reference/URL for published protocol	-	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Cardiovascular disease; risk; risk tools; prediction; lipid modification.	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated

ID	Field	Content	
		☐	Discontinued
34.	Additional information	NA	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018) • International HTA database (INAHTA) – all years • Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.

Studies included in the 2014 CG181 update and published between 2007 and 2014 CG181 cut-off date (November 2013) will be reconsidered for inclusion as per this protocol. Studies identified in the update search published since 2007 will be considered for inclusions as per this protocol (some additional risk tools have been added since the 2014 update so all years were considered not just those since the search cut off from the 2014 CG181 update in line with the clinical review).

Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[17]

Inclusion and exclusion criteria

- If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.
- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

	Health economic study type: • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2007 or later but that depend on unit costs and resource data entirely or predominantly from before 2007 will be rated as 'Not applicable'. • Studies published before 2007 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

Cardiovascular risk assessment tools in adults without established cardiovascular disease

The literature searches detailed below are for the review:

What is the most accurate tool for determining 10-year and lifetime cardiovascular risk in adults without established cardiovascular disease?

They complied with the methodology outlined in Developing NICE guidelines: the manual.[17]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 12: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 9 June 2022	Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 9 June 2022	Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 6 of 12, June 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 9 June 2022	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/

4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32
34.	letter/
35.	editorial/
36.	news/
37.	exp historical article/
38.	Anecdotes as Topic/
39.	comment/
40.	case report/
41.	(letter or comment*).ti.
42.	or/34-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43

45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	limit 52 to english language
54.	(QRisk* or QDiabetes* or JBS3 or ClinRisk*).ti,ab,kf.
55.	("systematic coronary risk evaluation" or risk chart* or HeartScore*).ti,ab,kf.
56.	(SCORE adj2 chart*).ti,ab,kf.
57.	(SCORE adj3 (10 y* or 10y* or lifetime or life time)).ti,ab,kf.
58.	(risk* adj2 (lifetime or life time)).ti,ab,kf.
59.	(SCORE2 or SCORE 2).ti,ab,kf.
60.	ASCVD.ti,ab,kf.
61.	LIFE CVD.ti,ab,kf.
62.	(CCRISK or CRISK).ti,ab,kf.
63.	PRIMROSE.ti,ab,kf.
64.	or/54-63
65.	53 and 64
66.	Meta-Analysis/
67.	Meta-Analysis as Topic/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	exp Cohort studies/
78.	(cohort adj (study or studies or analys* or data)).ti,ab.
79.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
80.	or/77-79
81.	randomized controlled trial.pt.
82.	controlled clinical trial.pt.
83.	randomi#ed.ab.
84.	placebo.ab.

85.	randomly.ab.
86.	clinical trials as topic.sh.
87.	trial.ti.
88.	or/81-87
89.	65 and (76 or 80)

Embase (Ovid) search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/
23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34

36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.
39.	case report/ or case study/
40.	(letter or comment*).ti.
41.	(conference abstract or conference paper).pt.
42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to english language
55.	(QRisk* or QDiabetes* or JBS3 or ClinRisk*).ti,ab,kf.
56.	("systematic coronary risk evaluation" or risk chart* or HeartScore*).ti,ab,kf.
57.	(SCORE adj2 chart*).ti,ab,kf.
58.	(SCORE adj3 (10 y* or 10y* or lifetime or life time)).ti,ab,kf.
59.	(risk* adj2 (lifetime or life time)).ti,ab,kf.
60.	(SCORE2 or SCORE 2).ti,ab,kf.
61.	ASCVD.ti,ab,kf.
62.	LIFE CVD.ti,ab,kf.
63.	(CCRISK or CRISK).ti,ab,kf.
64.	PRIMROSE.ti,ab,kf.
65.	or/55-64
66.	54 and 65
67.	systematic review/
68.	Meta-Analysis/
69.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
70.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
71.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
72.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
73.	(search* adj4 literature).ab.
74.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
75.	cochrane.jw.

76.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
77.	or/67-76
78.	longitudinal study/
79.	retrospective study/
80.	prospective study/
81.	cohort analysis/
82.	(cohort adj (study or studies or analys* or data)).ti,ab.
83.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
84.	or/78-83
85.	66 and (77 or 84)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Cardiovascular Diseases] this term only
#2.	MeSH descriptor: [Heart Diseases] this term only
#3.	MeSH descriptor: [Myocardial Ischemia] this term only
#4.	MeSH descriptor: [Angina Pectoris] explode all trees
#5.	MeSH descriptor: [Coronary Disease] this term only
#6.	MeSH descriptor: [Coronary Artery Disease] this term only
#7.	MeSH descriptor: [Coronary Stenosis] explode all trees
#8.	MeSH descriptor: [Myocardial Infarction] this term only
#9.	MeSH descriptor: [Heart Failure] explode all trees
#10.	MeSH descriptor: [Arrhythmias, Cardiac] this term only
#11.	MeSH descriptor: [Vascular Diseases] this term only
#12.	MeSH descriptor: [Atrial Fibrillation] this term only
#13.	MeSH descriptor: [Hypertension] this term only
#14.	MeSH descriptor: [Atherosclerosis] this term only
#15.	MeSH descriptor: [Peripheral Vascular Diseases] this term only
#16.	MeSH descriptor: [Peripheral Arterial Disease] this term only
#17.	MeSH descriptor: [Arteriosclerosis] this term only
#18.	MeSH descriptor: [Cerebrovascular Disorders] this term only
#19.	MeSH descriptor: [Stroke] explode all trees
#20.	MeSH descriptor: [Brain Ischemia] explode all trees
#21.	MeSH descriptor: [Heart Arrest] explode all trees
#22.	((cardiovascular or cardio vascular) near/3 (event* or disease* or disorder*)):ti,ab,kw
#23.	((coronary or peripheral vascular or heart or peripheral arter*) near/3 (disease* or event* or disorder*)):ti,ab,kw
#24.	(MI or myocardial infarct*):ti,ab,kw
#25.	((heart or cardiopulmonary or cardiac) near/3 (death* or arrest* or attack*)):ti,ab,kw
#26.	(CVD or CHD or CAD or PAD or CVA):ti,ab,kw
#27.	(hypertension or hypertensive*):ti,ab,kw
#28.	((high or raised or elevated) near/2 (blood pressure or bp)):ti,ab,kw

#29.	(atheroscleros* or arterioscleros*):ti,ab,kw
#30.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke):ti,ab,kw
#31.	(ACS or angina or acute coronary syndrome*):ti,ab,kw
#32.	(AF or atrial fibrillation):ti,ab,kw
#33.	((chronic or congestive) near/2 heart failure):ti,ab,kw
#34.	(or #1-#33)
#35.	conference:pt or (clinicaltrials or trialsearch):so
#36.	#34 not #35
#37.	(QRisk* or QDiabetes* or JBS3 or ClinRisk*):ti,ab
#38.	("systematic coronary risk evaluation" or risk chart* or HeartScore*):ti,ab
#39.	(SCORE near/2 chart*):ti,ab
#40.	(SCORE near/3 ("10 y*" or "10y*" or lifetime or "life time")):ti,ab
#41.	(risk* near/2 (lifetime or life time)):ti,ab
#42.	("SCORE2" or "SCORE 2"):ti,ab
#43.	ASCVD:ti,ab
#44.	LIFE CVD:ti,ab
#45.	(CCRISK or CRISK):ti,ab
#46.	PRIMROSE:ti,ab
#47.	18-#46
#48.	#36 and #47

Epistemonikos search terms

1.	(title:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*") OR abstract:(Cardiovascular Disease* OR "Heart disease*" OR "Myocardial Ischemia" OR "Angina Pectoris" OR "Coronary Disease*" OR "Coronary Artery Disease*" OR "Coronary Stenosis" OR "Myocardial Infarction*" OR "Heart Failure" OR Arrhythmia* OR "Atrial fibrillation" OR "Vascular Disease*" OR Hypertension OR Atherosclerosis OR "Peripheral Arterial Disease*" OR "Peripheral Vascular Disease*" OR Arteriosclerosis OR "Cerebrovascular Disorder*" OR Stroke OR strokes OR "brain ischemia" OR "heart arrest*" OR "heart attack*" OR "cardiac arrest*" OR "cardiac attack*" OR "heart failure*" OR "high blood pressure" OR angina OR "acute coronary syndrome*")) AND (title:((title:(QRisk1 OR QRisk2 OR QRisk3 OR QDiabetes OR JBS3 OR ClinRisk OR SCORE2 OR HEARTscore OR ASCVD OR LIFE CVD OR CCRISK OR CRISK OR PRIMROSE) OR abstract:(QRisk1 OR QRisk2 OR QRisk3 OR QDiabetes OR JBS3 OR ClinRisk OR SCORE2 OR HEARTscore OR ASCVD OR "LIFE CVD" OR CCRISK OR CRISK OR PRIMROSE))) OR abstract:((title:(QRisk1 OR QRisk2 OR QRisk3 OR QDiabetes OR JBS3 OR ClinRisk OR SCORE2 OR HEARTscore OR ASCVD OR LIFE CVD OR CCRISK OR CRISK OR PRIMROSE) OR abstract:(QRisk1 OR QRisk2 OR QRisk3 OR QDiabetes OR

	JBS3 OR ClinRisk OR SCORE2 OR HEARTscore OR ASCVD OR "LIFE CVD" OR CCRISK OR CRISK OR PRIMROSE))))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting literature searches as below. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 13 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 13 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 13 June 2022	English language

Medline (Ovid) search terms

1.	*Cardiovascular Diseases/
2.	*Heart diseases/
3.	*Myocardial Ischemia/

4.	exp *Angina Pectoris/
5.	*Coronary Disease/
6.	*Coronary Artery Disease/
7.	exp *Coronary Stenosis/
8.	*Myocardial Infarction/
9.	exp *Heart Failure/
10.	*Arrhythmias, cardiac/ or *Atrial fibrillation/
11.	*Vascular Diseases/
12.	*Hypertension/
13.	*Atherosclerosis/
14.	*Peripheral Arterial Disease/
15.	*Peripheral Vascular Diseases/
16.	*Arteriosclerosis/
17.	*Cerebrovascular Disorders/
18.	exp *Stroke/
19.	exp *brain ischemia/
20.	exp *heart arrest/
21.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
22.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
23.	(MI or myocardial infarct*).ti,ab.
24.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
25.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
26.	(hypertension or hypertensive*).ti,ab.
27.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
28.	(atheroscleros* or arterioscleros*).ti,ab.
29.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
30.	(ACS or angina or acute coronary syndrome*).ti,ab.
31.	(AF or atrial fibrillation).ti,ab.
32.	((chronic or congestive) adj2 heart failure).ti,ab.
33.	or/1-32
34.	letter/
35.	editorial/
36.	news/
37.	exp historical article/
38.	Anecdotes as Topic/
39.	comment/
40.	case report/
41.	(letter or comment*).ti.
42.	or/34-41
43.	randomized controlled trial/ or random*.ti,ab.

44.	42 not 43
45.	animals/ not humans/
46.	exp Animals, Laboratory/
47.	exp Animal Experimentation/
48.	exp Models, Animal/
49.	exp Rodentia/
50.	(rat or rats or mouse or mice or rodent*).ti.
51.	or/44-50
52.	33 not 51
53.	limit 52 to english language
54.	(QRisk* or QDiabetes* or JBS3 or ClinRisk*).ti,ab,kf.
55.	("systematic coronary risk evaluation" or risk chart* or HeartScore*).ti,ab,kf.
56.	(SCORE adj2 chart*).ti,ab,kf.
57.	(SCORE adj3 (10 y* or 10y* or lifetime or life time)).ti,ab,kf.
58.	(risk* adj2 (lifetime or life time)).ti,ab,kf.
59.	(SCORE2 or SCORE 2).ti,ab,kf.
60.	ASCVD.ti,ab,kf.
61.	LIFE CVD.ti,ab,kf.
62.	(CCRISK or CRISK).ti,ab,kf.
63.	PRIMROSE.ti,ab,kf.
64.	or/54-63
65.	53 and 64
66.	economics/
67.	value of life/
68.	exp "costs and cost analysis"/
69.	exp Economics, Hospital/
70.	exp Economics, medical/
71.	Economics, nursing/
72.	economics, pharmaceutical/
73.	exp "Fees and Charges"/
74.	exp budgets/
75.	budget*.ti,ab.
76.	cost*.ti.
77.	(economic* or pharmaco?economic*).ti.
78.	(price* or pricing*).ti,ab.
79.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
80.	(financ* or fee or fees).ti,ab.
81.	(value adj2 (money or monetary)).ti,ab.
82.	or/66-81
83.	65 and 82

84.	limit 83 to yr="2014 -Current"

Embase (Ovid) search terms

1.	*cardiovascular disease/
2.	*coronary artery disease/
3.	*vascular disease/
4.	*coronary artery atherosclerosis/
5.	*peripheral vascular disease/
6.	*peripheral occlusive artery disease/
7.	*arteriosclerosis/
8.	*ischemic heart disease/
9.	exp *Stroke/ or *stroke patient/
10.	*coronary artery obstruction/
11.	*hypertension/
12.	*heart disease/
13.	*heart arrhythmia/
14.	*heart fibrillation/ or *heart atrium fibrillation/
15.	*heart failure/ or exp *congestive heart failure/
16.	*acute coronary syndrome/ or exp *angina pectoris/ or *heart infarction/
17.	*cerebrovascular disease/
18.	*cerebrovascular accident/
19.	exp *brain ischemia/
20.	exp *heart arrest/ or *heart death/
21.	*brain infarction/
22.	*atherosclerosis/
23.	((cardiovascular or cardio vascular) adj3 (event* or disease* or disorder*)).ti,ab.
24.	((coronary or peripheral vascular or heart or peripheral arter*) adj3 (disease* or event* or disorder*)).ti,ab.
25.	(MI or myocardial infarct*).ti,ab.
26.	((heart or cardiopulmonary or cardiac) adj3 (death* or arrest* or attack*)).ti,ab.
27.	(CVD or CHD or CAD or PAD or CVA).ti,ab.
28.	(hypertension or hypertensive*).ti,ab.
29.	((high or raised or elevated) adj2 (blood pressure or bp)).ti,ab.
30.	(atheroscleros* or arterioscleros*).ti,ab.
31.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke).ti,ab.
32.	(ACS or angina or acute coronary syndrome*).ti,ab.
33.	(AF or atrial fibrillation).ti,ab.
34.	((chronic or congestive) adj2 heart failure).ti,ab.
35.	or/1-34
36.	letter.pt. or letter/
37.	note.pt.
38.	editorial.pt.

39.	case report/ or case study/
40.	(letter or comment*).ti.
41.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
42.	or/36-41
43.	randomized controlled trial/ or random*.ti,ab.
44.	42 not 43
45.	animal/ not human/
46.	nonhuman/
47.	exp Animal Experiment/
48.	exp Experimental Animal/
49.	animal model/
50.	exp Rodent/
51.	(rat or rats or mouse or mice or rodent*).ti.
52.	or/44-51
53.	35 not 52
54.	limit 53 to english language
55.	(QRisk* or QDiabetes* or JBS3 or ClinRisk*).ti,ab,kf.
56.	("systematic coronary risk evaluation" or risk chart* or HeartScore*).ti,ab,kf.
57.	(SCORE adj2 chart*).ti,ab,kf.
58.	(SCORE adj3 (10 y* or 10y* or lifetime or life time)).ti,ab,kf.
59.	(risk* adj2 (lifetime or life time)).ti,ab,kf.
60.	(SCORE2 or SCORE 2).ti,ab,kf.
61.	ASCVD.ti,ab,kf.
62.	LIFE CVD.ti,ab,kf.
63.	(CCRISK or CRISK).ti,ab,kf.
64.	PRIMROSE.ti,ab,kf.
65.	or/55-64
66.	54 and 65
67.	health economics/
68.	exp economic evaluation/
69.	exp health care cost/
70.	exp fee/
71.	budget/
72.	funding/
73.	budget*.ti,ab.
74.	cost*.ti.
75.	(economic* or pharmaco?economic*).ti.
76.	(price* or pricing*).ti,ab.
77.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
78.	(financ* or fee or fees).ti,ab.
79.	(value adj2 (money or monetary)).ti,ab.

80.	or/67-79
81.	66 and 80
82.	limit 81 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Cardiovascular Diseases
#2.	MeSH DESCRIPTOR Heart diseases
#3.	MeSH DESCRIPTOR Myocardial Ischemia
#4.	MeSH DESCRIPTOR Angina Pectoris EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Coronary Disease
#6.	MeSH DESCRIPTOR Coronary Artery Disease
#7.	MeSH DESCRIPTOR Coronary Stenosis EXPLODE ALL TREES
#8.	MeSH DESCRIPTOR Myocardial Infarction
#9.	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES
#10.	MeSH DESCRIPTOR Arrhythmias, cardiac
#11.	MeSH DESCRIPTOR Atrial fibrillation
#12.	MeSH DESCRIPTOR Vascular Diseases
#13.	MeSH DESCRIPTOR Hypertension
#14.	MeSH DESCRIPTOR Atherosclerosis
#15.	MeSH DESCRIPTOR Peripheral Arterial Disease
#16.	MeSH DESCRIPTOR Peripheral Vascular Diseases
#17.	MeSH DESCRIPTOR Arteriosclerosis
#18.	MeSH DESCRIPTOR Cerebrovascular Disorders
#19.	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES
#20.	MeSH DESCRIPTOR brain ischemia EXPLODE ALL TREES
#21.	MeSH DESCRIPTOR heart arrest EXPLODE ALL TREES
#22.	(cardiovascular or cardio vascular) AND (event* or disease* or disorder*)
#23.	(coronary or peripheral vascular or heart or peripheral arter*) AND (disease* or event* or disorder*)
#24.	(MI or myocardial infarct*)
#25.	(heart or cardiopulmonary or cardiac) AND (death* or arrest* or attack*)
#26.	(CVD or CHD or CAD or PAD or CVA)
#27.	(hypertension or hypertensive*)
#28.	(high or raised or elevated) AND (blood pressure or bp)
#29.	(atheroscleros* or arterioscleros*)
#30.	(cerebrovascular accident* or cerebrovascular disorder* or strokes or stroke)
#31.	(ACS or angina or acute coronary syndrome*)
#32.	(AF or atrial fibrillation)
#33.	(chronic or congestive) AND (heart failure)
#34.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33

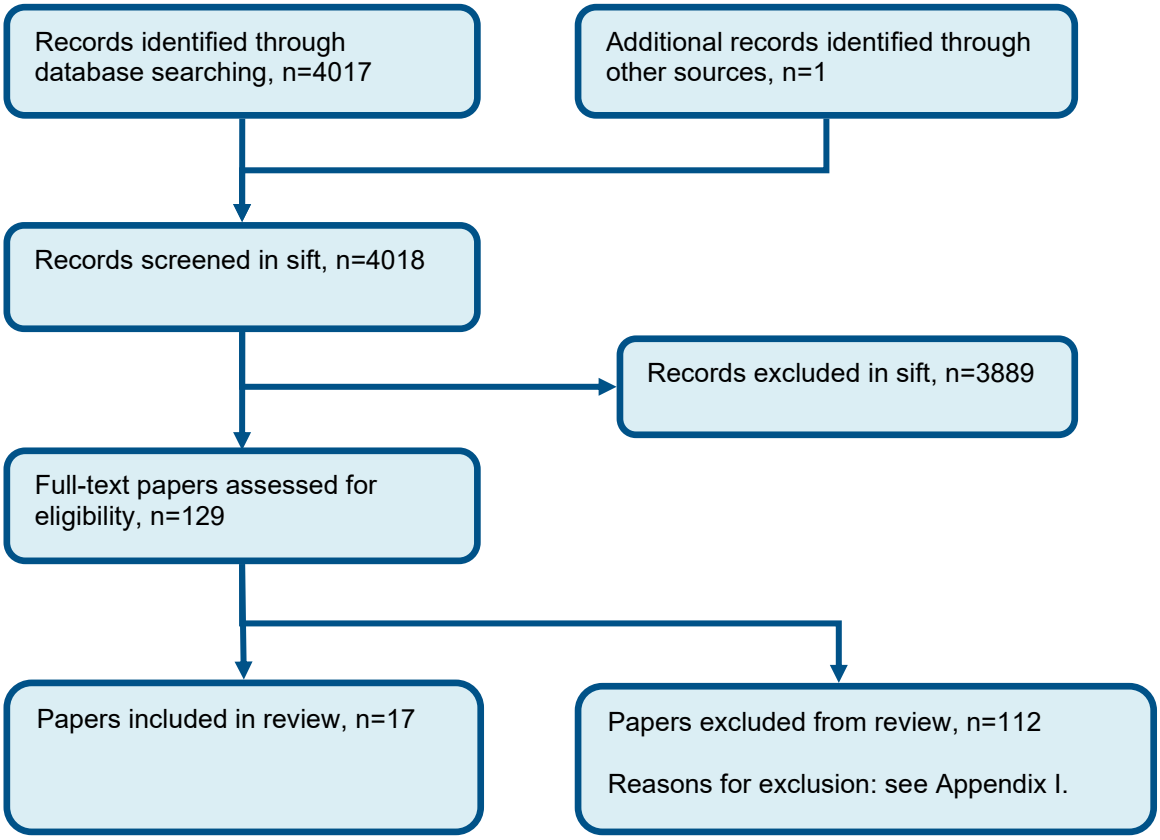
#35.	(QRisk* or QDiabetes* or JBS3 or ClinRisk*)
#36.	("systematic coronary risk evaluation" or risk chart* or HeartScore*)
#37.	(SCORE and chart*)
#38.	(SCORE and (10 y* or 10y* or lifetime or life time))
#39.	(risk* and (lifetime or life time))
#40.	(SCORE2 or SCORE 2)
#41.	(ASCVD)
#42.	(LIFE CVD)
#43.	(CCRISK or CRISK)
#44.	(PRIMROSE)
#45.	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
#46.	#34 AND #45
#47.	* IN NHSEED
#48.	#46 AND #47
#49.	* IN HTA
#50.	#46 AND #49

INAHTA search terms

1.	("Cardiovascular Diseases"[mhe]) AND ((QRisk* or QDiabetes* or JBS3 or ClinRisk* or "systematic coronary risk evaluation" or "risk chart*" or HeartScore*) OR (SCORE and chart*) OR (SCORE and ("10 y*" or "10y*" or lifetime or "life time")) OR (risk* and (lifetime or life time)) OR ("SCORE2" or "SCORE 2" or ASCVD or "LIFE CVD" or CCRISK or CRISK or PRIMROSE))

Appendix C Prognostic evidence study selection

Figure 14: Flow chart of clinical study selection for the review of CVD risk assessment tools



Appendix D Prognostic evidence

D.1 Risk factors and variables included in the risk assessment tools

Table 13: Risk factors and variables included in QRISK tools

Risk factors/variables	QRISK2	QRISK3	QRISK lifetime
Self-assigned ethnicity	White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed	White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed	White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed
Age	Years	Years	Years
Sex	Male/Female	Male/Female	Male/Female
Smoking status	Non-smoker, ex-smoker, light smoker (less than 10), moderate smoker (10-19), heavy smoker (20 or more)	Non-smoker, ex-smoker, light smoker (less than 10), moderate smoker (10-19), heavy smoker (20 or more)	Non-smoker, ex-smoker, light smoker (less than 10), moderate smoker (10-19), heavy smoker (20 or more)
Systolic blood pressure	Continuous (mmHg)	Continuous (mmHg)	Continuous (mmHg)
Total serum cholesterol and high-density lipoprotein cholesterol	Ratio of total to HDL-C; continuous	Ratio of total to HDL-C; continuous	Ratio of total to HDL-C; continuous
Body mass index (BMI)	Continuous	Continuous	Continuous
Family history of coronary heart disease in first degree relative under 60 years	Yes/No	Yes/No	Yes/No
Townsend deprivation score (output area level 2001 census data evaluated as a continuous variable)	Postcode	Postcode	Postcode
Treated hypertension	Yes/No	Yes/No	Yes/No
Rheumatoid arthritis	Yes/No	Yes/No	Yes/No
Atrial fibrillation	Yes/No	Yes/No	Yes/No
Type 1 diabetes	Yes/No	Yes/No	–

Risk factors/variables	QRISK2	QRISK3	QRISK lifetime
Type 2 diabetes	Yes/No	Yes/No	Yes/No
Duration of diabetes	–	–	–
Chronic kidney disease (stage 3, 4, or 5)	Yes/No	Yes/No	Yes/No
Had a heart attack, angina, stroke or TIA?	–	–	Yes/No
Measure of systolic blood pressure variability	–	Standard deviation of repeated measures	–
Migraine	–	Yes/No	–
Corticosteroids	–	Yes/No	–
Systemic lupus erythematosus (SLE)	–	Yes/No	–
Atypical antipsychotics	–	Yes/No	–
Severe mental illness	–	Yes/No	–
HIV/AIDs	–	-	–
Erectile dysfunction (men)	–	Yes/No	–

Table 14: Risk factors and variables included in CRISK tools

Risk factors/variables	CRISK (covariates the same as QRISK3 with Fine-Gray competing risk modelling)	CRISK-CCI (covariates the same as QRISK3 with the addition of Charlson comorbidity score and with Fine-Gray competing risk modelling)
Self-assigned ethnicity	White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed	White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed
Age	Years	Years
Sex	Male/Female	Male/Female
Smoking status	Non-smoker, ex-smoker, light smoker (less than 10), moderate smoker (10-19), heavy smoker (20 or more)	Non-smoker, ex-smoker, light smoker (less than 10), moderate smoker (10-19), heavy smoker (20 or more)
Systolic blood pressure	Continuous (mmHg)	Continuous (mmHg)

