# Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eMethods**

Variables included in PCE and QRISK3

We calculated mean systolic blood pressure from two measurements taken seated after two minutes rest using an appropriate cuff and an Omron HEM-7015IT digital BP monitor or manual reading. To define treated hypertension, we used information from a nurse administered questionnaire on blood pressure lowering medication. Standing height was measured using a Seca 202 device. BMI was calculated as weight (kg) measured using an electronic weighing scales (Tanita BC-418)[1] divided by height squared ($m^2$). Smoking was based on self-reported information on current smokers ("most or all days" and "occasional" smokers), previous smokers and never smokers (coded as non-smokers in PCE).

Serum data were corrected for laboratory dilution effects and were excluded if they fell outside limits defined according to UK Biobank specifications[2]. Total serum cholesterol and HDL cholesterol were obtained from enzymatic assays (Backman Coulter AU5800) and their ratio calculated[2]. We corrected total and HDL cholesterol values for individuals on lipid lowering treatment by dividing the total cholesterol value by 0.73 and HDL cholesterol by 1.03[3].

Definition of additional QRISK3 variables

Townsend deprivation index is available for all participants corresponding to the census output area in which their residential postcode is located. smoking intensity (number of cigarettes smoked per day or amount of tobacco currently smoked). We imputed smoking intensity among current smokers where information on amount smoked ("light", "moderate", "heavy") was missing. We considered missing smoking intensity data among

self-reported current smokers as Missing Not at Random (N = 9,465) and performed imputation on 40 continuous numeric smoking-related features with predictive mean matching using the *mice* package in R. We then categorized the continuous feature of "number of cigarettes smoked per day" into one of three ordinal factors for current smoking intensity analogous to those used by QRISK3 (light smoker: 0-9 cigarettes/day; moderate smoker: 10-19 cigarettes/day; heavy smoker: 20 or more cigarettes/day). All current pipe smokers were considered light smokers. The features used for smoking intensity imputation included demographic/socio-economic information, age when started smoking, measures of physical activity, biometric information, alcohol consumption (translated from an ordinal feature), and all but two of the available serum markers (due to missingness > 50%). Information on prevalent diseases was obtained from the nurse administered questionnaire or from relevant International Classification of Disease (ICD) codes or Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision, OPCS-4) codes in hospital episode statistics (HES) data with a date of event preceding the date of assessment centre attendance. Erectile dysfunction was additionally defined by relevant self-reported medication. Family history of CAD in a first degree relative was constructed from self-reported history of heart disease in father, mother or sibling. Type 1 and 2 diabetes were defined as self-reported diagnoses or from ICD codes in HES data prior to date of assessment; type 2 diabetes was additionally defined by relevant self-reported medication and HbA1c measurement at baseline ≥48 mmol/mol (measured by HPLC analysis on a Bio-Rad Variant II Turbo[2]). The definitions of all variables according to ICD-9, ICD-10, OPCS-4 and UK Biobank field codes are shown in Supplementary Material Online, Table S1.

Calculation of Polygenic Risk Scores (PRS)

A PRS is typically calculated as a weighted sum of an individual's risk alleles. During PRS calculation, decisions must be made on (i) the weights to use for each SNP, (ii) how many SNPs to include in the score, and (iii) how to account for correlations between the SNPs (linkage disequilibrium [LD]).

We considered two methods for PRS calculation which address these issues in different ways:

1. *Clumping and thresholding (C+T).* This approach is widely used and involves taking the estimated SNP effects (from summary statistics) from the largest available GWAS as the SNP weights. LD is accounted for using a clumping algorithm, which yields a subset of independent SNPs while preferentially selecting those that are most strongly associated with the phenotype. The number of SNPs in this subset to be included in the PRS is chosen by applying a threshold on the *P*-value for association from the original GWAS. Typically, many *P*-value thresholds are explored with the aim of maximizing the ability of the PRS to predict the target phenotype.
2. *Lassosum.* Lassosum has similar aims to an alternative method, LDpred. Both lassosum and LDpred aim to calculate a PRS that is maximally predictive of the phenotype, by optimising the weights given to each SNP whilst accounting for LD. Lassosum achieves this by using penalized regression to carry out shrinkage and selection on the SNP effects from the base GWAS, accounting for LD information from a reference panel [4]. Two model parameters (s and lambda) must be chosen; PRS are calculated across a grid of values of s and lambda with the aim of maximizing phenotypic prediction. LDpred uses a Bayesian model to estimate the posterior mean SNP effects based on the SNP effects from the base GWAS, a point-normal

mixture prior (which allows a proportion of SNPs to have an effect of zero) and LD information from a reference panel [5]. The relative performance of lassosum and LDpred will depend on whether the true distribution of SNP effects is closer to a point-normal mixture distribution or a double exponential distribution[6]. However, for CAD lassosum has been shown to perform similarly to or better than LDpred [4,5], and lassosum is less computationally intensive[5].

Reclassification metrics

We calculated the net reclassification index (NRI) at the current recommended threshold for treatment in the US (7.5%) and UK (10%), the associated integrated discrimination improvement (IDI), and the category free NRI. The NRI is calculated for nested models (PCE and PCE+PRS in our analysis) via a 2x2 classification table using defined thresholds. The 'upward' movement in categories for subjects with the outcome highlights better classification, and any 'downward movement' highlights worse reclassification. The improvement in reclassification is quantified as the sum of differences in proportions of individuals moving up minus the proportion moving down for those with the outcome, and the proportion of individuals moving down minus the proportion moving up for those without the outcome (NRI) [6]. Studies have shown that NRI is sensitive to the number and choice of thresholds selected [7]. To account for this, the continuous (category-free) NRI has been proposed. This is the relative increase in the predicted probabilities for people who experience events and the decrease for those who do not[8]. Finally, IDI is proposed as a measure that integrates the NRI over all possible cut-offs for the probability of the outcome; the IDI is equivalent to the difference in discrimination slopes of 2 models [6].

**eReferences**


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**eTable 1.** Definition of QRISK3 Variables in UK Biobank

| | HES statistics ICD-10 and ICD9 codes (with date of event < date of visit) | Self-reported Data-Field 20002 | Treatment and medication code Data-Field 20003 | Other data fields |
|---|---|---|---|---|
| **Atrial Fibrillation** | ICD-10 I48; ICD-9 4273 and 4270; OPCS-4 K622 and K623 | 1471; 1483 | | |
| **Migraine** | ICD-10 G43, G440, N943; ICD-9 346 | 1265 | | |
| **Type 1 diabetes** | ICD-10 E10, O230; ICD9 25001, 25011, 25021, 25031, 25041, 25051, 25061, 25071, 25081, 25091, 25003, 25013, 25023, 25033, 25043, 25053, 25063, 25073, 25083, 25093 | 1222 | | |
| **Type 2 diabetes** | ICD-10 E11, O231; ICD-9 25000, 25010, 25020, 25030, 25040, 25050, 25060, 25070, 25080, 25090, 25002, 25012, 25022, 25032, 25042, 25052, 25062, 25072, 25082, 25092 | 1223, 1220 | 1140868902, 1140874646, 1140874674, 1140874718, 1140874744, 1140883066, 1140884600, 1141152590, 1141157284, 1141168660, 1141171646, 1141173882, 1141189090 | Biobank field 2443 = 1; HbA1c measurement ≥ 48 mmol/mol |
| **Chronic kidney disease** | ICD-10 N183, N184, N185; ICD-10 5853, 5954, 5855 | 1192, 1193 | | |
| **Rheumatoid arthritis** | ICD-10 M05, M06; ICD-9 714 | 1464 | | |
| **Systemic lupus erythematosus** | ICD-10 M32; ICD-9 7100 | 1381 | | |
| **Severe mental illness** | ICD-10 F03, F068, F09, F20, F22, F23, F259, F28, F29, F31, F39, F53, F333; ICD9 295, 298, 296 | 1289, 1291 | | |
| **Erectile disfunction** | ICD-10 N484, N52; ICD-9 60784 | 1518 | 1141168936, 1141168948, 1141168944, 1141168946, 1140869100, 1140883010 | |
| **CAD in a 1st degree relative** | | | | Biobank fields 20107, 20110, 20111 = 1 |
| **Atypical antipsychotic medication** | | | 1140867420, 1140867444, 1140927956, 1140928916, 1141152848, 1141153490, 1141169714, 1141195974 | |
| **Steroid medications** | | | 1140874790, 1140874816, 1140874896.00, 1140874930, 1140874976, 1141145782, 1141173346 | |
| **Lipid lowering medications** | | | 1140861954, 1140861958, 1140888594, 1140888648, 1141146234, 1141192410, 1141192736 | |
| **Blood pressure lowering medications** | | | 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 | Biobank fields 6177, 6153 = 2 |

