

**Predictive value of metabolic profiling in cardiovascular risk scores:
analysis of 75,000 adults in UK Biobank**

Supplementary Appendix

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Supplementary Methods

QRISK3 variables and mapping in UK Biobank^{1,2}

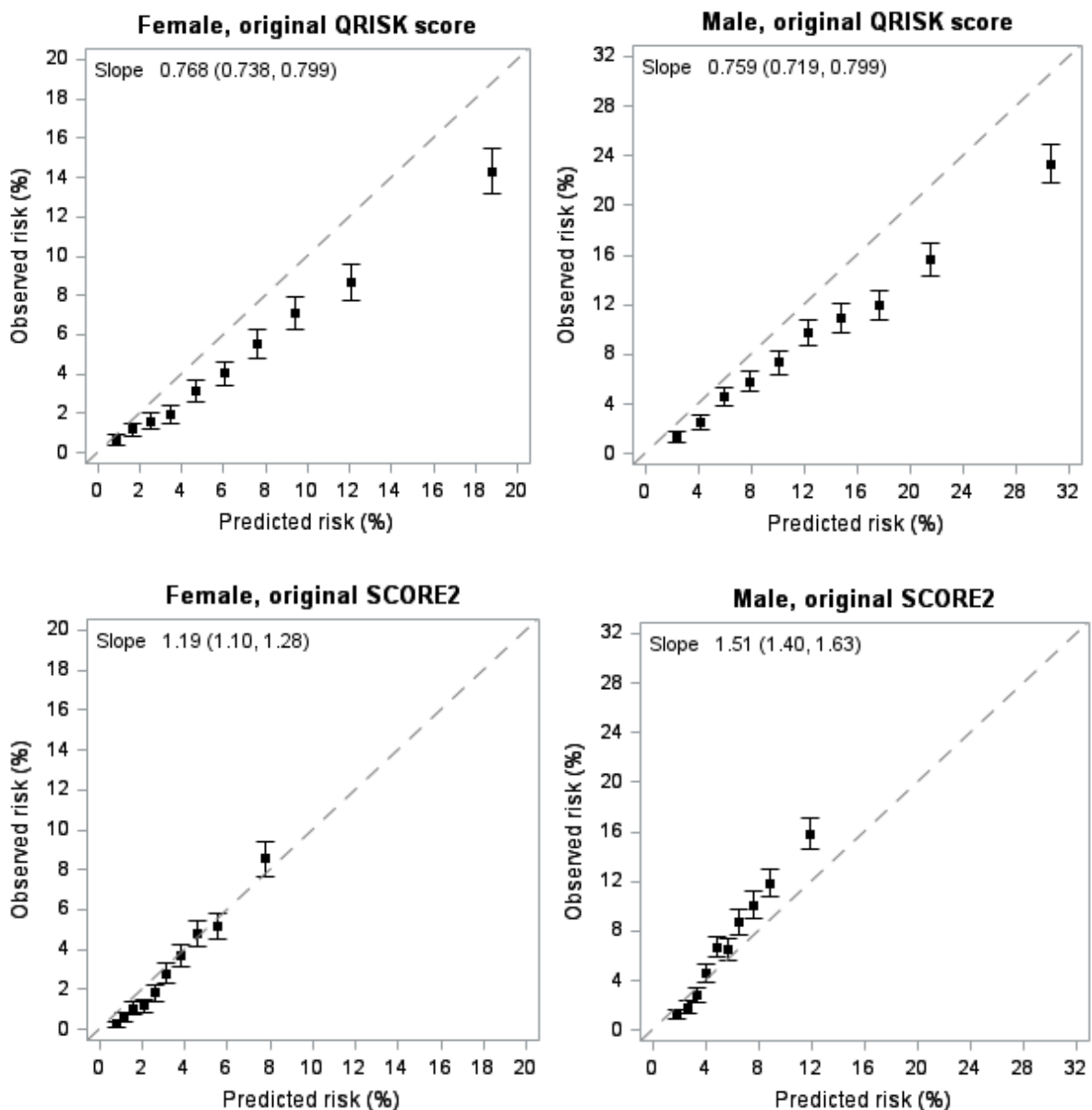
- Age at study entry (years)
- Ethnic origin (White or not state; Indian; Pakistani; Bangladeshi; Other Asian; Black Caribbean; Black African; Chinese; Other ethnic group): *our study only included White participants for analyses*
- Deprivation (as measured by the Townsend score, where higher values indicate higher levels of material deprivation)
- Systolic blood pressure (SBP) (mmHg)
- Measure of systolic blood pressure variability (standard deviation of repeated measures): *UK Biobank does not include information on variability in SBP. Our study derived this variable by the standard deviation between two automated or manual SBP readings at baseline (Variable ID 4080 and 93).*
- Body mass index (kg/m²)
- Total cholesterol-to-high density lipoprotein cholesterol ratio
- Smoking status (non-smoker, former smoker, light smoker (1-9/day), moderate smoker (10-19/day), or heavy smoker (≥ 20 /day)):
- Family history of coronary heart disease in a first-degree relative aged less than 60 years: *UK Biobank includes illnesses in father (Variable ID 20107), illnesses in mother (Variable ID 20110), and illnesses of siblings (Variable ID 20111), but does not have information on age at diagnosis. Our study assumed age less than 60 years at diagnosis.*
- Diabetes (type 1, type 2, or no diabetes)
- Treated hypertension (diagnosis of hypertension and treatment with at least one antihypertensive drug)
- Rheumatoid arthritis (diagnosis of rheumatoid arthritis, Felty's syndrome, Caplan's syndrome, adult onset Still's disease, or inflammatory polyarthropathy not otherwise specified)
- Atrial fibrillation (including atrial fibrillation, atrial flutter, and paroxysmal atrial fibrillation)
- Chronic kidney disease (stage 3, 4 or 5) and major chronic renal disease (including nephrotic syndrome, chronic glomerulonephritis, chronic pyelonephritis, renal dialysis, and renal transplant)
- Diagnosis of migraine (including classic migraine, atypical migraine, abdominal migraine, cluster headaches, basilar migraine, hemiplegic migraine, and migraine with or without aura)
- Corticosteroid use (including oral or parenteral prednisolone, betamethasone, cortisone, dexamethasone, deflazacort, ef cortisol, hydrocortisone, methylprednisolone, or triamcinolone)
- Systemic lupus erythematosus (including diagnosis of SLE, disseminated lupus erythematosus, or Libman-Sacks disease)
- Second generation "atypical" antipsychotic use (including amisulpride, aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, or zotepine)
- Diagnosis of severe mental illness (including psychosis, schizophrenia, or bipolar affective disease)
- Diagnosis of erectile dysfunction or treatment for erectile dysfunction (including alprostadil, phosphodiesterase type 5 inhibitors, papaverine, or phentolamine)

SCORE2 variables³

- Age at study entry (years)
- Smoking (current vs. other)
- Systolic blood pressure (SBP) (mmHg)
- Diabetes (yes or no)
- Total cholesterol (mmol/L)
- HDL cholesterol (mmol/L)
- Smoking x age interaction
- SBP x age interaction
- Total cholesterol x age interaction
- HDL cholesterol x age interaction
- Diabetes x age interaction

Recalibration of QRISK3 and SCORE2

The participants in UK Biobank are in overall healthier than the general UK population, with lower incidence of CVD in both men and women, and the calibration plot also showed that the original QRISK3 score was overestimated and original SCORE2 was underestimated when applying to the study population (Figure below). Therefore, following TRIPOD guidelines,⁴ our study only used the predicted hazard ratios calculated by the original algorithm⁵, and refitted the baseline survival function from the study population to obtain recalibrated predicted probabilities. After refitting the baseline risk, the recalibrated predicted risk from QRISK3 and SCORE2 was well calibrated to the observed risk of each individual (in main Figure and Figure S2, respectively).



Elastic-net^{6,7}

Elastic-net is a regularization and variable selection method that linearly combines the L1 and L2 penalties in the regression model. The method overcomes the limitations of the LASSO when dealing with highly correlated variables.