Risk factors/variables	CRISK (covariates the same as QRISK3 with Fine-Gray competing risk modelling)	CRISK-CCI (covariates the same as QRISK3 with the addition of Charlson comorbidity score and with Fine-Gray competing risk modelling)
Total serum cholesterol and high-density lipoprotein cholesterol	Ratio of total to HDL-C; continuous	Ratio of total to HDL-C; continuous
Body mass index (BMI)	Continuous	Continuous
Family history of coronary heart disease in first degree relative under 60 years	Yes/No	Yes/No
Townsend deprivation score (output area level 2001 census data evaluated as a continuous variable)	Postcode	Postcode
Treated hypertension	Yes/No	Yes/No
Rheumatoid arthritis	Yes/No	Yes/No
Atrial fibrillation	Yes/No	Yes/No
Type 1 diabetes	Yes/No	Yes/No
Type 2 diabetes	Yes/No	Yes/No
Duration of diabetes	–	–
Chronic kidney disease (stage 3, 4, or 5)	Yes/No	Yes/No
Had a heart attack, angina, stroke or TIA?	–	–
Measure of systolic blood pressure variability	Standard deviation of repeated measures	Standard deviation of repeated measures
Migraine	Yes/No	Yes/No
Corticosteroids	Yes/No	Yes/No
Systemic lupus erythematosus (SLE)	Yes/No	Yes/No
Atypical antipsychotics	Yes/No	Yes/No
Severe mental illness	Yes/No	Yes/No
HIV/AIDs	Yes/No	Yes/No

Risk factors/variables	CRISK (covariates the same as QRISK3 with Fine-Gray competing risk modelling)	CRISK-CCI (covariates the same as QRISK3 with the addition of Charlson comorbidity score and with Fine-Gray competing risk modelling)
Erectile dysfunction (men)	Yes/No	Yes/No

Table 15: Risk factors and variables included in ASCVD and LIFE-CVD tools

Risk factors/variables	ASCVD	Revised ASCVD	LIFE-CVD
Self-assigned ethnicity	White, African American, Other	White, African American, Other	–
Age	Years	Years	Years
Sex	Male/Female	Male/Female	Male/Female
Smoking status	Yes/no	Current, former, and never	Current, former, and never
Systolic blood pressure	Continuous (mmHg)	Continuous (mmHg)	Continuous (mmHg)
Diastolic blood pressure	–	Continuous (mmHg)	–
On a statin	–	Yes/No	–
On aspirin	–	Yes/No	–
Total serum cholesterol and high-density lipoprotein cholesterol	Total and high-density lipoprotein cholesterol, continuous	Total and high-density lipoprotein cholesterol, continuous	Non-high density lipoprotein cholesterol, continuous
Body mass index (BMI)	–	–	Continuous
Family history of coronary heart disease in first degree relative under 60 years	–		Family history of myocardial infarction Yes/No
Social deprivation score	–	–	–
Treated hypertension	Yes/No	Yes/No	–
Rheumatoid arthritis	–	–	–
Atrial fibrillation	–	–	–
Type 1 diabetes	History of diabetes: Yes/No	History of diabetes: Yes/No	History of diabetes: Yes/No
Type 2 diabetes			
Duration of diabetes	–	–	–
Chronic kidney disease (stage 3, 4, or 5)	–	–	–

Risk factors/variables	ASCVD	Revised ASCVD	LIFE-CVD
Measure of systolic blood pressure variability	–	–	–
Migraine	–	–	–
Corticosteroids	–	–	–
Systemic lupus erythematosus (SLE)	–	–	–
Atypical antipsychotics	–	–	–
Severe mental illness	–	–	–
HIV/AIDs	–	–	–
Erectile dysfunction (men)	–	–	–

Table 16: Risk factors and variables included in SCORE2 and SCORE2-OP tools

Risk factors/variables	SCORE2-OP (estimating incident cardiovascular event risk in older persons in four geographical risk regions)	SCORE2 (provides risk estimates for the combined outcome of fatal and non-fatal CVD events in Europe)
Self-assigned ethnicity	–	–
Age	Years	Years
Sex	Male/Female	Male/Female
Smoking status	Current	Current
Systolic blood pressure	Continuous (mmHg)	Continuous (mmHg)
Total serum cholesterol and high-density lipoprotein cholesterol	Total- and HDL-cholesterol	Total- and HDL-cholesterol
Body mass index (BMI)	–	–
Family history of coronary heart disease in first degree relative under 60 years	–	–
Social deprivation score	–	–
Treated hypertension	–	–

Risk factors/variables	SCORE2-OP (estimating incident cardiovascular event risk in older persons in four geographical risk regions)	SCORE2 (provides risk estimates for the combined outcome of fatal and non-fatal CVD events in Europe)
Rheumatoid arthritis	–	–
Chronic kidney disease	–	–
Atrial fibrillation	–	–
Type 1 diabetes	Yes/No	Yes/No
Type 2 diabetes	Yes/No	Yes/No
Duration of diabetes	–	–
Chronic kidney disease (stage 3, 4, or 5)	–	–
Measure of systolic blood pressure variability	–	–
Migraine	–	–
Corticosteroids	–	–
Systemic lupus erythematosus (SLE),	–	–
Atypical antipsychotics	–	–
Severe mental illness	–	–
HIV/AIDs	–	–
Erectile dysfunction (men)	–	–

Table 17: Risk factors and variables included in PRIMROSE tools

Risk factors/variables	PRIMROSE BMI	PRIMROSE lipid
Self-assigned ethnicity	–	–
Age	Years	Years
Sex	Male/Female	Male/Female
Smoking status	Smoking history	Smoking history
Systolic blood pressure	Continuous (mmHg)	Continuous (mmHg)

Risk factors/variables	PRIMROSE BMI	PRIMROSE lipid
Total serum cholesterol and high-density lipoprotein cholesterol	–	Ratio of total to HDL-C; continuous
Body mass index (BMI)	Continuous	–
Family history of coronary heart disease in first degree relative under 60 years	–	–
Townsend deprivation score (quintile of score, 1 being least deprived, 5 being most deprived)	Quintile	Quintile
Treated hypertension	–	–
Rheumatoid arthritis	–	–
Atrial fibrillation	–	–
Type 1 diabetes	Yes/No	Yes/No
Type 2 diabetes	Yes/No	Yes/No
Duration of diabetes	–	–
Chronic kidney disease (stage 3, 4, or 5)	–	–
Had a heart attack, angina, stroke or TIA?	–	–
Measure of systolic blood pressure variability	–	–
Migraine	–	–
Corticosteroids	–	–
Systemic lupus erythematosus (SLE),	–	–
First generation antipsychotics at baseline	Yes/No	–
Second generation antipsychotics at baseline	Yes/No	Yes/No
Antidepressant use	Yes/No	Yes/No
Severe mental illness	Yes/No	Yes/No
Heavy alcohol use	Yes/No	Yes/No
HIV/AIDs	–	–
Erectile dysfunction (men)	–	–

D.2 Evidence tables from the 2014 version of CG181

Collins 2012[339]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Collins 2012B. Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2. BMJ 2012. Funding: this research received no specific grant from any	Cohort study. THIN database. 364 general practices in the UK.	n=2,084,445 Inclusion criteria: age 30-85. Exclusion criteria: patients who had a previous diagnosis of cardiovascular disease, were registered for less than 12 months with the general practice, had invalid dates, had missing Townsend scores (social deprivation), or were	Patient registered from 27 June 1994 and 30 June 2008. Baseline characteristics: see Table 18.	- QRISK2 - modified Framingham tool	First diagnosis of CVD (myocardial infarction, angina, CHD, stroke, transient ischaemic attacks). n=93,564 (42,224 in women)	Median 5.75 years (interquartile range 2.48-8.49)	QRISK2 (women)		Method of imputing missing values (smoking status and BMI): multiple imputation using all predictors plus the outcome variable. This involves creating multiple copies of the data and imputing the missing values for each dataset with sensible values randomly
							R^2	48.3 (47.9–48.7)	
							D statistic	1.98 (1.96–1.99)	
							ROC statistic	0.835 (0.834–0.837)	
							QRISK2 (men)		
							R^2	41.6 (41.2–42.0)	
							D statistic	1.73 (1.71–1.75)	
							ROC statistic	0.809 (0.807–0.811)	
							Modified Framingham (women)		
							R^2	34.2 (33.6–34.9)	

funding agency in the public, commercial, or not for profit sectors		prescribed statins at baseline.					D statistic	1.48 (1.46–1.50)	selected from their predicted distribution. Ten imputed datasets were generated and we combined the results from analyses on each of the imputed values using Rubin's rules to produce estimates and confidence intervals that incorporate the uncertainty of imputed values.
							ROC statistic	0.776 (0.773–0.779)	
							Modified Framingham (men)		
							R^2	29.2 (28.7–29.7)	
							D statistic	1.31 (1.30–1.33)	
							ROC statistic	0.750 (0.747–0.752)	

Table 18: Collins 2012[339] baseline characteristics of patients aged 30 to 84 years in The Health Improvement Network database. Values are numbers (percentages) of patients unless stated otherwise

Characteristics	Women (n=1 066 127)	Men (n=1 018 318)
Mean (SD) age (years)	49.6 (14.7)	47.7 (13.4)
Mean (SD) body mass index (mg/kg2)	26.0 (5)	26.5 (4.1)

Characteristics	Women (n=1 066 127)	Men (n=1 018 318)
Body mass index not recorded	220 012 (20.6)	300 787 (29.5)
Mean (SD) systolic blood pressure (mm Hg)	130.5 (21.3)	134.3 (19.0)
Systolic blood pressure not recorded	84 802 (8.0)	183 852 (18.1)
Mean (SD) total cholesterol: HDL cholesterol ratio	3.9 (1.2)	4.5 (1.4)
Total cholesterol: HDL cholesterol ratio not recorded	830 407 (77.9)	791 281 (77.7)
Smoking status:		
Non-smoker	608 942 (57.1)	440 245 (43.2)
Former smoker	154 544 (14.5)	180 952 (17.8)
Current smoker (cigarettes/day):		
Light (<10)	58 254 (5.5)	56 176 (5.5)
Moderate (10-19)	96 970 (9.1)	92 200 (9.1)
Heavy (≥20)	69 517 (6.5)	102 955 (10.1)
Amount not recorded	11 760 (1.1)	29 072 (2.9)
Smoking status not recorded	66 140 (6.2)	116 718 (11.5)
Ethnic group:		
White/not recorded	1 041 209 (97.7)	994 798 (97.7)
Indian	5793 (0.5)	5907 (0.6)
Pakistani	1648 (0.2)	1786 (0.2)
Bangladeshi	520 (0.1)	708 (0.1)
Other Asian	2887 (0.3)	2774 (0.3)
Black Caribbean	2893 (0.3)	2238 (0.2)
Black African	4422 (0.4)	3900 (0.4)
Chinese	1142 (0.1)	848 (0.1)
Other, including mixed race	5613 (0.5)	5359 (0.5)
Clinical condition:		
Treated hypertension	68 061 (6.4)	45 079 (4.4)
Type 2 diabetes	18 295 (1.7)	22 056 (2.2)
Family history of early coronary heart disease	46 974 (4.4)	38 491 (3.8)

Characteristics	Women (n=1 066 127)	Men (n=1 018 318)
Atrial fibrillation	6276 (0.6)	7474 (0.7)
Chronic renal disease	1579 (0.15)	1467 (0.1)
Cardiovascular disease*	42 224	51 340
Person years of observation	6 159 929	5 702 452

**Cardiovascular disease events before death and deaths due to cardiovascular disease*

Table 19: Hippisley-Cox 2008[657]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures	Effect sizes	Comments
Hippisley-Cox 2008. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ 2008. Funding: No external funding. The authors	Cohort study. QRESEARCH database. 531 practices in England and Wales. Derivation (2/3 of practices) and internal validation (1/3 of practices) of QRISK2.	n=2,285,815 Inclusion criteria: age 35-74 at study entry. Exclusion criteria: patients with a prior recorded diagnosis of cardiovascular or cerebrovascular disease, temporary residents, patients with interrupted periods of registration	Patients registered from 1 Jan 1993 and 31 March 2008. Baseline characteristics: see Table 20	- QRISK2 - NICE-Framingham (validation cohort) See Table 21 for adjusted hazard ratios for QRISK2 model.	First recorded diagnosis of CVD: coronary heart disease (angina and myocardial infarction), stroke, or transient ischaemic attacks in the term cardiovascular disease but not peripheral vascular disease. n=96,709 (41,042 in women)	Adequate: time to event	QRISK2 (women)		Method of imputing missing values: assumed that the absence of a recorded diagnosis of diabetes or family history is equivalent to the person not having that factor; where ethnicity was not recorded, the person
							R^2	43.47 (42.78–44.16)	
							D statistic	1.795 (1.769–1.820)	
							ROC statistic	0.817 (0.814–0.820)	
							Brier score	0.086 (0.083–0.089)	
							QRISK2 (men)		
							R^2	38.38 (37.75–39.01)	
							D statistic	1.615 (1.594–1.637)	

were funded as part of their clinical or academic positions and meeting expenses were met by the University of Nottingham	UK	with the practice, those who did not have a valid Townsend deprivation score and those who were taking statins at baseline.					ROC statistic	0.792 (0.789–0.794)	was included on the white ethnic group.
							Brier score	0.136 (0.134–0.139)	
							Modified Framingham (women)		
							R^2	38.87 (38.12–39.62)	
							D statistic	1.632 (1.606–1.658)	
							ROC statistic	0.800 (0.797–0.803)	
							Brier score	0.093 (0.090–0.096)	
							Modified Framingham (men)		
							R^2	34.78 (34.12–35.45)	
							D statistic	1.495 (1.473–1.517)	
							ROC statistic	0.779 (0.776–0.782)	
							Brier score	0.177 (0.174–0.180)	

Table 20: Hippisley-Cox 2008[657]; baseline characteristics

	Derivation cohort		Validation cohort	
	No (%) of women	No (%) of men	No (%) of women	No (%) of men
No of patients	773 291	762 292	375 763	374 469
Total person years observation	5 645 104	5 280 571	2 594 842	2 470 729
Median age (IQR)	49 (41-60)	48 (40-58)	49 (41-59)	47 (40-57)
Ethnicity:				
White or not recorded	752 241 (97.3)	743 159 (97.5)	363 516 (96.7)	363 097 (97.0)
Indian	3635 (0.47)	3693 (0.48)	2241 (0.60)	2200 (0.59)
Pakistani	2035 (0.26)	2033 (0.27)	1114 (0.30)	1246 (0.33)
Bangladeshi	1213 (0.26)	1269 (0.17)	611 (0.16)	723 (0.19)
Other Asian	1802 (0.16)	1422 (0.19)	1086 (0.29)	988 (0.26)
Black Caribbean	3928 (0.51)	3109 (0.41)	1870 (0.50)	1495 (0.40)
Black African	3655 (0.47)	3316 (0.44)	2423 (0.64)	2201 (0.59)
Chinese	1128 (0.15)	859 (0.11)	675 (0.18)	478 (0.13)
Other including mixed	3654 (0.47)	3432 (0.45)	2227 (0.59)	2041 (0.55)
Risk factors:				
Ethnicity recorded	209 214 (27.1)	181 110 (23.8)	108 540 (28.9)	94 522 (25.2)
BMI recorded	622 741(80.5)	562 278 (73.8)	304 084 (80.9)	274 403 (73.3)
Smoking recorded	703 574 (91.0)	650 460 (85.3)	344 194 (91.6)	319 800 (85.4)
Cholesterol/HDL ratio recorded	265 402 (34.3)	247 116 (32.4)	210 638 (56.1)	125 037 (33.4)
Systolic blood pressure recorded	711 935 (92.1)	647 782 (85.0)	344 967 (91.8)	313 125 (83.6)
Complete BMI and smoking	615 301 (79.6)	554 070 (72.7)	301 016 (80.1)	270 956 (72.4)
Positive family history of CHD	97 448 (12.6)	73 740 (9.7)	48 610 (12.9)	36 761 (9.8)
Current smoker	176 202 (22.8)	208 913 (27.4)	88 672 (23.6)	104 829 (28.0)
Treated hypertension	55 069 (7.12)	42 607 (5.59)	25 953 (6.91)	20 083 (5.36)
Type 2 diabetes	13 127 (1.70)	17 107 (2.24)	6186 (1.65)	8179 (2.18)
Rheumatoid arthritis	7187 (0.93)	2996 (0.39)	3310 (0.88)	1380 (0.37)
Atrial fibrillation	2692 (0.35)	1880 (0.25)	1242 (0.33)	2155 (0.58)

	Derivation cohort		Validation cohort	
	No (%) of women	No (%) of men	No (%) of women	No (%) of men
Chronic kidney disease	1227 (0.16)	1117 (0.15)	621 (0.17)	498 (0.13

IQR=interquartile range; BMI=body mass index; HDL=high density lipoprotein cholesterol; CHD=coronary heart disease.

Table 21: Hippisley-Cox 2008[657]; adjusted hazard ratios (95% CI) for cardiovascular disease for QRISK2 model in derivation cohort

	Women	Men
White/not recorded	1	1
Indian	1.43 (1.24 to 1.65)	1.45 (1.29 to 1.63)
Pakistani	1.80 (1.5 to 2.17)	1.97 (1.70 to 2.29)
Bangladeshi	1.35 (1.06 to 1.72)	1.67 (1.40 to 2.01)
Other Asian	1.15 (0.86 to 1.54)	1.37 (1.09 to 1.72)
Black Caribbean	1.08 (0.94 to 1.24)	0.62 (0.53 to 0.73)
Black African	0.58 (0.42 to 0.82)	0.63 (0.47 to 0.85)
Chinese	0.69 (0.44 to 1.10)	0.51 (0.32 to 0.83)
Other	1.04 (0.85 to 1.28)	0.91 (0.75 to 1.10)
Age (10% increase)*	1.66 (1.65 to 1.68)	1.59 (1.58 to 1.60)
BMI (5 unit increase)	1.08 (1.06 to 1.10)	1.09 (1.07 to 1.11)
Townsend score (5 unit increase)	1.37 (1.34 to 1.40)	1.18 (1.16 to 1.20)
Systolic blood pressure (mm Hg) (20 unit increase)	1.20 (1.18 to 1.22)	1.19 (1.17 to 1.20)
Cholesterol/HDL ratio	1.17 (1.16 to 1.18)	1.19 (1.18 to 1.20)
Family history coronary heart disease	1.99 (1.92 to 2.05)	2.14 (2.08 to 2.20)
Current smoker	1.80 (1.75 to 1.86)	1.65 (1.60 to 1.70)
Treated hypertension	1.54 (1.45 to 1.63)	1.68 (1.60 to 1.77)
Type 2 diabetes	2.54 (2.33 to 2.77)	2.20 (2.06 to 2.35)
Rheumatoid arthritis	1.50 (1.39 to 1.61)	1.38 (1.25 to 1.52)
Atrial fibrillation	3.06 (2.39 to 3.93)	2.40 (2.07 to 2.79)
Renal disease	1.70 (1.43 to 2.03)	1.75 (1.51 to 2.02)

	Women	Men
Age* BMI interaction	0.976 (0.970 to 0.982)	0.985 (0.979 to 0.991)
Age* Townsend interaction (5 unit increase in score)	0.938 (0.930 to 0.946)	0.973 (0.967 to 0.98)
Age* systolic blood pressure interaction (20 unit increase in systolic blood pressure)	0.966 (0.961 to 0.971)	0.964 (0.96 to 0.969)
Age* family history interaction	0.927 (0.914 to 0.94)	0.923 (0.912 to 0.935)
Age* smoking interaction	0.931 (0.920 to 0.943)	0.932 (0.922 to 0.942)
Age* treated hypertension interaction	0.952 (0.934 to 0.971)	0.916 (0.901 to 0.931)
Age* type 2 diabetes interaction	0.904 (0.877 to 0.931)	0.902 (0.881 to 0.924)
Age* atrial fibrillation interaction	0.858 (0.795 to 0.926)	0.893 (0.852 to 0.935)

BMI=body mass index; HDL=high density lipoprotein cholesterol.
**All age terms expressed as 10% increase in age (for example, 50 to 55 years).*

Table 22: Hippisley-Cox 2010[655]

Reference	Study type	Number of patients	Patient characteristics	Index tests (risk assessment tools)	Patient outcome/target condition	Length of follow-up	Statistical measures (10-year model)	Effect sizes	Comments
Hippisley-Cox 2010. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease:	Cohort study. QRESEARCH database. 563 practices in England and Wales. Derivation (2/3 of practices) and	n=3,601,918 Inclusion criteria: age 30-84. Exclusion criteria: patients who did not have a postcode related Townsend deprivation score, those who had been	Patient registered from 1 Jan 1994 and 30 April 2010. Baseline characteristics: see Table 23	QRISK2-2010 (lifetime risk calculator) (also compared to the modified Framingham tool in the validation cohort)	First recorded diagnosis of CVD or death. CVD includes CHD (angina and MI), stroke, or transient ischaemic attacks but not peripheral vascular disease.	Up to 16 years	QRISK2 (women)		Multiple imputation to replace missing values for systolic blood pressure, total cholesterol: HDL cholesterol ratio, smoking
							R^2	47.0 (46.5–47.5)	
							ROC statistic	0.842 (0.840–0.844)	
							QRISK2 (men)		
							R^2	43.4 (42.9–43.9)	
							ROC statistic	0.828 (0.826–0.830)	

cohort study using QResearch database. BMJ 2010. Funding: No external funding.	internal validation (1/3 of practices) of lifetime QRISK2 tool. UK	prescribed statins before the study start date, and those with pre-existing cardiovascular disease.			n=121,623 (including CVD events before death and death due to CVD) and n=148,671 deaths from other causes.			status, and BMI.

Table 23: Hippisley-Cos 2010[655]: baseline characteristics of the derivation and validation cohorts. Patients are free from cardiovascular disease and not prescribed statins at baseline. Values are numbers (percentages) of patients unless otherwise stated.

	Derivation cohort (n=2 343 759)	Validation cohort (n=1 267 159)
Women	1 189 845 (50.8)	645 012 (50.9)
Mean (SD) age (years)	48.1 (14.3)	48.0 (14.2)
Mean (SD) Townsend score	−0.2 (3.4)	−0.3 (3.5)
Smoking status:		
Non-smoker	1 176 386 (50.2)	631 545 (49.8)
Former smoker	356 697 (15.2)	193 974 (15.3)
Current smoker (amount not recorded)	99 100 (4.2)	59 178 (4.7)
Light smoker (<10 cigarettes/day)	142 369 (6.1)	71 037 (5.6)
Moderate smoker (10-19/day)	175 419 (7.5)	91 679 (7.2)
Heavy smoker (≥20/day)	136 202 (5.8)	74 056 (5.8)
Smoking status not recorded	257 586 (11.0)	145 690 (11.5)
Ethnic group:		
White or not recorded	2 229 834 (95.1)	1 219 987 (96.3)

	Derivation cohort (n=2 343 759)	Validation cohort (n=1 267 159)
Indian	22 598 (1.0)	7 577 (0.6)
Pakistani	11 137 (0.5)	3 663 (0.3)
Bangladeshi	6 432 (0.3)	2 632 (0.2)
Other Asian	12 581 (0.5)	5 032 (0.4)
Caribbean	13 454 (0.6)	4 666 (0.4)
Black African	20 801 (0.8)	9 471 (0.8)
Chinese	5 915 (0.3)	3 068 (0.2)
Other	21 007 (0.9)	11 063 (0.8)
Clinical conditions:		
Treated hypertension*	132 585 (5.7)	67 986 (5.4)
Type 2 diabetes	40 504 (1.7)	20 868 (1.7)
Family history of early coronary heart disease†	247 981 (10.6)	143 593 (11.3)
Atrial fibrillation	12 031 (0.5)	6 589 (0.5)
Chronic renal disease	3 594 (0.2)	1 917 (0.2)
Clinical values:		
Systolic blood pressure recorded	2 027 470 (86.5)	1 081 944 (85.4)
Mean (SD) systolic blood pressure (mm Hg)	131.9 (20.5)	131.7 (20.5)
BMI recorded	1 773 567 (75.7)	949 434 (74.9)
Mean (SD) BMI (kg/m^2)	26.1 (4.5)	26.1 (4.5)
Smoking status and BMI recorded	1 754 250 (74.9)	937 808 (74.0)
Serum total and HDL cholesterol recorded	692 590 (29.6)	354 853 (28.0)
Mean (SD) total cholesterol:HDL cholesterol ratio	4.2 (1.3)	4.2 (1.3)

**A recorded diagnosis of hypertension and treatment that could include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, β blockers, thiazides, or calcium channel blockers.*
†Heart disease in a first degree relative aged <60 years.

Table 24: Hippisley-Cox 2010[655]: adjusted hazard ratios* for cardiovascular disease for individual predictor variables in the derivation cohort of 2 343 759 patients

Variables	Adjusted hazard ratio (95% CI)	
	Women	Men
Body mass index†	1.32 (1.22 to 1.44)	1.54 (1.45 to 1.63)
Systolic blood pressure (per 20 mm Hg increase)	1.13 (1.12 to 1.14)	1.11 (1.10 to 1.12)
Total cholesterol:HDL cholesterol ratio (per unit increase)	1.17 (1.16 to 1.18)	1.18 (1.17 to 1.18)
Townsend score (per 5 unit increase)‡	1.13 (1.11 to 1.14)	1.06 (1.05 to 1.07)
Smoking status:		
Non-smoker	1.00	1.00
Former smoker	1.17 (1.14 to 1.21)	1.18 (1.16 to 1.21)
Light smoker (<10 cigarettes/day)	1.39 (1.33 to 1.45)	1.38 (1.34 to 1.43)
Moderate smoker (10-19/day)	1.57 (1.52 to 1.63)	1.55 (1.51 to 1.60)
Heavy smoker (≥20/day)	1.84 (1.77 to 1.91)	1.79 (1.74 to 1.84)
Ethnic group:		
White or not recorded	1.00	1.00
Indian	1.42 (1.28 to 1.58)	1.50 (1.38 to 1.63)
Pakistani	2.04 (1.78 to 2.34)	2.05 (1.84 to 2.28)
Bangladeshi	1.61 (1.30 to 1.98)	2.14 (1.85 to 2.46)
Other Asian	1.14 (0.92 to 1.4 0)	1.32 (1.12 to 1.56)
Caribbean	1.03 (0.91 to 1.16)	0.71 (0.63 to 0.81)
Black African	0.69 (0.54 to 0.89)	0.70 (0.56 to 0.86)
Chinese	0.77 (0.55 to 1.08)	0.79 (0.58 to 1.06)
Other	0.99 (0.85 to 1.16)	0.90 (0.78 to 1.04)
Clinical conditions:		
Family history of early coronary heart disease§	1.67 (1.63 to 1.71)	1.84 (1.80 to 1.88)
Type 2 diabetes	1.67 (1.60 to 1.73)	1.60 (1.55 to 1.66)
Treated hypertension	1.33 (1.30 to 1.36)	1.37 (1.34 to 1.40)
Rheumatoid arthritis	1.43 (1.35 to 1.53)	1.37 (1.26 to 1.50)

Variables	Adjusted hazard ratio (95% CI)	
	Women	Men
Atrial fibrillation	1.89 (1.78 to 2.01)	1.63 (1.54 to 1.72)
Chronic renal disease	1.67 (1.44 to 1.95)	1.59 (1.39 to 1.83)

**Hazard ratios were adjusted for all other variables listed in the table.*
†Fractional polynomial terms for body mass index: for women, (body mass index/10)0.5; for men, ln(body mass index/10).
‡Increasing Townsend scores indicate increasing levels of deprivation.
§Heart disease in a first degree relative aged <60 years.