**eTable 2.** Definition of Coronary Artery Disease (CAD) and Cardiovascular Disease (CVD)

| ICD-10 | ICD-9 | OPCS-4 | Non-cancer illness code (Biobank field: 20002) | Operation code (Biobank field: 20004) | Vascular/heart problems diagnosed by doctor (Biobank field: 6150) |
|---|---|---|---|---|---|
| CAD | | | | | |
| I21 | 410 | K40.1-4 | 1075: Heart attack/myocardial infarction | 1070: Coronary angioplasty | 1: Heart attack |
| I22 | 411 | K41.1-4 | | 1095: Coronary artery bypass grafts | |
| I23 | 412 | K45.1-5 | | | |
| I24.1 | 429.79 | K49.1-2 | | | |
| I25.2 | | K49.8-9 | | | |
| | | K50.2 | | | |
| | | K75.1-4 | | | |
| | | K75.8-9 | | | |
| CVD | | | | | |
| G45 | 410 | K40 | 1074: Angina | 1070: Coronary angioplasty | 1: Heart attack |
| I20 | 411 | K41 | 1075: Heart attack/myocardial infarction | 1071: Other arterial surgery/revascularisation procedures | 2: Angina |
| I21 | 412 | K42 | 1082: Transient ischaemic attack | 1095: Coronary artery bypass grafts | 3: Stroke |
| I22 | 413 | K43 | 1583: Ischaemic stroke | 1105: Carotid artery surgery/endarterectomy | |
| I23 | 414 | K44 | | 1109: Carotid artery angioplasty +/- stent | |
| I24 | 434 | K45 | | 1514: Coronary angiogram | |
| I25 | 436 | K46 | | | |
| I63 | | K47.1 | | | |
| I64 | | K49 | | | |
| | | K50 | | | |
| | | K75 | | | |

**eTable 3A.** Descriptive Characteristics of Tuning (Case-Control) Set (N=80,103)

| | Women | Men | Number of missing |
|---|---|---|---|
| **N** | 25,444 | 54,659 | 12740 |
| **Age (years) (mean (SD)) *** | 60.0 (7.1) | 59.7 (7.1) | |
| **Mean SBP (mmHg) (mean (SD)) *** | 138.0 (19.2) | 141.1 (18.0) | 95 |
| **SD of SBP (mmHg) (mean (SD))** | 5.9 (4.8) | 5.5 (4.5) | 178 |
| **BMI (kg/m²) (mean (SD))** | 28.1 (5.5) | 28.3 (4.4) | 440 |
| **Townsend deprivation score (mean (SD))** | -1.0 (3.2) | -1.2 (3.2) | 103 |
| **Reported Ethnicity (%) *** | | | 88 |
| **African** | 140 (0.6) | 282 (0.5) | |
| **Caribbean** | 278 (1.1) | 292 (0.5) | |
| **White/Not stated** | 24122 (94.8) | 52055 (95.2) | |
| **Bangladeshi** | 12 (0.0) | 38 (0.1) | |
| **Chinese** | 59 (0.2) | 105 (0.2) | |
| **Indian** | 303 (1.2) | 758 (1.4) | |
| **Other** | 380 (1.5) | 607 (1.1) | |
| **Other Asian** | 75 (0.3) | 238 (0.4) | |
| **Pakistani** | 75 (0.3) | 284 (0.5) | |
| **Smoking category (%) *** | | | 2479 |
| **Non-smoker** | 13852 (54.8) | 23137 (42.6) | |
| **Ex-smoker** | 9058 (35.8) | 24997 (46.0) | |
| **Light Smoker (0-9/day)** | 524 (2.1) | 1635 (3.0) | |
| **Moderate Smoker (10-19/day)** | 1044 (4.1) | 2110 (3.9) | |
| **Heavy Smoker (20+/day)** | 805 (3.2) | 2456 (4.5) | |
| **Type 1 diabetes (%)** | 82 (0.3) | 205 (0.4) | |
| **Type 2 diabetes (%)** | 2213 (8.7) | 6512 (11.9) | |
| **Erectile disfunction (%)** | | 610 (1.1) | |
| **Atrial fibrillation (%)** | 480 (1.9) | 1782 (3.3) | |
| **Rheumatoid arthritis (%)** | 595 (2.3) | 579 (1.1) | |
| **Systemic lupus erythematosus (%)** | 94 (0.4) | 24 (0.0) | |
| **Migraine (%)** | 1063 (4.2) | 774 (1.4) | |
| **Severe mental health (%)** | 141 (0.6) | 269 (0.5) | |
| **Chronic kindey disease(%)** | 38 (0.1) | 124 (0.2) | |
| **Blood pressure lowering medication (%) *** | 10237 (40.2) | 25411 (46.5) | |
| **Systemic steroid medications (%)** | 398 (1.6) | 661 (1.2) | |
| **Atypical antipsychotic medications (%)** | 74 (0.3) | 167 (0.3) | |
| **First degree relative with CHD (%)** | 13711 (53.9) | 25819 (47.2) | |
| **Cholesterol (mean (SD)) *** | 242.4 (46.6) | 227.7 (44.6) | 3802 |
| **HDL cholesterol (mean (SD)) *** | 58.9 (14.9) | 47.6 (12.1) | 9996 |
| **Diabetes medication (%) *** | 1461 (5.7) | 4428 (8.1) | |
| **Cholesterol medication (%) *** | 9569 (37.6) | 24949 (45.6) | |

*Variables used in PCE. Note: PCE is considering Black vs. all other ethnicities, current smokers vs. non-current smokers and diabetes as a binary variable

**eTable 3B.** Descriptive Characteristics of the PCE Prospective Cohort/Testing Set (N=352,660)

| | Full population | | Incident CAD | | Incident CVD | |
|---|---|---|---|---|---|---|
| | Women | Men | Women | Men | Women | Men |
| **N** | 205,297 | 147,363 | 1779 | 4493 | 5158 | 8595 |
| **Age (years) (mean (SD))** | 56.00 (8.01) | 55.79 (8.35) | 60.84 (6.43) | 59.60 (6.92) | 60.64 (6.63) | 59.87 (6.96) |
| **Mean SBP (mmHg) (mean (SD))** | 135.05 (19.16) | 140.92 (17.29) | 146.16 (20.99) | 147.08 (18.10) | 143.81 (20.54) | 146.73 (18.48) |
| **Reported Ethnicity (%)** | | | | | | |
| **Black** | 3865 (1.9) | 2567 (1.7) | 15 (0.8) | 30 (0.7) | 82 (1.6) | 86 (1.0) |
| **White/Others** | 201432 (98.1) | 144796 (98.3) | 1764 (99.2) | 4463 (99.3) | 5076 (98.4) | 8509 (99.0) |
| **Smoking category (%)** | | | | | | |
| **Current smokers** | 16680 (8.1) | 17140 (11.6) | 895 (50.3) | 2635 (58.6) | 2473 (47.9) | 5025 (58.5) |
| **Non-current smokers** | 13852 (91.9) | 130223 (88.4) | 884 (49.7) | 1858 (41.4) | 2685 (52.0) | 3570 (41.5) |
| **Type 1 diabetes (%)** | 7322 (3.6) | 9540 (6.5) | 159 ( 8.9) | 514 (11.4) | 473 ( 9.2) | 1072 (12.5) |
| **Blood pressure lowering medication (%)** | 35291 (17.2) | 30743 (20.9) | 615 (34.6) | 1410 (31.4) | 1784 (34.6) | 2913 (33.9) |
| **Cholesterol (mean (SD))** | 235.52 (44.8) | 227.03 (42.86) | 257.24 (50.59) | 241.85 (46.39) | 251.52 (48.29) | 236.30 (45.88) |
| **HDL cholesterol (mean (SD))** | 61.39 (14.7) | 49.42 (11.97) | 56.39 (13.71) | 46.83 (10.76) | 57.92 (14.48) | 47.55 (11.87) |
| **Person-years of observation (mean (SD))** | 8.01 (1.04) | 7.89 (1.31) | 4.60 (2.37) | 4.33 (2.38) | 4.50 (2.38) | 4.36 (2.38) |

