An independent external validation of the QRISK3 cardiovascular risk prediction model using UK Biobank

SUPPLEMENTARY MATERIAL

S.1 DEFINITION OF VARIABLES FOR QRISK3

This section outlines the UK Biobank field identifications (FIDs) and linked records that we have used for each of the QRISK3 variables, along with any assumptions made. In cases where variables required in QRISK3 had non-perfect UK Biobank field matches, we used the fields with the closest matches.

Diagnosis of disease variables

We used either self-reported non-cancer illness at baseline (FID 20002) or linked Hospital Episode Statistics (HES) data prior to baseline to derive the diagnosis of rheumatoid arthritis, diabetes (type 1 and 2), systemic lupus erythematosus, atrial fibrillation, chronic kidney disease, migraine, severe mental illness, and erectile dysfunction variables. Disease status was obtained according to International Classification of Disease (ICD) -9 and -10 codes and the Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 codes (OPCS-4) for the HES data, as in the derivation of QRISK3, these can be seen in Table S.1.

Table S.1
Definitions of diagnosis of disease variables for QRISK3 according to ICD-9, ICD-10, OPCS-4 and UK Biobank FIDs.

Variable	Self-Reported Data Field Code (FID 20002)	ICD9, ICD10 and OPSC-4 Codes	Treatment and Medication Data Field Code (FID 20003)	Other data fields
Type 1 Diabetes	1222	ICD-10 E10, O240; ICD9 25001, 25011, 25021, 25031, 25041, 25051, 25061, 25071, 25081, 25091, 25003, 25013, 25023, 25033, 25043, 25053, 25063, 25073, 25083, 25093		

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Type 2 Diabetes	1223,1220	ICD-10 E11, O241; ICD-9 25000, 25010, 25020, 25030, 25040, 25050, 25060, 25070, 25080, 25090, 25002, 25012, 25022, 25032, 25042, 25052, 25062, 25072, 25082, 25092	1140868902, 1140874646, 1140874674, 1140874718, 1140874744, 1140883066, 1140884600, 1141152590, 1141157284, 1141168660, 1141171646, 1141173882, 1141189090	FID 2443 = 1, FID 30750 ≥ 48 (HbA1c measurement ≥ 48 mmol/mol)
Rheumatoid Arthritis Including rheumatoid arthritis, Felty's syndrome, Caplan's syndrome, adult onset Still's disease, or inflammatory polyarthropathy not otherwise specified	1464	ICD-10 M05, M06; ICD-9 714		
Atrial Fibrillation Including atrial fibrillation, atrial flutter, and paroxysmal atrial fibrillation	1471, 1483	ICD-10 I48; ICD-9 4273 and 4270; OPCS-4 K622 and K623		
Chronic Kidney Disease Including chronic kidney disease stages 3, 4 or 5 and major chronic renal disease; nephrotic syndrome, chronic glomerulonephritis, chronic pyelonephritis, renal dialysis, and renal transplant),	1192, 1519, 1609	ICD-10 N183, N184, N185; ICD-9 5853, 5855, 5810, 5820, 5900, V420, V451		
Migraine Including classic migraine, atypical migraine, abdominal migraine, cluster headaches, basilar migraine, hemiplegic migraine, and migraine with or without aura	1265	ICD-10 G43, G440, N943; ICD-9 346		
Systemic Lupus Erythematosus Including diagnosis of systemic lupus erthematosus, disseminated lupus erythematosus, or Libman-Sacks disease	1381	ICD-10 M32; ICD-9 7100		
Severe Mental Illness Including psychosis, schizophrenia, or bipolar affective disease	1289, 1291	ICD-10 F03, F068, F09, F20, F22, F23, F259, F28, F29, F31, F39, F53, F333; ICD9 295, 298, 296		

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Erectile Dysfunction Including treatment for erectile dysfunction (BNF chapter 7.4.5 including alprostadil, phosphodiesterase type 5 inhibitors, papaverine, or phentolamine	1518	ICD-10 N484; ICD-9 60784	1141168936, 1141168948, 1141168944, 1141168946, 1140869100, 1140883010	

We additionally used self-reported treatment and medication reported to clinic nurses at baseline (FID 20003) to determine a diagnosis of diabetes type 2 and erectile dysfunction, under the assumption that those who take related medication have a diagnosis of the disease. Additionally, a reported diagnosis of diabetes by a doctor (FID 2443) with a measurement of glycated haemoglobin (HbA1c) greater than or equal to 48 mmol/mol (FID 30750) was seen to indicate a diagnosis of diabetes type 2, as was done in a previous mapping.