D.3 Appendix D1. Evidence tables from update search

Anonymous., 2021

Bibliographic Reference	Anonymous.; SCORE2 risk prediction algorithms: New models to estimate 10-year risk of cardiovascular disease in Europe; European Heart Journal; 2021; vol. 42 (no. 25); 2439-2454

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Prospective cohort study
Study location	Derivation cohort: Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Spain, Sweden, UK, Canada, USA External validation: Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, UK, Czech Republic, Estonia, Poland, Lithuania, Russia
Study setting	Population-based cohorts

Secondary publication of another included study- see primary study for details	NA
Study dates	Cohort with baseline data after 1990
Sources of funding	Programme grants from the British Heart Foundation, BHF Centre of Research Excellence, the UK Medical Research Council, and the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre Project-specific support received from the UK NIHR, British United Provident Association UK Foundation and an unrestricted educational grant from GlaxoSmithKline.
Study sample	Derivation cohort: individual-participant data from 45 prospective cohorts involving 677684 participants in 13 countries (Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Spain, Sweden, UK, Canada, USA). External validation: 25 prospective cohorts not in the model derivation involving 1,133,181 individuals in 15 European countries (Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, UK, Czech Republic, Estonia, Poland, Lithuania, Russia). Derived in participants aged 40–79 years at baseline without previous CVD.
Inclusion criteria	Prospective studies that met all of the following criteria: Recorded baseline information on risk factors necessary to derive risk prediction models (age, sex, smoking status, history of diabetes mellitus, systolic blood pressure, and total- and HDL-cholesterol); were population-based [i.e. did not select participants on the basis of having previous disease (e.g. case-control studies) and were not active treatment arms of intervention studies]; had a median year of baseline survey after 1990; had recorded cause-specific deaths and/or non-fatal CVD events (i.e. non-fatal myocardial infarction or stroke) for at least 1-year of follow-up for validation only: made individual participant data available.
Exclusion criteria	Not stated
Population subgroups	Data reported separately for men and women
Risk tool(s)	SCORE2 for estimation of 10-year risk of fatal and non-fatal CVD events
Predictors	The sex-specific models included the following predictors: age, current smoking, history of diabetes mellitus, systolic blood pressure, and total- and HDL-cholesterol. The risk factors were selected due to their predictive ability as well as their availability in: derivation cohorts, target populations for screening, and population statistics needed for model recalibration.

Secondary publication of another included study- see primary study for details	NA
	Since previous research showed that associations of these risk factors with CVD decline with increasing age, age-interactions were added for all predictors.
Model development and validation	For model derivation, sex-specific associations [i.e. sub-distribution hazard ratios] were estimated using Fine and Gray competing risk-adjusted models stratified by cohort. Risk models were recalibrated to risk regions using age- and sex-specific mean risk factor levels and CVD incidence rates. External validation was performed in a cohorts not included in the model derivation.
Outcome	Fatal or non-fatal cardiovascular disease. Cause-specific mortality due to: Hypertensive disease Ischemic heart disease Arrhythmias, heart failure Cerebrovascular disease Atherosclerosis/abdominal aortic aneurysm Sudden death and death within 24h of symptom onset Non-fatal cardiovascular disease Non-fatal myocardial infarction Non-fatal stroke
Duration of follow-up	Median in derivation cohorts: 10.7 (5.0 to 18.6) years Median in validation cohorts: 3.8 - 22.1 years
Indirectness	None detected
Additional comments	

Study arms

SCORE2 derivation/internal validation (N = 677684)

677684 from Europe (of which 476072, 79% were from the UK)

SCORE2 - low risk; UK (external validation) (N = 981370)

SCORE2 - CPRD (external validation) (N = 927079)

2nd risk tool

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Derivation cohort No of events	% = 56
Validation cohort (Europe) No of events	% = 50.9
Validation cohort (CPRD) No of events	% = 51
Derivation cohort Mean (SD)	57 (9)
Validation cohort (CPRD) Mean (SD)	53 (8.3)
Validation cohort (Europe) range of mean ages across cohorts Range	50 to 60.4
Ethnicity Nominal	NA
Type 1 diabetes While the SCORE2 risk models are not intended for use in individuals with diabetes, participants with a history of diabetes were included at the model derivation stage (with appropriate adjustment for diabetes status), since it wasn't possible to exclude people with diabetes from population-level mortality statistics and risk factor data used in recalibration. Nominal	NA
Derivation cohort Diabetes (not stated if type 1 or 2) No of events	n = 31413 ; % = 4.6

Characteristic	Study (N =)
Type 2 diabetes Nominal	NA
CKD Nominal	NA
Socioeconomic status Nominal	NA
Autoimmune disease Nominal	NA
Serious mental illness Nominal	NA

Outcomes

Study timepoints

- 10 year (Estimates of 10-year risk)

Discrimination

Outcome	SCORE2 derivation/internal validation, 10 year, N = 677684	SCORE2 - low risk; UK (external validation), 10 year, N = 981370	SCORE2 - CPRD (external validation), 10 year, N = 927079
C-statistic Mean (95% CI)	0.74 (0.74 to 0.74)	0.72 (0.72 to 0.73)	0.72 (0.72 to 0.72)
Age 40-50 Mean (95% CI)	-	-	0.7 (0.69 to 0.71)
Age 50-59 Mean (95% CI)	-	-	0.65 (0.65 to 0.66)
Age 60-69	-	-	0.62 (0.61 to 0.63)

Outcome	SCORE2 derivation/internal validation, 10 year, N = 677684	SCORE2 - low risk; UK (external validation), 10 year, N = 981370	SCORE2 - CPRD (external validation), 10 year, N = 927079
Mean (95% CI)			

Calibration

Outcome	SCORE2 derivation/internal validation, 10 year, N =	SCORE2 - low risk; UK (external validation), 10 year, N =	SCORE2 - CPRD (external validation), 10 year, N = 927079
Observed:predicted risk Custom value	-	-	see graph

in CPRD data set

Critical appraisal - PROBAST tool (derivation cohort)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	High (Insufficient calibration data)
Overall Risk of bias and Applicability	Concerns for applicability	Low

Critical appraisal - PROBAST tool (CPRD cohort)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Anonymous., 2021

Bibliographic Reference	Anonymous.; SCORE2-OP risk prediction algorithms: Estimating incident cardiovascular event risk in older persons in four geographical risk regions; European Heart Journal; 2021; vol. 42 (no. 25); 2455-2467

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Prospective cohort study
Study location	Derivation cohort: Norway Validation cohort: USA, Europe, and UK
Study setting	Derivation cohort was from the CONOR study: population-based cohort Validation cohorts were 3 population-based cohorts (ARIC, MESA and CPRD) and 3 clinical trials (HYVET, PROSPER and SPRINT)
Study dates	Derivation cohort: 1994-2003 ARIC: 2016-2017 CPRD: 2006-2017 HYVET: 2001-2007 MESA: 2000-2002 PROSPER: 1997-1999 SPRINT: 2010-2013
Sources of funding	N/A
Study sample	Derivation cohort: CONOR study External validation: cohort studies and clinical trials (the Atherosclerosis Risk in Communities (ARIC) study; the Clinical Practice Research Datalink (CPRD); the Hypertension in the Very Elderly Trial (HYVET); the Multi-Ethnic Study of Atherosclerosis (MESA); the 'PROspective Study of Pravastatin in Elderly at Risk' (PROSPER) trial; and the Systolic Blood Pressure Intervention Trial (SPRINT). Derived in participants aged 65 years or over without previous CVD.
Inclusion criteria	Target population: individuals aged 65 years or over.

Secondary publication of another included study- see primary study for details	NA
Exclusion criteria	Individuals with a history of CVD (i.e. coronary heart disease, stroke, or peripheral artery disease).
Population subgroups	NA
Risk tool(s)	SCORE-OP for estimation of 5- and 10-year risk of fatal and non-fatal CVD events AHA/ASCVD or estimation of 10-year risk of fatal and non-fatal CVD events
Predictors	SCORE-OP. The sex-specific models included the following predictors: age, smoking status, diabetes, systolic blood pressure, and total- and high-density lipoprotein cholesterol AHA/ASCVD: age, gender, smoking status, race, diabetes, systolic blood pressure, treatment for hypertension, and total- and high-density lipoprotein cholesterol
Model development and validation	For model derivation, sex-specific associations [i.e. sub-distribution hazard ratios] were estimated using Fine and Gray competing risk-adjusted models stratified by cohort. Risk models were recalibrated to risk regions using age- and sex-specific mean risk factor levels and CVD incidence rates. External validation was performed in a cohorts not included in the model derivation.
Outcome	Fatal or non-fatal cardiovascular disease. Cause-specific mortality due to: Hypertensive disease Ischemic heart disease Arrhythmias, heart failure Cerebrovascular disease Atherosclerosis/abdominal aortic aneurysm Sudden death and death within 24h of symptom onset Non-fatal cardiovascular disease Non-fatal myocardial infarction Non-fatal stroke
Duration of follow-up	Median in derivation cohort: 13 (8-15) years Median in validation cohorts: 3-13 years
Indirectness	None detected

Study arms

SCORE-OP (derivation/internal validation) (N = 28503)

SCORE-OP (external validation, CPRD) (N = 319390)

ASCVD (external validation, CPRD) (N = 319390)
2nd risk tool

Characteristics

Study-level characteristics

Characteristic	Study (N =)
CONOR derivation cohort No of events	% = 50
CPRD validation cohort No of events	% = 58
CONOR derivation cohort Mean (SD)	73 (5)
CPRD validation cohort Mean (SD)	74 (6)
Ethnicity Nominal	NR
Type 1 diabetes Nominal	NR
CONOR derivation cohort No of events	% = 6

Characteristic	Study (N =)
CPRD Validation cohort No of events	% = 10
CKD Nominal	NR
Socioeconomic status Nominal	NR
Autoimmune disease Nominal	NR
Serious mental illness Nominal	NR

Outcomes

Study timepoints

- 10 year (risk estimate)

Discrimination

Outcome	SCORE-OP (derivation/internal validation), 10 year, N = 28503	SCORE-OP (external validation, CPRD), 10 year, N = 319390	ASCVD (external validation, CPRD), 10 year, N = 319390
C-statistic Mean (95% CI)	0.66 (0.65 to 0.66)	0.66 (0.66 to 0.66)	0.66 (0.66 to 0.67)

Calibration

Outcome	SCORE-OP (derivation/internal validation), 10 year, N = 28503	SCORE-OP (external validation, CPRD), 10 year, N = 319390	ASCVD (external validation, CPRD), 10 year, N = 319390
Observed/expected events Custom value	see graph	see graph	NR

Critical appraisal - PROBAST tool (CPRD cohort)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Collins, 2012

Bibliographic Reference	**Collins, Gary S; Altman, Douglas G; Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2.; BMJ (Clinical research ed.); 2012; vol. 344; e4181**

Study details

Secondary publication of another included study- see primary study for details	**See full details in the 2014 version of CG181 evidence report**

Study arms

QRISK2-2008 (N = 2084445)

QRISK2-2010 (N = 2084445)

QRISK2-2011 (N = 2084445)

Outcomes

Study timepoints

- 10 year (risk estimate)

Discrimination

Outcome	QRISK2-2008, 10 year, N = 2084445	QRISK2-2010, 10 year, N = 2084445	QRISK2-2011, 10 year, N = 2084445

Critical appraisal - PROBAST tool (QRISK2 2008, 2010 and 2011)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Dziopa, 2022

Bibliographic Reference	Dziopa, Katarzyna; Asselbergs, Folkert W; Gratton, Jasmine; Chaturvedi, Nishi; Schmidt, Amand F; Cardiovascular risk prediction in type 2 diabetes: a comparison of 22 risk scores in primary care settings.; Diabetologia; 2022; vol. 65 (no. 4); 644-656

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Prospective cohort study

Secondary publication of another included study- see primary study for details	NA
Study location	UK
Study setting	Linked Bespoke studies and Electronic health Records (CALIBER), linking three English EHR sources: primary care records from the Clinical Practice Research Datalink (CPRD), Hospital Episodes Statistics (HES) and national death registration from the Office for National Statistics
Study dates	Start date: not reported, end date: 5 February 2018. Median follow-up: 9.0 years
Sources of funding	National Productivity Investment Fund–MRC Doctoral Training Programme, UCL Hospitals NIHR Biomedical Research Centre. BHF, UCL BHF Research Accelerator AA/18/6/34223, MRC
Study sample	168,871 UK-based individuals
Inclusion criteria	Type 2 diabetes (age ≥18 years without pre-existing CVD+, where CVD+ denotes the addition of heart failure and atrial fibrillation to CVD (defined as the first occurrence of fatal or non-fatal myocardial infarction, sudden cardiac death, ischaemic heart disease, fatal or non-fatal stroke, or PAD)
Population subgroups	NA
Risk tool(s)	QRISK2, QRISK3, ASCVD
Predictors	QRISK2: •Age •Gender •Ethnic origin (9 categories) •Deprivation •Systolic blood pressure •Body mass index •Ratio of total cholesterol : HDLc •Smoking status •Family history of coronary heart disease •Treated hypertension •Rheumatoid arthritis •Atrial fibrillation •CKD (stage 4 or 5) and major chronic renal disease

Secondary publication of another included study- see primary study for details	NA
	QRISK3: •Age •Gender •Ethnic origin (9 categories) •Deprivation •Systolic blood pressure •Body mass index •Ratio of total cholesterol : HDLc •Smoking status •Family history of coronary heart disease •Diabetes (type 1, type 2, or no) •Treated hypertension •Rheumatoid arthritis •Atrial fibrillation •CKD (stage 4 or 5) and major chronic renal disease In addition to QRISK2 •Chronic kidney disease stage 3 •SBP variability •Migraine •Corticosteroids •SLE •Atypical antipsychotics •Severe mental illness •Erectile dysfunction ASCVD •Age

Secondary publication of another included study- see primary study for details	NA
	•Gender •Ethnic origin (3 categories) •Systolic blood pressure •Smoking status •Treated hypertension
Model development and validation	NA
Outcome	CVD defined as the first occurrence of fatal or non-fatal myocardial infarction, sudden cardiac death, ischaemic heart disease, fatal or non-fatal stroke, or PAD CVD+ defined as CVD plus heart failure and atrial fibrillation
Duration of follow-up	Median (Q1; Q3): 9.0 (5.3; 10.0) years
Indirectness	No indirectness

Study arms

QRISK2 (N = 168871)

QRISK3 (N = 168871)
2nd risk tool

ASCVD (N = 168871)
3rd risk tool

Characteristics

Study-level characteristics

Characteristic	Study (N = 168871)
% Female Sample size	n = 78204 ; % = 46
Mean age (SD) Mean (SD)	59.3 (13.9)
Type 2 diabetes Sample size	n = 168871 ; % = 100
Townsend deprivation score 1 (least deprived) Sample size	n = 32058 ; % = 19
Townsend deprivation score 2 Sample size	n = 35090 ; % = 20.8
Townsend deprivation score 3 Sample size	n = 35255 ; % = 20.9
Townsend deprivation score 4 Sample size	n = 37365 ; % = 22.1
Townsend deprivation score 5 (most deprived) Sample size	n = 28990 ; % = 17.2

Outcomes

C Statistic

Outcome	QRISK2, N = 168871	QRISK3, N = 168871	ASCVD, N = 168871
C-statistic for CVD only Custom value	0.664 (95%CI 0.660 to 0.667)	0.664 (95%CI 0.660 to 0.668)	0.668 (95%CI 0.664 to 0.671)
C-statistic for CVD+ Custom value	0.683 (95%CI 0.680 to 0.686)	0.683 (95%CI 0.680 to 0.686)	0.689 (95%CI 0.686 to 0.693)

C-statistic for CVD only - Polarity - Higher values are better

Critical appraisal - PROBAST tool (QRISK2, QRISK3, ASCVD)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Goff, 2014

Bibliographic Reference	**Goff, David C.; Lloyd-Jones, Donald M.; Bennett, Glen; Coady, Sean; D'Agostino, Ralph B.; Gibbons, Raymond; Greenland, Philip; Lackland, Daniel T.; Levy, Daniel; O'Donnell, Christopher J.; Robinson, Jennifer G.; Schwartz, J. Sanford; Shero, Susan T.; Smith, Sidney C.; Sorlie, Paul; Stone, Neil J.; Wilson, Peter W. F.; 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk; Circulation; 2014; vol. 129 (no. 25suppl2); 49-s73**

Study details

Secondary publication of another included study- see primary study for details	**NA**
Other publications associated with this study included in review	NA
Trial name / registration number	NA
Study type	Prospective cohort study
Study location	USA
Study setting	Primary care cohorts
Study dates	Not given
Sources of funding	NHLBI
Study sample	ARIC (Atherosclerosis Risk in Communities) study, the Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts

Secondary publication of another included study- see primary study for details	**NA**
Inclusion criteria	Aged 40 to 79 years, apparently healthy, African American or White, and free of a previous history of MI (recognised or unrecognised), stroke, congestive heart failure, percutaneous coronary intervention, coronary bypass surgery, or atrial fibrillation.
Population subgroups	NA
Risk tool(s)	ASCVD
Predictors	Age, total cholesterol, high-density lipoprotein cholesterol, systolic BP (including treated or untreated status), diabetes mellitus, and current smoking status
Model development and validation	Model developed in ARIC (Atherosclerosis Risk in Communities) study, the Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts. Model validated in (1) Multi-Ethnic Study of Atherosclerosis (MESA) cohort (2) REasons for Geographic And Racial Differences in Stroke study (REGARDS) cohort and (3) Contemporary cohort (ARIC visit 4, Framingham cohort cycles 22, 23 (highest attended), and Framingham Offspring cycles 5, 6 (highest attended))
Outcome	Nonfatal myocardial infarction or coronary heart disease death, or fatal or nonfatal stroke
Duration of follow-up	10 years
Indirectness	Indirect population

Study arms

White women derivation cohort (N = 11240)
ARIC (Atherosclerosis Risk in Communities) study, the Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts

White men derivation cohort (N = 9098)
ARIC (Atherosclerosis Risk in Communities) study, the Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts

African American women derivation cohort (N = 2641)
ARIC (Atherosclerosis Risk in Communities) study, the Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts

African American men derivation cohort (N = 1647)
ARIC (Atherosclerosis Risk in Communities) study, the Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts

MESA white women validation cohort (N = 1273)
Multi-Ethnic Study of Atherosclerosis cohort, based on 6-year prediction

MESA white men validation cohort (N = 1184)
Multi-Ethnic Study of Atherosclerosis cohort, based on 6-year prediction

MESA African American women validation cohort (N = 978)
Multi-Ethnic Study of Atherosclerosis cohort, based on 6-year prediction

REGARDS white women validation cohort (N = 6333)
REasons for Geographic And Racial Differences in Stroke study, based on on 4-year prediction

REGARDS white men validation cohort (N = 5296)
REasons for Geographic And Racial Differences in Stroke study, based on on 4-year prediction

REGARDS African American women validation cohort (N = 5275)
REasons for Geographic And Racial Differences in Stroke study, based on on 4-year prediction

REGARDS African American men validation cohort (N = 2969)
REasons for Geographic And Racial Differences in Stroke study, based on on 4-year prediction

MESA African American men validation cohort (N = 799)
Multi-Ethnic Study of Atherosclerosis cohort, based on 6-year prediction

Contemporary white women validation cohort (N = 6509)
Includes ARIC visit 4, Framingham cohort cycles 22, 23 (highest attended), and Framingham Offspring cycles 5, 6 (highest attended)

Contemporary white men validation cohort (N = 5041)
Includes ARIC visit 4, Framingham cohort cycles 22, 23 (highest attended), and Framingham Offspring cycles 5, 6 (highest attended)

Contemporary African American women validation cohort (N = 1367)
Includes ARIC visit 4, Framingham cohort cycles 22, 23 (highest attended), and Framingham Offspring cycles 5, 6 (highest attended)

Contemporary African American men validation cohort (N = 735)
Includes ARIC visit 4, Framingham cohort cycles 22, 23 (highest attended), and Framingham Offspring cycles 5, 6 (highest attended)

Characteristics

Study-level characteristics

Characteristic	Study (N = 24626)
% Female Sample size	n = 13881 ; % = 56
ARIC cohort African American women Mean (SD)	53.1 (5.7)
CARDIA cohort African American women Mean (SD)	40.4 (1)
CHS cohort African American women Mean (SD)	71.2 (4)
ARIC cohort white women Mean (SD)	53.9 (5.7)
CARDIA cohort white women Mean (SD)	40.1 (0.3)
CHS cohort white women Mean (SD)	70.8 (3.8)
ARIC cohort African American men Mean (SD)	53.6 (5.9)
CARDIA cohort African American men Mean (SD)	40.3 (0.8)
CHS cohort African American men Mean (SD)	70.9 (3.9)
ARIC cohort white men Mean (SD)	54.5 (5.7)
CARDIA cohort white men Mean (SD)	40.2 (0.4)
CHS cohort white men Mean (SD)	71.2 (3.8)
Framingham white women Mean (SD)	53.5 (8.7)
Framingham white men Mean (SD)	52.8 (8.5)

Characteristic	Study (N = 24626)
African American No of events	n = 4288 ; % = 17
White No of events	n = 20338 ; % = 83
ARIC cohort African American women Custom value	17.1%
CARDIA cohort African American women Custom value	6.4%
CHS cohort African American women Custom value	22.3%
ARIC cohort white women Custom value	6.1%
CARDIA cohort white women Custom value	1.5%
CHS cohort white women Custom value	9.9%
ARIC cohort African American men Custom value	15.0%
CARDIA cohort African American men Custom value	3.1%
CHS cohort African American men Custom value	25.6%
ARIC cohort white men Custom value	7.8%
CARDIA cohort white men Custom value	2.9%
CHS cohort white men Custom value	15.4%
Framingham white women Custom value	4.7%

Characteristic	Study (N = 24626)
Framingham white men Custom value	7.7%

Outcomes

C-statistic

Outcome	White women derivation cohort, , N = 11240	White men derivation cohort, , N = 5041	African American women derivation cohort, , N = 2641	African American men derivation cohort, , N = 1647	MESA white women validation cohort, , N = 1273	MESA white men validation cohort, , N = 1184	MESA African American women validation cohort, , N = 978	REGARDS white women validation cohort, , N = 6333	REGARDS white men validation cohort, , N = 5296	REGARDS African American women validation cohort, , N = 5275	REGARDS African American men validation cohort, , N = 2969	MESA African American men validation cohort, , N = 1184	Contemporary white women validation cohort, , N = 6509	Contemporary white men validation cohort, , N = 5041	Contemporary African American women validation cohort, , N = 1367	Contemporary African American men validation cohort, , N = 735
C-statistic Custom value	0.8058	0.7462	0.8182	0.7130	0.7109	0.7044	0.7684	0.6599	0.5950	0.6625	0.6625	0.7684	0.7377	0.6843	0.7068	0.7109

Critical appraisal - PROBAST tool (ASCVD validation cohorts)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	High (non-UK cohort)

Hippisley-Cox, 2014

Bibliographic Reference	**Hippisley-Cox, Julia; Coupland, Carol; Brindle, Peter; The performance of seven QPrediction risk scores in an independent external sample of patients from general practice: a validation study.; BMJ open; 2014; vol. 4 (no. 8); e005809**

Study details

Secondary publication of another included study- see primary study for details	
Study type	Prospective cohort study
Study location	UK
Study setting	357 practices in England in CPRD which had linked Office for National Statistics (ONS) mortality and hospital admissions data
Study dates	For each patient an entry date to the cohort was the latest of the following dates: 25th birthday, date of registration with the practice plus 1 year, date on which the practice computer system was installed plus 1 year and the beginning of the study period (1 January 1998). Patients were censored at the earliest date of the relevant outcome, de-registration with the practice, last upload of computerised data or the study end date (31 July 2012).
Sources of funding	National Institute for Health Research
Study sample	An open cohort of patients aged 25–99 years at entry from the CPRD.
Inclusion criteria	Not stated
Exclusion criteria	Existing CVD or statins at study entry Missing Townsend score or temporary resident
Population subgroups	Reported separately for men and women
Risk tool(s)	QRISK2-2014
Predictors	In men and women: age, smoking status ethnic group (nine categories), systolic blood pressure, cholesterol/HDL ratio, body mass index, family history of cardiovascular disease in first degree relative under 60 years, Townsend deprivation score, treated hypertension, rheumatoid arthritis, chronic renal disease, type 2 diabetes, atrial fibrillation.
Model development and validation	The algorithm was applied to eligible patients in the CPRD study cohort to obtain predicted risks for each of the relevant clinical outcomes.