**eTable 3C**. Descriptive Characteristics of the PCE Prospective Cohort and Excluded Participants.

| | Prospective cohort (N=352,660) | | Excluded (N=69,773) | | |
|---|---|---|---|---|---|
| | Women | Men | Women | Men | Missing counts |
| **N** | 205,297 | 147,363 | 42661 | 27112 | 64670 |
| **Age (years) (mean (SD))** | 56.00 (8.01) | 55.79 (8.35) | 55.87 (8.05) | 56.01 (8.36) | |
| **Mean SBP (mmHg) (mean (SD))** | 135.05 (19.16) | 140.92 (17.29) | 134.96 (19.35) | 140.54 (17.50) | 1230 |
| **Reported Ethnicity (%)** | | | | | |
| **Black** | 3865 (1.9) | 2567 (1.7) | 988 (2.3) | 537 (2.0) | |
| **White/Others** | 201432 (98.1) | 144796 (98.3) | 41673 (97.7) | 26575 (98.0) | |
| **Smoking category (%)** | | | | | 2216 |
| **Current smokers** | 16680 (8.1) | 17140 (11.6) | 16614 (40.1) | 13007 (49.8) | |
| **Non-current smokers** | 13852 (91.9) | 130223 (88.4) | 24820 (59.9) | 13116 (50.2) | |
| **Diabetes (%)** | 7322 (3.6) | 9540 (6.5) | 1708 (4.0) | 1984 (7.3) | |
| **Blood pressure lowering medication (%)** | 35291 (17.2) | 30743 (20.9) | 7630 (17.9) | 6024 (22.2) | |
| **Cholesterol (mean (SD))** | 235.52 (44.8) | 227.03 (42.86) | 234.69 (44.73) | 226.14 (43.98) | 29119 |
| **HDL cholesterol (mean (SD))** | 61.39 (14.7) | 49.42 (11.97) | 59.91 (14.63) | 48.51 (12.25) | 62646 |
| **Person-years of observation (mean (SD))** | 8.01 (1.04) | 7.89 (1.31) | 8.06 (1.22) | 7.94 (1.52) | |

**eTable 3D.** Descriptive Characteristics of the QRISK3 Prospective Cohort/Testing Set (N=350,730)

| | Full population | | Incident CAD | | Incident CVD | |
|---|---|---|---|---|---|---|
| | Women | Men | Women | Men | Women | Men |
| **N** | 204157 | 146573 | 1768 | 4471 | 5114 | 8534 |
| **Age (years) (mean (SD))** | 56.0 (8.0) | 55.8 (8.3) | 60.8 (6.4) | 59.6 (6.9) | 60.7 (6.6) | 59.9 (7.0) |
| **Mean SBP (mmHg) (mean (SD))** | 135.0 (19.1) | 140.9 (17.3) | 146.0 (20.8) | 147.1 (18.1) | 143.8 (20.4) | 146.7 (18.5) |
| **SD of SBP (mmHg) (mean (SD))** | 5.5 (4.5) | 5.3 (4.3) | 6.1 (5.1) | 5.6 (4.6) | 6.1 (5.0) | 5.7 (4.7) |
| **BMI (kg/m²) (mean (SD))** | 26.9 (5.1) | 27.7 (4.2) | 28.1 (5.1) | 28.4 (4.1) | 28.3 (5.4) | 28.5 (4.3) |
| **Townsend deprivation score (mean (SD))** | -1.4 (3.0) | -1.3 (3.1) | -1.0 (3.2) | -1.3 (3.1) | -1.0 (3.2) | -1.2 (3.2) |
| **Reported Ethnicity (%)** | | | | | | |
| **African** | 1178 (0.6) | 1154 (0.8) | 3 (0.2) | 8 (0.2) | 21 (0.4) | 35 (0.4) |
| **Bangladeshi** | 48 (0.0) | 97 (0.1) | 1 (0.1) | 4 (0.1) | 3 (0.1) | 6 (0.1) |
| **Caribbean** | 2055 (1.0) | 1110 (0.8) | 12 (0.7) | 12 (0.3) | 51 (1.0) | 35 (0.4) |
| **Chinese** | 745 (0.4) | 391 (0.3) | 3 (0.2) | 3 (0.1) | 10 (0.2) | 6 (0.1) |
| **Indian** | 2039 (1.0) | 1751 (1.2) | 22 (1.2) | 84 (1.9) | 51 (1.0) | 148 (1.7) |
| **Other** | 3330 (1.6) | 2066 (1.4) | 20 (1.1) | 46 (1.0) | 72 (1.4) | 80 (0.9) |
| **Other Asian** | 627 (0.3) | 631 (0.4) | 9 (0.5) | 22 (0.5) | 20 (0.4) | 39 (0.5) |
| **Pakistani** | 500 (0.2) | 682 (0.5) | 5 (0.3) | 36 (0.8) | 22 (0.4) | 56 (0.7) |
| **White/Not stated** | 193635 (94.8) | 138691 (94.6) | 1693 (95.8) | 4256 (95.2) | 4864 (95.1) | 8129 (95.3) |
| **Smoking category (%)** | | | | | | |
| **Non-smoker** | 121888 (59.7) | 74007 (50.5) | 881 (49.8) | 1849 (41.4) | 2664 (52.1) | 3543 (41.5) |
| **Ex-smoker** | 65692 (32.2) | 55521 (37.9) | 587 (33.2) | 1929 (43.1) | 1772 (34.6) | 3689 (43.2) |
| **Light Smoker (0-9/day)** | 4725 (2.3) | 4762 (3.2) | 49 (2.8) | 152 (3.4) | 119 (2.3) | 266 (3.1) |
| **Moderate Smoker (10-19/day)** | 7171 (3.5) | 6025 (4.1) | 127 (7.2) | 239 (5.3) | 302 (5.9) | 455 (5.3) |
| **Heavy Smoker (20+/day)** | 4681 (2.3) | 6258 (4.3) | 124 (7.0) | 302 (6.8) | 257 (5.0) | 581 (6.8) |
| **Type 1 diabetes (%)** | 283 (0.1) | 262 (0.2) | 13 (0.7) | 18 (0.4) | 35 (0.7) | 40 (0.5) |
| **Type 2 diabetes (%)** | 7544 (3.7) | 9310 (6.4) | 153 (8.7) | 493 (11.0) | 448 (8.8) | 1021 (12.0) |
| **Erectile disfunction (%)** | | 971 (0.7) | | 52 (1.2) | | 98 (1.1) |
| **Atrial fibrillation (%)** | 1022 (0.5) | 1825 (1.2) | 13 (0.7) | 78 (1.7) | 101 (2.0) | 223 (2.6) |
| **Rheumatoid arthritis (%)** | 2914 (1.4) | 1027 (0.7) | 58 (3.3) | 55 (1.2) | 125 (2.4) | 108 (1.3) |
| **Systemic lupus erythematosus (%)** | 406 (0.2) | 43 (0.0) | 9 (0.5) | 4 (0.1) | 23 (0.4) | 7 (0.1) |
| **Migraine (%)** | 8913 (4.4) | 2194 (1.5) | 75 (4.2) | 64 (1.4) | 237 (4.6) | 116 (1.4) |
| **Severe mental health (%)** | 883 (0.4) | 735 (0.5) | 9 (0.5) | 28 (0.6) | 40 (0.8) | 51 (0.6) |
| **Chronic kindey disease(%)** | 123 (0.1) | 136 (0.1) | 5 (0.3) | 13 (0.3) | 14 (0.3) | 30 (0.4) |
| **Blood pressure lowering medication (%)** | 34994 (17.1) | 30513 (20.8) | 611 (34.6) | 1399 (31.3) | 1761 (34.4) | 2883 (33.8) |
| **Systemic steroid medications (%)** | 1794 (0.9) | 1152 (0.8) | 31 (1.8) | 72 (1.6) | 99 (1.9) | 126 (1.5) |
| **Atypical antipsychotic medications (%)** | 443 (0.2) | 423 (0.3) | 4 (0.2) | 10 (0.2) | 19 (0.4) | 24 (0.3) |
| **First degree relative with CHD (%)** | 90542 (44.3) | 55506 (37.9) | 1023 (57.9) | 2249 (50.3) | 2873 (56.2) | 4088 (47.9) |
| **Cholesterol / HDL ratio (mean (SD))** | 4.0 (1.1) | 4.8 (1.3) | 4.8 (1.3) | 5.4 (1.4) | 4.6 (1.3) | 5.2 (1.4) |
| **Diabetes medication (%)** | 4427 (2.2) | 5860 (4.0) | 114 (6.4) | 335 (7.5) | 324 (6.3) | 698 (8.2) |
| **Cholesterol medication (%)** | 21242 (10.4) | 24645 (16.8) | 364 (20.6) | 1106 (24.7) | 1124 (22.0) | 2258 (26.5) |
| **Person-years of observation (mean (SD))** | 8.0 (1.0) | 7.9 (1.3) | 4.6 (2.4) | 4.3 (2.4) | 4.5 (2.4) | 4.3 (2.4) |