In our study, elastic-net was applied in Cox proportional hazards model, using the Python package of *sksurv.linear_model.CoxnetSurvivalAnalysis*.⁸ The key parameters include:

- `n_alphas` (int, default: 100) – Number of alphas along the regularization path.
- `alphas` (array-like or None) – List of alphas where to compute the models.
- `alpha_min_ratio` (float or "auto", default: "auto") – Determines minimum alpha of the regularization path if `alphas` is None. The smallest value for alpha is computed as the fraction of the data derived maximum alpha (i.e. the smallest value for which all coefficients are zero). If set to "auto", the value will depend on the sample size relative to the number of features. If `n_samples > n_features`, the default value is 0.0001. If `n_samples ≤ n_features`, 0.01 is the default value.
- `l1_ratio` (float, default: 0.5) – The ElasticNet mixing parameter, with $0 < \text{l1_ratio} \leq 1$. For `l1_ratio = 0` the penalty is an L2 penalty. For `l1_ratio = 1` it is an L1 penalty. For $0 < \text{l1_ratio} < 1$, the penalty is a combination of L1 and L2.

XGBoost^{9,10}

XGBoost (eXtreme Gradient Boosting) is a gradient boosting decision tree algorithm that can include higher-order interactions and account for complex nonlinear relationships of variables. Boosting is an ensemble technique where new models are added to correct the errors made by existing models. Models are added sequentially until no further improvements can be made. Gradient boosting is an approach where new models are created that predict the residuals or errors of prior models and then added together to make the final prediction, using a gradient descent algorithm to minimize the loss when adding new models. This approach supports both regression and classification predictive modeling problems, including hazard risk prediction. XGBoost handles sparse data and enables quicker model exploration, and often achieves higher accuracy than a single decision tree.

In our study, XGBoost was applied in Cox proportional hazards model, using the Python package of *xgboost*.¹¹ The key parameters include:

- objective: Learning objective.
 - survival:cox: Cox regression for right censored survival time data
- eval_metric: Evaluation metrics for validation data
 - cox-nloglik: negative partial log-likelihood for Cox proportional hazards regression
- n_estimators (range: (0,∞], default: 100): The number of trees (or rounds)
- learning_rate (range: [0,1], default: 0.3): Step size shrinkage used in update to prevents overfitting.
- max_depth (range: [0,∞], default: 6): Maximum depth of a tree. Increasing this value will make the model more complex and more likely to overfit. 0 indicates no limit on depth.
- subsample (range: (0,1], default: 1): Subsample ratio of the training instances. Setting it to 0.5 means that XGBoost would randomly sample half of the training data prior to growing trees. and this will prevent overfitting. Subsampling will occur once in every boosting iteration.
- colsample_bytree (range: (0,1], default: 1): Subsample ratio of columns when constructing each tree. Subsampling occurs once for every tree constructed.
- min_child_weight (range: [0,∞], default: 1): Minimum sum of instance weight (hessian) needed in a child. If the tree partition step results in a leaf node with the sum of instance weight less than min_child_weight, then the building process will give up further partitioning. The larger min_child_weight is, the more conservative the algorithm will be.
- reg_lambda (default: 1): L2 regularization term on weights. Increasing this value will make model more conservative.
- reg_alpha (default: 0): L1 regularization term on weights. Increasing this value will make model more conservative.

BorutaSHAP¹²

SHAP (SHapley Additive exPlanations) is a unified approach to explain how much each factor in a model has contributed to the prediction, in other words, it measures the impact in model predictions with and without a particular feature. BorutaSHAP is a wrapper feature selection method, which combines both the Boruta feature selection algorithm with shapley values. This combination has proven to outperform the original Permutation Importance method in both speed, and the quality of the feature subset produced. Not only does this algorithm provide a better subset of features, but it can also simultaneously provide the most accurate and consistent global feature rankings, which can be used for model inference too. BorutaSHAP allows the user to choose any Tree Based learner as the base model in the feature selection process.

In our study, BorutaSHAP was applied in XGBoost survival model, using the Python package of *BorutaShap*,¹³ The key parameters include:

- importance_measure ("shap", "gain" or "permutation", default: "shap"): BorutaShap object
- n_trials (range: (0,∞], default: 100): Number of iterations for Boruta algorithm

Assessment of prediction performance

Discrimination: The ability of a model to separate cases from controls

Harrell's C-index: Goodness of fit measure to evaluate risk models in survival analysis. It measures the probability that a randomly selected subject with shorter time-to-event will have a higher predicted probability of event than a randomly selected subject with longer time-to-event.

Reclassification: The ability of a new model to improve on an old model

Integrated discrimination improvement (IDI): It summarises the extent a new model increases risk in events and decreases risk in non-event compared with the old model. (\bar{P} represents the average predicted probability for that group)

$$\text{IDI} = (\bar{P}_{\text{new,events}} - \bar{P}_{\text{old,events}}) - (\bar{P}_{\text{new,non-events}} - \bar{P}_{\text{old,non-events}})$$

Net reclassification improvement (NRI): It quantifies the appropriateness of the change in predicted probabilities or categorised risk group when changing from old to new model (\hat{P} represents the proportion and D the occurrence of death)

- Continuous NRI = Continuous NRI_{event} + Continuous NRI_{non-event}
Continuous NRI_{event} = $\hat{P}_{\text{higher predicted prob, D=1}} - \hat{P}_{\text{lower predicted prob, D=1}}$
Continuous NRI_{non-event} = $\hat{P}_{\text{lower predicted prob, D=0}} - \hat{P}_{\text{higher predicted prob, D=0}}$
- Categorical NRI = Categorical NRI_{event} + Categorical NRI_{non-event}
Categorical NRI_{event} = $\hat{P}_{\text{higher risk group, D=1}} - \hat{P}_{\text{lower risk group, D=1}}$
Categorical NRI_{non-event} = $\hat{P}_{\text{lower risk group, D=0}} - \hat{P}_{\text{higher risk group, D=0}}$

Calibration: How close the predicted probability is to the actual (observed) risk

Calibration plot: It reflects how close the predicted probability is to the actual risk in each decile group of predicted probability.

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Table S1: List of clinically validated metabolites for main analyses

| | Clinically validated metabolites* | Abbreviation |
|----|---|---------------------|
| | Cholesterols, mmol/L | |
| 1 | Total cholesterol | Total_C |
| 2 | VLDL cholesterol | VLDL_C |
| 3 | LDL cholesterol | LDL_C |
| 4 | HDL cholesterol | HDL_C |
| | Triglycerides, mmol/L | |
| 5 | Total triglycerides | Total_TG |
| | Fatty acids, mmol/L | |
| 6 | Total fatty acids | TotFA |
| 7 | Omega-3 fatty acids | FAw3 |
| 8 | Omega-6 fatty acids | FAw6 |
| 9 | Polyunsaturated fatty acids | PUFA |
| 10 | Monounsaturated fatty acids | MUFA |
| 11 | Saturated fatty acids | SFA |
| 12 | Docosahexenoic acid | DHA |
| 13 | Linoleic acid | LA |
| | Fatty acids ratios | |
| 14 | Omega-3 fatty acids to total fatty acids | FAw3_FA |
| 15 | Omega-6 fatty acids to total fatty acids | FAw6_FA |
| 16 | Polyunsaturated fatty acids to total fatty acids | PUFA_FA |
| 17 | Monounsaturated fatty acids to total fatty acids | MUFA_FA |
| 18 | Saturated fatty acids to total fatty acids | SFA_FA |
| 19 | Docosahexaenoic acid to total fatty acids | DHA_FA |
| 20 | Linoleic acid to total fatty acids | LA_FA |
| 21 | Polyunsaturated to monounsaturated fatty acids | PUFA_MUFA |
| 22 | Omega-6 fatty acids to omega-3 fatty acids | FAw6_FAw3 |
| | Apolipoproteins | |
| 23 | Apolipoprotein B, g/l | ApoB |
| 24 | Apolipoprotein A1, g/l | ApoA1 |
| 25 | Apolipoprotein B ratio to apolipoprotein A1 | ApoB_ApoA1 |
| | Amino acids, mmol/L | |
| 26 | Alanine | Ala |
| 27 | Glycine | Gly |
| 28 | Histidine | His |
| | Branched-chain amino acids, mmol/L | |
| 29 | Isoleucine | Ile |
| 30 | Leucine | Leu |
| 31 | Valine | Val |
| 32 | Total concentration of branched-chain amino acids | BCAA |
| | Aromatic amino acids, mmol/L | |
| 33 | Phenylalanine | Phe |
| 34 | Tyrosine | Tyr |
| | Glycolysis related metabolites, mmol/L | |
| 35 | Glucose | Glc |
| 36 | Lactate | Lac |
| | Fluid balance | |
| 37 | Creatinine, mmol/L | Crea |
| 38 | Albumin, g/L | Alb |
| | Inflammation, mmol/L | |
| 39 | Glycoprotein acetyls | GlycA |

*Clinically and analytically validated biomarkers, which are comparable with other clinically and analytically validated laboratory method, such as photometric or enzymatic methods.