Secondary publication of another included study- see primary study for details	
	In order to assess calibration (i.e., degree of similarity between predicted and observed risks), the mean predicted risk and the observed risk1 were obtained using the Kaplan-Meier estimate and compared the ratio of the mean predicted risk to the observed risk for patients in the validation cohort in each decile of predicted risk. The area under the ROC statistic and D statistic were calculated to assess discrimination (i.e., ability of a risk prediction equation to distinguish between those who do and do not have an event during the follow-up period).
Outcome	The same definition as in the original derivation of the risk scores using QResearch.
Duration of follow-up	Unclear In women 69 202 cases of CVD occurred; standardised rate per 1000 person years 6.72 (6.67 to 6.77) In men 70 283 cases of CVD occurred; standardised rate per 1000 person years 7.38 (7.33 to 7.44)
Indirectness	NA
Additional comments	Since 2008 QRISK2 has been updated annually and recalibrated to the latest version of the QResearch database; the age range across which it applies has also been extended from 35-74 years to 25-84 years, type 1 diabetes has been included as a separate variable, smoking is assessed at five levels instead of two, and the Townsend score has been updated using the most recent values from the 2011 census.

Study arms

QRISK2-2014 (external validation: CPRD): men (N = 1588803)

QRISK2-2014 (external validation: CPRD): women (N = 1682709)

Characteristics

Study-level characteristics

Characteristic	Study (N =)
% Female No of events	% = 51
Serious mental illness	NR

Nominal	

Arm-level characteristics

Characteristic	QRISK2-2014 (external validation: CPRD): men (N = 1588803)	QRISK2-2014 (external validation: CPRD): women (N = 1682709)
25-34 No of events	% = 26.9	% = 27.8
35-44 No of events	% = 25	% = 21.6
45-54 No of events	% = 18.5	% = 16.5
55-64 No of events	% = 13.4	% = 12.6
65-74 No of events	% = 9.3	% = 9.8
75 or over No of events	% = 6.9	% = 11.8
White or not recorded No of events	% = 95.4	% = 95.2
Indian No of events	% = 1	% = 1
Pakistani No of events	% = 0.4	% = 0.4
Bangladeshi No of events	% = 0.2	% = 0.1
Other Asian No of events	% = 0.7	% = 0.7
Caribbean No of events	% = 0.3	% = 0.4
Black African	% = 0.8	% = 0.9

No of events		
Chinese No of events	% = 0.2	% = 0.2
Other ethnic group No of events	% = 1	% = 1.2
Type 1 diabetes No of events	% = 0.4	% = 0.3
Type 2 diabetes No of events	% = 3.2	% = 2.6
CKD No of events	% = 0.2	% = 0.2
Socioeconomic status mean Townsend deprivation score Mean (SD)	-0.5 (3.2)	-0.5 (3.2)
Autoimmune disease rheumatoid arthritis or SLE No of events	% = 0.5	% = 1.1

Outcomes

Study timepoints

- 10 year (risk estimate)

Discrimination

Outcome	QRISK2-2014 (external validation: CPRD): men, 10 year, N = 1588803	QRISK2-2014 (external validation: CPRD): women, 10 year, N = 1682709
ROC statistic Mean (95% CI)	0.88 (0.88 to 0.88)	0.86 (0.86 to 0.86)

D statistic Mean (95% CI)	2.33 (2.31 to 2.34)	2.09 (2.07 to 2.1)

Classification measures

Outcome	QRISK2-2014 (external validation: CPRD): men vs QRISK2-2014 (external validation: CPRD): women, 10 year, N2 = 1588803, N1 = 1682709
Sensitivity (%) Nominal	49.9
Specificity (%) Nominal	91.9
Observed risk (%) Nominal	31.8

at 20.7% threshold (top decile)

Calibration
see graph

Critical appraisal - PROBAST tool (QRISK2-2014, men and women)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Hippisley-Cox, 2017

Bibliographic Reference	Hippisley-Cox, Julia; Coupland, Carol; Brindle, Peter; Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study.; BMJ (Clinical research ed.); 2017; vol. 357; j2099

Study details

Study type	Prospective cohort study
Study location	UK
Study setting	General practices in England providing data for the QResearch database (version 41).
Study sample	Open cohort of patients aged 25-84 years registered (between 1 January 1998 and 31 December 2015) with all practices in England that had been using the EMIS computer system for at least one year. Three quarters of practices were randomly allocated to the derivation dataset and the remainder to a validation dataset.
Inclusion criteria	Member of the above cohort
Exclusion criteria	No postcode related Townsend score Pre-existing cardiovascular disease (on general practice records or linked hospital records), Using prescribed statins at cohort entry.
Population subgroups	Reported separately for men and women. Subgroup data also reported by: • age • ethnicity • AF • atypical antipsychotics • corticosteroids • erectile dysfunction • migraine • rheumatoid arthritis • CKD • SMI • SLE • treated hypertension • type 1 diabetes • type 2 diabetes • family history of coronary heart disease
Risk tool(s)	QRISK3-2017
Predictors	•Age •Ethnic origin (9 categories) •Deprivation

	•Systolic blood pressure •Body mass index •Ratio of total cholesterol : HDLc •Smoking status •Family history of coronary heart disease •Diabetes (type 1, type 2, or no) •Treated hypertension •Rheumatoid arthritis •Atrial fibrillation •CKD (stage 4 or 5) and major chronic renal disease In addition to QRISK2 •Chronic kidney disease stage 3 •SBP variability in model C (or latest SBP value where only the current reading is available as in model B) •Migraine •Corticosteroids •SLE •Atypical antipsychotics •Severe mental illness •Erectile dysfunction
Model development and validation	Derivation Cox's proportional hazards models were used to estimate the coefficients for each risk factor in women and men separately. Included variables from existing QRISK2 models and then retained additional variables if they had an adjusted hazard ratio of less than 0.90 or greater than 1.10 (for binary variables) and were statistically significant at the 0.01 level. From the final models regression coefficients for each variable were used as weights, which were combined with the baseline survivor function evaluated up to 15 years to derive risk equations over a period of 15 years of follow-up.
Outcome	Incident cardiovascular disease recorded on any of the following three linked data sources: general practice, mortality, or hospital admission records: composite outcome of coronary heart disease, ischaemic stroke, or transient ischaemic attack.
Duration of follow-up	In the derivation cohort the median follow-up was 4.4 years (interquartile range 1.6-10.8) and 2 141 841 patients had 10 years or more of follow-up.

	In the validation cohort, the median follow up was 4.4 years (interquartile range 1.6-10.8) and 728 704 patients had 10 years or more of follow-up.
Indirectness	NA

Study arms

QRISK3 derivation: women (N = 4019956)

QRISK3 derivation: men (N = 3869847)

QRISK3 internal validation: women (N = 1360457)
Models B and C, without and with standard deviation of serial systolic blood pressure values included, respectively

QRISK3 internal validation: men (N = 1310841)
Models B and C, without and with standard deviation of serial systolic blood pressure values included, respectively

QRISK2-2017 validation: women (N = 1360457)
Model A in study (2nd risk tool)

QRISK2-2017 validation: men (N = 1310841)
Model A in study (2nd risk tool)

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Derivation cohort No of events	% = 51
Validation cohort No of events	% = 51

Arm-level characteristics

Characteristic	QRISK3 derivation: women (N = 4019956)	QRISK3 derivation: men (N = 3869847)	QRISK3 internal validation: women (N = 1360457)	QRISK3 internal validation: men (N = 1310841)	QRISK2-2017 validation: women (N = 1360457)	QRISK2-2017 validation: men (N = 1310841)
Mean age (SD) Mean (SD)	43.3 (15.3)	42.6 (14)	43.3 (15.3)	42.6 (13.8)	-	-
Recorded No of events	% = 64.9	% = 59.7	% = 62.5	% = 57.3	-	-
White or not recorded No of events	% = 88.7	% = 88.8	% = 89.6	% = 89.4	-	-
Indian No of events	% = 1.9	% = 2.1	% = 1.7	% = 2	-	-
Pakistani No of events	% = 1	% = 1.2	% = 0.8	% = 1.1	-	-
Bangladeshi No of events	% = 0.8	% = 1.1	% = 0.6	% = 0.9	-	-
Other Asian No of events	% = 1.3	% = 1.2	% = 1.3	% = 1.2	-	-
Black Caribbean No of events	% = 0.9	% = 0.8	% = 1	% = 0.8	-	-
Black African No of events	% = 1.9	% = 1.8	% = 2	% = 1.9	-	-

Chinese No of events	% = 0.8	% = 0.6	% = 0.7	% = 0.5	-	-
Other No of events	% = 2.6	% = 2.4	% = 2.4	% = 2.2	-	-
Type 1 diabetes No of events	n = 10060 ; % = 0.3	n = 11617 ; % = 0.3	n = 3351 ; % = 0.2	n = 3932 ; % = 0.3	-	-
Type 2 diabetes No of events	n = 48022 ; % = 1.2	n = 58393 ; % = 1.5	n = 15872 ; % = 1.2	n = 19318 ; % = 1.5	-	-
CKD stage 3, 4 or 5 No of events	n = 19396 ; % = 0.5	n = 12254 ; % = 0.3	n = 6949 ; % = 0.5	n = 4232 ; % = 0.3	-	-
Socioeconomic status Townsend score Mean (SD)	0.4 (3.2)	0.5 (3.3)	0.4 (3.3)	0.5 (3.3)	-	-
Rheumatoid arthritis No of events	n = 45700 ; % = 1.1	n = 20997 ; % = 0.5	n = 15139 ; % = 1.1	n = 7055 ; % = 0.5	-	-
Systemic lupus erythematosus No of events	n = 4010 ; % = 0.1	n = 365 ; % = 0	n = 1349 ; % = 0.1	n = 134 ; % = 0	-	-
Serious mental illness No of events	n = 274069 ; % = 6.8	n = 167115 ; % = 4.3	n = 94724 ; % = 7	n = 57830 ; % = 4.4	-	-

Outcomes

Study timepoints

- 10 year (estimated risk)

Discrimination

Outcome	QRISK3 derivation: women, 10 year, N =	QRISK3 derivation: men, 10 year, N =	QRISK3 internal validation: women, 10 year, N = 1360457	QRISK3 internal validation: men, 10 year, N = 1310841	QRISK2-2017 validation: women, 10 year, N = 1360457	QRISK2-2017 validation: men , 10 year, N = 1310841
C Statistic						
Model A Mean (95% CI)	-	-	-	-	0.88 (0.88 to 0.88)	0.86 (0.86 to 0.86)
Model B Mean (95% CI)	-	-	0.88 (0.88 to 0.88)	0.86 (0.86 to 0.86)	-	-
Model C Mean (95% CI)	-	-	0.88 (0.88 to 0.88)	0.86 (0.86 to 0.86)	-	-
Model B: CKD stage 3, 4 or 5 subgroup Mean (95% CI)	-	-	0.74 (0.72 to 0.76)	0.74 (0.72 to 0.76)	-	-
Model B: type 1 diabetes subgroup Mean (95% CI)	-	-	0.82 (0.79 to 0.86)	0.8 (0.78 to 0.83)	-	-
Model B: type 2 diabetes subgroup Mean (95% CI)	-	-	0.7 (0.69 to 0.71)	0.7 (0.69 to 0.7)	-	-
Model B: SMI subgroup Mean (95% CI)	-	-	0.84 (0.84 to 0.85)	0.82 (0.81 to 0.83)	-	-
D statistic						
Model A Mean (95% CI)	-	-	-	-	2.48 (2.46 to 2.5)	2.25 (2.24 to 2.27)
Model B Mean (95% CI)	-	-	2.48 (2.46 to 2.5)	2.26 (2.24 to 2.27)	-	-
Model C	-	-	2.49 (2.47 to 2.51)	2.26 (2.25 to 2.28)	-	-

Mean (95% CI)						
Model B: CKD stage 3, 4 or 5 subgroup Mean (95% CI)	-	-	1.32 (1.17 to 1.47)	1.28 (1.13 to 1.44)	-	-
Model B: type 1 diabetes subgroup Mean (95% CI)	-	-	1.94 (1.66 to 2.22)	1.87 (1.64 to 2.11)	-	-
Model B: type 2 diabetes subgroup Mean (95% CI)	-	-	1.19 (1.12 to 1.25)	1.12 (1.06 to 1.17)	-	-
Model B: SMI subgroup Mean (95% CI)	-	-	-	2.16 (2.1 to 2.22)	1.94 (1.87 to 2.02)	-

Harrell's C - Polarity - Higher values are better
D statistic - Polarity - Higher values are better

Calibration

Outcome	QRISK3 internal validation: women vs QRISK3 internal validation: men, 10 year, N2 = 1360457, N1 = 1310841
Women Models A, B and C Custom value	Predicted: 4.7%; Observed: 5.8 (95% CI: 5.8-5.9)%
Men Models A, B and C Custom value	Predicted: 6.4%; Observed: 7.5 (95% CI: 7.5-7.6)%

Reclassification
see narrative summary

Critical appraisal - PROBAST tool (QRISK2)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low (Note possible risk of bias in analysis: lack of accounting for competing risks and unclear if overfitting accounted for)
Overall Risk of bias and Applicability	Concerns for applicability	Low (Note outcome definition includes TIA)

Critical appraisal - PROBAST tool (QRISK3)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low (Note possible risk of bias in analysis: lack of accounting for competing risks)
Overall Risk of bias and Applicability	Concerns for applicability	Low (Note outcome definition includes TIA)

Hippisley-Cox, 2010

Bibliographic Reference	Hippisley-Cox, Julia; Coupland, Carol; Robson, John; Brindle, Peter; Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database.; BMJ (Clinical research ed.); 2010; vol. 341; c6624

Study details

Secondary publication of another included study- see primary study for details	**See full details in the 2014 version of CG181 evidence table**
Study type	Prospective cohort study
Study location	UK
Study setting	GP practices in the QResearch database
Study dates	Patients registered with practices between 1 January 1994 and 30 April 2010.

Study sample	All participating practices in England and Wales who had been using their EMIS (Egton Medical Information System) computer system for at least a year. Two thirds of practices randomly allocated to a derivation dataset and a third retained for a validation dataset.
Inclusion criteria	Part of the cohort above.
Exclusion criteria	Excluded patients who: did not have a postcode related Townsend deprivation score (5.2% of patients), had been prescribed statins before the study start date (3.0% of patients), had pre-existing cardiovascular disease (3.6%).
Population subgroups	Reported separately for men and women.
Risk tool(s)	QRISK-lifetime
Predictors	Same predictor variables as QRISK2, with the exception of smoking status (which we categorised as a five level variable) and age (which we included as the underlying time function rather than as a predictor variable). The following variables were included in the final models for men and women separately: • Smoking status (heavy smoker (≥20 cigarettes/day), moderate smoker (10–19/day), light smoker (<10/day), former smoker, non-smoker) • Self-assigned ethnicity (white (or not recorded), Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other (including mixed)) • Systolic blood pressure (continuous) • Ratio of total serum cholesterol to high density lipoprotein (HDL) cholesterol (continuous) • Body mass index (weight (kg)/(height (m)2) (continuous) • Family history of coronary heart disease in first degree relative aged <60 years (yes/no) • Townsend deprivation score (output area level 2001 census data evaluated as a continuous variable) • Treated hypertension (diagnosis of hypertension and at least one current prescription of at least one antihypertensive agent) • Rheumatoid arthritis (yes/no) • Atrial fibrillation (yes/no) • Type 2 diabetes (yes/no) • Chronic renal disease (yes/no), based on presence of diagnostic codes as in QRISK2 rather than defined by glomerular filtration rates.
Model development and validation	Development

	Model developed to estimate the lifetime risk of cardiovascular disease, with death (non-cardiovascular) accounted for as a competing risk. Used cause-specific hazard models to account for competing risks, which involved fitting two separate Cox models—one for cardiovascular disease and one for deaths from other causes —including the same predictor variables in both models. Patients who didn't die or have cardiovascular disease were censored at the earliest date of deregistration with the practice, last upload of computerised data, or the study end date (30 April 2010). Used age as the underlying time function in the Cox regression by setting the origin as the patient's date of birth. Validation To validate the performance of the lifetime model at 10 years, the algorithms were applied to the validation cohort and calculated measures of discrimination. In order to determine the calibration of the lifetime risk model, observed with predicted lifetime risks were compared by 10th of predicted risk, taking account of competing risks in the calculation of observed risks.
Outcome	Cases of cardiovascular disease based on the first recorded diagnosis of cardiovascular disease recorded on the general practice computer system or their linked death certificate during the study period. The term cardiovascular includes: coronary heart disease (angina and myocardial infarction), stroke, transient ischaemic attacks.
Duration of follow-up	up to 16 years
Indirectness	

Study arms

QRISK lifetime validation cohort (N = 1267159)
based on QRISK2-2010

Outcomes

Study timepoints

- 10 year (risk estimate)

Discrimination: C statistic

Outcome	QRISK lifetime validation cohort, 10 year, N = 1267159
Women Mean (95% CI)	0.84 (0.84 to 0.84)
Men Mean (95% CI)	0.83 (0.83 to 0.83)

Calibration

Outcome	QRISK lifetime validation cohort, 10 year, N = 1267159
Women: decile 1 Median (IQR)	0.83 (18.5 to 22.4)
Women: decile 2 Median (IQR)	0.82 (21.3 to 25.9)
Women: decile 3 Median (IQR)	0.84 (22.9 to 27.3)
Women: decile 4 Median (IQR)	0.86 (24.4 to 28.5)
Women: decile 5 Median (IQR)	0.88 (26 to 29.4)
Women: decile 6 Median (IQR)	0.87 (27.8 to 31.9)
Women: decile 7 Median (IQR)	0.87 (30.2 to 34.8)
Women: decile 8 Median (IQR)	0.92 (33.7 to 36.8)
Women: decile 9 Median (IQR)	0.96 (39.5 to 41.3)
Women: decile 10 Median (IQR)	1.02 (51.9 to 50.8)
Men: decile 1 Median (IQR)	0.9 (22.5 to 25)
Men: decile 2	0.85 (27.2 to 32.1)

Median (IQR)	
Men: decile 3 Median (IQR)	0.85 (29.8 to 34.9)
Men: decile 4 Median (IQR)	0.86 (32 to 37.3)
Men: decile 5 Median (IQR)	0.87 (34.2 to 39.3)
Men: decile 6 Median (IQR)	0.87 (36.6 to 42.1)
Men: decile 7 Median (IQR)	0.88 (39.5 to 44.9)
Men: decile 8 Median (IQR)	0.92 (43.5 to 47.5)
Men: decile 9 Median (IQR)	0.98 (49.9 to 51)
Men: decile 10 Median (IQR)	1.01 (64.4 to 63.7)

Reclassification
see narrative summary in report

Critical appraisal - PROBAST tool (QRISK2 lifetime)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Hippisley-Cox, 2008

Bibliographic Reference	Hippisley-Cox, Julia; Coupland, Carol; Vinogradova, Yana; Robson, John; Minhas, Rubin; Sheikh, Aziz; Brindle, Peter; Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2.; BMJ (Clinical research ed.); 2008; vol. 336 (no. 7659); 1475-82

Study details

Secondary publication of another included study- see primary study for details	**See full details in the 2014 version of CG181 evidence table**

Study arms

QRISK2 derivation (N = 1535583)

QRISK2 internal validation (N = 750232)

Outcomes

Study timepoints

- 10 year (risk estimation)

Discrimination

Outcome	QRISK2 derivation, 10 year, N =	QRISK2 internal validation, 10 year, N =

ROC statistic - Polarity - Higher values are better

Critical appraisal - PROBAST tool

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low (Competing risks and model overfitting possibly not accounted for)
Overall Risk of bias and Applicability	Concerns for applicability	Low

Jaspers, 2020

Bibliographic Reference	Jaspers, Nicole E M; Blaha, Michael J; Matsushita, Kunihiro; van der Schouw, Yvonne T; Wareham, Nicholas J; Khaw, Kay-Tee; Geisel, Marie H; Lehmann, Nils; Erbel, Raimund; Jockel, Karl-Heinz; van der Graaf, Yolanda; Verschuren, W M Monique; Boer, Jolanda M A; Nambi, Vijay; Visseren, Frank L J; Dorresteijn, Jannick A N; Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people.; European heart journal; 2020; vol. 41 (no. 11); 1190-1199

Study details

Study type	Retrospective cohort study
Study location	Development and internal validation: USA External validation: USA, Germany, Netherlands, and UK
Study setting	Development and internal validation: Multi-Ethnic Study of Atherosclerosis - American population-based cohort (enrolment period: 2000-2002) External validation: EPIC-Norfolk - UK population-based cohort (enrolment period: 1993-1997)
Study dates	Derivation cohort based on patients enrolled between 2000 and 2002 UK validation cohort based on patients enrolled between 1993 and 1997
Sources of funding	Netherlands Heart Foundation (2016T026).
Study sample	Development (MESA; n=6715): Recruited men and women aged 45-84 years of age, free of known (self-reported) clinical cardiovascular disease, active cancer treatment, pregnancy, any serious medical condition which would prevent long-term participation; weight >136 kg; cognitive inability as judged by the interviewer; living in a nursing home or on the waiting list for a nursing home; plans to leave the community within five years; language barrier; chest computerized tomography scan in the past year. Probability sampling from four communities in pre-defined sex and race/ethnicity proportions.

	External validation (EPIC-Norfolk, n=23548): Recruited men and women aged 39-79 from the county of Norfolk from the population-based sampling frame of people registered with 35 participating General Practices.
Inclusion criteria	Participants in the development or validation cohorts.
Exclusion criteria	Participants <45 years, with a history of CVD, heart failure, chronic kidney disease epidemiology collaboration estimated glomerular filtration rate (CKD-EPI eGFR) <30mL/min/1.73m2, and terminal malignancy at baseline. As the model aims to estimate 10-year and lifetime risk for people aged 45–80 years, those >80 years at baseline were not included in validation cohorts. Patients aged >80 years at baseline were included in the development cohort to stabilize estimations between the 80th and 90th life-years.
Population subgroups	NA
Risk tool(s)	Lifetime-perspective Cardiovascular Disease (LIFE-CVD) model for the estimation of individual-level 10 years and lifetime treatment-effects of cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people
Predictors	Predictors were pre-specified based on the literature and availability in clinical practice: gender, systolic blood pressure (SBP, mmHg), non-high density lipoprotein cholesterol (non-HDLc, mmol/L), body mass index (kg/m2), smoking status (current, former, and never), presence of diabetes mellitus (yes/no, 2007 American Diabetes Association fasting criteria), a positive history of premature (prior to age 60) myocardial infarction (MI) in either parent.
Model development and validation	Development The model was developed in the MESA cohort due to the wide range of baseline ages, relatively recent commencement (2000), and a high degree of racial/ethnic diversity. The model comprises of two complementary Fine and Gray competing-risk adjusted left-truncated sub-distribution hazard functions: one for CVD-events and one for non-CVD mortality. Age was used as the time-scale meaning participants contributed from the age at cohort entry to the age at end of follow-up. Internal validation was performed on a set of MESA participants drawn by bootstrapping from the dataset of individuals aged 45–80 years at baseline. The expected vs. observed ratio of CVD-events and non-CVD mortality in MESA was used to recalibrate the intercepts.

	External validation was then performed in ARIC, HNR, EPIC-NL, and EPIC-Norfolk. Geographical differences in event rates were corrected based on the intercept recalibration in the HNR-study, and the same recalibration coefficients were used for the other European cohorts.
Outcome	Cardiovascular disease-events were defined as fatal or non-fatal MI or stroke, resuscitated cardiac arrest, and coronary heart disease (CHD)-death. The competing-risk outcome was death from any non-CVD cause.
Duration of follow-up	In MESA, 621 CVD-events and 795 non-CVD deaths occurred over a median follow-up duration of 13.0 years.
Indirectness	Derivation and internal validation cohorts based on an indirect population.
Additional comments	

Study arms

Derivation cohort (MESA) (N = 6715)
Multi-Ethnic Study of Atherosclerosis

Internal validation (MESA) (N = 6526)
Of the 6715 participants used for derivation, the 6526 individuals aged 45-80 years at baseline were resampled with replacement.