We coded diagnosis of each disease as a binary variable, as in the original QRISK3 model, with 1 indicating the diagnosis of the disease and 0 indicating no diagnosis of the disease.

Treatment and medication variables

We ascertained the use of antihypertensives, corticosteroids and atypical antipsychotics from FID 20003, self-reported treatment and medication reported to clinic nurses at baseline, which excluded short-term medications or prescribed medication that was not taken. We additionally used FIDs 6177 and 6152, the regular use of antihypertensives for males and females respectively. Table S.2 contains definitions of the treatment and medication variables according to the coding of UK Biobank FIDs.

The QRISK3 derivation defines the use of treatments and medications at baseline as being from at least two prescriptions, with the most recent one no more than 28 days before baseline. It is not possible to ascertain this level of information from the fields in UK Biobank. For this reason, we have used the information that is available in UK Biobank FID 20003, 6177 and 6152 under the assumption that they meet this definition.

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We coded use of each treatment or medication in QRISK3 as a binary variable, as in the original QRISK3 model, with 1 indicating the use of the treatment or medication and 0 indicating no use of the treatment or medication.

Table S.2
Definitions of treatment and medication variables for QRISK3 according to ICD-9, ICD-10, OPCS-4 and UK Biobank FIDs.

Variable	Self-Reported Data Field Code (FID 20002)	ICD9, ICD10 and OPSC-4 Codes	Treatment and Medication Data Field Code (FID 20003)	Other data fields
Treated Hypertension Diagnosis of hypertension and treatment with at least one antihypertensive drug			1140860192, 1140860292, 1140860696, 1140860728, 1140860750, 1140860806, 1140860882, 1140860904, 1140861088, 1140861190, 1140861276, 1140866072, 1140866078, 1140866090, 1140866102, 1140866108, 1140866122, 1140866138, 1140866156, 1140866162, 1140866724, 1140866738, 1140868618, 1140872568, 1140874706, 1140874744, 1140875808, 1140879758, 1140879760, 1140879762, 1140879802, 1140879806, 1140879810, 1140879818, 1140879822, 1140879826, 1140879830, 1140879834, 1140879842, 1140879866, 1140884298, 1140888552, 1140888556, 1140888560, 1140888646, 1140909706, 1140910442, 1140910614, 1140916356, 1140923272, 1140923336, 1140923404, 1140923712, 1140926778, 1140928226, 1141145660, 1141146126, 1141152998, 1141153026, 1141164276, 1141165470, 1141166006, 1141169516, 1141171336, 1141180592, 1141180772, 1141180778, 1141184722, 1141193282, 1141194794, 1141194810	FID 6177 = "Blood Pressure Medication" or FID 6152 = "Blood Pressure Medication"
Corticosteroid Use British National Formulary (BNF) chapter			1140874790, 1140874816, 1140874896.00, 1140874930,	

6.3.2 including oral or parenteral prednisolone, betamethasone, cortisone, depo-medrone, dexamethasone, deflazacort, efcortesol, hydrocortisone, methylprednisolone, or triamcinolone			1140874976, 1141145782, 1141173346	
Second Generation 'atypical' Antipsychotic Use Including amisulpride, aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, or zotepine			1140867420, 1140867444, 1140927956, 1140928916, 1141152848, 1141153490, 1141169714, 1141195974	

Sociodemographic and lifestyle variables

Other than diagnoses of disease and treatment and medication status, additional sociodemographic and lifestyle variables required for QRISK3 (Box 1) were derived using a range of fields from the UK Biobank study. QRISK3 requires some of these variables to be coded as binary, some as categorical and some as continuous, the nature of these variables can be seen in Table S.3, along with the levels for categorical variables.

We derived the QRISK3 variables; ethnic origin, Townsend deprivation scores and sex from the exact matches of these variables in UK Biobank; FID 21000, FID 189 and FID 31. Townsend deprivation score was calculated immediately prior to the participant joining the UK Biobank cohort, based on place of residence and the census.

We generated BMI by dividing UK Biobank FID 50, weight at baseline, by the square of standing height at baseline (FID 21002) converted to meters. We derived the age of participants in years by calculating the time between the year of birth (FID 34), month of birth (FID 52), and the date that the individual attended the baseline assessment centre (FID 53).

The UK Biobank study collected data on smoking habits of participants using multiple variables, for this reason it was not possible to derive a variable with the exact levels used in QRISK3. We obtained the levels of smoking status by assuming that individuals reporting their current smoking as 'only occasionally' at

baseline (FID 1239) were light smokers, individuals reporting their smoking status as 'never' (FID 20116) were non-smokers, and individuals reporting their smoking status as 'previous' (FID 20116) were former smokers. For individuals reporting that they currently smoked in FID 1239 or 20116, the number of cigarettes smoked daily (FID 3456) was used to derive their level of smoking.