**eTable 3E.** Descriptive Characteristics of the QRISK3 Prospective Cohort and Excluded Participants

| | Prospective cohort (N=350,730) | | Excluded (N=71,703) | | |
|---|---|---|---|---|---|
| | **Women** | **Men** | **Women** | **Men** | **Missing count** |
| **N** | 204157 | 146573 | 43801 | 27902 | |
| **Age (years) (mean (SD))** | 56.0 (8.0) | 55.8 (8.3) | 55.86 (8.05) | 55.98 (8.37) | |
| **Mean SBP (mmHg) (mean (SD))** | 135.0 (19.1) | 140.9 (17.3) | 135.03 (19.43) | 140.55 (17.56) | 1230 |
| **SD of SBP (mmHg) (mean (SD))** | 5.5 (4.5) | 5.3 (4.3) | 5.51 (4.55) | 5.25 (4.37) | 1655 |
| **BMI (kg/m²) (mean (SD))** | 26.9 (5.1) | 27.7 (4.2) | 27.22 (5.44) | 27.75 (4.35) | 2665 |
| **Townsend deprivation score (mean (SD))** | -1.4 (3.0) | -1.3 (3.1) | -1.19 (3.11) | -1.06 (3.25) | 520 |
| **Reported Ethnicity (%)** | | | | | |
| **African** | 1178 (0.6) | 1154 (0.8) | 367 (0.8) | 273 (1.0) | |
| **Bangladeshi** | 48 (0.0) | 97 (0.1) | 14 (0.0) | 27 (0.1) | |
| **Caribbean** | 2055 (1.0) | 1110 (0.8) | 537 (1.2) | 245 (0.9) | |
| **Chinese** | 745 (0.4) | 391 (0.3) | 186 (0.4) | 88 (0.3) | |
| **Indian** | 2039 (1.0) | 1751 (1.2) | 597 (1.4) | 503 (1.8) | |
| **Other** | 3330 (1.6) | 2066 (1.4) | 839 (1.9) | 445 (1.6) | |
| **Other Asian** | 627 (0.3) | 631 (0.4) | 156 (0.4) | 131 (0.5) | |
| **Pakistani** | 500 (0.2) | 682 (0.5) | 142 (0.3) | 154 (0.6) | |
| **White/Not stated** | 193635 (94.8) | 138691 (94.6) | 40963 (93.5) | 26036 (93.3) | |
| **Smoking category (%)*** | | | | | 3854 |
| **Non-smoker** | 121888 (59.7) | 74007 (50.5) | 25474 (61.0) | 13522 (51.8) | |
| **Ex-smoker** | 65692 (32.2) | 55521 (37.9) | 13479 (32.3) | 10114 (38.8) | |
| **Light Smoker (0-9/day)** | 4725 (2.3) | 4762 (3.2) | 751 (1.8) | 692 (2.7) | |
| **Moderate Smoker (10-19/day)** | 7171 (3.5) | 6025 (4.1) | 1190 (2.8) | 825 (3.2) | |
| **Heavy Smoker (20+/day)** | 4681 (2.3) | 6258 (4.3) | 868 (2.1) | 934 (3.6) | |
| **Type 1 diabetes (%)** | 283 (0.1) | 262 (0.2) | 1813 (4.1) | 2074 (7.4) | |
| **Type 2 diabetes (%)** | 7544 (3.7) | 9310 (6.4) | 6 (0.0) | 194 (0.7) | |
| **Erectile disfunction (%)** | | 971 (0.7) | 243 (0.6) | 354 (1.3) | |
| **Atrial fibrillation (%)** | 1022 (0.5) | 1825 (1.2) | 649 (1.5) | 205 (0.7) | |
| **Rheumatoid arthritis (%)** | 2914 (1.4) | 1027 (0.7) | 90 (0.2) | 14 (0.1) | |
| **Systemic lupus erythematosus (%)** | 406 (0.2) | 43 (0.0) | 1840 (4.2) | 348 (1.2) | |
| **Migraine (%)** | 8913 (4.4) | 2194 (1.5) | 215 (0.5) | 207 (0.7) | |
| **Severe mental health (%)** | 883 (0.4) | 735 (0.5) | 45 (0.1) | 28 (0.1) | |
| **Chronic kidney disease (%)** | 123 (0.1) | 136 (0.1) | 7927 (18.1) | 6254 (22.4) | |
| **Blood pressure lowering medication (%)** | 34994 (17.1) | 30513 (20.8) | 418 (1.0) | 279 (1.0) | |
| **Systemic steroid medications (%)** | 1794 (0.9) | 1152 (0.8) | 128 (0.3) | 111 (0.4) | |
| **Atypical antipsychotic medications (%)** | 443 (0.2) | 423 (0.3) | 19237 (43.9) | 10486 (37.6) | |
| **First degree relative with CHD (%)** | 90542 (44.3) | 55506 (37.9) | 234.56 (44.87) | 225.96 (44.06) | |
| **Cholesterol / HDL ratio (mean (SD))** | 4.0 (1.1) | 4.8 (1.3) | 59.36 (14.67) | 48.35 (12.37) | 62712 |
| **Diabetes medication (%)** | 4427 (2.2) | 5860 (4.0) | 1204 (2.7) | 1327 (4.8) | |
| **Cholesterol medication (%)** | 21242 (10.4) | 24645 (16.8) | 4869 (11.1) | 5136 (18.4) | |
| **Person-years of observation (mean (SD))** | 8.0 (1.0) | 7.9 (1.3) | 8.05 (1.23) | 7.93 (1.52) | |

*Smoking intensity was imputed for current smokers in the prospective cohort.

**eTable 4.** Association of Different Polygenic Risk Scores (PRS) With Coronary Artery Disease (CAD) and Cardiovascular Disease (CVD) in Tuning Case-Control Studies and in Prospective Cohort Study

| | | | AUC (95% CI) PRS | | | |
|---|---|---|---|---|---|---|
| | | | CAD | | CVD | |
| **Method** | **P value/ tuning parameter** | **N SNPs in the PRS** | **Case control study (N=15,947)** | **Prospective study (N=6,272)** | **Case control study (N=33,458)** | **Prospective study (N=13,753)** |
| Clumping & Thresholding | 0.000001 | 109 | 0.597 (0.591-0.603) | 0.588 (0.581-0.595) | 0.549 (0.545-0.554) | 0.549 (0.544-0.554) |
| Clumping & Thresholding | 0.000005 | 156 | 0.600 (0.594-0.606) | 0.590 (0.583-0.598) | 0.552 (0.547-0.556) | 0.551 (0.546-0.556) |
| Clumping & Thresholding | 0.00001 | 177 | 0.603 (0.597-0.609) | 0.593 (0.585-0.600) | 0.553 (0.549-0.558) | 0.552 (0.547-0.557) |
| Clumping & Thresholding | 0.00005 | 274 | 0.609 (0.603-0.615) | 0.598 (0.591-0.606) | 0.557 (0.553-0.561) | 0.555 (0.550-0.560) |
| Clumping & Thresholding | 0.0001 | 342 | 0.607 (0.600-0.613) | 0.598 (0.591-0.605) | 0.559 (0.554-0.563) | 0.554 (0.550-0.559) |
| Clumping & Thresholding | 0.0002 | 459 | 0.609 (0.602-0.615) | 0.598 (0.591-0.605) | 0.560 (0.556-0.565) | 0.556 (0.551-0.561) |
| Clumping & Thresholding | 0.0003 | 539 | 0.610 (0.603-0.616) | 0.599 (0.592-0.606) | 0.561 (0.557-0.566) | 0.557 (0.552-0.562) |
| Clumping & Thresholding | 0.0004 | 614 | 0.611 (0.605-0.617) | 0.600 (0.593-0.607) | 0.562 (0.557-0.566) | 0.558 (0.553-0.563) |
| Clumping & Thresholding | 0.0005 | 671 | 0.611 (0.605-0.618) | 0.600 (0.593-0.607) | 0.562 (0.558-0.567) | 0.558 (0.554-0.563) |
| Clumping & Thresholding | 0.0006 | 740 | 0.612 (0.606-0.618) | 0.600 (0.593-0.608) | 0.563 (0.558-0.567) | 0.559 (0.554-0.564) |
| Clumping & Thresholding | 0.0007 | 812 | 0.612 (0.606-0.618) | 0.600 (0.593-0.607) | 0.563 (0.559-0.567) | 0.559 (0.554-0.564) |
| Clumping & Thresholding | 0.0008 | 869 | 0.612 (0.606-0.619) | 0.600 (0.593-0.607) | 0.563 (0.559-0.568) | 0.558 (0.553-0.563) |
| Clumping & Thresholding | 0.0009 | 930 | 0.612 (0.605-0.618) | 0.599 (0.592-0.606) | 0.563 (0.558-0.567) | 0.558 (0.553-0.563) |
| Clumping & Thresholding | 0.001 | 987 | 0.612 (0.606-0.618) | 0.599 (0.592-0.606) | 0.563 (0.559-0.567) | 0.558 (0.553-0.563) |
| Clumping & Thresholding | 0.002 | 1,488 | 0.612 (0.606-0.618) | 0.599 (0.592-0.606) | 0.563 (0.559-0.567) | 0.559 (0.554-0.563) |
| Clumping & Thresholding | 0.003 | 1,934 | 0.612 (0.606-0.618) | 0.597 (0.590-0.604) | 0.564 (0.560-0.569) | 0.558 (0.553-0.563) |
| Clumping & Thresholding | 0.004 | 2,363 | 0.613 (0.606-0.619) | 0.595 (0.588-0.602) | 0.565 (0.561-0.570) | 0.557 (0.552-0.562) |
| Clumping & Thresholding | 0.005 | 2,795 | 0.611 (0.605-0.617) | 0.594 (0.587-0.602) | 0.565 (0.561-0.569) | 0.557 (0.552-0.562) |
| Genome-wide significant | 5.00E-08 | 455 | 0.551 (0.545-0.557) | 0.552 (0.545-0.560) | 0.524 (0.519-0.528) | 0.527 (0.522-0.532) |
| Lassosum (INFO score>0.999 (N=1,037,385 variants)) | s=0.5; lambda=0.00428 (CAD) s=0.9; lambda=0.00207 (CVD) | 40,079 (CAD) 297,862 (CVD) | 0.629 (0.623-0.635) | 0.608 (0.601-0.615) | 0.582 (0.577-0.586) | 0.564 (0.559-0.569) |
| Lassosum (INFO score>0.3 (N=6,750,670 variants)) | s=0.2; lambda=0.00546 (CAD) s=0.2; lambda=0.00886 (CVD) | 39,219 (CAD) 1,227 (CVD) | 0.618 (0.612-0.624) | 0.605 (0.598-0.612) | 0.548 (0.543-0.552) | 0.544 (0.539-0.549) |