External validation (EPIC-Norfolk) (N = 23548)
European Prospective Investigation into Cancer and Nutrition - Norfolk

Characteristics

Study-level characteristics

Characteristic	Study (N =)
CKD Nominal	NR
Socioeconomic status	NR

Nominal	
Autoimmune disease Nominal	NR
Serious mental illness Nominal	NR

Arm-level characteristics

Characteristic	Derivation cohort (MESA) (N = 6715)	Internal validation (MESA) (N = 6526)	External validation (EPIC-Norfolk) (N = 23548)
% Female No of events	% = 47	-	% = 56
Mean age (SD) Median (IQR)	62 (53 to 70)	-	59 (52 to 67)
Caucasian No of events	% = 39	-	% = 100
African-American No of events	% = 28	-	% = 0
Other No of events	% = 34	-	% = 0
Diabetes No of events	% = 14	-	% = 2

Outcomes

Study timepoints

- 10 year (Validation is for 10 year risk only as not feasible to perform validation over a lifetime)

Discrimination

Outcome	Derivation cohort (MESA), 10 year, N =	Internal validation (MESA), 10 year, N = 6526	External validation (EPIC-Norfolk), 10 year, N = 23548
C-statistic Mean (95% CI)	-	0.74 (0.73 to 0.75)	0.76 (0.75 to 0.76)

Calibration
see graphs

Critical appraisal - PROBAST tool (EPIC-Norfolk validation cohort)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Lindbohm, 2019

Bibliographic Reference	Lindbohm, Joni V; Sipila, Pyry N; Mars, Nina J; Pentti, Jaana; Ahmadi-Abhari, Sara; Brunner, Eric J; Shipley, Martin J; Singh-Manoux, Archana; Tabak, Adam G; Kivimaki, Mika; 5-year versus risk-category-specific screening intervals for cardiovascular disease prevention: a cohort study.; The Lancet. Public health; 2019; vol. 4 (no. 4); e189-e199

Study details

Secondary publication of another included study- see primary study for details	Lindbohm 2021
Trial name / registration number	NA
Study type	Prospective cohort study
Study location	UK

Study setting	Whitehall II longitudinal, prospective cohort study
Study dates	Attaining risk factors at between Aug 7, 1991, and May 10, 1993; April 24, 1997, and Jan 8, 1999; Oct 8, 2002, and Sept 10, 2004; Oct 10, 2007, and Nov 18, 2009; and Jan 27, 2012, and Oct 30, 2013
Sources of funding	Medical Research Council, British Heart Association, National Institutes on Aging, NordForsk, Academy of Finland
Study sample	6964
Inclusion criteria	Participants were eligible for the analysis if they had participated in at least two risk-factor assessments between Aug 7, 1991, to May 10, 1993 and Jan 27, 2012, to Oct 30, 2013, or had participated in one screening and had a major cardiovascular event or died during follow-up
Exclusion criteria	Evidence of stroke, myocardial infarction, heart failure, atrial fibrillation, coronary artery bypass graft, or percutaneous coronary intervention at baseline
Population subgroups	NA
Risk tool(s)	Revised ASCVD algorithm: revised version to estimates the 10-year risk of a major cardiovascular event at each of the five clinical screenings
Predictors	Age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication (yes or no), smoking (yes or no), and diabetes (yes or no).
Model development and validation	NA
Outcome	Fatal coronary heart disease, non-fatal myocardial infarction, and fatal or non-fatal stroke.
Duration of follow-up	Mean (SD): 22.0 (5.0) years
Indirectness	No indirectness

Characteristics

Study-level characteristics

Characteristic	Study (N = 6964)
% Female Sample size	n = 2098 ; % = 30.1
Mean age (SD) Mean (SD)	50 (6)
Type 2 diabetes	n = 137 ; % = 2

Sample size	

Outcomes

Harrell's C statistic

Outcome	Study, , N = 6964
Revised ASCVD Custom value	0.72
ASCVD Custom value	0.71

Critical appraisal - PROBAST tool (ASCVD and revised ASCVD)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Lindbohm, 2021

Bibliographic Reference	Lindbohm, Joni V; Sipila, Pyry N; Mars, Nina; Knuppel, Anika; Pentti, Jaana; Nyberg, Solja T; Frank, Philipp; Ahmadi-Abhari, Sara; Brunner, Eric J; Shipley, Martin J; Singh-Manoux, Archana; Tabak, Adam G; Batty, G David; Kivimaki, Mika; Association between change in cardiovascular risk scores and future cardiovascular disease: analyses of data from the Whitehall II longitudinal, prospective cohort study.; The Lancet. Digital health; 2021; vol. 3 (no. 7); e434-e444

Study details

Secondary publication of another included	**Lindbohm 2019**

study- see primary study for details	
Other publications associated with this study included in review	Lindbohm 2019
Trial name / registration number	NA
Study type	Retrospective cohort study
Study location	UK
Study setting	Whitehall II longitudinal, prospective cohort study
Study dates	April 24, 1997, and Oct 2, 2019
Sources of funding	UK Medical Research Council, British Heart Foundation, Wellcome Trust, and US National Institute on Aging
Study sample	British Whitehall II cohort study. In 1985, all civil servants aged 35–55 years and working in 20 government departments in London, UK, were invited by letter to participate. The clinical examination at study entry between Sept 10, 1985, and March 29, 1988, did not include all cardiovascular risk factors. Participants underwent clinical examinations for a comprehensive set of risk factors in line with European, British, and US guidelines at 5-year intervals between Aug 7, 1991, and May 10, 1993; April 24, 1997, and Jan 8, 1999; Oct 8, 2002, and Sept 10, 2004; Oct 10, 2007, and Nov 18, 2009; and Jan 27, 2012, and Oct 30, 2013.
Inclusion criteria	No history of stroke, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, definite angina, heart failure, or peripheral artery disease at baseline
Exclusion criteria	Prevalent cardiovascular disease
Population subgroups	Low risk (<2·5%) Mean time spent: 8·7 (8·4–9·0) years Intermediate-low risk (2·5% to <5·0%) Mean time spent: 7·2 (7·0–7·5) years Intermediate-high risk (5·0% to <7·5%) Mean time spent: 3·9 (3·7–4·1) years High risk (7·5% to <15·0%) Mean time spent: 6·7 (6·3–7·1) years
Risk tool(s)	(1) Revised Atherosclerotic Cardiovascular Disease (ASCVD) algorithm (2) Systematic Coronary Risk Evaluation (SCORE)
Predictors	Age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication (yes or no), smoking (yes or no), and diabetes (yes or no).
Model development and validation	NA

Outcome	Major cardiovascular events as defined as fatal coronary heart disease, non-fatal myocardial infarction, and fatal or non-fatal stroke
Duration of follow-up	Mean (SD): 18·7 (5.5) years
Indirectness	No indirectness

Characteristics

Study-level characteristics

Characteristic	Study (N = 7996)
% Female No of events	n = 2464 ; % = 30.8
Mean age (SD) Mean (SD)	50 (6)
White Sample size	n = 7212 ; % = 90.5
Other Sample size	n = 754 ; % = 9.5
Type 2 diabetes Sample size	n = 155 ; % = 1.9

Outcomes

Harrell's C statistic

Outcome	Study, , N = 7996
ASCVD Custom value	0.699

Critical appraisal - PROBAST tool (ASCVD)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Livingstone, 2022

Bibliographic Reference	Livingstone, Shona J; Guthrie, Bruce; Donnan, Peter T; Thompson, Alexander; Morales, Daniel R; Predictive performance of a competing risk cardiovascular prediction tool CRISK compared to QRISK3 in older people and those with comorbidity: population cohort study.; BMC medicine; 2022; vol. 20 (no. 1); 152

Study details

Other publications associated with this study included in review	**Same cohort as Livingstone 2021 - split in this study to create a derivation and a validation set**
Trial name / registration number	NA
Study type	Prospective cohort study
Study location	UK
Study setting	Clinical Practice Research Datalink (CPRD) GOLD GP practices
Study dates	Cohort entry was the latest date of Jan 1, 2004, a patient's 25th birthday, or contribution of up-to-standard data for at least 1 year. Cohort exit was the date of a first CVD event, death, prescription of a statin, deregistration from the primary care practice, date of the last data collection from the practice, or the end of the study on March 31, 2016, whichever came first.
Sources of funding	National Institute for Health Research (NIHR) Health Services and Delivery Research Programme (project reference 15/12/22).
Study sample	CPRD Gold which does not overlap with the QRISK3 derivation dataset, although it is similar in its inclusion of linked primary care, hospital, and mortality data. Patients were randomly allocated to a fixed derivation and test dataset in a 2:1 ratio with the split balanced in terms of age and final event status.

Inclusion criteria	Patients in CPRD who: • were permanently registered with a primary care practice, • contributed up-to-standard data for at least 1 year, • had linkage to Hospital Episode Statistics (HES) discharge data and Office of National Statistics (ONS) mortality data • were aged 25–84 years • had no previous history of CVD • had no history of previous statin treatment.
Exclusion criteria	Patients in CPRD who: had missing Townsend deprivation scores
Population subgroups	Stratified results given by age modified Charlson Comorbidity Index (mCCI).
Risk tool(s)	Derivation and validation of a competing risk model alone (CRISK) and with Charlson Comorbidity score (CRISK-CCI). External validation of QRISK3-2017 model with the following adaptations: • a later cohort entry date (Jan 1, 2004, rather than Jan 1, 1998), • if no cholesterol values were available at baseline, QRISK3 derivation allowed cholesterol values from after the index date to be used if they were measured before any event; instead, this validation only included values recorded before the index date to avoid using future information in prediction, • Townsend deprivation score evaluated as the median of the vigintile (equal 20th) of the score for the area within which an individual lived, as individual values were not available.
Predictors	CRISK: Age, ethnicity, deprivation, systolic blood pressure, body mass index, total cholesterol to high density lipoprotein cholesterol ratio, smoking, family history of coronary heart disease in a first degree relative aged less than 60 years, type 1 diabetes, type 2 diabetes, treated hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease (stage 3, 4, or 5), systolic blood pressure variability (standard deviation of repeated measures), migraine, atypical antipsychotics, corticosteroids, systemic lupus erythematosus (SLE), severe mental illness, HIV/AIDs, and erectile dysfunction diagnosis or treatment in men. Covariates the same as QRISK3 with Fine-Gray competing risk modelling. CRISK-CCI: Age, ethnicity, deprivation, systolic blood pressure, body mass index, total cholesterol to high density lipoprotein cholesterol ratio, smoking, family history of coronary heart disease in a first degree relative aged less than 60 years, type 1 diabetes, type 2 diabetes, treated hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease (stage 3, 4, or 5), Charlson comorbidity score, systolic blood pressure variability (standard deviation of repeated measures), migraine, atypical antipsychotics,

	corticosteroids, systemic lupus erythematosus (SLE), severe mental illness, HIV/AIDs, and erectile dysfunction diagnosis or treatment in men. Covariates the same as QRISK3 with the addition of Charlson comorbidity score and with Fine-Gray competing risk modelling. QRISK3: Age, ethnicity, deprivation, systolic blood pressure, body mass index, total cholesterol to high density lipoprotein cholesterol ratio, smoking, family history of coronary heart disease in a first degree relative aged less than 60 years, type 1 diabetes, type 2 diabetes, treated hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease (stage 3, 4, or 5), systolic blood pressure variability (standard deviation of repeated measures), migraine, atypical antipsychotics, corticosteroids, systemic lupus erythematosus (SLE), severe mental illness, HIV/AIDs, and erectile dysfunction diagnosis or treatment in men.
Model development and validation	Development The derivation dataset was used to derive CRISK, a new Fine-Gray model to predict the 10-year risk of experiencing a CVD event accounting for the competing risk of non-CVD death. Separate models were estimated for men and women. The Fine-Gray model calculates the sub-distribution hazard ratio that is the instantaneous risk of failure from the CVD event in subjects who have not yet experienced a CVD event, whilst simultaneously accounting for the occurrence of non-CVD death. To facilitate comparison with QRISK3, all the same main effects and age interactions were included, but non-CVD death was additionally accounted for as a second (competing) outcome. 10-fold cross validation was conducted in the derivation data set. Next, a further model (CRISK-CCI) was derived which additionally included the CCI score in the model (categorised as 0, 1, 2, ≥ 3) as a validated predictor of total mortality. Validation The performance of CRISK and CRISK-CCI was compared to QRISK3 in the independent validation dataset by examining discrimination and calibration of all models, as well as patient reclassification into high risk (eligible for treatment).
Outcome	A first CVD event was defined as the earliest recording of any fatal or non-fatal coronary heart disease, ischaemic stroke, or transient ischaemic attack. Fatal CVD events were identified with codes from the International Classification of Diseases, tenth version (ICD-10), recorded in ONS death registration. Non-fatal events were identified either in primary care electronic health records (using Read codes, the standard coding system used in UK clinics) or HES discharge diagnoses (ICD-10 codes).
Duration of follow-up	Median follow-up in the whole cohort was 5·0 years (IQR 1·9–9·2), with 641 596 (22·1%) of 2 904 773 patients remaining in the cohort and CVD event-free at 10-year follow-up. In the derivation cohort, there were 14,150 incident cases of CVD observed in women in 2,865,660 years of follow-up (4.9 [95%CI 4.89–4.99] per 1000 person-years), compared to 17,689 incident cases in men in 2,632,804 years of follow-up (6.7 [95%CI 6.66–6.78] per 1000 person-years).

Study arms

Derivation cohort (CRISK and CRISK-CCI) (N = 1936516)

CRISK-CCI validation: women (N = 494865)

CRISK-CCI validation: men (N = 473392)

CRISK validation: women (N = 494865)

CRISK validation: men (N = 473392)

QRISK3 validation: women (N = 494865)

QRISK3 validation: men (N = 473392)

Outcomes

Study timepoints

- 10 year (risk estimate)

Discrimination

Outcome	Derivation cohort (CRISK and CRISK-CCI), 10 year, N = 1936516	CRISK-CCI validation: women, 10 year, N = 494865	CRISK-CCI validation: men, 10 year, N = 473392	CRISK validation: women, 10 year, N = 494865	CRISK validation: men, 10 year, N = 473392	QRISK3 validation: women, 10 year, N = 494865	QRISK3 validation: men, 10 year, N = 473392
Harrell's C-statistic QRISK3 cohort overlaps with Livingstone 2021 Mean (95% CI)	-	0.86 (0.86 to 0.87)	0.82 (0.82 to 0.82)	0.86 (0.86 to 0.87)	0.83 (0.83 to 0.84)	0.86 (0.86 to 0.87)	0.83 (0.83 to 0.84)
Age: 25-44 Mean (95% CI)	-	0.76 (0.75 to 0.78)	0.73 (0.72 to 0.75)	0.76 (0.74 to 0.78)	0.74 (0.73 to 0.76)	0.77 (0.75 to 0.78)	0.74 (0.73 to 0.75)
Age: 45–64 Mean (95% CI)	-	0.71 (0.7 to 0.72)	0.66 (0.65 to 0.67)	0.71 (0.7 to 0.72)	0.68 (0.68 to -)	0.71 (0.7 to 0.72)	0.68 (0.67 to 0.68)
Age 65-74 Mean (95% CI)	-	0.65 (0.64 to 0.66)	0.59 (0.58 to 0.6)	0.65 (0.63 to 0.66)	0.61 (0.6 to 0.62)	0.64 (0.63 to 0.65)	0.61 (0.6 to 0.62)
Age: 75-84 Mean (95% CI)	-	0.62 (0.61 to 0.62)	0.57 (0.56 to 0.58)	0.61 (0.61 to 0.62)	0.59 (0.58 to 0.6)	0.61 (0.6 to 0.62)	0.59 (0.58 to 0.6)
CCI 0 Mean (95% CI)	-	0.86 (0.86 to 0.87)	0.81 (0.81 to 0.82)	0.86 (0.86 to 0.87)	0.83 (0.82 to 0.83)	0.86 (0.86 to 0.87)	0.82 (0.82 to 0.83)
CCI 1 Mean (95% CI)	-	0.84 (0.83 to 0.85)	0.82 (0.81 to 0.83)	0.84 (0.83 to 0.85)	0.83 (0.82 to 0.84)	0.84 (0.83 to 0.85)	0.83 (0.82 to 0.84)
CCI 2 Mean (95% CI)	-	0.79 (0.77 to 0.81)	0.7 (0.69 to 0.72)	0.79 (0.77 to 0.81)	0.73 (0.71 to 0.75)	0.79 (0.77 to 0.81)	0.73 (0.71 to 0.75)
CCI 3+ Mean (95% CI)	-	0.75 (0.73 to 0.78)	0.67 (0.64 to 0.7)	0.75 (0.73 to 0.78)	0.7 (0.67 to 0.73)	0.75 (0.73 to 0.78)	0.7 (0.67 to 0.72)

Calibration

See graphs

Critical appraisal - PROBAST tool (CRISK and CRISK-CCI internal validation)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low (Note outcome definition includes TIA)

Livingstone, 2021

Bibliographic Reference	Livingstone, Shona; Morales, Daniel R; Donnan, Peter T; Payne, Katherine; Thompson, Alexander J; Youn, Ji-Hee; Guthrie, Bruce; Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study.; The Lancet. Healthy longevity; 2021; vol. 2 (no. 6); e352-e361

Study details

Other publications associated with this study included in review	**Livingstone 2022 uses the same cohort**
Study type	Retrospective cohort study
Study location	UK
Study setting	Clinical Practice Research Datalink (CPRD) Gold GP practices
Study dates	Cohort entry was the latest date of Jan 1, 2004, a patient's 25th birthday, or contribution of up-to-standard data for at least 1 year. Cohort exit was the date of a first CVD event, death, prescription of a statin, deregistration from the primary care practice, date of the last data collection from the practice, or the end of the study on March 31, 2016, whichever came first.
Sources of funding	National Institute for Health Research (NIHR) Health Services and Delivery Research Programme (project reference 15/12/22).
Study sample	CPRD Gold which does not overlap with the QRISK3 derivation dataset, although it is similar in its inclusion of linked primary care, hospital, and mortality data.
Inclusion criteria	Patients in CPRD who: were permanently registered with a primary care practice,

	contributed up-to-standard data for at least 1 year, had linkage to Hospital Episode Statistics (HES) discharge data and Office of National Statistics (ONS) mortality data were aged 25–84 years had no previous history of CVD had no history of previous statin treatment.
Exclusion criteria	Patients in CPRD who: had missing Townsend deprivation scores
Population subgroups	Stratified results given by age modified Charlson Comorbidity Index (mCCI).
Risk tool(s)	QRISK3-2017 model with the following adaptations: • a later cohort entry date (Jan 1, 2004, rather than Jan 1, 1998), • if no cholesterol values were available at baseline, QRISK3 derivation allowed cholesterol values from after the index date to be used if they were measured before any event; instead, this validation only included values recorded before the index date to avoid using future information in prediction, • Townsend deprivation score evaluated as the median of the vigintile (equal 20th) of the score for the area within which an individual lived, as individual values were not available.
Predictors	Age, ethnicity, deprivation, systolic blood pressure, body mass index, total cholesterol to high density lipoprotein cholesterol ratio, smoking, family history of coronary heart disease in a first degree relative aged less than 60 years, type 1 diabetes, type 2 diabetes, treated hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease (stage 3, 4, or 5), systolic blood pressure variability (standard deviation of repeated measures), migraine, atypical antipsychotics, corticosteroids, systemic lupus erythematosus (SLE), severe mental illness, HIV/AIDs, and erectile dysfunction diagnosis or treatment in men.
Model development and validation	External validation of QRISK3 Those with missing data on ethnicity were assumed to be White, and multiple imputation was used for missing body-mass index, total cholesterol to HDL cholesterol ratio, systolic blood pressure and its variability, and smoking status. Calculated the 10-year risk of having a cardiovascular event for each patient using the published QRISK3 equation without recalibration.
Outcome	A first CVD event was defined as the earliest recording of any fatal or non-fatal coronary heart disease, ischaemic stroke, or transient ischaemic attack. Fatal CVD events were identified with codes from the International Classification of Diseases, tenth version (ICD-10), recorded in ONS death registration.

	Non-fatal events were identified either in primary care electronic health records (using Read codes, the standard coding system used in UK clinics) or HES discharge diagnoses (ICD-10 codes).
Duration of follow-up	Median follow-up in the whole cohort was 5·0 years (IQR 1·9–9·2), with 641 596 (22·1%) of 2 904 773 patients remaining in the cohort and CVD event-free at 10-year follow-up. By 10 years, CVD events occurred in 39 048 (2·6%) of 1 484 597 women compared with 49 146 (3·5%) of 1 420 176 men, and non-CVD deaths occurred in 40 839 (2·8%) women compared with 38 226 (2·7%) men. Censoring due to statin initiation was more common than that due to non-CVD death, but almost two thirds of both men and women were censored due to deregistration or to having less than 10 years of follow-up before the end of the study. Sensitivity analysis using a censoring-adjusted C-statistic found a somewhat lower discrimination than in the main analysis, but did not alter the overall interpretation.

Characteristic	**Study (N = 2904773)**
% Female No of events	n = 1484597 ; % = 51.1
Women Mean (SD)	46 (15.3)
Men Mean (SD)	44.8 (13.9)
White or not recorded Custom value	Women: 91.8%; Men: 94.1%
Indian Custom value	Women: 1.5%; Men: 1.1%
Pakistani Custom value	Women: 0.6%; Men: 0.5%
Bangladeshi Custom value	Women: 0.2%; Men: 0.2%
Other Asian Custom value	Women: 0.9%; Men: 0.7%
Black Caribbean	Women: 91.8%; Men: 94.1%

Custom value	
Black African Custom value	Women: 0.6%; Men: 0.5%
Chinese Custom value	Women: 0.5%; Men: 0.2%
Other Custom value	Women: 2.6%; Men: 1.9%
Women No of events	n = 3752 ; % = 0.3
Men No of events	n = 4843 ; % = 0.3
Women No of events	n = 17022 ; % = 1.1
Men No of events	n = 21077 ; % = 1.5
Women No of events	n = 6918 ; % = 0.5
Men No of events	n = 5659 ; % = 0.4
Socioeconomic status Nominal	NR
Systemic lupus erythematosus: Women No of events	n = 1725 ; % = 0.1
Systemic lupus erythematosus: Men No of events	n = 165 ; % = 0.01
Rheumatoid arthritis: Women No of events	n = 12702 ; % = 0.9
Rheumatoid arthritis: Men No of events	n = 4724 ; % = 0.3
Women No of events	n = 110799 ; % = 7.5

Men No of events	n = 57264 ; % = 4

Outcomes

Study timepoints

- 10 year (risk estimate)

Discrimination

Outcome	QRISK3 external validation: women, 10 year, N = 1484597	QRISK3 external validation: men, 10 year, N = 1420176
Harrell's C statistic full cohort Mean (95% CI)	0.87 (0.86 to 0.87)	0.83 (0.83 to 0.84)
Age: 25-44 Mean (95% CI)	0.76 (0.75 to 0.77)	0.76 (0.75 to 0.76)
Age: 45–64 Mean (95% CI)	0.71 (0.7 to 0.71)	0.68 (0.68 to 0.69)
Age 65-74 Mean (95% CI)	0.64 (0.64 to 0.65)	0.61 (0.61 to 0.62)
Age: 75-84 Mean (95% CI)	0.61 (0.61 to 0.62)	0.59 (0.58 to 0.59)
mCCI: 0 Mean (95% CI)	0.86 (0.86 to 0.87)	0.83 (0.82 to 0.83)
mCCI: 1 Mean (95% CI)	0.85 (0.84 to 0.85)	0.83 (0.82 to 0.84)
mCCI: 2 Mean (95% CI)	0.79 (0.78 to 0.8)	0.73 (0.72 to 0.74)
mCCI: ≥3 Mean (95% CI)	0.74 (0.73 to 0.76)	0.7 (0.68 to 0.71)

Royston's D Mean (95% CI)	2.43 (2.41 to 2.45)	2.1 (2.08 to 2.12)
Age: 25-44 Mean (95% CI)	1.69 (1.63 to 1.76)	1.57 (1.52 to 1.61)
Age: 45–64 Mean (95% CI)	1.25 (1.22 to 1.28)	1.04 (1.02 to 1.07)
Age 65-74 Mean (95% CI)	0.82 (0.77 to 0.86)	0.63 (0.59 to 0.66)
Age: 75-84 Mean (95% CI)	0.61 (0.56 to 0.66)	0.46 (0.42 to 0.51)
mCCI: 0 Mean (95% CI)	2.4 (2.38 to 2.43)	2.02 (2 to 2.04)
mCCI: 1 Mean (95% CI)	2.2 (2.17 to 2.24)	2 (1.96 to 2.03)
mCCI: 2 Mean (95% CI)	1.73 (1.67 to 1.78)	1.28 (1.22 to 1.34)
mCCI: ≥3 Mean (95% CI)	1.4 (1.32 to 1.48)	1.13 (1.04 to 1.21)

Calibration

Outcome	QRISK3 external validation: women, 10 year, N = 1484597	QRISK3 external validation: men, 10 year, N = 1420176
Calibration plots Custom value	See graph	See graph

Critical appraisal - PROBAST tool (QRISK3)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low (Note outcome definition includes TIA)

Osborn, 2019

Bibliographic Reference	Osborn, D; Burton, A; Walters, K; Atkins, L; Barnes, T; Blackburn, R; Craig, T; Gilbert, H; Gray, B; Hardoon, S; Heinkel, S; Holt, R; Hunter, R; Johnston, C; King, M; Leibowitz, J; Marston, L; Michie, S; Morris, R; Morris, S; Nazareth, I; Omar, R; Petersen, I; Peveler, R; Pinfold, V; Stevenson, F; Zomer, E; Primary care management of cardiovascular risk for people with severe mental illnesses: the Primrose research programme including cluster RCT; Programme Grants for Applied Research; 2019

Study details

Secondary publication of another included study- see primary study for details	**Secondary report of Osborn 2015**

Osborn, 2015

Bibliographic Reference	Osborn, David P J; Hardoon, Sarah; Omar, Rumana Z; Holt, Richard I G; King, Michael; Larsen, John; Marston, Louise; Morris, Richard W; Nazareth, Irwin; Walters, Kate; Petersen, Irene; Cardiovascular risk prediction models for people with severe mental illness: results from the prediction and management of cardiovascular risk in people with severe mental illnesses (PRIMROSE) research program.; JAMA psychiatry; 2015; vol. 72 (no. 2); 143-51

Study details

Other publications associated with this study included in review	**Osborn 2019**
Trial name / registration number	N/A

Study type	Prospective cohort study
Study location	UK
Study setting	UK primary care database: THIN
Study dates	Data collected between January 1995 and December 2010.
Sources of funding	National Institute for Health Research (NIHR)
Study sample	De-identified data from the THIN database
Inclusion criteria	Age 30 to 90 years with a diagnostic entry in their primary care electronic health record for an SMI at any time during their follow-up period. SMI defined as: (1) schizophrenia and schizoaffective disorder, (2) bipolar affective disorder, and (3) other nonorganic psychoses.
Exclusion criteria	Individual patients who: • had less than a year's follow-up data after registration to allow time for patient history and risk factor information to be captured • had a diagnosis of CVD prior to baseline • were already prescribed statins at baseline (since risk scores are used to guide statin treatment) • had a record of dementia within one year of their SMI diagnosis (as the diagnosis of SMI was likely to be misclassification of dementia) • had missing Townsend deprivation data.
Population subgroups	Reported separately for men and women
Risk tool(s)	PRIMROSE BMI PRIMROSE lipid
Predictors	PRIMROSE BMI: sex, age, SBP, weight, height, history of diabetes, smoking history, calendar year at baseline, use of anti-depressants, history of heavy drinking, Townsend quintile of deprivation, SMI diagnosis (schizophrenia, bipolar disorder, other psychosis, unknown - on SMI register), use of second generation antipsychotics at baseline, use of first generation antipsychotics at baseline. PRIMROSE lipid: sex, age, SBP, total cholesterol, HDL cholesterol, history of diabetes, smoking history, calendar year at baseline, use of anti-depressants, history of heavy drinking, Townsend quintile of deprivation, SMI diagnosis (schizophrenia, bipolar disorder, other psychosis, unknown - on SMI register), use of second generation antipsychotics at baseline.