Table S2: List of metabolites for sensitivity analyses

| Biomarker name | Abbreviation | Biomarker name | Abbreviation |
|---|--------------|---|--------------|
| Total lipids, mmol/L | | Fatty acids (concentration), mmol/L | |
| Total cholesterol* | Total_C | Polyunsaturated fatty acids* | PUFA |
| VLDL cholesterol* | VLDL_C | Monounsaturated fatty acids* | MUFA |
| IDL cholesterol | IDL_C | Saturated fatty acids* | SFA |
| LDL cholesterol* | LDL_C | Docosaheptaenoic acid* | DHA |
| HDL cholesterol* | HDL_C | Linoleic acid* | LA |
| Total cholesterol minus HDL-C | non_HDL_C | Omega-3 fatty acids* | FAw3 |
| Remnant cholesterol | Remnant_C | Omega-6 fatty acids* | FAw6 |
| Total esterified cholesterol | Total_CE | Total fatty acids* | TotFA |
| Total free cholesterol | Total_FC | Fatty acids ratio, % | |
| Total phospholipids | Total_PL | Polyunsaturated fatty acids to total* | PUFA_FA |
| Total triglycerides* | Total_TG | Monounsaturated fatty acids to total* | MUFA_FA |
| Lipoprotein particle concentration, mmol/L | | Saturated fatty acids to total* | SFA_FA |
| Chylomicrons&extremely large VLDL | XXL_VLDL_P | Docosaheptaenoic acid to total* | DHA_FA |
| Very large VLDL | XL_VLDL_P | Linoleic acid to total* | LA_FA |
| Large VLDL | L_VLDL_P | Omega-3 fatty acids to total* | FAw3_FA |
| Medium VLDL | M_VLDL_P | Omega-6 fatty acids to total* | FAw6_FA |
| Small VLDL | S_VLDL_P | Polyunsaturated to monounsaturated fatty acids* | PUFA_MUFA |
| Very small VLDL | XS_VLDL_P | Omega-6 to omega-3 fatty acids* | FAw6_FAw3 |
| Total VLDL | VLDL_P | Cholines, mmol/L | |
| IDL | IDL_P | Total cholines | TotCho |
| Large LDL | L_LDL_P | Phosphatidylcholine | PC |
| Medium LDL | M_LDL_P | Sphingomyelins | SM |
| Small LDL | S_LDL_P | Phosphoglycerides | Phosphoglyc |
| Total LDL | LDL_P | Amino acids, mmol/L | |
| Very large HDL | XL_HDL_P | Alanine* | Ala |
| Large HDL | L_HDL_P | Glutamine | Gln |
| Medium HDL | M_HDL_P | Glycine* | Gly |
| Small HDL | S_HDL_P | Histidine* | His |
| Total HDL | HDL_P | Isoleucine* | Ile |
| Mean lipoprotein particle size, nm | | Leucine* | Leu |
| VLDL | VLDL_D | Valine* | Val |
| LDL | LDL_D | Branched-chain amino acids* | BCAA |
| HDL | HDL_D | Phenylalanine* | Phe |
| Lipoprotein particle composition | | Tyrosine* | Tyr |
| Esterified cholesterol in VLDL | VLDL_CE | Glycolysis related metabolites, mmol/L | |
| Free cholesterol in VLDL | VLDL_FC | Lactate* | Lac |
| Phospholipids in VLDL | VLDL_PL | Citrate | Cit |
| Triglycerides in VLDL | VLDL_TG | Glucose* | Glc |
| Esterified cholesterol in IDL | IDL_CE | Pyruvate | Pyruvate |
| Free cholesterol in IDL | IDL_FC | Ketone bodies, mmol/L | |
| Phospholipids in IDL | IDL_PL | Acetate | Ace |
| Triglycerides in IDL | IDL_TG | Aceto acetate | AcAce |
| Esterified cholesterol in LDL | LDL_CE | Acetone | Acetone |
| Free cholesterol in LDL | LDL_FC | Beta-hydroxybutyrate | bOHBut |
| Phospholipids in LDL | LDL_PL | Fluid balance | |
| Triglycerides in LDL | LDL_TG | Albumin*, g/L | Alb |
| Esterified cholesterol in HDL | HDL_CE | Creatinine*, mmol/L | Crea_nmr |
| Free cholesterol in HDL | HDL_FC | Inflammation, mmol/L | |
| Triglycerides in HDL | HDL_TG | Glycoprotein acetyls* | Gp |
| Phospholipids in HDL | HDL_PL | | |
| Apolipoproteins, g/L | | | |
| Apolipoprotein A-I* | ApoA-1 | | |
| Apolipoprotein B* | ApoB | | |
| Apolipoprotein B to A-1 ratio* | ApoB_ApoA-1 | | |

*The clinical-validated metabolites used in the main analyses

Table S3: Disease and medication codes of QRISK3 variables in UK biobank

| | ICD-10 code | Verbal interview or questionnaire code | Medication code or other measurement |
|--|----------------------------|--|--|
| Diabetes | | | |
| Type 1 | E10 | 1222; Variable ID 2443=1 & age≤20 | If recode both type1 & type2, then categorize as type1 |
| Type 2 | E11;E13;E14 | 1220;1223; Variable ID 2443=1 & age>20 | HbA1c≥48 & ≤184 mmol/mol |
| Chronic kidney disease (stage 3, 4, 5) | N183; N184; N185; N180 | 1193 | eGFR <60 ml/min |
| Atrial fibrillation | I48 | 1471;1483 | |
| Hypertension treatment | | Variable ID 6177, 6153 =2 | 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 |
| Migraines | G43 | 1265 | |
| Rheumatoid arthritis | M05; M06 | 1464 | |
| Systemic lupus erythematosus | M32 | 1381 | |
| Severe mental illness* | F20; F31; F331; F332; F333 | 1289;1291; Variable ID 20126=1,2,3,4 | |
| Atypical antipsychotic medication | | | 1140867420, 1140867444, 1140927956, 1140928916, 1141152848, 1141153490, 1141169714, 1141195974 |
| Regular steroid tablets | | | 1140874790, 1140874816, 1140874896, 1140874930, 1140874976, 1141145782, 1141173346 |
| Erectile dysfunction | N484 | 1518 | 1141168936, 1141168948, 1141168944, 1141168946, 1140869100, 1140883010 |