Clumping parameter: R2=0.6 (no clumping for genome wide)
To allow recalculation of the PRS, Lassosum coefficients for CAD and CVD models can be downloaded from 10.6084/m9.figshare.11778534 (CAD) and 10.6084/m9.figshare.11778543 (CVD).

**eTable 5.** Recalibration Coefficients for CAD and CVD Analyses From Cox Regression (PCE)

| | | PRS | | PCE | | Sex | | Age 1** | | Age 2** | | Age 3** | | Age 4** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S0 | β | SE | β | SE | β | SE | β | SE | β | SE | β | SE | β | SE |
| **CAD** | | | | | | | | | | | | | | | |
| PCE | 0.984 | | | 0.58 | 0.01 | 1.06 | 0.03 | | | | | | | | |
| PRS | 0.978 | 2.79 | 0.09 | | | | | | | | | | | | |
| Age + sex | 0.984 | | | | | 1.29 | 0.03 | 2.13 | 0.14 | 2.13 | 0.11 | 4.36 | 0.33 | 2.09 | 0.11 |
| PRS + age + sex | 0.985 | 2.99 | 0.09 | | | 1.31 | 0.03 | 2.15 | 0.14 | 2.15 | 0.11 | 4.41 | 0.33 | 2.15 | 0.11 |
| PCE + PRS | 0.986 | 2.79 | 0.09 | 0.57 | 0.01 | 1.08 | 0.03 | | | | | | | | |
| **CVD** | | | | | | | | | | | | | | | |
| PCE | 0.963 | | | 0.57 | 0.01 | 0.66 | 0.02 | | | | | | | | |
| PRS | 0.952 | 0.29 | 0.01 | | | | | | | | | | | | |
| Age + sex | 0.961 | | | | | 0.88 | 0.02 | 1.95 | 0.09 | 2.07 | 0.07 | 4.21 | 0.22 | 2.27 | 0.07 |
| PRS + age + sex | 0.962 | 0.32 | 0.01 | | | 0.89 | 0.02 | 1.97 | 0.09 | 2.09 | 0.07 | 4.24 | 0.22 | 2.3 | 0.07 |
| PCE + PRS | 0.963 | 0.28 | 0.01 | 0.56 | 0.01 | 0.67 | 0.02 | | | | | | | | |

*S0: recalibrated baseline survival at 10 years

**Non-linear effects of age are modelled with cubic splines (breakpoints at quartiles of age)

**eTable 6.** C Statistics (Derived From Cox Regression) for CVD Using Recalibrated Models in the PCE Prospective Cohort. Results are presented for the full population and stratified by gender and age class (above or below 55 years of age).

A. All participants

| | All (N=352,660 13,753 events) | < 55 years old (N=147,985 2,854 events) | >= 55 years old (N=204,675 10,899 events) | Men (N=147,363 8,595 events) | Women (N=205,297 5,158 events) |
|---|---|---|---|---|---|
| PRS | 0.56 (0.56-0.57) | 0.59 (0.58-0.60) | 0.56 (0.55-0.56) | 0.57 (0.56-0.57) | 0.56 (0.56-0.57) |
| Age and sex | 0.70 (0.70-0.71) | 0.68 (0.67-0.69) | 0.65 (0.64-0.65) | 0.65 (0.65-0.66) | 0.68 (0.67-0.68) |
| PRS + age and sex | 0.71 (0.71-0.72) | 0.70 (0.69-0.71) | 0.66 (0.65-0.66) | 0.67 (0.66-0.67) | 0.69 (0.68-0.69) |
| PCE | 0.72 (0.72-0.73) | 0.73 (0.72-0.74) | 0.67 (0.67-0.68) | 0.68 (0.67-0.69) | 0.71 (0.70-0.72) |
| PRS + PCE | 0.73 (0.73-0.74) | 0.74 (0.73-0.75) | 0.68 (0.68-0.69) | 0.69 (0.68-0.70) | 0.72 (0.71-0.72) |
| B. Participants not receiving lipid lowering treatment at baseline | | | | | |
| | All (N=306,421 10,332 events) | < 55 years old (N=140,266 2,432 events) | >= 55 years old (N=166,155 7,900 events) | Men (N=122,546 6,313 events) | Women (N=183,875 4,019 events) |
| PRS | 0.57 (0.56-0.57) | 0.59 (0.58-0.61) | 0.56 (0.56-0.57) | 0.57 (0.56-0.58) | 0.56 (0.55-0.57) |
| Age and sex | 0.71 (0.70-0.71) | 0.68 (0.67-0.69) | 0.65 (0.65-0.66) | 0.66 (0.65-0.67) | 0.68 (0.67-0.69) |
| PRS + age and sex | 0.72 (0.71-0.72) | 0.70 (0.69-0.71) | 0.66 (0.66-0.67) | 0.68 (0.67-0.68) | 0.69 (0.68-0.70) |
| PCE | 0.73 (0.72-0.73) | 0.72 (0.71-0.73) | 0.68 (0.67-0.68) | 0.69 (0.68-0.69) | 0.71 (0.70-0.72) |
| PRS + PCE | 0.74 (0.73-0.74) | 0.73 (0.72-0.74) | 0.68 (0.68-0.69) | 0.70 (0.69-0.70) | 0.72 (0.71-0.72) |

**eTable 7.** Recalibration Coefficients for CAD and CVD Analysis From Cox Regression (QRISK3)

| | | PRS | | PCE | | Sex | | Age 1** | | Age 2** | | Age 3** | | Age 4** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | S0 | β | SE | β | SE | β | SE | β | SE | β | SE | β | SE | β | SE |
| **CAD** | | | | | | | | | | | | | | | |
| PCE | 0.987 | | | 1.01 | 0.02 | 1.3 | 0.03 | | | | | | | | |
| PRS | 0.978 | 2.79 | 0.09 | | | | | | | | | | | | |
| Age + sex | 0.984 | | | | | 1.29 | 0.03 | 2.12 | 0.14 | 2.12 | 0.11 | 4.31 | 0.33 | 2.09 | 0.11 |
| PRS + age + sex | 0.985 | 2.99 | 0.09 | | | 1.31 | 0.03 | 2.14 | 0.14 | 2.14 | 0.11 | 4.36 | 0.33 | 2.15 | 0.11 |
| PCE + PRS | 0.987 | 2.68 | 0.09 | 0.99 | 0.02 | 1.32 | 0.03 | | | | | | | | |
| **CVD** | | | | | | | | | | | | | | | |
| PCE | 0.967 | | | 0.97 | 0.01 | 0.89 | 0.02 | | | | | | | | |
| PRS | 0.952 | 0.29 | 0.01 | | | | | | | | | | | | |
| Age + sex | 0.961 | | | | | 0.88 | 0.02 | 1.97 | 0.09 | 2.08 | 0.07 | 4.24 | 0.22 | 2.28 | 0.07 |
| PRS + age + sex | 0.962 | 0.32 | 0.01 | | | 0.89 | 0.02 | 1.98 | 0.09 | 2.1 | 0.07 | 4.28 | 0.22 | 2.31 | 0.07 |
| PCE + PRS | 0.968 | 0.26 | 0.01 | 0.96 | 0.01 | 0.9 | 0.02 | | | | | | | | |