Model development and validation	Derivation: both PRIMROSE risk models were derived using Cox proportional hazards regression modelling. Robust standard errors were used to account for clustering of patients within general practices. The assumption of proportional hazards was checked using Schoenfeld residuals4 and plots of the log cumulative hazard function. Continuous variables (age, SBP, total cholesterol, HDL cholesterol, height, weight, calendar year) were centered around their mean value and the assumption of a linear relationship was assessed using fractional polynomials and transformations made when linear relationships were not confirmed. Backwards elimination was used to determine which of the additional SMI-specific variables above (e.g. SMI diagnosis) should be retained, using the Akaike's Information Criteria. Validation: 10-fold internal cross validation. The cohort was split into 10 random "test sets", based on the general practices patients were registered with, each containing an equal number of practices. The discriminative performance of the PRIMROSE models was assessed by separately for each test set and an overall point estimate was calculated by combining predicted values from all the test sets from each separate validation.
Outcome	Newly recorded fatal and nonfatal cardiovascular events - a diagnostic record for: • myocardial infarction, • angina pectoris, • coronary heart disease, • major coronary surgery and revascularization, • cerebrovascular accident, • transient ischemic attack.
Duration of follow-up	Median follow-up period 5.6 years (interquartile range, 2.5-9.2 years). 20.7% had 10 years or more of follow-up.
Indirectness	NA
Additional comments	There were 2324 newly recorded CVD events during the follow-up period, corresponding to a crude incidence rate of 9.72 (95%CI, 9.33-10.1) per 1000 person-years. The incidence of CVD increased with age and was higher in men within all age categories except for the very oldest category. The most common events were ischemic or unspecified stroke (778 [33.5%] of the total events),myocardial infarction (414[17.8%]),TIA ((349[15.0%]),angina(325 [14.0%]), coronary heart disease unspecified (304 [13.1%]), unstable angina (65 [2.8%]), and haemorrhagic stroke (46 [2.0%]).

Study arms

PRIMROSE derivation (N = 38824)

Derivation set for lipid and BMI models

PRIMROSE BMI internal validation (N = 38824)

PRIMROSE lipid internal validation (N = 38824)
2nd risk tool

Characteristics

Study-level characteristics

Characteristic	Study (N =)
% Female No of events	n = 20407 ; % = 52.6
Mean age (SD) Mean (SD)	49.5 (15.6)
Ethnicity Nominal	NR
Type 1 diabetes History of diabetes No of events	n = 1356 ; % = 3.5
CKD Nominal	NR
Quintile 1 Least deprived No of events	n = 6021 ; % = 15.5
Quintile 2 No of events	n = 6599 ; % = 17
Quintile 3	n = 7967 ; % = 20.6

No of events	
Quintile 4 No of events	n = 9252 ; % = 23.8
Quintile 5 Most deprived No of events	n = 8985 ; % = 23.1
Autoimmune disease Nominal	NR
Schizophrenia No of events	n = 13232 ; % = 34.1
Bipolar disorder No of events	n = 10098 ; % = 26
Other No of events	n = 11205 ; % = 28.9
Unknown (on SMI register) No of events	n = 4289 ; % = 11

Outcomes

Study timepoints

- 10 year (risk estimate)

Discrimination

Outcome	PRIMROSE derivation, 10 year, N =	PRIMROSE BMI internal validation, 10 year, N = 3882	PRIMROSE lipid internal validation, 10 year, N = 3882
C statistic			
Men n=1842 Mean (95% CI)	-	0.78 (0.74 to 0.83)	0.8 (0.76 to 0.83)

Women n=2041 Mean (95% CI)	-	0.78 (0.75 to 0.81)	0.79 (0.76 to 0.82)
D statistic			
Men Mean (95% CI)	-	1.84 (1.73 to 1.96)	1.92 (1.8 to 2.03)
Women Mean (95% CI)	-	1.8 (1.7 to 1.9)	1.87 (1.76 to 1.98)

Calibration

Outcome	PRIMROSE derivation, 10 year, N =	PRIMROSE BMI internal validation, 10 year, N = 38824	PRIMROSE lipid internal validation, 10 year, N = 38824
Calibration plot Custom value	-	see graph	see graph

Critical appraisal - PROBAST tool (PRIMROSE BMI and lipid internal validation)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	High (Missing data and internal validation only)
Overall Risk of bias and Applicability	Concerns for applicability	Low

Tillin, 2014

Bibliographic Reference	Tillin, Therese; Hughes, Alun D; Whincup, Peter; Mayet, Jamil; Sattar, Naveed; McKeigue, Paul M; Chaturvedi, Nish; SABRE Study, Group; Ethnicity and prediction of cardiovascular disease: performance of QRISK2 and Framingham scores in a U.K. tri-ethnic prospective cohort study (SABRE--Southall And Brent REvisited).; Heart (British Cardiac Society); 2014; vol. 100 (no. 1); 60-7

Study details

Secondary publication of another included study- see primary study for details	**N/A**
Other publications associated with this study included in review	N/A
Trial name / registration number	N/A
Study type	Prospective cohort study
Study location	UK
Study setting	Southall and Brent, West London
Study dates	Baseline: 1988–1991 Follow-up: 10 years
Sources of funding	Medical Research Council, Diabetes UK and British Heart Foundation and at follow-up by the Wellcome Trust and British Heart Foundation
Study sample	European, South Asian, and African Caribbean men and women in a UK population based cohort in West London
Inclusion criteria	Randomly selected from primary care lists
Exclusion criteria	None stated
Population subgroups	(1) White Europeans (2) South Asians (3) African Caribbeans
Risk tool(s)	QRISK2 for estimation of 10-year risk of fatal and non-fatal CVD events Framingham risk score for estimation of 10-year risk of fatal and non-fatal CVD events
Model development and validation	QRISK2 scores at baseline were calculated applying the published algorithm (http://svn.clinrisk.co.uk/ qrisk2 XML source: Q68_qrisk2_2012_1_1.xml, STATA dta time stamp: 2 January 2012, 23:10). The Framingham risk score was calculated using the published algorithm with South Asian ethnicity adjustment.
Outcome	Fatal or non-fatal CVD: First myocardial infarction, angina, CHD, stroke, transient ischaemic attack, revascularisation

Duration of follow-up	10 years
Indirectness	No indirectness

Study arms

European White Men (N = 1359)

South Asian Men (N = 1076)

African Caribbean Men (N = 307)

European White Women (N = 444)

South Asian Women (N = 241)

African Caribbean Women (N = 247)

Characteristics

Study-level characteristics

Characteristic	Study (N = 3821)
% Female Sample size	n = 932 ; % = 25

European White Men Out of a total number of men Sample size	n = 1359 ; % = 48
South Asian Men Out of a total number of men Sample size	n = 1076 ; % = 39
African Caribbean Men Out of a total number of men Sample size	n = 307 ; % = 11
European White Women Out of a total number of women Sample size	n = 444 ; % = 48
Asian Women Out of a total number of women Sample size	n = 241 ; % = 26
African Caribbean Women Out of a total number of women Sample size	n = 247 ; % = 27
Mean age	
European White Men Mean (SD)	52.8 (7.1)
South Asian Men Mean (SD)	50.8 (6.9)
African Caribbean Men Mean (SD)	53.5 (5.8)
European White Women Mean (SD)	53 (6.8)
South Asian Women Mean (SD)	50.3 (6.5)
African Caribbean Women Mean (SD)	52.6 (6)
Ethnicity	

European White Sample size	n = 1803 ; % = 49
South Asians Sample size	n = 1317 ; % = 36
African Caribbean Sample size	n = 554 ; % = 15
Diabetes	
European White Men Sample size	n = 81 ; % = 6
South Asian Men Sample size	n = 209 ; % = 19
African Caribbean Men Sample size	n = 53 ; % = 17
European White Women Sample size	n = 17 ; % = 4
South Asian Women Sample size	n = 38 ; % = 6
African Caribbean Women Sample size	n = 53 ; % = 21
Socioeconomic status	
European White Men Townsend score Mean (95% CI)	2.5 (2.3 to 2.6)
South Asian Men Townsend score Mean (95% CI)	3.5 (3.4 to 3.7)
African Caribbean Men Townsend score Mean (95% CI)	4.3 (4 to 4.6)
European White Women Townsend score	3.3 (3 to 3.5)

Mean (95% CI)	
South Asian Women Townsend score Mean (95% CI)	3.3 (3.1 to 3.5)
African Caribbean Women Townsend score Mean (95% CI)	4.9 (4.5 to 5.3)

Outcomes

Study timepoints

- 10 year

Discrimination and ratio of predicted to observed risk: QRISK2 and Framingham risk score by sex and ethnicity (95% CIs)

Outcome	European White Men, 10 year, N = 1359	South Asian Men, 10 year, N = 1076	African Caribbean Men, 10 year, N = 307	European White Women, 10 year, N = 444	South Asian Women, 10 year, N = 241	African Caribbean Women, 10 year, N = 247
AUROC QRISK2 score (AUCROC (95%CI)) Custom value	0.70 (0.66 to 0.74)	0.73 (0.69 to 0.77)	0.67 (0.57 to 0.77)	0.75 (0.67 to 0.82)	0.75 (0.66 to 0.84)	0.65 (0.54 to 0.76)
QRISK2 score D statistic (95%CI) Custom value	1.06 (0.82 to 1.30)	1.22 (0.99 to 1.45)	0.96 (0.32 to 1.59)	1.33 (0.79 to 1.87)	1.55 (0.91 to 2.19)	0.74 (0 to 1.63)
QRISK2 score observed: predicted (95%CI) Custom value	0.78 (0.72 to 0.85)	0.71 (0.64 to 0.78)	0.95 (0.80 to 1.00)	0.95 (0.80 to 1.00)	0.52 (0.34 to 0.72)	1.22 (1.04 to 1.84)

AUROC QRISK2 score - Polarity - Higher values are better
QRISK2 score D statistic (95%CI) - Polarity - Higher values are better

Critical appraisal - PROBAST tool (African Caribbean Men, European White Women, South Asian Women, African Caribbean Women)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	High (Low event rate)
Overall Risk of bias and Applicability	Concerns for applicability	Low

Critical appraisal - PROBAST tool (European White Men, South Asian Men)

Section	Question	Answer
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

Appendix E Forest plots and summary ROC curves

E.1 Summary of C statistic data

Figure 15: AUC of CVD risk prediction tools in women without established CVD

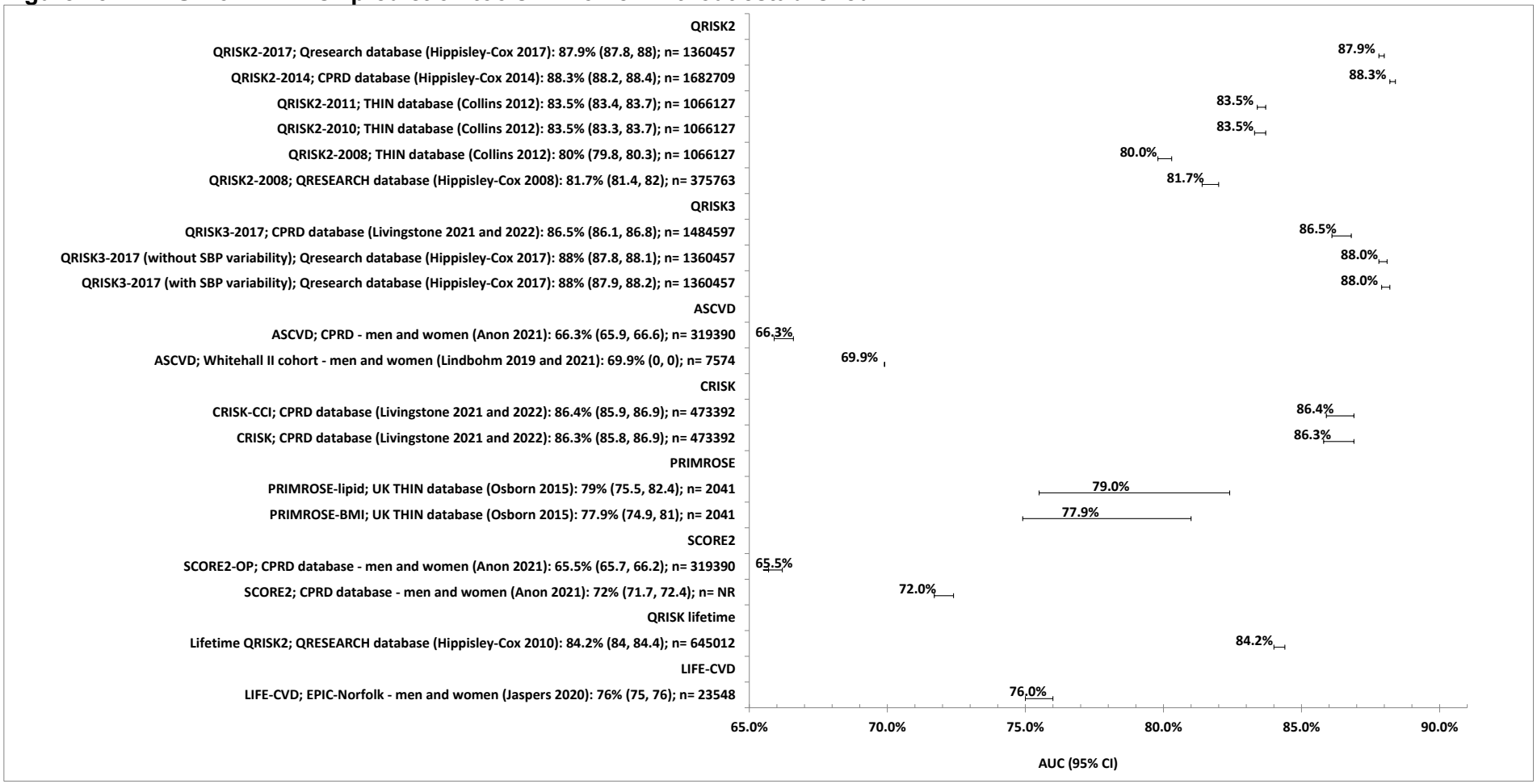
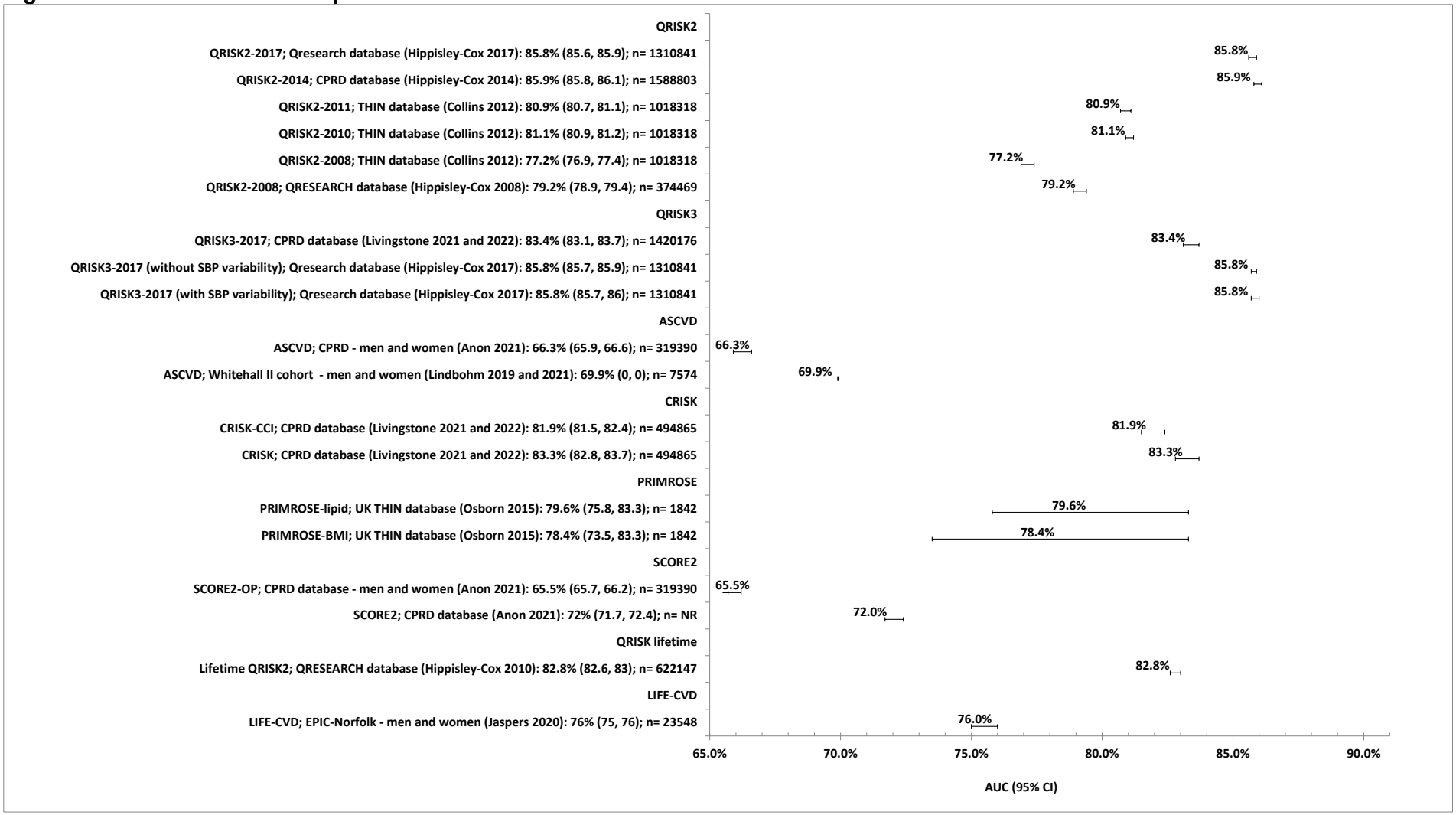


Figure 16: AUC of CVD risk prediction tools in men without established CVD



E.2 Sensitivity and specificity data

Figure 17: QRISK3 in women

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Livingstone 2022 (A: 7.5% threshold)	9718	90678	3238	391231	0.75 [0.74, 0.76]	0.81 [0.81, 0.81]
Livingstone 2022 (B: 10% threshold)	8849	70976	4107	410933	0.68 [0.67, 0.69]	0.85 [0.85, 0.85]
Livingstone 2022 (C: 20% threshold)	6084	33135	6872	448774	0.47 [0.46, 0.48]	0.93 [0.93, 0.93]

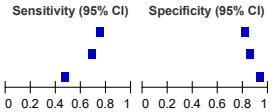


Figure 18: QRISK3 in men

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Livingstone 2022 (A: 7.5% threshold)	12967	130457	3334	326634	0.80 [0.79, 0.80]	0.71 [0.71, 0.72]
Livingstone 2022 (B: 10% threshold)	11620	101012	4677	356079	0.71 [0.71, 0.72]	0.78 [0.78, 0.78]
Livingstone 2022 (C: 20% threshold)	7350	41419	8951	415672	0.45 [0.44, 0.46]	0.91 [0.91, 0.91]

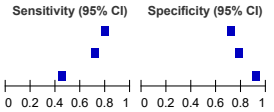


Figure 19: CRISK-CCI in women

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Livingstone 2022 (A: 7.5% threshold)	9498	84357	3458	397552	0.73 [0.73, 0.74]	0.82 [0.82, 0.83]
Livingstone 2022 (B: 10% threshold)	8542	64487	4414	417422	0.66 [0.65, 0.67]	0.87 [0.87, 0.87]
Livingstone 2022 (C: 20% threshold)	5344	26467	7612	455442	0.41 [0.40, 0.42]	0.95 [0.94, 0.95]

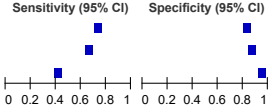
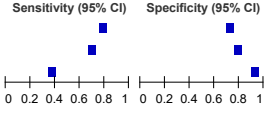


Figure 20: CRISK-CCI in men

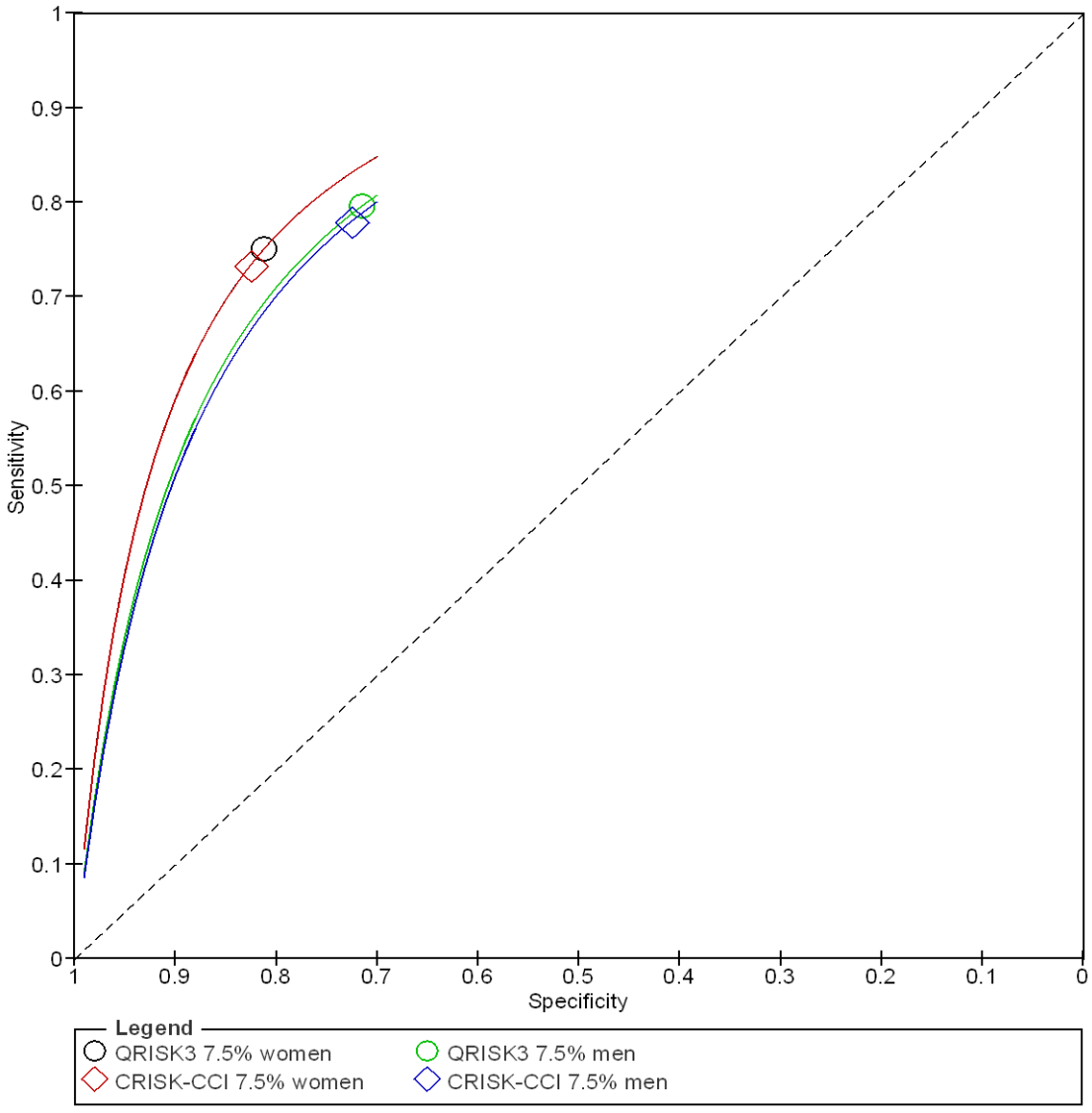
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Livingstone 2022 (A: 7.5% threshold)	12703	125649	3598	331442	0.78 [0.77, 0.79]	0.73 [0.72, 0.73]
Livingstone 2022 (B: 10% threshold)	11272	96099	5029	360992	0.69 [0.68, 0.70]	0.79 [0.79, 0.79]
Livingstone 2022 (C: 20% threshold)	6125	35392	10176	421699	0.38 [0.37, 0.38]	0.92 [0.92, 0.92]