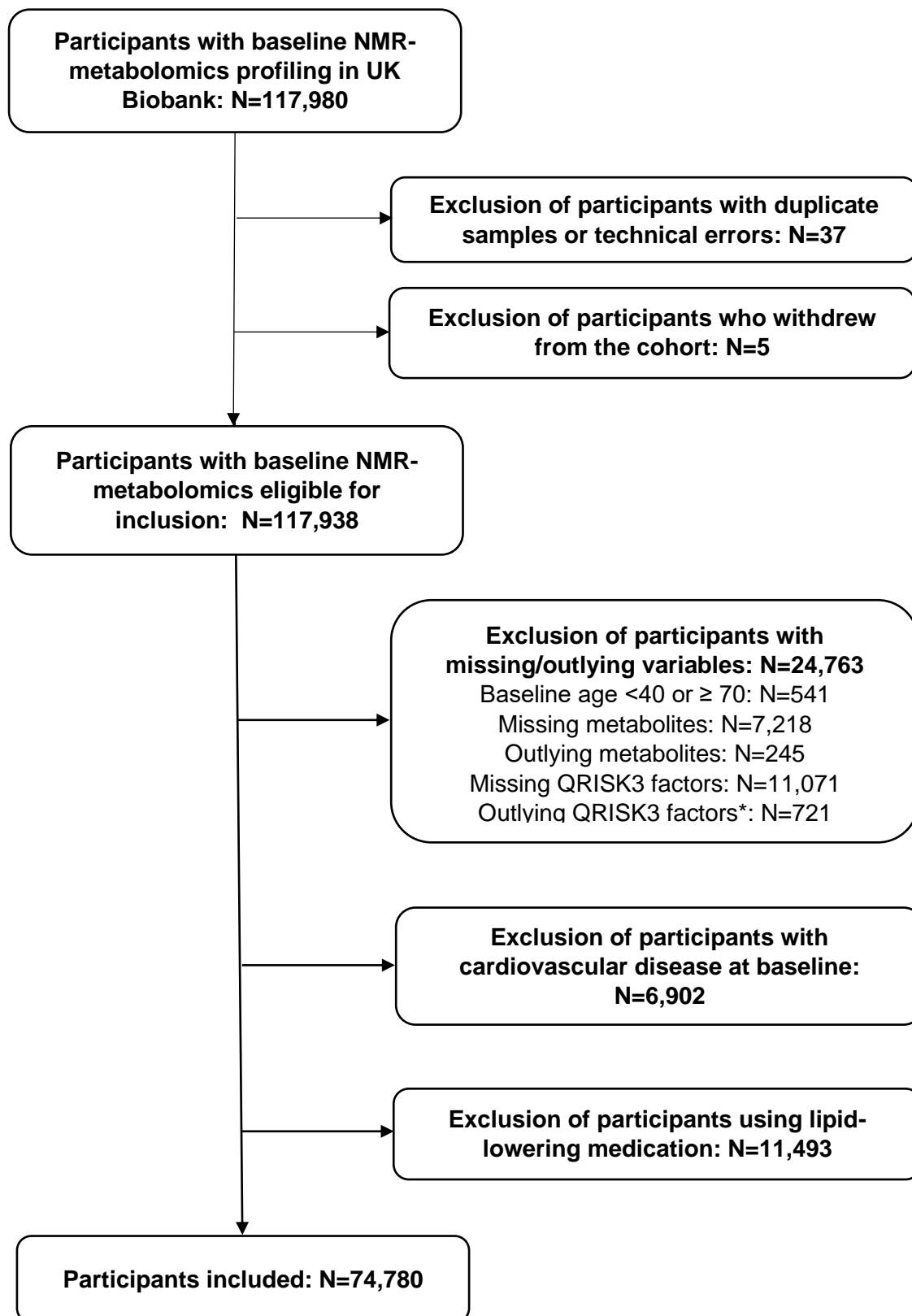
* Includes schizophrenia, bipolar disorder and moderate/severe depression.

Table S4: ICD-10 and operation code of cardiovascular disease

| ICD/OPCS category | Disease category | Code definition |
|-------------------|---|---|
| I20 | Angina pectoris | I20.0 Unstable angina I20.1 Angina pectoris with documented spasm I20.8 Other forms of angina pectoris I20.9 Angina pectoris, unspecified angina |
| I21 | Acute myocardial infarction | I21.0 Acute transmural myocardial infarction of anterior wall I21.1 Acute transmural myocardial infarction of inferior wall I21.2 Acute transmural myocardial infarction of other sites I21.3 Acute transmural myocardial infarction of unspecified site I21.4 Acute subendocardial myocardial infarction I21.9 Acute myocardial infarction, unspecified |
| I22 | Subsequent myocardial infarction | I22.0 Subsequent myocardial infarction of anterior wall I22.1 Subsequent myocardial infarction of inferior wall I22.8 Subsequent myocardial infarction of other sites I22.9 Subsequent myocardial infarction of unspecified site |
| I23 | Certain current complications following acute myocardial infarction | I23.0 Haemopericardium as current complication following acute myocardial infarction; I23.1 Atrial septal defect as current complication following acute myocardial infarction; I23.2 Ventricular septal defect as current complication following acute myocardial infarction; I23.3 Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction; I23.4 Rupture of chordae tendineae as current complication following acute myocardial infarction I23.5 Rupture of papillary muscle as current complication following acute myocardial infarction I23.6 Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction; I23.8 Other current complications following acute myocardial infarction |
| I24 | Other acute ischaemic heart diseases | I24.0 Coronary thrombosis not resulting in myocardial infarction I24.1 Dressler's syndrome I24.8 Other forms of acute ischaemic heart disease I24.9 Acute ischaemic heart disease, unspecified (excl. ischaemic heart disease (chronic) NOS) |
| I25 | Chronic ischaemic heart disease | I25.0 Atherosclerotic cardiovascular disease, so described I25.1 Atherosclerotic heart disease I25.2 Old myocardial infarction I25.3 Aneurysm of heart I25.4 Coronary artery aneurysm I25.5 Ischaemic cardiomyopathy I25.6 Silent myocardial ischaemia I25.8 Other forms of chronic ischaemic heart disease - Any condition in I21-I22 and I24.- specified as chronic I25.9 Chronic ischaemic heart disease, unspecified - Ischaemic heart disease (chronic) NOS |
| I63 | Cerebral infarction | I63.0 Cerebral infarction due to thrombosis of precerebral arteries I63.1 Cerebral infarction due to embolism of precerebral arteries I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries I63.3 Cerebral infarction due to thrombosis of cerebral arteries I63.4 Cerebral infarction due to embolism of cerebral arteries I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries |

| | | |
|-----|--------------------------------------|---|
| | | I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic I63.8 Other cerebral infarction I63.9 Cerebral infarction, unspecified |
| I64 | Stroke | Stroke, not specified as haemorrhage or infarction |
| G45 | Transient cerebral ischaemic attacks | G45.0 Vertebro-basilar artery syndrome G45.1 Carotid artery syndrome (hemispheric) G45.2 Multiple and bilateral precerebral artery syndromes G45.3 Amaurosis fugax G45.4 Transient global amnesia G45.8 Other transient cerebral ischaemic attacks and related syndromes G45.9 Transient cerebral ischaemic attack, unspecified |
| K40 | | Saphenous vein graft replacement of coronary artery |
| K41 | | Other autograft replacement of coronary artery |
| K42 | | Allograft replacement of coronary artery |
| K43 | | Prosthetic replacement of coronary artery |
| K44 | | Other replacement of coronary artery |
| K45 | | Connection of thoracic artery to coronary artery |
| K46 | | Other bypass of coronary artery |
| K47 | | Repair of coronary artery |
| K49 | | Transluminal balloon angioplasty of coronary artery |
| K50 | | Other therapeutic transluminal operations on coronary artery |
| K75 | | Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery |

Figure S1: Flowchart of exclusion criteria for study population in UK Biobank



*Exclude outlying of baseline standard deviation of systolic blood pressure >20, most missing in QRISK3 variables come from clinical chemistry measurement of total cholesterol to HDL cholesterol ratio (n=10,794)

Table S5: Fine-tuning of hyper-parameters (QRISK3)

| Model | Package (Python) | Hyperparameter* | Tuning Range | Tuning Step† | Selected Value | |
|---------|---|--------------------|---|--------------|----------------|---------------|
| | | | | | Women | Men |
| Model 1 | CoxPHSurvivalAnalysis | - | - | - | | |
| Model 2 | CoxnetSurvivalAnalysis (Penalized Cox Model) | L1_ratio alphas | (0.7, 1.0) alpha_min_ratio=0.01, max_iter=1000 to search for 1000 α values up to 1% of estimated maximum. | 0.05 | 0.9 0.00041 | 0.9 0.0012 |
| Model 3 | XGBoost | objective | - | - | survival:cox | |
| | | eval_metric | - | - | cox-nloglik | |
| | | learning_rate | [0.01, 0.02, 0.05, 0.1] | | 0.01 | 0.01 |
| | | max_depth | (2,5) | 1 | 4 | 4 |
| | | n_estimators | (50,2000) | 50 | 550 | 450 |
| | | subsample | (0.5, 1.0) | 0.1 | 0.8 | 0.6 |
| | | colsample_bytree | (0.5, 1.0) | 0.1 | 0.5 | 0.9 |
| | | min_child_weight | (6,30) | 1 | 21 | 18 |
| | | reg_lambda | Start from [1e-6, 1e-4, 0.01, 0.1, 1, 10, 100] | | 2.3 | 1.6 |
| | | reg_alpha | Start from [0, 1e-6, 1e-4, 0.01, 0.1, 1, 10, 100] | | 0.18 | 0.0036 |
| | BorutaShap | importance_measure | - | - | SHAP | |
| | | n_trials | - | - | 100 | |
| | CoxPHSurvivalAnalysis | - | - | - | | |

*The meaning of each hyperparameter is explained in eMethods; †Tuning the hyperparameter from the lowest value to the highest value in the tuning range, with increase of the tuning step each time, and selected the hyperparameter with the best performance.