*S0: recalibrated baseline survival at 10 years

**Non-linear effects of age are modelled with cubic splines (breakpoints at quartiles of age)

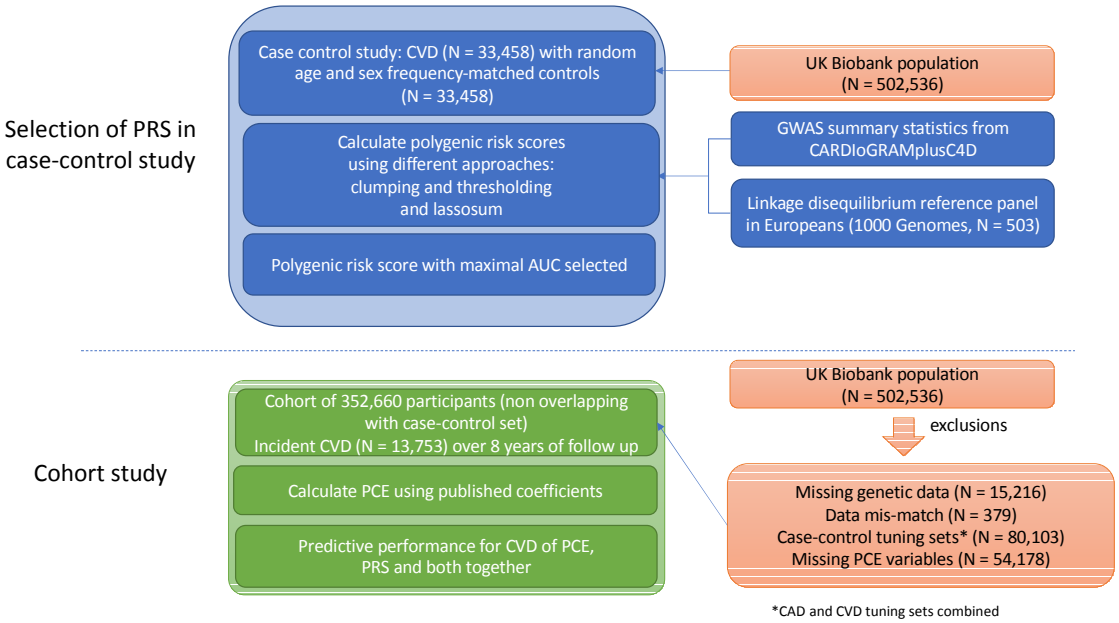
**eTable 8.** C Statistics (Derived From Cox Regression) for CAD and CVD Using Recalibrated Models in the QRISK3 Prospective Cohort. Results are presented for the full population and stratified by gender and age class (above or below 55 years of age).

| **CAD** | | | | | |
|---|---|---|---|---|---|
| | Full population | < 55 years old | >= 55 years old | Men | Women |
| | (N=350,730 | (N=147,110 | (N=203,620 | (N=146,573 | (N=204,157 |
| | 6,239 events) | 1,339 events) | 4,900 events) | 4,471 events) | 1,768 events) |
| QRISK3 | 0.61 (0.60-0.62) | 0.64 (0.63-0.66) | 0.60 (0.59-0.61) | 0.61 (0.60-0.62) | 0.61 (0.60-0.63) |
| Age (and sex*) | 0.73 (0.72-0.74) | 0.73 (0.72-0.75) | 0.68 (0.68-0.69) | 0.64 (0.63-0.65) | 0.68 (0.67-0.70) |
| PRS + age (and sex*) | 0.76 (0.75-0.76) | 0.76 (0.75-0.78) | 0.71 (0.70-0.72) | 0.68 (0.67-0.69) | 0.71 (0.70-0.73) |
| QRISK3* | 0.78 (0.77-0.79) | 0.81 (0.80-0.83) | 0.73 (0.73-0.74) | 0.71 (0.70-0.72) | 0.76 (0.75-0.78) |
| PRS + QRISK3* | 0.79 (0.79-0.80) | 0.83 (0.81-0.84) | 0.75 (0.74-0.76) | 0.73 (0.72-0.74) | 0.78 (0.76-0.79) |
| Participants not receiving lipid lowering treatment at baseline | | | | | |
| | All | < 55 years old | >= 55 years old | Men | Women |
| | (N=304,843 | (N=139,475 | (N=165,368 | (N=121,928 | (N=182,915 |
| | 4,769 events) | 1,139 events) | 3,630 events) | 3,365 events) | 1,404 events) |
| QRISK3 | 0.61 (0.60-0.62) | 0.65 (0.63-0.66) | 0.61 (0.60-0.62) | 0.62 (0.61-0.63) | 0.61 (0.60-0.63) |
| Age (and sex*) | 0.74 (0.73-0.75) | 0.74 (0.72-0.75) | 0.69 (0.68-0.70) | 0.65 (0.64-0.66) | 0.69 (0.67-0.71) |
| PRS + age (and sex*) | 0.76 (0.76-0.77) | 0.77 (0.75-0.79) | 0.72 (0.71-0.73) | 0.70 (0.69-0.71) | 0.72 (0.70-0.73) |
| QRISK3* | 0.79 (0.78-0.80) | 0.81 (0.80-0.83) | 0.74 (0.73-0.75) | 0.72 (0.71-0.73) | 0.77 (0.75-0.78) |
| PRS + QRISK3* | 0.81 (0.80-0.81) | 0.83 (0.81-0.85) | 0.76 (0.75-0.77) | 0.75 (0.74-0.76) | 0.78 (0.77-0.80) |
| **CVD** | | | | | |
| | Full population | < 55 years old | >= 55 years old | Men | Women |
| | (N=350,730 | (N=147,110 | (N=203,620 | (N=146,573 | (N=204,157 |
| | 13,650 events) | 2,826 events) | 10,824 events) | 8,536 events) | 5,114 events) |
| QRISK3 | 0.56 (0.56-0.57) | 0.59 (0.58-0.61) | 0.56 (0.55-0.56) | 0.57 (0.56-0.57) | 0.56 (0.56-0.57) |
| Age (and sex*) | 0.70 (0.70-0.71) | 0.68 (0.67-0.69) | 0.65 (0.64-0.65) | 0.65 (0.65-0.66) | 0.68 (0.67-0.68) |
| PRS + age (and sex*) | 0.71 (0.71-0.72) | 0.70 (0.69-0.71) | 0.66 (0.65-0.66) | 0.67 (0.66-0.67) | 0.69 (0.68-0.69) |
| QRISK3* | 0.75 (0.74-0.75) | 0.76 (0.75-0.77) | 0.70 (0.69-0.70) | 0.71 (0.70-0.71) | 0.74 (0.73-0.74) |
| PRS + QRISK3* | 0.75 (0.75-0.76) | 0.77 (0.76-0.78) | 0.70 (0.70-0.71) | 0.71 (0.71-0.72) | 0.74 (0.73-0.75) |
| Participants not receiving lipid lowering treatment at baseline | | | | | |
| | All | < 55 years old | >= 55 years old | Men | Women |
| | (N=304,843 | (N=139,475 | (N=165,368 | (N=121,928 | (N=182,915 |
| | 10,267 events) | 2,408 events) | 7,859 events) | 6,277 events) | 3,990 events) |
| QRISK3 | 0.57 (0.56-0.57) | 0.59 (0.58-0.61) | 0.56 (0.56-0.57) | 0.57 (0.56-0.58) | 0.56 (0.55-0.57) |
| Age (and sex*) | 0.71 (0.70-0.71) | 0.68 (0.67-0.69) | 0.65 (0.65-0.66) | 0.66 (0.65-0.67) | 0.68 (0.67-0.69) |
| PRS + age (and sex*) | 0.72 (0.71-0.72) | 0.70 (0.69-0.71) | 0.66 (0.66-0.67) | 0.68 (0.67-0.68) | 0.69 (0.68-0.70) |
| QRISK3* | 0.75 (0.75-0.76) | 0.76 (0.75-0.77) | 0.70 (0.69-0.71) | 0.71 (0.71-0.72) | 0.74 (0.73-0.74) |
| PRS + QRISK3* | 0.76 (0.75-0.76) | 0.76 (0.75-0.78) | 0.71 (0.70-0.71) | 0.72 (0.72-0.73) | 0.74 (0.73-0.75) |