Note: data from CRISK-CCI internal validation cohort

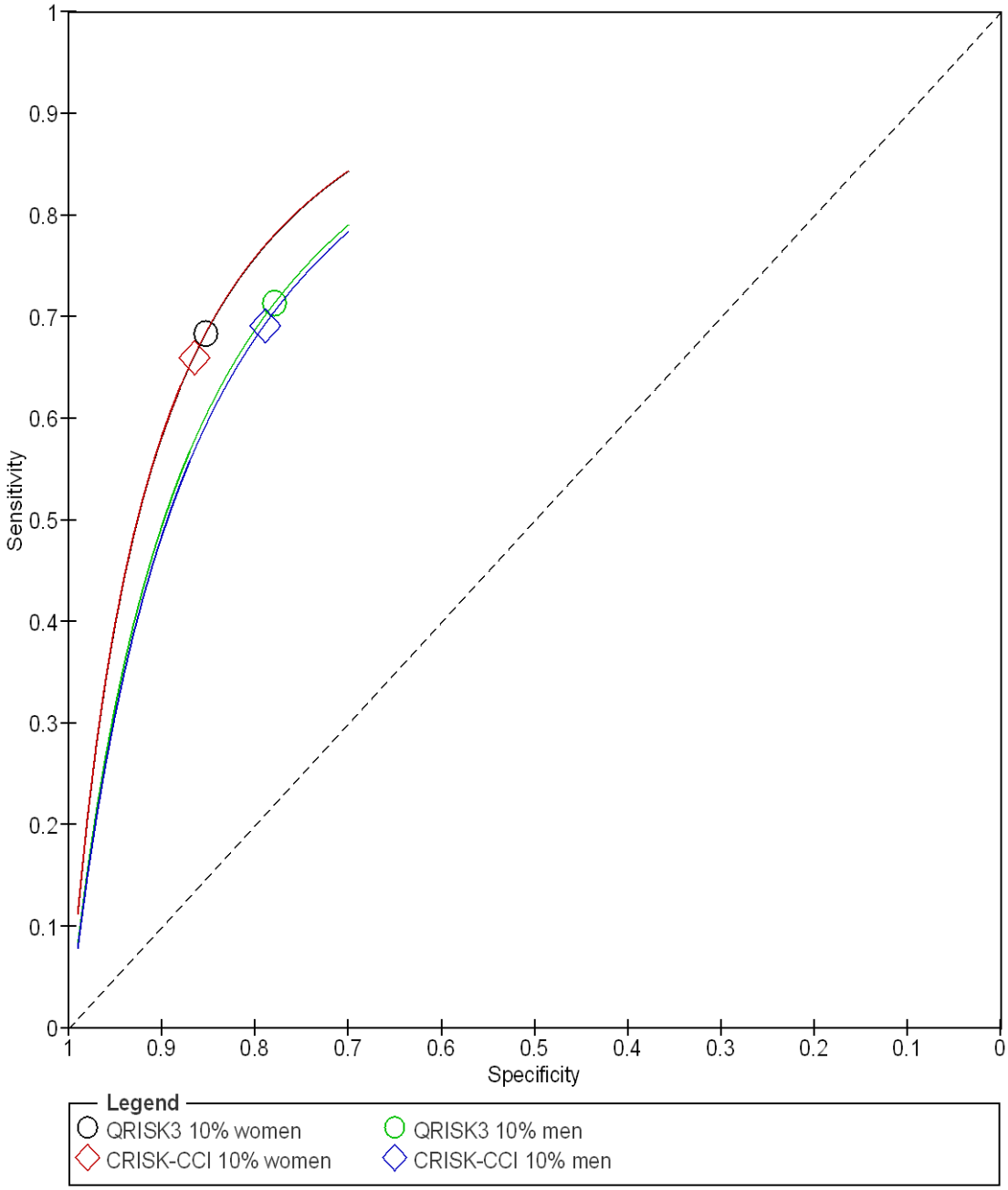
E.3 Summary ROC curves

Figure 21: Summary ROC curves comparing QRISK3 and CRISK-CCI at 7.5% threshold (data CRISK-CCI internal validation cohort)



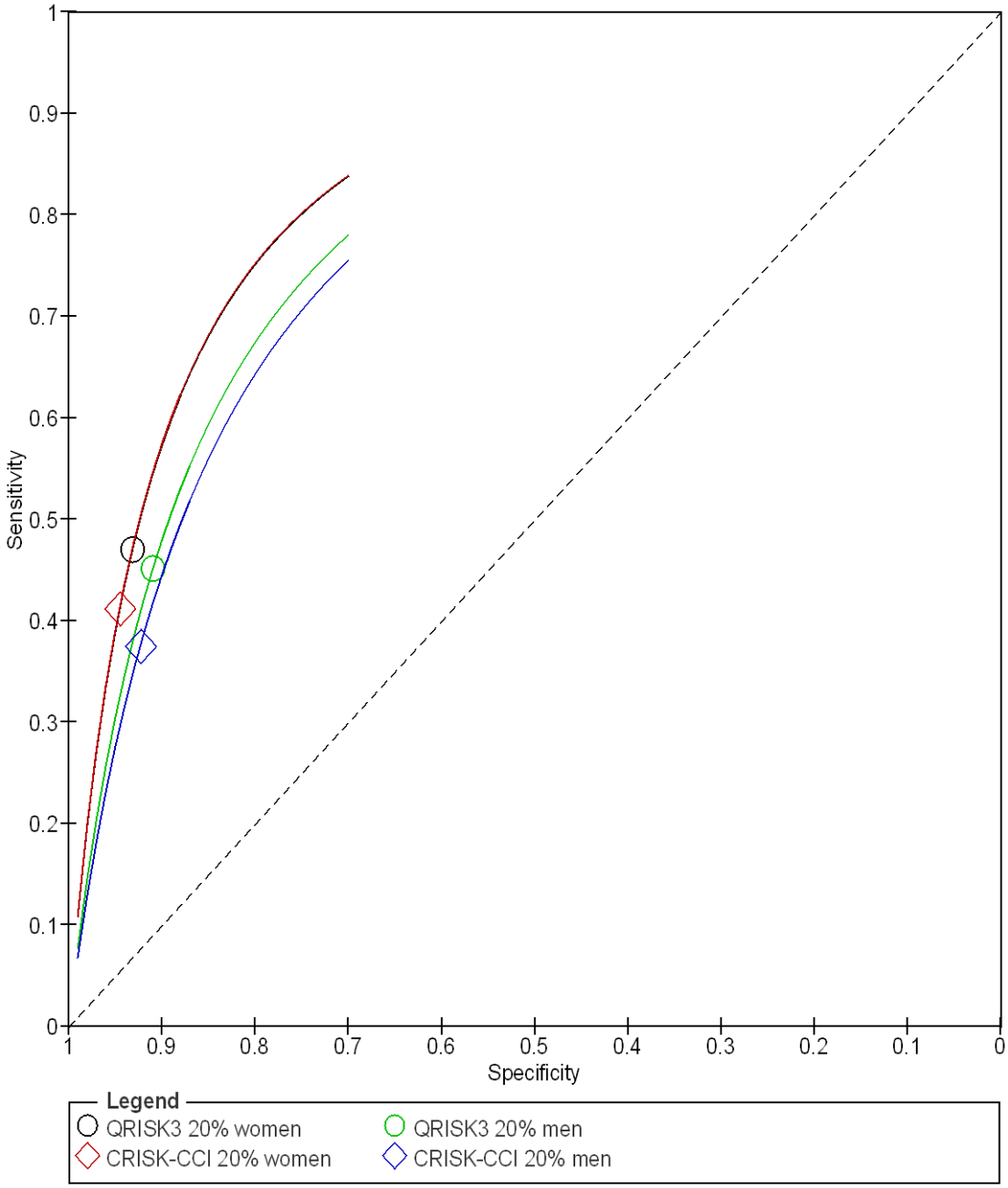
Note: data from CRISK-CCI internal validation cohort

Figure 22: Summary ROC curves comparing QRISK3 and CRISK-CCI at 10% threshold (data CRISK-CCI internal validation cohort)



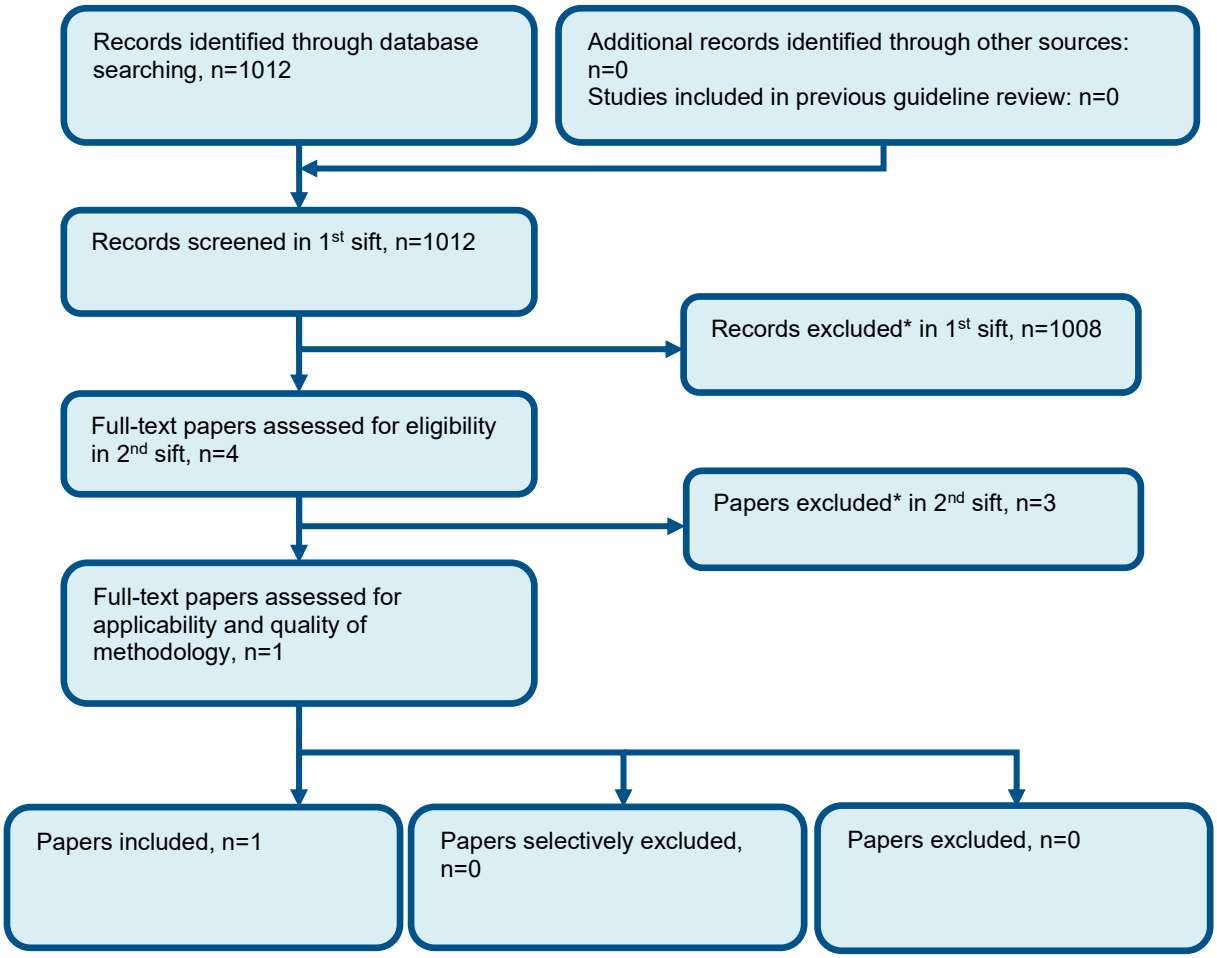
Note: data from CRISK-CCI internal validation cohort

Figure 23: Summary ROC curves comparing QRISK3 and CRISK-CCI at 20% threshold (data CRISK-CCI internal validation cohort)



Note: data from CRISK-CCI internal validation cohort

Appendix F Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G Economic evidence tables

Study	Zomer 2017[24]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** patient-level simulation **Approach to analysis:** decision tree to categorise based on risk algorithm and existing treatment; Markov model (1 year cycles) with CVD states (no CVD event, primary CVD event (CHD event: stable angina, unstable angina, MI, coronary artery surgery and unclassified CHD; CVA event: TIA, haemorrhagic stroke, ischemic/unclassified stroke and unspecified cerebrovascular disease), secondary CVD event (MI and stroke), CVD death, all-cause death). Statin relative treatment effects for CHD and stroke applied.	**Population:** people with serious mental illness (SMI) (schizophrenia or schizoaffective disorder, bipolar disorder, other long-term psychotic illness (non-organic psychoses) and/or were listed on the SMI register) and no CVD. **Population characteristics:** SMI without CVD cohort is from UK THIN primary care dataset (n=33,206). A random sample of 1000 people was used: Mean age: 50yrs (SD: 12) Male: 49% **Intervention 1:** D'Agostino general population lipid algorithm (adapted Framingham using UK THIN data) **Intervention 2:** D'Agostino general population BMI algorithm (adapted Framingham using UK THIN data) **Intervention 3:** PRIMROSE lipid risk algorithm **Intervention 4:** PRIMROSE BMI risk algorithm	**Total costs (mean per patient):** Intervention 1: £1,666 Intervention 2: £1,677 Intervention 3: £1,671 Intervention 4: £1,659 Incremental (2-1): £11 (95% CI: NR; p=NR) Incremental (3-1): £5 (95% CI: NR; p=NR) Incremental (4-1): -£7 (95% CI: NR; p=NR) **Currency & cost year:** 2012/13 UK pounds **Cost components incorporated:** Risk assessment (GP time and blood tests); statins; CVD event costs (first and subsequent years).	**QALYs (mean per patient):** Intervention 1: 6.828 Intervention 2: 6.826 Intervention 3: 6.827 Intervention 4: 6.830 Incremental (2-1): -0.002 (95% CI: NR; p=NR) Incremental (3-1): -0.001 (95% CI: NR; p=NR) Incremental (4-1): 0.002 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 4 is dominant (lower costs and higher QALYs) 95% CI: NR Probability cost effective (£20K/30K threshold): 5. ~22%/~22% 6. ~17%/~17% 7. ~13%/~13% 8. ~43%/~43% (Probability no risk algorithm CE ~5%) **Analysis of uncertainty:** A range of sensitivity analyses were also conducted: • Doubling costs • Alternative utility values for people with SMI • Varying statin treatment effects to lower and upper bound of confidence interval • Reducing statin adherence to 50%

Perspective: UK NHS **Time horizon:** 10 years **Treatment effect duration:**[(a)] 10 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	For all groups, people assessed as ≥10% 10-year CV risk receive and statin treatment (20mg atorvastatin). People already on statin therapy (in THIN) remained on treatment irrespective of risk level. A 'No risk assessment' group without additional statin treatment was also estimated but is not presented here as did not meet the protocol.			The general population lipid algorithm became the most cost-effective option
Data sources				
Health outcomes: Risk was calculated for each individual in the cohort using the different risk algorithms and the individual patient characteristics. General population risk tool was D'Agostino 2008.[4] SMI specific risk tool was PRIMROSE.[21] Baseline transition probabilities for first CVD event were calculated from 10 imputed datasets of the SMI with CVD cohort from the UK THIN primary care dataset using a survival model. Separate models were estimated for CHD and CVA; covariates included age, sex, systolic blood pressure, use of antihypertensive therapy, HDL cholesterol, use of cholesterol-lowering/cholesterol-altering therapy, height, weight, presence of diabetes, smoking status, history of heavy drinking, type of SMI, use of first-generation antipsychotic therapy, use of second-generation antipsychotic therapy, and history of depression or use of antidepressant therapy. Proportions of people experiencing fatal/nonfatal events and each type of CVD/CVA event was based on the THIN SMI cohort data. Baseline transition probabilities for secondary CVD event was calculated from the model in the Reduction of Atherothrombosis for Continued Health (REACH) Registry (not SMI population) for secondary CVD and secondary fatal CVD. Secondary events were split into MI and stroke based on REACH data. Non-CVD death probabilities were based on analysis of the THIN SMI dataset. Effectiveness of statin treatment applied was CHD 0.73 and stroke 0.78 from a Cochrane review (Taylor 2013). **Quality-of-life weights:** People with SMI from published time-trade-off experiment. Utility decrements for non-fatal CVD events from Statins TA model (Ward 2007) applied for time horizon. **Cost sources:** Standard UK national sources and published CV costs from Statins TA model (Ward 2007) inflated to 2012/13.			
Comments				
Source of funding: NIHR. **Limitations:** Doesn't include comparison to general population algorithms used in current practice (general population algorithms were UK adjusted Framingham equations which do not meet the update review protocol [QRISK2 recommended in the 2014 CG181 update over Framingham-based assessments]). 2012/13 cost year and some based on resource use before 2007 may not reflect current NHS context. Cost of blood test excluded for BMI-based algorithms but would be required in patients starting statin therapy so can monitor impact of treatment. The PRIMROSE SMI-specific risk tool has not been externally validated (see clinical review).				
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; CUA = cost–utility analysis; CHD = coronary heart disease; CV = cardiovascular; CVA = cerebrovascular disease; da= deterministic analysis; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]), negative values mean worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix H Health economic model

This area was not prioritised for new cost-effectiveness analysis.

Appendix I Excluded studies

I.1 Clinical studies

Table 25: Studies excluded from the clinical review

Study	Exclusion reason(s)
Abeles, Robin D, Mullish, Benjamin H, Forlano, Roberta et al. (2019) Derivation and validation of a cardiovascular risk score for prediction of major acute cardiovascular events in non-alcoholic fatty liver disease; the importance of an elevated mean platelet volume. Alimentary pharmacology & therapeutics 49(8): 1077-1085	- Analysis not relevant to this protocol: prediction of 1-year risk only
Albarqouni, Loai, Doust, Jennifer A, Magliano, Dianna et al. (2019) External validation and comparison of four cardiovascular risk prediction models with data from the Australian Diabetes, Obesity and Lifestyle study. The Medical journal of Australia 210(4): 161-167	- Population not relevant to this review protocol: Australia
Alemao, Evo, Cawston, Helene, Bourhis, Francois et al. (2017) Comparison of cardiovascular risk algorithms in patients with vs without rheumatoid arthritis and the role of C-reactive protein in predicting cardiovascular outcomes in rheumatoid arthritis. Rheumatology (Oxford, England) 56(5): 777-786	- Analysis not relevant to this protocol: Prediction of 5 and 3-year risk only
Arts, E E A, Popa, C D, Den Broeder, A A et al. (2016) Prediction of cardiovascular risk in rheumatoid arthritis: performance of original and adapted SCORE algorithms. Annals of the rheumatic diseases 75(4): 674-80	- Study does not contain a risk tool relevant to this review protocol: SCORE - Population not relevant to this review protocol: Netherlands
Arts, E E A, Popa, C, Den Broeder, A A et al. (2015) Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Annals of the rheumatic diseases 74(4): 668-74	- Population not relevant to this review protocol: Netherlands
Ashraf, Tariq, Mengal, Muhammad Naeem, Muhammad, Atif Sher et al. (2020) Ten years risk assessment of atherosclerotic cardiovascular disease using Astro-CHARM and pooled cohort equation in a south Asian sub-population. BMC public health 20(1): 403	- Population not relevant to this review protocol: Pakistan - Study design not relevant to this review protocol: cross sectional
Aspelund, Thor, Thorgeirsson, Gudmundur, Sigurdsson, Gunnar et al. (2007) Estimation of 10-year risk of fatal cardiovascular disease and coronary heart disease in Iceland with results comparable with those of the Systematic Coronary Risk Evaluation project. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 14(6): 761-8	- Population not relevant to this review protocol: Iceland

Study	Exclusion reason(s)
Bae, Jae Hyun, Moon, Min Kyong, Oh, Sohee et al. (2020) Validation of Risk Prediction Models for Atherosclerotic Cardiovascular Disease in a Prospective Korean Community-Based Cohort. Diabetes & metabolism journal 44(3): 458-469	- Population not relevant to this review protocol: Korea
Bell, Katy J L, White, Sam, Hassan, Omar et al. (2022) Evaluation of the Incremental Value of a Coronary Artery Calcium Score Beyond Traditional Cardiovascular Risk Assessment: A Systematic Review and Meta-analysis. JAMA internal medicine 182(6): 634-642	- Population not relevant to this review protocol: US, Netherlands, Germany and South Korea
Bertomeu-Gonzalez, Vicente, Soriano Maldonado, Cristina, Bleda-Cano, Jesus et al. (2019) Predictive validity of the risk SCORE model in a Mediterranean population with dyslipidemia. Atherosclerosis 290: 80-86	- Population not relevant to this review protocol: Spain - Study does not contain a risk tool relevant to this review protocol: SCORE
Cacciapaglia, Fabio, Fornaro, Marco, Venerito, Vincenzo et al. (2020) Cardiovascular risk estimation with 5 different algorithms before and after 5 years of bDMARD treatment in rheumatoid arthritis. European journal of clinical investigation 50(12): e13343	- Population not relevant to this review protocol: Italy - Study design not relevant to this review protocol:
Campos-Staffico, Alessandra M, Cordwin, David, Murthy, Venkatesh L et al. (2021) Comparative performance of the two pooled cohort equations for predicting atherosclerotic cardiovascular disease. Atherosclerosis 334: 23-29	- Population not relevant to this review protocol: USA
Cauwenberghs, Nicholas, Hedman, Kristofer, Kobayashi, Yukari et al. (2019) The 2013 ACC/AHA risk score and subclinical cardiac remodeling and dysfunction: Complementary in cardiovascular disease prediction. International journal of cardiology 297: 67-74	- Population not relevant to this review protocol: Belgium
Cedeno Mora, Santiago, Goicoechea, Marian, Torres, Esther et al. (2017) Cardiovascular risk prediction in chronic kidney disease patients. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia 37(3): 293-300	- Population not relevant to this review protocol: Spain
Chew, K W, Bhattacharya, D, Horwich, T B et al. (2017) Performance of the Pooled Cohort atherosclerotic cardiovascular disease risk score in hepatitis C virus-infected persons. Journal of viral hepatitis 24(10): 814-822	- Population not relevant to this review protocol: USA
Chia, Yook Chin; Lim, Hooi Min; Ching, Siew Mooi (2014) Validation of the pooled cohort risk score in an Asian population - a retrospective cohort study. BMC cardiovascular disorders 14: 163	- Population not relevant to this review protocol: Malaysia
Chlabicz, Malgorzata, Jamiolkowski, Jacek, Laguna, Wojciech et al. (2021) A Similar Lifetime CV Risk and a Similar Cardiometabolic Profile in the Moderate and High Cardiovascular Risk Populations: A Population-Based Study. Journal of clinical medicine 10(8)	- Study design not relevant to this review protocol: cross sectional study with no calibration or discrimination data - Population not relevant to this review protocol: Poland

Study	Exclusion reason(s)
Clark, Christopher E, Warren, Fiona C, Boddy, Kate et al. (2021) Associations Between Systolic Interarm Differences in Blood Pressure and Cardiovascular Disease Outcomes and Mortality: Individual Participant Data Meta-Analysis, Development and Validation of a Prognostic Algorithm: The INTERPRESS-IPD Collaboration. Hypertension (Dallas, Tex. : 1979) 77(2): 650-661	- Population not relevant to this review protocol: Validation not in a UK population (USA, China, Spain and Netherlands); 18.3% had established CVD - Study does not contain a risk tool relevant to this review protocol: Validation only for prediction of fatal events
Colaco, Keith, Ocampo, Vanessa, Ayala, Ana Patricia et al. (2020) Predictive Utility of Cardiovascular Risk Prediction Algorithms in Inflammatory Rheumatic Diseases: A Systematic Review. The Journal of rheumatology 47(6): 928-938	- Systematic review used as source of primary studies
Colantonio, Lisandro D, Richman, Joshua S, Carson, April P et al. (2017) Performance of the Atherosclerotic Cardiovascular Disease Pooled Cohort Risk Equations by Social Deprivation Status. Journal of the American Heart Association 6(3)	- Population not relevant to this review protocol: USA - Analysis not relevant to this protocol: prediction of 5-year risk only
Collins, Gary S and Altman, Douglas G (2009) An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. BMJ (Clinical research ed.) 339: b2584	- Study does not contain a risk tool relevant to this review protocol: QRISK
Collins, Gary S and Altman, Douglas G (2010) An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. BMJ (Clinical research ed.) 340: c2442	- Validation cohort overlaps with an included study with also reports on QRISK2-2008 using data from THIN, and includes a larger, more-applicable sample
Conroy, R M, Pyorala, K, Fitzgerald, A P et al. (2003) Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. European heart journal 24(11): 987-1003	- Study does not contain a risk tool relevant to this review protocol: SCORE: fatal events only
Cooney, Marie Therese, Selmer, Randi, Lindman, Anja et al. (2016) Cardiovascular risk estimation in older persons: SCORE O.P. European journal of preventive cardiology 23(10): 1093-103	- Study does not contain a risk tool relevant to this review protocol: SCORE-OP
Corrales, Alfonso, Vegas-Revenga, Nuria, Atienza-Mateo, Belen et al. (2021) Combined use of QRISK3 and SCORE as predictors of carotid plaques in patients with rheumatoid arthritis. Rheumatology (Oxford, England) 60(6): 2801-2807	- Study design not relevant to this review protocol: diagnostic accuracy for carotid plaques
Courand, Pierre-Yves, Lenoir, Jerome, Grandjean, Adrien et al. (2022) SCORE underestimates cardiovascular mortality in hypertension: insight from the OLD-HTA and NEW-HTA Lyon cohorts. European journal of preventive cardiology 29(1): 136-143	- Population not relevant to this review protocol: France - Study does not contain a risk tool relevant to this review protocol: SCORE: fatal events only
Crowson, Cynthia S, Gabriel, Sherine E, Semb, Anne Grete et al. (2017) Rheumatoid arthritis-specific cardiovascular risk scores are not	- Population not relevant to this review protocol: Includes 7 countries (UK, Norway, Netherlands,