We ascertained systolic blood pressure (SBP) using the mean of the automated (FID 4080) or manual (FID 93) readings at the initial assessment visit and the first repeat assessment visit, as has been done in a previous study. There is no field in UK Biobank for variability in SBP, we therefore derived this variable as the standard deviation between two automated or manual SBP readings at baseline (FID 4080 and 93).

Total serum cholesterol and high-density lipoprotein (HDL) cholesterol were derived from enzymatic assays collected at baseline of the UK Biobank study and reported in FID 30690 and FID 30760, respectively. We subsequently calculated the ratio of these measurements to obtain the ratio measure required in QRISK3.

The QRISK3 derivation defines family history of coronary heart disease (CHD) as CHD in a first degree relative aged less than 60 years, however, it is not possible to obtain this level of information from the fields of UK Biobank. We therefore used the UK Biobank fields illnesses in father (FID 20107), illnesses in mother (FID 20110), and illnesses of siblings (FID 20111), under the assumption that the level 'heart disease' of these illnesses was CHD and that the relative was aged less than 60 years at diagnosis.

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Table S.3
Coding of the levels of the sociodemographic and lifestyle variables in QRISK3.

Risk Factor	QRISK3 variable
Ethnic origin	Categorical with levels: 1 White or not stated 2 Indian 3 Pakistani 4 Bangladeshi 5 Other Asian 6 Black Caribbean 7 Black African 8 Chinese 9 Other ethnic group
Townsend deprivation score	Continuous
Body mass index	Continuous
Smoking	Categorical with levels: 1 non-smoker 2 ex-smoker 3 light smoker (less than 10) 4 moderate smoker (10 to 19) 5 heavy smoker (20 or over)
Age	Continuous
Sex	Binary: 0 male 1 female
Systolic blood pressure	Continuous
Systolic blood pressure variability	Continuous
Total cholesterol to HDL ratio	Continuous
Family history of coronary heart disease (CHD) in first degree relative aged less than 60 years	Binary: 0 no 1 yes

Outcome

The outcome of interest is CVD defined in the original QRISK3 derivation by a diagnosis of coronary heart disease, ischaemic stroke or transient ischaemic attack (TIA). We derived this outcome from the linked HES and operative procedures (using the Office of Population Censuses and Surveys (OPCS) 4 codes) for CVD, using codes listed in Table S.4. These TIA events are not captured by the touchscreen questionnaire at the baseline assessment of the UK Biobank, because TIA is not a pre-coded category of its data field 6150 "Vascular/heart problems diagnosed by doctor". We note that TIA is category of the verbal interview (data field 20002), which was included when identifying prevalent cases for exclusion from the study population. In this study, we have used both HES records and UK Biobank data field 6150 to derive the CVD outcome including TIA (Table S.4). Since GP data was only available for around 45% of the UK Biobank cohort, we did not incorporate CVD diagnosis by GP in our outcome.

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We coded the outcome as a binary variable, with 1 indicating a participant who experienced an outcome and 0 indicating a participant who did not experience an outcome.

Table S.4
Coding for cardiovascular disease for QRISK3 according to ICD-9, ICD-10, OPCS-4 and UK Biobank FIDs.
ICD-9, ICD-10, OPCS-4 and UK Biobank FIDs were used for identifying individuals with prevalent CVD at baseline for exclusion from the analysis population.
ICD-9, ICD-10 and OPCS-4 were used for incident outcome definition.

Data source	ICD-10	ICD-9	OPCS-4	Non-Cancer Illness Code (FID 20002)	Operation Code (FID 20004)	Vascular/heart problems diagnosed by a doctor (FID 6150)
Codes	G45, I20, I21, I22, I23, I24, I25, I63, I64	410, 411, 412, 413, 414, 434, 436	K40, K41, K42, K43, K44, K45, K46, K47.1, K49, K50, K75	1074, 1075, 1082, 1583	1070, 1071. 1095, 1105, 1109, 1514	1, 2, 3

Supplementary exclusion criteria

Data from 502,488 participants in the UK Biobank study were reviewed for eligibility in this study (Figure 1). In line with the QRISK3 derivation exclusion criteria we excluded 623 participants with missing Townsend deprivation scores, a further 90,296 using statins at baseline and finally 8199 with previous diagnosis of CVD (Table S.4).