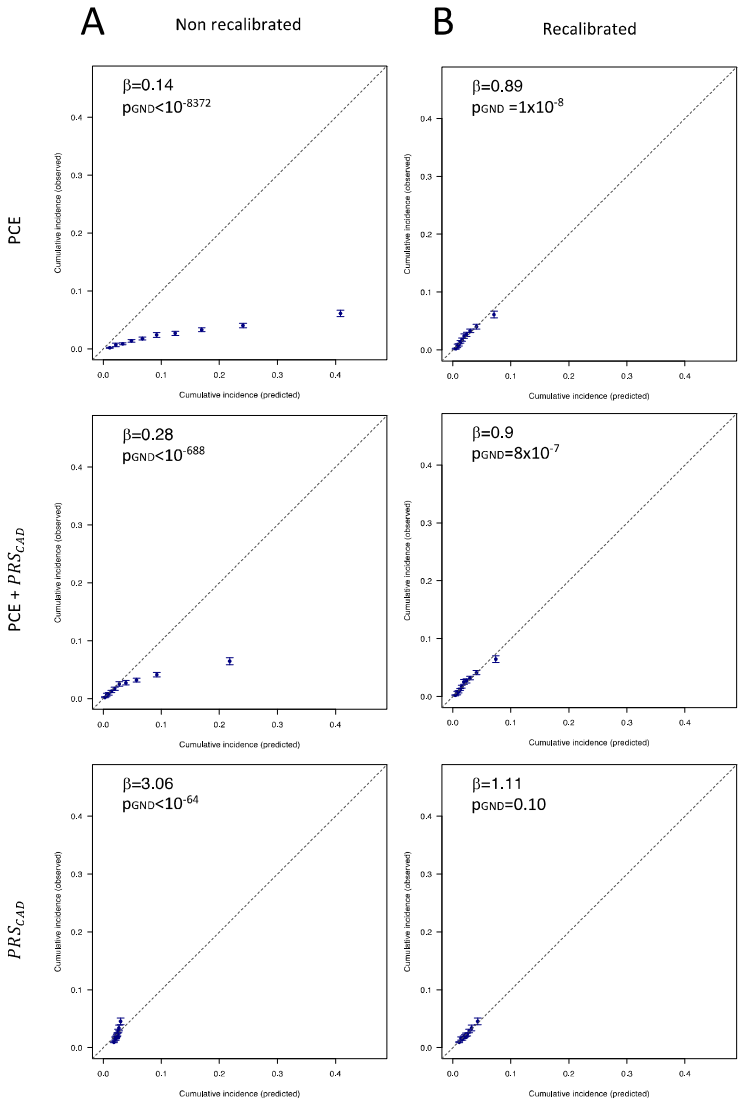
**eTable 9.** Risk Reclassification at 7.5% and 10% Thresholds for CAD and CVD Using Recalibrated Models: QRISK3 and QRISK3 Plus PRS.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **CAD (7.5% threshold)** | | | | | | | |
| | | | QRISK3 + PRS | | | | |
| | | | <7.5% | >=7.5% | % reclassified | Categorical NRI: | Continuous NRI: |
| QRISK3 | <7.5% | Cases | 4347 | 585 | 11.86 | 0.052 (0.043;0.061) | 0.149 (0.125;0.174) |
| | >=7.5% | Cases | 260 | 1047 | 19.89 | | |
| | <7.5% | Non-cases | 319802 | 7154 | 2.19 | -0.005 (-0.006;-0.005) | 0.147 (0.143;0.150) |
| | >=7.5% | Non-cases | 5365 | 12170 | 30.6 | | |
| | | | | | NRI in the full population: | 0.047 (0.038;0.056) | 0.296 (0.271;0.321) |
| | IDI: | 0.0064 (0.0058-0.007) | | | | | |
| **CAD (10% threshold)** | | | | | | | |
| | | | QRISK3 + PRS | | | | |
| | | | <10% | >=10% | % reclassified | Categorical NRI: | Continuous NRI: |
| QRISK3 | <10% | Cases | 5175 | 411 | 7.36 | 0.043 (0.036;0.051) | 0.149 (0.125;0.174) |
| | >=10% | Cases | 141 | 512 | 21.59 | | |
| | <10% | Non-cases | 332698 | 4521 | 1.34 | -0.006 (-0.007;-0.006) | 0.147 (0.143;0.150) |
| | >=10% | Non-cases | 2359 | 4913 | 32.44 | | |
| | | | | | NRI in the full population: | 0.037 (0.030;0.044) | 0.296 (0.271;0.321) |
| | IDI: | 0.0064 (0.0058-0.007) | | | | | |
| **CVD (7.5% threshold)** | | | | | | | |
| | | | QRISK3 + PRS | | | | |
| | | | <7.5% | >=7.5% | % reclassified | Categorical NRI: | Continuous NRI: |
| QRISK3 | <7.5% | Cases | 5831 | 628 | 9.72 | 0.008 (0.003;0.013) | 0.079 (0.062;0.096) |
| | >=7.5% | Cases | 521 | 6670 | 7.25 | | |
| | <7.5% | Non-cases | 260120 | 8104 | 3.02 | 0.003 (0.002;0.004) | 0.075 (0.072;0.078) |
| | >=7.5% | Non-cases | 9171 | 59685 | 13.32 | | |
| | | | | | NRI in the full population: | 0.011 (0.006;0.016) | 0.154 (0.137;0.171) |
| | IDI: | 0.0032 (0.0029-0.0036) | | | | | |
| **CVD (10% threshold)** | | | | | | | |
| | | | QRISK3 + PRS | | | | |
| | | | <10% | >=10% | % reclassified | Categorical NRI: | Continuous NRI: |
| QRISK3 | <10% | Cases | 7967 | 682 | 7.89 | 0.014 (0.009;0.018) | 0.079 (0.062;0.096) |
| | >=10% | Cases | 497 | 4504 | 9.94 | | |
| | <10% | Non-cases | 290884 | 6570 | 2.21 | -0.0005 (-0.001;0.000) | 0.075 (0.072;0.078) |
| | >=10% | Non-cases | 6404 | 33222 | 16.16 | | |
| | | | | | NRI in the full population: | 0.013 (0.008;0.018) | 0.154 (0.137;0.171) |
| | IDI: | 0.0032 (0.0029-0.0036) | | | | | |

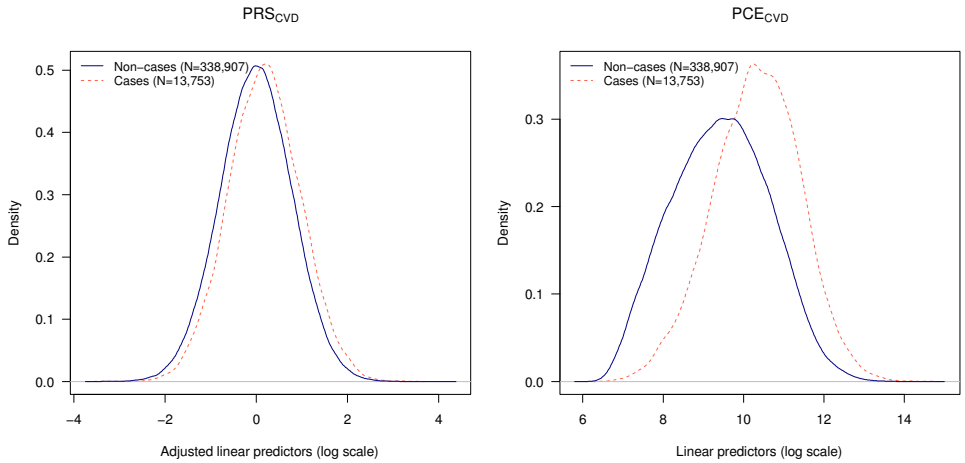
**eFigure 1.** Study Design and Flowchart for Cardiovascular Disease With PCE



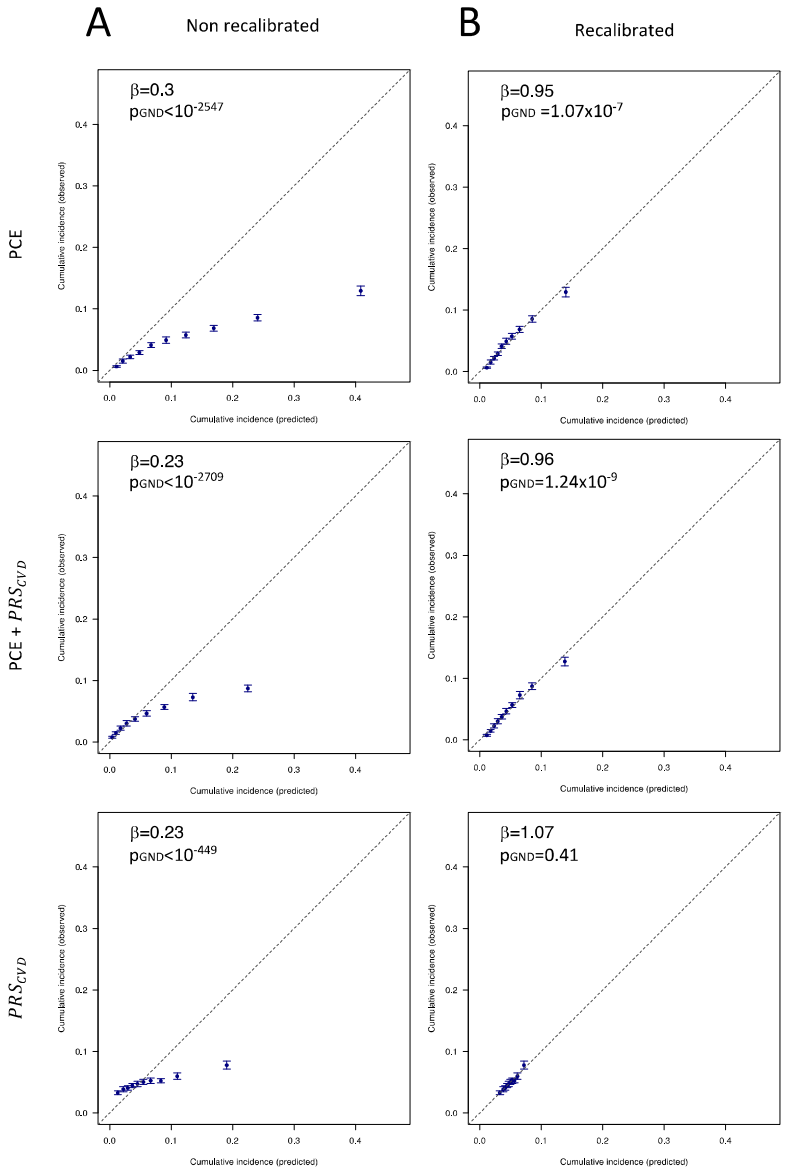
**eFigure 2.** Calibration Plots for PCE, Polygenic Risk Score for Coronary Artery Disease (CAD) ($PRS_{CAD}$) and Both Combined, Using a UK Biobank Prospective Cohort Sample (N = 352,660) **A)** Non-recalibrated model performance. **B)** Recalibrated model performance. Recalibration was undertaken by fitting the predicted log hazard from original models as a covariate in a Cox survival model. $P_{GND}$ is the P-value associated with the Greenwood-Nam-D'Agostino test statistic and tests the null hypothesis that the observed and expected probabilities are identical in each group.