Study	Exclusion reason(s)
superior to general risk scores: a validation analysis of patients from seven countries. Rheumatology (Oxford, England) 56(7): 1102-1110	USA, South Africa, Canada and Mexico) and proportions are unclear.
Dalton, Jarrod E, Perzynski, Adam T, Zidar, David A et al. (2017) Accuracy of Cardiovascular Risk Prediction Varies by Neighborhood Socioeconomic Position: A Retrospective Cohort Study. Annals of internal medicine 167(7): 456-464	- Population not relevant to this review protocol: USA - Study design not relevant to this review protocol: prediction of 5-year risk only
De Bacquer, Dirk and De Backer, Guy (2010) Predictive ability of the SCORE Belgium risk chart for cardiovascular mortality. International journal of cardiology 143(3): 385-90	- Population not relevant to this review protocol: Belgium - Study does not contain a risk tool relevant to this review protocol: SCORE: fatal events only
de la Iglesia, Beatriz, Potter, John F, Poulter, Neil R et al. (2011) Performance of the ASSIGN cardiovascular disease risk score on a UK cohort of patients from general practice. Heart (British Cardiac Society) 97(6): 491-9	- Study does not contain a risk tool relevant to this review protocol: ASSIGN and Framingham
De Las Heras Gala, T., Geisel, M.H., Peters, A. et al. (2016) Recalibration of the ACC/AHA risk score in two population-based German cohorts. PLoS ONE 11(10): e0164688	- Population not relevant to this review protocol: Germany
DeFilippis, Andrew P, Young, Rebekah, Carrubba, Christopher J et al. (2015) An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Annals of internal medicine 162(4): 266-75	- Population not relevant to this review protocol: USA
DeFilippis, Andrew Paul, Young, Rebekah, McEvoy, John W et al. (2017) Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. European heart journal 38(8): 598-608	- Population not relevant to this review protocol: USA
Di Battista, Marco, Tani, Chiara, Elefante, Elena et al. (2020) Framingham, ACC/AHA or QRISK3: which is the best in systemic lupus erythematosus cardiovascular risk estimation?. Clinical and experimental rheumatology 38(4): 602-608	- Population not relevant to this review protocol: Italy
Drosos, George C, Konstantonis, George, Sfikakis, Petros P et al. (2020) Underperformance of clinical risk scores in identifying vascular ultrasound-based high cardiovascular risk in systemic lupus erythematosus. European journal of preventive cardiology: 2047487320906650	- Population not relevant to this review protocol: Greece
Edwards, N., Langford-Smith, A.W.W., Parker, B.J. et al. (2018) QRISK3 improves detection of cardiovascular disease risk in patients with	- Data not reported in an extractable format or a format that can be analysed no accuracy data

Study	Exclusion reason(s)
systemic lupus erythematosus. Lupus Science and Medicine 5(1): e000272	- Study design not relevant to this review protocol: cross sectional
Emdin, Connor A, Khera, Amit V, Natarajan, Pradeep et al. (2017) Evaluation of the Pooled Cohort Equations for Prediction of Cardiovascular Risk in a Contemporary Prospective Cohort. The American journal of cardiology 119(6): 881-885	- Population not relevant to this review protocol: USA
Fan, W., Wong, D.N., Li, X. et al. (2020) Cardiovascular Risk Prediction in Diabetes from Machine Learning: The ACCORD Study. Circulation 142(suppl3)	- Conference abstract
Fausto, S., Marina, C., Marco, D.C. et al. (2018) The expanded risk score in rheumatoid arthritis (ERS-RA): Performance of a disease-specific calculator in comparison with the traditional prediction scores in the assessment of the 10-year risk of cardiovascular disease in patients with rheumatoid arthritis. Swiss Medical Weekly 148(3334): w14656	- Population not relevant to this review protocol: Italy
Giavarina, Davide, Barzon, Elena, Cigolini, Massimo et al. (2007) Comparison of methods to identify individuals at increased risk of cardiovascular disease in Italian cohorts. Nutrition, metabolism, and cardiovascular diseases : NMCD 17(4): 311-8	- Study design not relevant to this review protocol: cross-sectional
Gidlow, C.J., Ellis, N.J., Cowap, L. et al. (2021) Cardiovascular disease risk communication in nhs health checks using qrisk 2 and jbs3 risk calculators: The rico qualitative and quantitative study. Health Technology Assessment 25(50): vii-102	- Study design not relevant to this review protocol: qualitative study with no predictive accuracy data
Goh, Louise Gek Huang; Welborn, Timothy Alexander; Dhaliwal, Satvinder Singh (2014) Independent external validation of cardiovascular disease mortality in women utilising Framingham and SCORE risk models: a mortality follow-up study. BMC women's health 14: 118	- Population not relevant to this review protocol: Australia - Study does not contain a risk tool relevant to this review protocol SCORE and Framingham: fatal events only
Gopal, Dipesh P and Usher-Smith, Juliet A (2016) Cardiovascular risk models for South Asian populations: a systematic review. International journal of public health 61(5): 525-34	- Systematic review used as source of primary studies
Grammer, Tanja B, Dressel, Alexander, Gergei, Ingrid et al. (2019) Cardiovascular risk algorithms in primary care: Results from the DETECT study. Scientific reports 9(1): 1101	- Population not relevant to this review protocol: Germany
Graversen, Peter, Abildstrom, Steen Z, Jespersen, Lasse et al. (2016) Cardiovascular risk prediction: Can Systematic Coronary Risk Evaluation (SCORE) be improved by adding simple risk markers? Results from the	- Population not relevant to this review protocol: Denmark - Study does not contain a risk tool relevant to this review protocol SCORE

Study	Exclusion reason(s)
Copenhagen City Heart Study. European journal of preventive cardiology 23(14): 1546-56	
Hageman, Steven H J, McKay, Ailsa J, Ueda, Peter et al. (2022) Estimation of recurrent atherosclerotic cardiovascular event risk in patients with established cardiovascular disease: the updated SMART2 algorithm. European heart journal 43(18): 1715-1727	- Population not relevant to this review protocol: Secondary prevention - Study does not contain a risk tool relevant to this review protocol SMART2
Hippisley-Cox, J, Coupland, C, Vinogradova, Y et al. (2008) Performance of the QRISK cardiovascular risk prediction algorithm in an independent UK sample of patients from general practice: a validation study. Heart (British Cardiac Society) 94(1): 34-9	- Study does not contain a risk tool relevant to this review protocol QRISK and Framingham
Hippisley-Cox, Julia, Coupland, Carol, Vinogradova, Yana et al. (2007) Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ (Clinical research ed.) 335(7611): 136	- Study does not contain a risk tool relevant to this review protocol QRISK, Framingham and ASSIGN
Johns, I., Moschonas, K.E., Medina, J. et al. (2018) Risk classification in primary prevention of CVD according to QRISK2 and JBS3 - - heart age', and prevalence of elevated high-sensitivity C reactive protein in the UK cohort of the EURIKA study. Open Heart 5(2): e000849	- Study design not relevant to this review protocol: cross sectional and no predictive accuracy outcome data
Jorstad, Harald T, Colkesen, Ersen B, Minneboo, Madelon et al. (2015) The Systematic COronary Risk Evaluation (SCORE) in a large UK population: 10-year follow-up in the EPIC-Norfolk prospective population study. European journal of preventive cardiology 22(1): 119-26	- Study does not contain a risk tool relevant to this review protocol SCORE: fatal events only
Jung, K.J., Jang, Y., Oh, D.J. et al. (2015) The ACC/AHA 2013 pooled cohort equations compared to a Korean Risk Prediction Model for atherosclerotic cardiovascular disease. Atherosclerosis 242(1): 367-375	- Population not relevant to this review protocol: Korea
Karmali, KN, Persell, SD, Perel, P et al. (2017) Risk scoring for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies none of the included studies used a tool specified in the review protocol
Karmali, Kunal N, Goff, David C Jr, Ning, Hongyan et al. (2014) A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. Journal of the American College of Cardiology 64(10): 959-68	- Study design not relevant to this review protocol: no predictive accuracy data reported
Khera, Rohan, Pandey, Ambarish, Ayers, Colby R et al. (2020) Performance of the Pooled Cohort Equations to Estimate Atherosclerotic Cardiovascular Disease Risk by Body Mass Index. JAMA network open 3(10): e2023242	- Population not relevant to this review protocol: USA
Kim, Tae Hyuk, Choi, Hoon Sung, Bae, Ji Cheol et al. (2014) Subclinical hypothyroidism in addition to common risk scores for prediction of	- Population not relevant to this review protocol: Korea

Study	Exclusion reason(s)
cardiovascular disease: a 10-year community-based cohort study. European journal of endocrinology 171(5): 649-57	
Kuragaichi, Takashi, Kataoka, Yuki, Miyakoshi, Chisato et al. (2019) External validation of pooled cohort equations using systolic blood pressure intervention trial data. BMC research notes 12(1): 271	- Population not relevant to this review protocol: USA
Lengele, Jean-Philippe, Vinck, Wouter J, De Plaen, Jean-Francois et al. (2007) Cardiovascular risk assessment in hypertensive patients: major discrepancy according to ESH and SCORE strategies. Journal of hypertension 25(4): 757-62	- Study design not relevant to this review protocol: cross sectional and no predictive accuracy outcome data
Li, Yan, Sperrin, Matthew, Ashcroft, Darren M et al. (2020) Consistency of variety of machine learning and statistical models in predicting clinical risks of individual patients: longitudinal cohort study using cardiovascular disease as exemplar. BMJ (Clinical research ed.) 371: m3919	- Data not reported in an extractable format or a format that can be analysed Confidence intervals not reported for accuracy data - Validation cohort overlaps with an included study of more direct relevance
Loprinzi, P D (2016) Predictive validity of the ACC/AHA pooled cohort equations in predicting cancer-specific mortality in a National Prospective Cohort Study of Adults in the United States. International journal of clinical practice 70(8): 691-5	- Study does not contain a risk tool relevant to this review protocol: cancer-specific mortality
Loprinzi, Paul D and Addoh, Ovuokerie (2016) Predictive Validity of the American College of Cardiology/American Heart Association Pooled Cohort Equations in Predicting All-Cause and Cardiovascular Disease-Specific Mortality in a National Prospective Cohort Study of Adults in the United States. Mayo Clinic proceedings 91(6): 763-9	- Population not relevant to this review protocol: USA
Lucaroni, Francesca, Cicciarella Modica, Domenico, Macino, Mattia et al. (2019) Can risk be predicted? An umbrella systematic review of current risk prediction models for cardiovascular diseases, diabetes and hypertension. BMJ open 9(12): e030234	- Systematic review used as source of primary studies
Mancini, G.B.J. and Ryomoto, A. (2014) Comparison of cardiovascular risk assessment algorithms to determine eligibility for statin therapy: Implications for practice in Canada. Canadian Journal of Cardiology 30(6): 661-666	- Study design not relevant to this review protocol: no predictive accuracy data
Mansoor, Hend, Jo, Ara, Beau De Rochars, V Madsen et al. (2019) Novel Self-Report Tool for Cardiovascular Risk Assessment. Journal of the American Heart Association 8(24): e014123	- Population not relevant to this review protocol: USA
Matsushita, K., Jassal, S.K., Sang, Y. et al. (2020) Incorporating kidney disease measures into cardiovascular risk prediction: Development and validation in 9 million adults from 72 datasets. EClinicalMedicine 27: 100552	- Study design not relevant to this review protocol: only estimates 5-year risk for the UK cohort

Study	Exclusion reason(s)
McKay, Ailsa J, Gunn, Laura H, Ference, Brian A et al. (2022) Is the SMART risk prediction model ready for real-world implementation? A validation study in a routine care setting of approximately 380 000 individuals. European journal of preventive cardiology 29(4): 654-663	- Population not relevant to this review protocol: secondary prevention
Mora, Samia, Wenger, Nanette K, Cook, Nancy R et al. (2018) Evaluation of the Pooled Cohort Risk Equations for Cardiovascular Risk Prediction in a Multiethnic Cohort From the Women's Health Initiative. JAMA internal medicine 178(9): 1231-1240	- Population not relevant to this review protocol: USA
Moral Pelaez, I., Brotons Cuixart, C., Fernandez Valverde, D. et al. (2021) External validation of the European and American equations for calculating cardiovascular risk in a Spanish working population. Revista Clinica Espanola 221(10): 561-568	- Population not relevant to this review protocol: Spain
Mosepele, M., Hemphill, L.C., Palai, T. et al. (2017) Cardiovascular disease risk prediction by the American College of Cardiology (ACC)/American Heart Association (AHA) Atherosclerotic Cardiovascular Disease (ASCVD) risk score among HIV-infected patients in sub-Saharan Africa. PLoS ONE 12(2): e0172897	- Population not relevant to this review protocol: Botswana - Study design not relevant to this review protocol: Cross sectional and no predictive accuracy outcome data
Motamed, N, Ajdarkosh, H, Perumal, D et al. (2021) Comparison of risk assessment tools for cardiovascular diseases: results of an Iranian cohort study. Public health 200: 116-123	- Population not relevant to this review protocol: Iran
Nanna, Michael G, Peterson, Eric D, Wojdyla, Daniel et al. (2020) The Accuracy of Cardiovascular Pooled Cohort Risk Estimates in U.S. Older Adults. Journal of general internal medicine 35(6): 1701-1708	- Population not relevant to this review protocol: USA
Navarini, Luca, Caso, Francesco, Costa, Luisa et al. (2020) Cardiovascular Risk Prediction in Ankylosing Spondylitis: From Traditional Scores to Machine Learning Assessment. Rheumatology and therapy 7(4): 867-882	- Population not relevant to this review protocol: Italy
Navarini, Luca, Margiotta, Domenico Paolo Emanuele, Caso, Francesco et al. (2018) Performances of five risk algorithms in predicting cardiovascular events in patients with Psoriatic Arthritis: An Italian bicentric study. PloS one 13(10): e0205506	- Population not relevant to this review protocol: Italy
Nguyen, Q.D., Odden, M.C., Peralta, C.A. et al. (2020) Predicting risk of atherosclerotic cardiovascular disease using pooled cohort equations in older adults with frailty, multimorbidity, and competing risks. Journal of the American Heart Association 9(18): e016003	- Population not relevant to this review protocol: USA
Ozen, Gulsen, Sunbul, Murat, Atagunduz, Pamir et al. (2016) The 2013 ACC/AHA 10-year atherosclerotic cardiovascular disease risk index is better than SCORE and QRisk II in	- Study design not relevant to this review protocol: Cross sectional

Study	Exclusion reason(s)
rheumatoid arthritis: is it enough?. Rheumatology (Oxford, England) 55(3): 513-22	
Pandey, Ambarish, Mehta, Anurag, Paluch, Amanda et al. (2021) Performance of the American Heart Association/American College of Cardiology Pooled Cohort Equations to Estimate Atherosclerotic Cardiovascular Disease Risk by Self-reported Physical Activity Levels. JAMA cardiology 6(6): 690-696	- Population not relevant to this review protocol: USA
Pate, Alexander, Emsley, Richard, Ashcroft, Darren M et al. (2019) The uncertainty with using risk prediction models for individual decision making: an exemplar cohort study examining the prediction of cardiovascular disease in English primary care. BMC medicine 17(1): 134	- Study does not contain a risk tool relevant to this review protocol: Unvalidated models based on QRISK2 and QRISK3
Patel, Aniruddh P, Wang, Minxian, Kartoun, Uri et al. (2021) Quantifying and Understanding the Higher Risk of Atherosclerotic Cardiovascular Disease Among South Asian Individuals: Results From the UK Biobank Prospective Cohort Study. Circulation 144(6): 410-422	- Data not reported in an extractable format or a format that can be analysed
Pennells, Lisa, Kaptoge, Stephen, Wood, Angela et al. (2019) Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. European heart journal 40(7): 621-631	- Population not relevant to this review protocol: Mixed cohorts: <80% UK-based
Piccininni, Marco, Rohmann, Jessica L, Huscher, Dorte et al. (2020) Performance of risk prediction scores for cardiovascular mortality in older persons: External validation of the SCORE OP and appraisal. PloS one 15(4): e0231097	- Population not relevant to this review protocol: Germany - Study does not contain a risk tool relevant to this review protocol: SCORE-OP
Plante, T.B., Juraschek, S.P., Zakai, N.A. et al. (2019) Pooled Cohort Equation performance in primary and secondary prevention subgroups of the systolicblood pressure intervention trial (SPRINT). Circulation 139(supplement1)	- Conference abstract
Prausmuller, Suriya, Resl, Michael, Arfsten, Henrike et al. (2021) Performance of the recommended ESC/EASD cardiovascular risk stratification model in comparison to SCORE and NT-proBNP as a single biomarker for risk prediction in type 2 diabetes mellitus. Cardiovascular diabetology 20(1): 34	- Population not relevant to this review protocol: Austria - Study does not contain a risk tool relevant to this review protocol: SCORE
Preiss, David and Kristensen, Soren L (2015) The new pooled cohort equations risk calculator. The Canadian journal of cardiology 31(5): 613-9	- Review article but not a systematic review
Raiko, Juho R H, Magnussen, Costan G, Kivimaki, Mika et al. (2010) Cardiovascular risk scores in the prediction of subclinical atherosclerosis in young adults: evidence from the cardiovascular risk in a young Finns study. European journal of cardiovascular prevention and rehabilitation : official journal of the	- Population not relevant to this review protocol: Finland - Study does not contain a risk tool relevant to this review protocol:

Study	Exclusion reason(s)
European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 17(5): 549-55	
Ramsay, Sheena E, Morris, Richard W, Whincup, Peter H et al. (2011) Prediction of coronary heart disease risk by Framingham and SCORE risk assessments varies by socioeconomic position: results from a study in British men. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 18(2): 186-93	- Study does not contain a risk tool relevant to this review protocol: Framingham and SCORE
Rana, Jamal S, Tabada, Grace H, Solomon, Matthew D et al. (2016) Accuracy of the Atherosclerotic Cardiovascular Risk Equation in a Large Contemporary, Multiethnic Population. Journal of the American College of Cardiology 67(18): 2118-2130	- Population not relevant to this review protocol: USA
Read, Stephanie H, van Diepen, Merel, Colhoun, Helen M et al. (2018) Performance of Cardiovascular Disease Risk Scores in People Diagnosed With Type 2 Diabetes: External Validation Using Data From the National Scottish Diabetes Register. Diabetes care 41(9): 2010-2018	- Analysis not relevant to this review protocol: 5-year risk estimate only
Romanens, Michel, Adams, Ansgar, Sudano, Isabella et al. (2021) Prediction of cardiovascular events with traditional risk equations and total plaque area of carotid atherosclerosis: The Arteris Cardiovascular Outcome (ARCO) cohort study. Preventive medicine 147: 106525	- Population not relevant to this review protocol: Switzerland and Germany - Study does not contain a risk tool relevant to this review protocol:
Saar, Aet, Lall, Kristi, Alver, Maris et al. (2019) Estimating the performance of three cardiovascular disease risk scores: the Estonian Biobank cohort study. Journal of epidemiology and community health 73(3): 272-277	- Population not relevant to this review protocol: Estonia
Santos-Ferreira, Catia, Baptista, Rui, Oliveira-Santos, Manuel et al. (2020) A 10- and 15-year performance analysis of ESC/EAS and ACC/AHA cardiovascular risk scores in a Southern European cohort. BMC cardiovascular disorders 20(1): 301	- Population not relevant to this review protocol: Portugal
Sawano, Mitsuaki, Kohsaka, Shun, Okamura, Tomonori et al. (2016) Validation of the european SCORE risk chart in the healthy middle-aged Japanese. Atherosclerosis 252: 116-121	- Population not relevant to this review protocol: Japan - Study does not contain a risk tool relevant to this review protocol:
Schiborn, Catarina, Kuhn, Tilman, Muhlenbruch, Kristin et al. (2021) A newly developed and externally validated non-clinical score accurately predicts 10-year cardiovascular disease risk in	- Population not relevant to this review protocol: Germany

Study	Exclusion reason(s)
the general adult population. Scientific reports 11(1): 19609	
Schulz, C.-A., Mavarani, L., Reinsch, N. et al. (2021) Prediction of future cardiovascular events by Framingham, SCORE and asCVD risk scores is less accurate in HIV-positive individuals from the HIV-HEART Study compared with the general population. HIV Medicine 22(8): 732-741	- Population not relevant to this review protocol: Germany
Siontis, George C M, Tzoulaki, Ioanna, Siontis, Konstantinos C et al. (2012) Comparisons of established risk prediction models for cardiovascular disease: systematic review. BMJ (Clinical research ed.) 344: e3318	- Systematic review used as source of primary studies
Sivakumaran, J., Harvey, P., Omar, A. et al. (2021) Assessment of cardiovascular risk tools as predictors of cardiovascular disease events in systemic lupus erythematosus. Lupus Science and Medicine 8(1): e000448	- Population not relevant to this review protocol: Canada
Tang, Xun, Zhang, Dudan, He, Liu et al. (2019) Performance of atherosclerotic cardiovascular risk prediction models in a rural Northern Chinese population: Results from the Fangshan Cohort Study. American heart journal 211: 34-44	- Population not relevant to this review protocol: China
Tolunay, Hatice and Kurmus, Ozge (2016) Comparison of coronary risk scoring systems to predict the severity of coronary artery disease using the SYNTAX score. Cardiology journal 23(1): 51-6	- Population not relevant to this review protocol: Turkey - Study does not contain a risk tool relevant to this review protocol:
Tralhao, Antonio, Ferreira, Antonio M, Goncalves, Pedro de Araujo et al. (2016) Accuracy of Pooled-Cohort Equation and SCORE cardiovascular risk calculators to identify individuals with high coronary atherosclerotic burden - implications for statin treatment. Coronary artery disease 27(7): 573-9	- Population not relevant to this review protocol: Portugal - Analysis not relevant to this review protocol: predicting risk of coronary atherosclerotic burden
Triant, Virginia A, Perez, Jeremiah, Regan, Susan et al. (2018) Cardiovascular Risk Prediction Functions Underestimate Risk in HIV Infection. Circulation 137(21): 2203-2214	- Population not relevant to this review protocol: USA
Ueda, Peter, Woodward, Mark, Lu, Yuan et al. (2017) Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. The lancet. Diabetes & endocrinology 5(3): 196-213	- Population not relevant to this review protocol: No accuracy data for UK
van der Heijden, Amber A W A, Ortegon, Monica M, Niessen, Louis W et al. (2009) Prediction of coronary heart disease risk in a general, pre-diabetic, and diabetic population during 10 years of follow-up: accuracy of the Framingham, SCORE, and UKPDS risk functions: The Hoorn Study. Diabetes care 32(11): 2094-8	- Population not relevant to this review protocol: Netherlands
van Dis, Ineke, Kromhout, Daan, Geleijnse, Johanna M et al. (2010) Evaluation of	- Population not relevant to this review protocol: Netherlands

Study	Exclusion reason(s)
cardiovascular risk predicted by different SCORE equations: the Netherlands as an example. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 17(2): 244-9	- Analysis not relevant to this review protocol: Fatal events only
Vassy, Jason L, Lu, Bing, Ho, Yuk-Lam et al. (2020) Estimation of Atherosclerotic Cardiovascular Disease Risk Among Patients in the Veterans Affairs Health Care System. JAMA network open 3(7): e208236	- Population not relevant to this review protocol: USA
Vega Alonso, A.T., Ordax Diez, A., Lozano Alonso, J.E. et al. (2019) Validation of the SCORE index and SCORE for old people in the Castilla y Leon cardiovascular disease risk cohort. Hipertension y Riesgo Vascular 36(4): 184-192	- Study not reported in English - Population not relevant to this review protocol: Spain
Verweij, Lotte, Peters, Ron J G, Scholte Op Reimer, Wilma J M et al. (2019) Validation of the Systematic COronary Risk Evaluation - Older Persons (SCORE-OP) in the EPIC-Norfolk prospective population study. International journal of cardiology 293: 226-230	- Study does not contain a risk tool relevant to this review protocol: SCORE-OP (not latest version)
Wang, M., Wang, W., Liu, J. et al. (2017) Updating 10-year atherosclerotic cardiovascular risk assessment equation for Chinese adults. Journal of the American College of Cardiology 70(16supplement1): c74-c75	- Conference abstract
Welsh, Paul, Hart, Carole, Papacosta, Olia et al. (2016) Prediction of Cardiovascular Disease Risk by Cardiac Biomarkers in 2 United Kingdom Cohort Studies: Does Utility Depend on Risk Thresholds For Treatment?. Hypertension (Dallas, Tex. : 1979) 67(2): 309-15	- Study does not contain a risk tool relevant to this review protocol: Model based on QRISK2 and modifications
WHO CVD Risk Chart Working, Group (2019) World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. The Lancet. Global health 7(10): e1332-e1345	- Study does not contain a risk tool relevant to this review protocol:
Xu, Yu, Li, Mian, Qin, Guijun et al. (2021) Cardiovascular Risk Based on ASCVD and KDIGO Categories in Chinese Adults: A Nationwide, Population-Based, Prospective Cohort Study. Journal of the American Society of Nephrology : JASN	- Population not relevant to this review protocol: China
Yang, Xueli, Li, Jianxin, Hu, Dongsheng et al. (2016) Predicting the 10-Year Risks of Atherosclerotic Cardiovascular Disease in Chinese Population: The China-PAR Project (Prediction for ASCVD Risk in China). Circulation 134(19): 1430-1440	- Population not relevant to this review protocol: China
Yu, Zhi, Yang, Nicole, Everett, Brendan M et al. (2018) Impact of Changes in Inflammation on Estimated Ten-Year Cardiovascular Risk in	- Population not relevant to this review protocol: USA

Study	Exclusion reason(s)
Rheumatoid Arthritis. Arthritis & rheumatology (Hoboken, N.J.) 70(9): 1392-1398	
Zafrir, Barak, Saliba, Walid, Widder, Rachel Shay Li et al. (2021) Value of addition of coronary artery calcium to risk scores in the prediction of major cardiovascular events in patients with type 2 diabetes. BMC cardiovascular disorders 21(1): 541	- Population not relevant to this review protocol: Israel
Zhu, Lisa, Singh, Manpreet, Lele, Sonia et al. (2022) Assessing the validity of QRISK3 in predicting cardiovascular events in systemic lupus erythematosus. Lupus science & medicine 9(1)	- Population not relevant to this review protocol: USA

I.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2007 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 26: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix J List of abbreviations

Table 27: List of abbreviations

BiomarCaREConsortium	Biomarker for Cardiovascular Risk Assessment across Europe consortium
DETECT	Dynamic Electronic Tracking and Escalation to reduce Critical Care Transfers
EHR	Electronic Health Records
EPIC-CVD	European Prospective Investigation into Cancer and Nutrition-cardiovascular disease
ERFC	Emerging Risk Factors Collaboration
ESC	European Society of Cardiology
GHS	Gutenberg Health Study
h	hours
HAPIEE	Health, Alcohol and Psychosocial factors In Eastern Europe
HNR	Heinz-Nixdorf Recall
HUNT	The Trøndelag Health Study
MORGAM	MOnica Risk, Genetics, Archiving and Monograph
NR	not reported
NHLBI	National Heart, Lung, and Blood Institute
PAD	Peripheral arterial disease
SABRE	Southall and Brent Revisited cohort