Table S6: Baseline characteristics in UK Biobank versus in study population

| | UK Biobank population | | Study Population | |
|--|-----------------------|--------------|------------------|--------------|
| | Women | Men | Women | Men |
| No. of participants | 232,744 | 169,405 | 42,427 | 32,353 |
| Age and socioeconomic factors | | | | |
| Baseline Age, years | 55.5 (8.0) | 55.3 (8.2) | 55.4 (7.9) | 55.1 (8.2) |
| White, % | 94.4 | 94.1 | 95.0 | 94.8 |
| Townsend deprivation index* | -1.4 (3.0) | -1.3 (3.1) | -1.5 (3.0) | -1.4 (3.0) |
| Anthropometry, blood pressure, and lipids by clinical chemistry | | | | |
| Body Mass Index, kg/m ² | 26.7 (5.0) | 27.4 (4.0) | 26.7 (4.9) | 27.4 (4.0) |
| Systolic blood pressure, mmHg | 134.4 (19.2) | 140.3 (17.3) | 134.0 (18.9) | 140.2 (17.2) |
| Standard deviation between two readings†, mmHg | 5.4 (4.5) | 5.2 (4.3) | 5.2 (4.1) | 5.0 (3.9) |
| Total cholesterol to HDL-C ratio | 3.9 (1.0) | 4.6 (1.1) | 3.9 (1.0) | 4.6 (1.1) |
| Smoking intensity, % | | | | |
| Ex-smoker | 30.7 | 34.9 | 30.9 | 35.0 |
| Light smoker (< 10 per day) | 3.9 | 6.1 | 3.9 | 5.9 |
| Moderate smoker (10-19 per day) | 3.0 | 3.1 | 3.0 | 3.0 |
| Heavy smoker (≥20 per day) | 1.9 | 3.4 | 1.8 | 3.3 |
| Family history of heart disease‡, % | | | | |
| Parents | 42.8 | 36.1 | 43.2 | 36.3 |
| Siblings | 40.1 | 33.7 | 40.5 | 33.9 |
| Disease and medication history, % | | | | |
| Type 1 diabetes | 0.5 | 0.2 | 0.5 | 0.2 |
| Type 2 diabetes | 1.3 | 2.4 | 1.3 | 2.3 |
| Chronic kidney disease | 1.7 | 1.1 | 1.8 | 1.2 |
| Atrial fibrillation | 0.6 | 1.4 | 0.6 | 1.3 |
| Migraines | 6.0 | 2.2 | 6.3 | 2.3 |
| Rheumatoid arthritis | 1.5 | 0.8 | 1.5 | 0.8 |
| Systemic lupus erythematosus | 0.2 | <0.1 | 0.2 | <0.1 |
| Severe mental illness§ | 0.5 | 0.5 | 5.9 | 3.8 |
| Erectile dysfunction | - | 0.5 | - | 0.6 |
| Hypertension treatment | 12.5 | 12.6 | 12.2 | 12.5 |
| Atypical antipsychotic medication | 0.2 | 0.3 | 0.2 | 0.3 |
| Regular steroid tablets | 0.8 | 0.7 | 0.8 | 0.8 |

Characteristics of QRISK factors at baseline by sex. Continuous variables are presented as mean (standard deviation) and categorical variables are presented as column percentages. *Higher values indicate higher levels of material deprivation; †QRISK asks for standard deviation of systolic blood pressure values recorded in the five years before study entry, but UK biobank only provided two automated or manual readings at study entry; ‡QRISK asks for the family history in first degree relatives aged less than 60 years, but UK biobank only identified family history in first degree relatives in all ages; §Includes schizophrenia, bipolar disorder and moderate/severe depression. HDL-C=high-density lipoproteins cholesterol.

Table S7: List of selected novel metabolites by different methods (QRISK3)

| Clinically validated metabolites | Women | | | | Men | | | |
|--|--|--|------------------------------|-----------------------------|---------------------------|---------------------------|-----------------|----------------|
| | Significant associated [*] | Independent associated [†] | Elastic -net [‡] | Boruta SHAP [¶] | Significant associated | Independent associated | Elastic -net | Boruta SHAP |
| Cholesterols&Triglycerides | | | | | | | | |
| Total_C | | | | | ✓ | | | |
| VLDL_C | ✓ | | | | ✓ | | | ✓ |
| LDL_C | ✓ | | | ✓ | ✓ | | | |
| HDL_C | ✓ | ✓ | | | ✓ | | ✓ | |
| Total_TG | ✓ | | ✓ | ✓ | ✓ | | ✓ | |
| Fatty acids | | | | | | | | |
| Total FA | ✓ | | | | ✓ | | | |
| Omega-3 FA | | | ✓ | | | ✓ | ✓ | |
| Omega-6 FA | | | | | ✓ | | | |
| PUFA | | | | | ✓ | | | |
| MUFA | ✓ | | | | ✓ | | | |
| SFA | ✓ | | | | ✓ | | | |
| DHA | | | | | | | | |
| LA | | | | | ✓ | | | |
| Omega-3 FA to total FA | | | | | ✓ | ✓ | ✓ | |
| Omega-6 FA to total FA | ✓ | ✓ | | ✓ | | | | |
| PUFA to total FA | ✓ | ✓ | | | ✓ | | | |
| MUFA to total FA | ✓ | ✓ | | ✓ | ✓ | | ✓ | |
| SFA to total FA | | | | ✓ | | | | ✓ |
| DHA to total FA | ✓ | ✓ | | | ✓ | | | |
| LA to total FA | ✓ | ✓ | ✓ | | | | | |
| PUFA to MUFA | ✓ | ✓ | ✓ | | ✓ | | | |
| Omega-6 to omega-3 FA | | | ✓ | | | | | ✓ |
| Apolipoproteins | | | | | | | | |
| ApoB | ✓ | | ✓ | | ✓ | | | |
| ApoA-1 | ✓ | ✓ | | | ✓ | | | |
| ApoB to ApoA-1 | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Amino acids | | | | | | | | |
| Alanine | | | | | | | ✓ | |
| Glycine | ✓ | | ✓ | | ✓ | | ✓ | ✓ |
| Histidine | ✓ | ✓ | ✓ | | | | | |
| Isoleucine | | | | | | | | |
| Leucine | | | | | | | ✓ | ✓ |
| Valine | | | ✓ | | | | ✓ | |
| BACC | | | | | | | | |
| Phenylalanine | ✓ | | ✓ | | ✓ | | ✓ | |
| Tyrosine | | | | ✓ | | | | ✓ |
| Glycolysis related | | | | | | | | |
| Glucose | | | | ✓ | | | | ✓ |
| Lactate | | | | | | | ✓ | |
| Fluid balance | | | | | | | | |
| Creatinine | | | | | ✓ | | | |
| Albumin | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Inflammation | | | | | | | | |
| Glycoprotein acetyls | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

*Association was calculated using Cox proportional-hazards regression with adjustment of established risk factors, including age, education, region, townsend deprivation index, smoking, alcohol intake, body mass index, systolic blood pressure, and baseline diabetes; Significant association was defined as p-value<0.01 after correction of false discovery rate using Benjamini-Hochberg method; [†]Association was calculated using Cox proportional-hazards regression with adjustment of QRISK3 score; [‡]Novel metabolites selected by elastic-net based on Cox proportional-hazards regression, when adding all metabolites into the model; [¶]Novel metabolites selected by BorutaSHAP from XGBoost survival model, when adding all metabolites into the model