Supplementary statistical analysis

We used the multivariate imputation by chained equations (MICE) package in R to impute missing data on total cholesterol/HDL cholesterol ratio, smoking status, weight, height, SBP and SBP variability, by gender. Ten imputations were carried out. In the imputation model for males, we included all QRISK3 model predictor risk factors, along with survival outcomes; and for females, we included all gender-specific

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predictors and survival outcomes but diagnosis of or treatment for erectile dysfunction was removed from the imputation model. We implemented the QRISK3-2017 prediction model using the user-written package 'QRISK3' in R [S.1]. Statistical estimates from the ten imputed datasets were pooled using Rubin's [S.2] rules to produce summary estimates and confidence limits, incorporating the additional uncertainty of the imputed datasets.

We calculated the R^2D statistic overall and in each age group as a measure of explained variation (the proportion to which the model accounts for the dispersion of the data set) tailored towards survival data, based on the D-index [S.3]. Higher values of the R^2_D statistic indicate that a higher proportion of the variation in CVD risk in UK Biobank is explained by the dependent covariates included in the QRISK3 model and suggests that there is less residual variation.

S.2 SUPPLEMENTARY RESULTS – OVERALL MODEL PERFORMANCE

Table S.5 displays explained variation for the QRISK3 model in the UK Biobank cohort overall and in age groups, using the R^2_D measure described by Royston and Sauerbrei [S.3]. Overall, for female participants QRISK3 explained 28.2% of the variation in time to a cardiovascular outcome, this was 22.6% for males. This contrasted with an R^2_D of 59.6% for female patients and 55.0% for male patients in the QResearch internal validation. The overall model performance decreases with age, with the best performance seen in the youngest age group (35 to 45 years) and the worst in the oldest age group (65 to 75 years) for both sexes.

Table S.5
R^2_D measure of explained variation for the UK Biobank external validation of QRISK3 Model in the UK Biobank cohort overall and for each age group, as well as overall for the QResearch internal validation.

	Female					**Males**				
Age Group (years)	**All**	**<45**	**45-55**	**55-65**	**>65**	**All**	**<45**	**45-55**	**55-65**	**>65**
UK Biobank External validation	28.2%	31.5%	25.5%	16.7%	9.7%	22.6%	30.1%	19.2%	11.8%	6.6%
Internal validation	59.6%	NA	NA	NA	NA	55.0%	NA	NA	NA	NA

NA = not applicable as these measures were not reported in the QResearch internal validation.

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Table S.6

Baseline characteristics of all participants in the UK Biobank cohort by incident CVD outcome before and after multiple imputation (MI). Values are number (percentages) unless otherwise stated. Note that the baseline characteristics of all ten imputed datasets were similar. Therefore, we only show the characteristics of a randomly chosen imputed dataset in "After MI" columns. The baseline characteristics are similar before and after MI, indicating that the "missing at random" assumption is met.