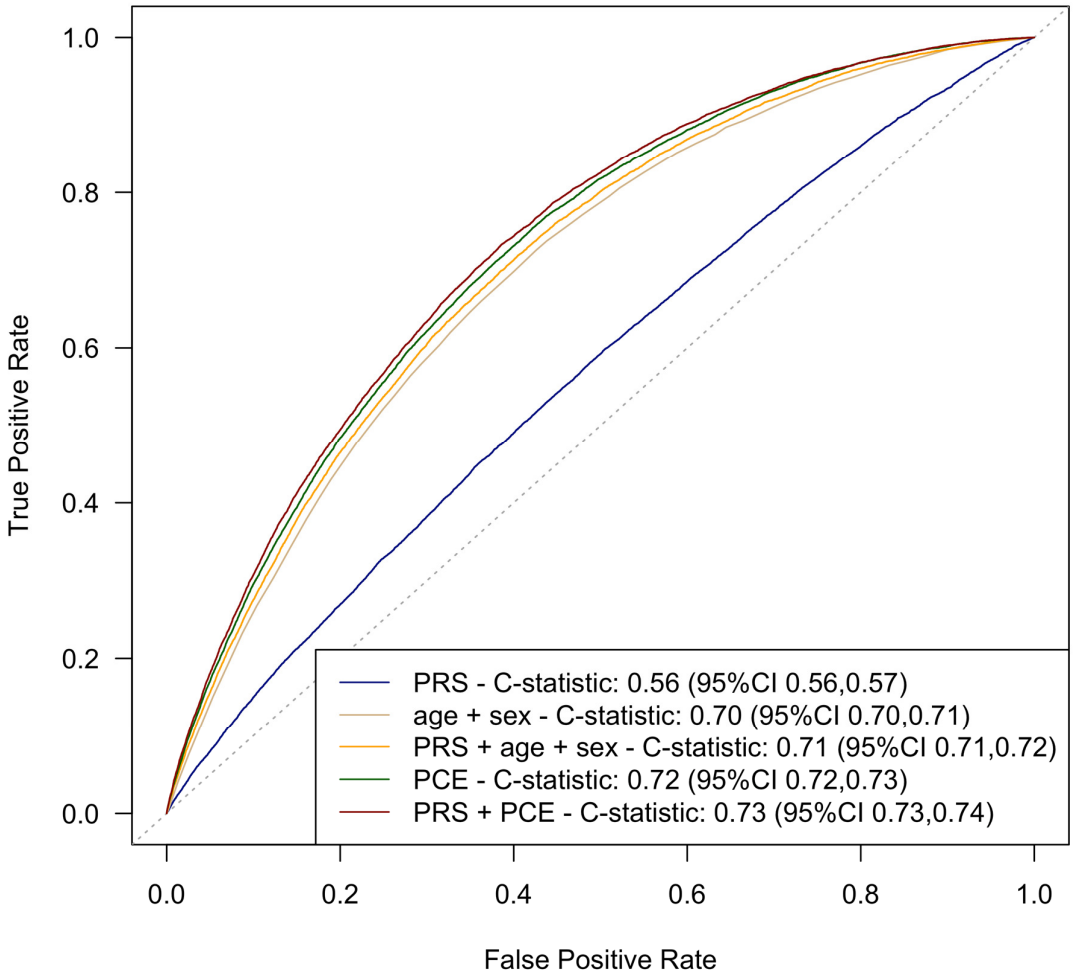
**eFigure 3.** Distributions of PRS and PCE for CVD in the Prospective Cohort



**eFigure 4.** Calibration Plots for PCE, Polygenic Risk Score for CVD ($PRS_{CVD}$) and Both Combined, Using a UK Biobank Prospective Cohort Sample (N=352,662). A. Non-recalibrated model performance. B. Recalibrated model performance. Recalibration was undertaken by fitting the predicted log hazard from original models as a covariate in a Cox survival model. $P_{GND}$ is the P-value associated with the Greenwood-Nam-D'Agostino test statistic.

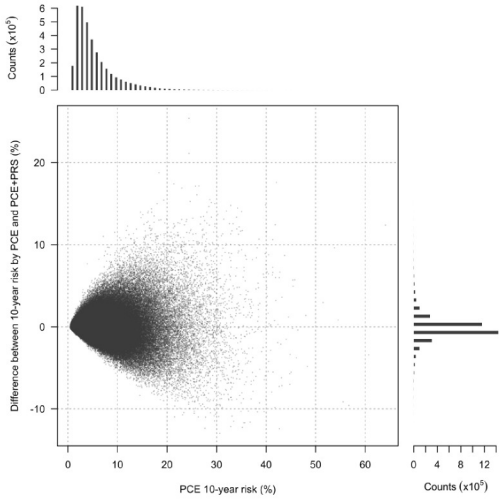


**eFigure 5.** ROC Curves and C Statistics for Different Models in Prospective Cohort Analyses for CVD



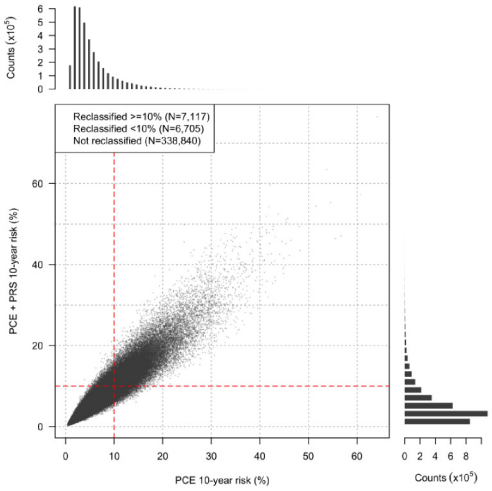
**eFigure 6.** Change in the Predicted Probabilities (Expressed as a Percentage) of the Recalibrated PCE Model After the Addition of the Polygenic Risk Score for Cardiovascular Disease (CVD) ($PRS_{CVD}$). The x-axis is the predicted probability from the original PCE model, and the y-axis is the difference in predicted probabilities between the $PRS_{CVD}$-augmented models and PCE. The associated table shows the percentage of participants whose predicted probabilities change by less than given thresholds. B. Predicted probabilities by PCE and PCE plus $PRS_{CVD}$ with dotted lines showing the 7.5% threshold. The associated table shows the reclassification percentages for 7.5% threshold as well as the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI).

A.




| % of sample | | Full sample |
|---|---|---|
| Change in probability lower than | 1% | 73.71 |
| | 5% | 98.95 |
| | 7.5% | 99.76 |
| | 10% | 99.94 |

B.




| | | | PCE + $PRS_{CVD}$ <7.5% | PCE + $PRS_{CVD}$ >=7.5% | % reclassified |
|---|---|---|---|---|---|
| PCE | <7.5% | Cases | 6780 | 682 | 9.14 |
| | >=7.5% | Cases | 495 | 5798 | 7.87 |
| | <7.5% | Non-cases | 267512 | 9083 | 3.28 |
| | >=7.5% | Non-cases | 8907 | 53405 | 14.29 |

C.

| | Continuous NRI | Categorical NRI | IDI |
|---|---|---|---|
| Cases (N=13,755) | 0.085 (0.069;0.102) | 0.014 (0.009;0.018) | |
| Non-cases (N=338,907) | 0.087 (0.084;0.090) | -0.001 (-0.001;0.000) | |
| Full population (N=352,662) | 0.172 (0.155;0.189) | 0.013 (0.008;0.018) | 0.0034 (0.0030-0.0037) |