Table S8. Associations of clinical metabolites independent from SCORE2

| | Hazard ratio (95% CI) | |
|--|---------------------------|---------------------------|
| | Women | Men |
| Recalibrated SCORE2 | 1.12 (1.10, 1.13) | 1.07 (1.06, 1.07) |
| Cholesterols & Triglycerides | | |
| Total cholesterol | 0.96 (0.92, 1.01) | 0.98 (0.95, 1.02) |
| VLDL cholesterol | 1.06 (1.01, 1.11) | 1.01 (0.97, 1.05) |
| LDL cholesterol | 0.99 (0.95, 1.04) | 0.99 (0.96, 1.03) |
| HDL cholesterol | 0.87 (0.83, 0.92)* | 0.95 (0.91, 0.99) |
| Total triglycerides | 1.05 (1.01, 1.10) | 0.99 (0.95, 1.03) |
| Fatty acids | | |
| Total fatty acids | 1.03 (0.99, 1.08) | 0.98 (0.95, 1.02) |
| Omega-3 fatty acids | 0.96 (0.92, 1.01) | 0.93 (0.90, 0.96)* |
| Omega-6 fatty acids | 0.98 (0.94, 1.03) | 0.99 (0.95, 1.02) |
| Polyunsaturated fatty acids | 0.97 (0.93, 1.02) | 0.97 (0.93, 1.00) |
| Monounsaturated fatty acids | 1.08 (1.03, 1.12)* | 1.00 (0.96, 1.04) |
| Saturated fatty acids | 1.04 (0.99, 1.08) | 0.98 (0.95, 1.02) |
| Docosahexenoic acid | 0.94 (0.90, 0.98) | 0.93 (0.90, 0.96)* |
| Linoleic acid | 0.97 (0.93, 1.02) | 0.99 (0.95, 1.02) |
| Omega-3 to total fatty acids | 0.94 (0.90, 0.98) | 0.92 (0.89, 0.96)* |
| Omega-6 to total fatty acids | 0.91 (0.87, 0.95)* | 1.01 (0.98, 1.05) |
| Polyunsaturated to total fatty acids | 0.89 (0.85, 0.93)* | 0.98 (0.95, 1.02) |
| Monounsaturated to total fatty acids | 1.16 (1.11, 1.22)* | 1.03 (0.99, 1.07) |
| Saturated to total fatty acids | 1.03 (0.99, 1.08) | 1.00 (0.96, 1.04) |
| Docosahexaenoic acid to total fatty acids | 0.92 (0.88, 0.96)* | 0.93 (0.90, 0.97)* |
| Linoleic acid to total fatty acids | 0.90 (0.86, 0.94)* | 1.00 (0.97, 1.04) |
| Polyunsaturated to monounsaturated fatty acids | 0.85 (0.81, 0.89)* | 0.97 (0.94, 1.01) |
| Omega-6 to omega-3 fatty acids | 1.03 (0.99, 1.08) | 1.06 (1.02, 1.09)* |
| Apolipoproteins | | |
| Apolipoprotein B | 1.03 (0.98, 1.08) | 1.01 (0.98, 1.05) |
| Apolipoprotein A-1 | 0.90 (0.86, 0.94)* | 0.94 (0.90, 0.97)* |
| Apolipoprotein B to apolipoproteinA-1 | 1.09 (1.04, 1.14)* | 1.07 (1.03, 1.11)* |
| Amino acids | | |
| Alanine | 1.03 (0.99, 1.08) | 0.98 (0.95, 1.02) |
| Glycine | 0.94 (0.89, 0.98) | 0.95 (0.92, 0.99) |
| Histidine | 0.91 (0.87, 0.95)* | 0.97 (0.93, 1.00) |
| Isoleucine | 1.04 (0.99, 1.08) | 1.03 (0.99, 1.06) |
| Leucine | 1.02 (0.98, 1.06) | 1.01 (0.98, 1.05) |
| Valine | 1.01 (0.97, 1.05) | 1.00 (0.96, 1.03) |
| Total branched-chain amino acids | 1.02 (0.98, 1.06) | 1.01 (0.97, 1.04) |
| Phenylalanine | 1.06 (1.02, 1.11) | 1.06 (1.03, 1.10)* |
| Tyrosine | 1.02 (0.97, 1.06) | 1.02 (0.99, 1.06) |
| Glycolysis related metabolites | | |
| Glucose | 1.03 (0.99, 1.07) | 1.03 (0.99, 1.06) |
| Lactate | 1.03 (0.99, 1.08) | 0.99 (0.95, 1.02) |
| Fluid balance | | |
| Creatinine | 1.05 (1.01, 1.09) | 1.03 (1.00, 1.06) |
| Albumin | 0.86 (0.82, 0.90)* | 0.89 (0.86, 0.93)* |
| Inflammation | | |
| Glycoprotein acetyls | 1.18 (1.13, 1.23)* | 1.08 (1.04, 1.12)* |

Hazard ratios (HR) per one score higher of concentration. HR of each metabolite was calculated by Cox proportional-hazards regression with adjustment of SCORE2. *Associations remained significant (p-value<0.01) by correction of false discovery rate using Benjamini-Hochberg method.

Table S9: List of selected metabolites using different methods (SCORE2)

| Clinically metabolites | validated | Women | | | | Men | | | |
|----------------------------|-----------|--|--|------------------------------|-----------------------------|---------------------------|---------------------------|-----------------|----------------|
| | | Significant associated [*] | Independent associated [†] | Elastic -net [‡] | Boruta SHAP [¶] | Significant associated | Independent associated | Elastic -net | Boruta SHAP |
| Cholesterols&Triglycerides | | | | | | | | | |
| Total_C | | | | | | ✓ | | | |
| VLDL_C | | ✓ | | | | ✓ | | | ✓ |
| LDL_C | | ✓ | | | ✓ | ✓ | | | |
| HDL_C | | ✓ | ✓ | | | ✓ | | | |
| Total_TG | | ✓ | | ✓ | ✓ | ✓ | | ✓ | |
| Fatty acids | | | | | | | | | |
| Total FA | | ✓ | | | | ✓ | | | |
| Omega-3 FA | | | | ✓ | | | ✓ | ✓ | |
| Omega-6 FA | | | | | | ✓ | | | |
| PUFA | | | | | | ✓ | | | |
| MUFA | | ✓ | ✓ | | | ✓ | | | |
| SFA | | ✓ | | | | ✓ | | | |
| DHA | | | | | | | ✓ | | |
| LA | | | | | | ✓ | | | |
| Omega-3 FA to total FA | | | | | | ✓ | ✓ | | |
| Omega-6 FA to total FA | | ✓ | ✓ | | ✓ | | | | |
| PUFA to total FA | | ✓ | ✓ | | | ✓ | | | |
| MUFA to total FA | | ✓ | ✓ | | ✓ | | | ✓ | |
| SFA to total FA | | | | | ✓ | | | | ✓ |
| DHA to total FA | | ✓ | ✓ | | | ✓ | ✓ | | |
| LA to total FA | | ✓ | ✓ | ✓ | | | | | |
| PUFA to MUFA | | ✓ | ✓ | ✓ | | ✓ | | | |
| Omega-6 to omega-3 FA | | | | ✓ | | | ✓ | | ✓ |
| Apolipoproteins | | | | | | | | | |
| ApoB | | ✓ | | ✓ | | ✓ | | | |
| ApoA-1 | | ✓ | ✓ | | | ✓ | ✓ | | |
| ApoB to ApoA-1 | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Amino acids | | | | | | | | | |
| Alanine | | | | | | | | ✓ | |
| Glycine | | ✓ | | ✓ | | ✓ | | ✓ | ✓ |
| Histidine | | ✓ | ✓ | ✓ | | | | | |
| Isoleucine | | | | | | | | | |
| Leucine | | | | | | | | | ✓ |
| Valine | | | | ✓ | | | | ✓ | |
| BACC | | | | | | | | | |
| Phenylalanine | | ✓ | | ✓ | | ✓ | ✓ | ✓ | |
| Tyrosine | | | | ✓ | ✓ | | | ✓ | ✓ |
| Glycolysis related | | | | | | | | | |
| Glucose | | | | ✓ | ✓ | | | | ✓ |
| Lactate | | | | ✓ | | | | ✓ | |
| Fluid balance | | | | | | | | | |
| Creatinine | | | | ✓ | | ✓ | | ✓ | |
| Albumin | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Inflammation | | | | | | | | | |
| Glycoprotein acetyls | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