	Before MI Incident CVD status		After MI Incident CVD status	
	No (N=375472)	Yes (N=27898)	No (N=375472)	Yes (N=27898)
Age (years) mean (SD)	55.6 (8.1)	60.0 (7.1)	55.6 (8.1)	60.0 (7.1)
Female	221895 (59.1)	11338 (40.6)	221895 (59.1)	11338 (40.6)
Systolic blood pressure (mmHg) mean (SD)	136.4 (18.5)	144.4 (19.2)	136.4 (18.5)	144.4 (19.2)
Missing	1260 (0.3)	147 (0.5)	--	--
Measure of systolic blood pressure variability (standard deviation of repeated measures) mean (SD)	5.3 (4.4)	5.7 (4.7)	5.3 (4.4)	5.7 (4.7)
Missing	1260 (0.3)	147 (0.5)	--	--
Total cholesterol: high-density lipoprotein cholesterol ratio (mmol/L) mean (SD)	4.2 (1.1)	4.6 (1.2)	4.2 (1.1)	4.6 (1.2)
Missing	54553 (14.5)	4021 (14.4)	--	--
Family history of coronary heart disease	147970 (39.4)	13379 (48.0)	147970 (39.4)	13379 (48.0)
Self-reported ethnicity				
White or not stated	355934 (94.8)	26666 (95.6)	355934 (94.8)	26666 (95.6)
Indian	3827 (1.0)	357 (1.3)	3827 (1.0)	357 (1.3)
Pakistani	1106 (0.3)	135 (0.5)	1106 (0.3)	135 (0.5)
Bangladeshi	124 (0.0)	16 (0.1)	124 (0.0)	16 (0.1)
Other Asian	1205 (0.3)	103 (0.4)	1205 (0.3)	103 (0.4)
Black Caribbean	3463 (0.9)	167 (0.6)	3463 (0.9)	167 (0.6)
Black African	2606 (0.7)	99 (0.4)	2606 (0.7)	99 (0.4)
Chinese	1330 (0.4)	35 (0.1)	1330 (0.4)	35 (0.1)
Other ethnic group	5877 (1.6)	320 (1.1)	5877 (1.6)	320 (1.1)
Townsend deprivation score mean (SD)	-1.4 (3.0)	-1.2 (3.2)	-1.4 (3.0)	-1.2 (3.2)
Body mass index (kg/m^2) mean (SD)	26.9 (4.6)	28.0 (4.7)	26.9 (4.6)	28.0 (4.7)
Missing	2021 (0.5)	225 (0.8)	--	--
Smoking status				
Non-smoker	215879 (59.7)	13299 (49.9)	223878 (59.6)	13900 (49.8)
Ex-smoker	120184 (33.3)	10233 (38.4)	125020 (33.3)	10712 (38.4)
Light smoker (Less than 10 a day)	4093 (1.1)	306 (1.1)	4273 (1.1)	324 (1.2)
Moderate smoker (10 to 19 a day)	12127 (3.4)	1343 (5.0)	12655 (3.4)	1409 (5.1)
Heavy smoker (20 or over a day)	9157 (2.5)	1463 (5.5)	9646 (2.6)	1553 (5.6)
Missing	14032 (3.7)	1254 (4.5)	--	--
Atrial fibrillation	1468 (0.4)	391 (1.4)	1468 (0.4)	391 (1.4)
Erectile dysfunction	596 (0.2)	102 (0.4)	596 (0.2)	102 (0.4)
Migraine	12214 (3.3)	820 (2.9)	12214 (3.3)	820 (2.9)
Rheumatoid arthritis	3894 (1.0)	516 (1.8)	3894 (1.0)	516 (1.8)
Chronic kidney disease	339 (0.1)	77 (0.3)	339 (0.1)	77 (0.3)
Severe mental illness	1699 (0.5)	195 (0.7)	1699 (0.5)	195 (0.7)
Systemic lupus erythematosus	428 (0.1)	57 (0.2)	428 (0.1)	57 (0.2)
Diabetes type 1	29 (0.0)	4 (0.0)	29 (0.0)	4 (0.0)
Diabetes type 2	3296 (0.9)	662 (2.4)	3296 (0.9)	662 (2.4)
Second generation "atypical" antipsychotic use	853 (0.2)	86 (0.3)	853 (0.2)	86 (0.3)
Corticosteroid use	2728 (0.7)	423 (1.5)	2728 (0.7)	423 (1.5)
Treated hypertension	42332 (11.3)	5924 (21.2)	42332 (11.3)	5924 (21.2)

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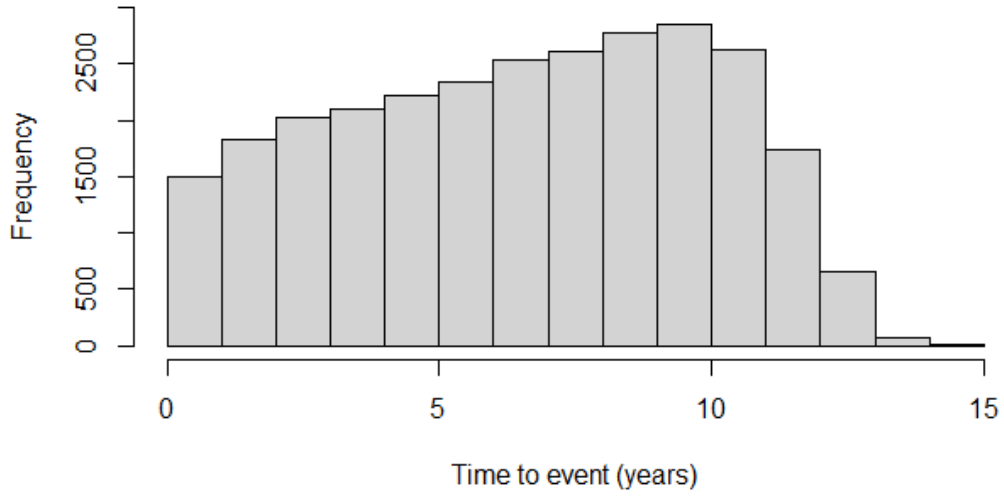
Figure S.1 Distribution of time (in years) between time of assessment and time of incident cardiovascular disease (CVD) events, N = 27898. Median (IQR) = 6.8 (3.8-9.4). Mean (SD) = 6.5 (3.4). IQR: interquartile range. SD: standard deviation.



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