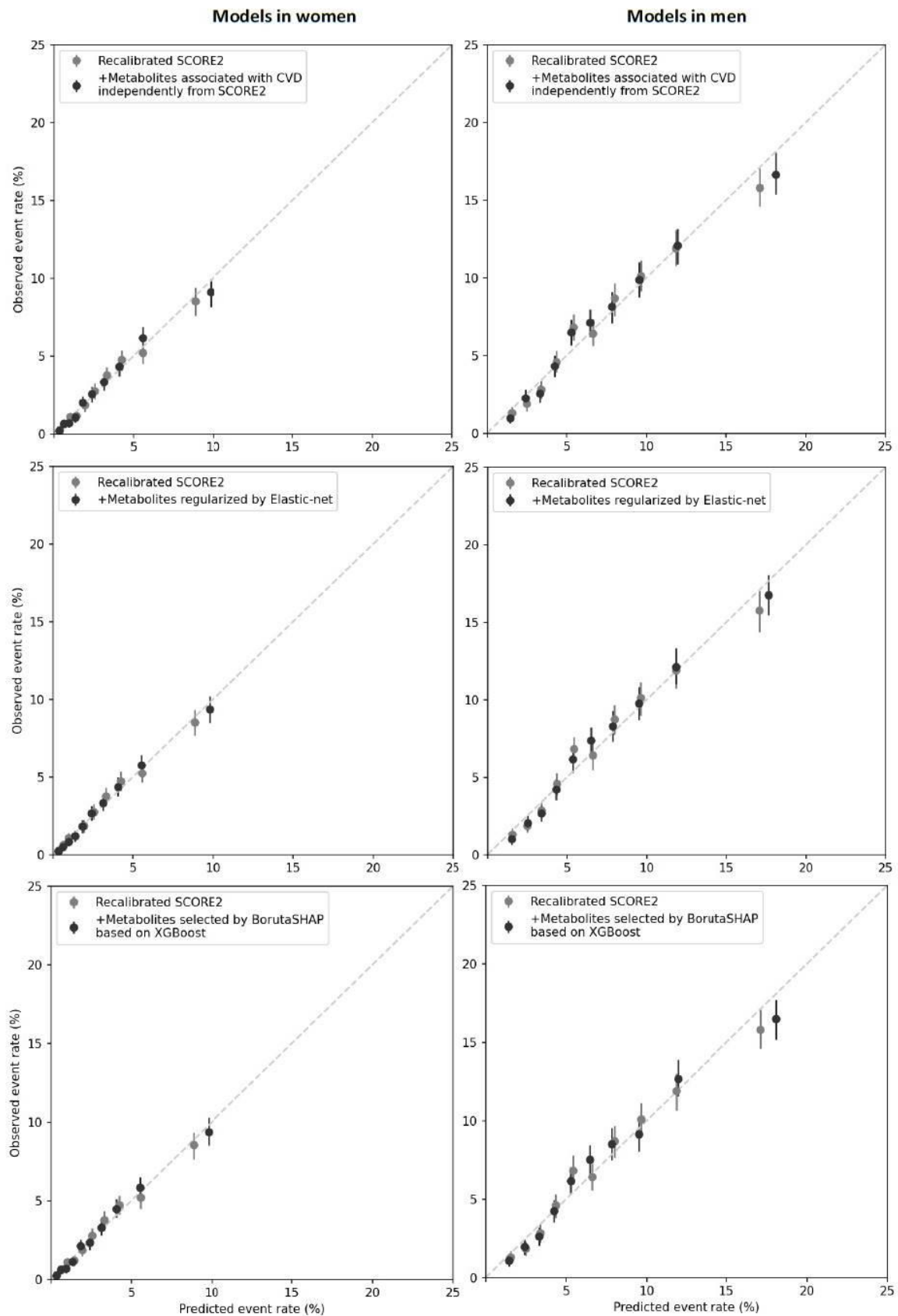
*Association was calculated using Cox proportional-hazards regression with adjustment of established risk factors, including age, education, region, townsend deprivation index, smoking, alcohol intake, body mass index, systolic blood pressure, and baseline diabetes; Significant association was defined as p-value<0.01 after correction of false discovery rate using Benjamini-Hochberg method; [†]Association was calculated using Cox proportional-hazards regression with adjustment of SCORE2; [‡] Novel metabolites selected by elastic-net based on Cox proportional-hazards regression, when adding all metabolites into the model; [¶] Novel metabolites selected by BorutaSHAP from XGBoost survival model, when adding all metabolites into the model.

Table S10: Comparing prediction performance of 10-year CVD risk w/o metabolites (SCORE2)

| Prediction Performance | Women (95% CI*) | Men (95% CI) |
|---|----------------------|----------------------|
| Recalibrated SCORE2 | | |
| Harrell's C-index † | 0.731 (0.718, 0.744) | 0.689 (0.679, 0.699) |
| Adding metabolites associated with CVD independently from SCORE2 | | |
| Harrell's C-index | 0.745 (0.732, 0.758) | 0.695 (0.686, 0.705) |
| IDI‡ (%) | 0.39 (0.24, 0.52) | 0.34 (0.20, 0.44) |
| Continuous NRI§ (%) | 21.1 (15.7, 26.3) | 15.3 (11.3, 19.3) |
| events | 9.2 (3.9, 14.3) | 6.2 (2.3, 10.0) |
| non-events | 12.0 (11.1, 12.9) | 9.1 (8.0, 10.2) |
| Categorical NRI (%) | 1.5 (-0.1, 2.8) | 0.4 (-1.0, 1.8) |
| events | 2.3 (0.8, 3.7) | -0.2 (-1.5, 1.2) |
| non-events | -0.9 (-1.0, -0.7) | 0.6 (0.3, 0.8) |
| Adding metabolites with regularization (using Elastic-net) | | |
| Harrell's C-index | 0.746 (0.734, 0.758) | 0.695 (0.685, 0.705) |
| IDI (%) | 0.36 (0.20, 0.49) | 0.21 (0.10, 0.30) |
| Continuous NRI (%) | 20.1 (14.5, 25.1) | 7.6 (3.3, 11.6) |
| events | 7.5 (2.0, 12.3) | 5.1 (0.6, 9.0) |
| non-events | 12.7 (11.7, 13.6) | 2.5 (1.4, 3.6) |
| Categorical NRI (%) | 1.4 (-0.1, 3.0) | 0.2 (-1.2, 1.6) |
| events | 2.3 (0.8, 3.8) | -0.4 (-1.7, 1.0) |
| non-events | -0.9 (-1.0, -0.7) | 0.6 (0.3, 0.9) |
| Adding metabolites selected by BorutaSHAP from XGBoost | | |
| Harrell's C-index | 0.747 (0.734, 0.758) | 0.694 (0.685, 0.704) |
| IDI (%) | 0.36 (0.21, 0.48) | 0.27 (0.14, 0.36) |
| Continuous NRI (%) | 21.9 (16.1, 27.3) | 13.3 (9.1, 17.7) |
| events | 5.2 (-0.4, 10.4) | 2.9 (-1.2, 6.8) |
| non-events | 16.7 (15.7, 17.6) | 10.4 (9.2, 11.5) |
| Categorical NRI (%) | 1.4 (0, 2.8) | 0.5 (-0.8, 1.7) |
| events | 2.2 (0.9, 3.7) | -0.1 (-1.4, 1.0) |
| non-events | -0.8 (-1.0, -0.7) | 0.6 (0.3, 0.9) |

Comparing prediction performance of 10-year CVD risk w/o metabolites. In all models, metabolites are added to recalibrated SCORE2 using Cox proportional-hazards regression. Hyper-parameters of each model are in appendix. *Bootstrap percentile confidence interval, bootstrap for 500 times; †Harrell's C-index, measuring the probability that a randomly selected subject with shorter time-to-event will have a higher predicted probability of event than a randomly selected subject with longer time-to-event; ‡Integrated discrimination improvement, summarising the extent a new model increases risk in events and decreases risk in non-event compared with the old model; §Net reclassification improvement, quantifying the appropriateness of the change in predicted probabilities or categorised risk group when changing from old to new model; Categorical NRI is based on a 10% risk threshold.

Figure S2: Calibration of risk prediction models for 10-year CVD risk (SCORE2)



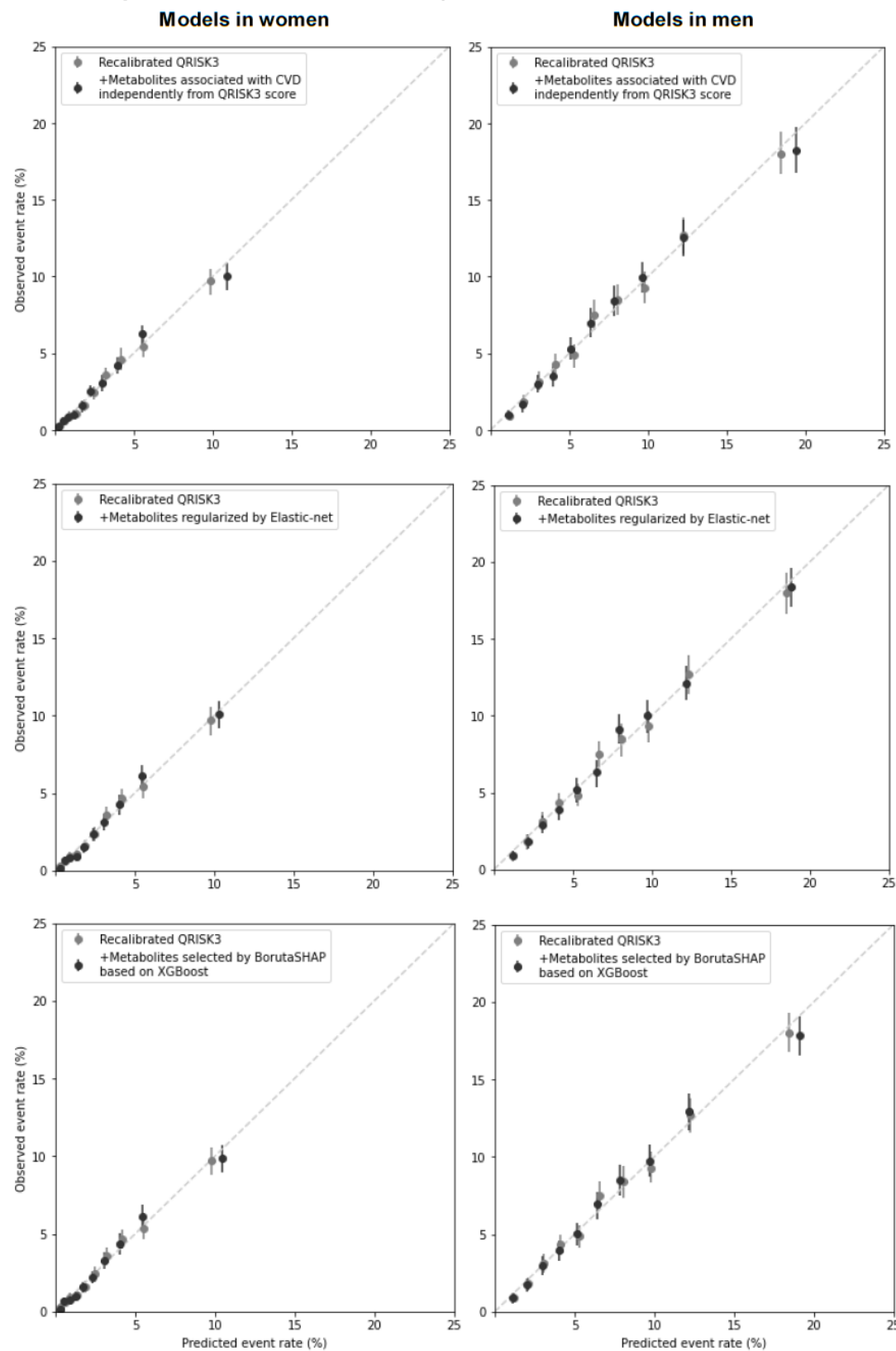
Calibration of risk prediction models for 10-year CVD risk. For each model, the observed and predicted CVD event rates are shown for each of 10 equally sized groups of absolute predicted risk. Vertical lines represent 95% CIs (bootstrap percentile confidence interval, bootstrap for 500 times).

Table S11: Prediction performance of 10-year ASCVD risk w/o metabolites (QRISK3 and wider scope of candidate metabolites)

| Prediction Performance | Women (95% CI*) | Men (95% CI) |
|---|----------------------|----------------------|
| Recalibrated QRISK3 | | |
| Harrell's C-index † | 0.750 (0.739, 0.763) | 0.706 (0.696, 0.716) |
| Adding metabolites associated with CVD independently from QRISK3 score | | |
| Harrell's C-index | 0.759 (0.748, 0.770) | 0.712 (0.702, 0.722) |
| IDI‡ (%) | 0.49 (0.21, 0.65) | 0.31 (0.18, 0.40) |
| Continuous NRI§ (%) | 17.3 (11.6, 22.2) | 10.0 (5.5, 13.8) |
| events | 7.1 (1.4, 12.2) | 1.6 (-2.6, 5.2) |
| non-events | 10.2 (9.3, 11.2) | 8.4 (7.3, 9.6) |
| Categorical NRI (%) | 1.5 (-0.2, 3.0) | 0.8 (-0.7, 2.2) |
| events | 2.3 (0.6, 3.8) | 0.2 (-1.3, 1.6) |
| non-events | -0.8 (-1.0, -0.7) | 0.6 (0.3, 0.9) |
| Adding metabolites with regularization (using Elastic-net) | | |
| Harrell's C-index | 0.760 (0.749, 0.772) | 0.711 (0.701, 0.720) |
| IDI (%) | 0.24 (0.08, 0.36) | 0.12 (0.01, 0.21) |
| Continuous NRI (%) | 6.7 (1.5, 11.9) | 2.8 (-1.5, 7.1) |
| events | 6.7 (1.6, 11.8) | 7.2 (3.1, 11.4) |
| non-events | -0.5 (-1.0, 0.9) | -4.4 (-5.4, -3.3) |
| Categorical NRI (%) | 0.8 (-0.9, 2.2) | 0.6 (-0.7, 1.8) |
| events | 1.2 (-0.4, 2.7) | 0.1 (-1.2, 1.3) |
| non-events | -0.5 (-0.6, -0.3) | 0.5 (0.2, 0.8) |
| Adding metabolites selected by BorutaSHAP from XGBoost | | |
| Harrell's C-index | 0.760 (0.748, 0.771) | 0.710 (0.700, 0.720) |
| IDI (%) | 0.35 (0.20, 0.47) | 0.19 (0.09, 0.27) |
| Continuous NRI (%) | 17.4 (12.0, 23.7) | 9.2 (5.0, 13.6) |
| events | 5.6 (0.4, 11.1) | 1.4 (-2.6, 5.4) |
| non-events | 11.8 (10.8, 12.7) | 7.8 (6.7, 8.9) |
| Categorical NRI (%) | 0.6 (-0.7, 2.0) | 1.0 (-0.2, 2.2) |
| events | 1.3 (-0.1, 2.7) | 0.6 (-0.7, 1.7) |
| non-events | -0.7 (-0.8, -0.5) | 0.5 (0.2, 0.7) |

Comparing prediction performance of 10-year ASCVD risk w/o metabolites. In all models, metabolites are added to recalibrated QRISK3 using Cox proportional-hazards regression. Hyper-parameters of each model are in appendix. *Bootstrap percentile confidence interval, bootstrap for 500 times; †Harrell's C-index, measuring the probability that a randomly selected subject with shorter time-to-event will have a higher predicted probability of event than a randomly selected subject with longer time-to-event; ‡Integrated discrimination improvement, summarising the extent a new model increases risk in events and decreases risk in non-event compared with the old model; §Net reclassification improvement, quantifying the appropriateness of the change in predicted probabilities or categorised risk group when changing from old to new model; Categorical NRI is based on a 10% risk threshold.

Figure S3: Calibration of risk prediction models for 10-year ASCVD risk (QRISK3 and wider scope of candidate metabolites)



Calibration of risk prediction models for 10-year ASCVD risk. For each model, the observed and predicted CVD event rates are shown for each of 10 equally sized groups of absolute predicted risk. Vertical lines represent 95% CIs (bootstrap percentile confidence interval, bootstrap for 500 times).