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CLINICAL RESEARCH
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Genetic, sociodemographic, lifestyle, and clinical risk factors of recurrent coronary artery disease events: a population-based cohort study

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Abstract

Aims Complications of coronary artery disease (CAD) represent the leading cause of death among adults globally. This study examined the associations and clinical utilities of genetic, sociodemographic, lifestyle, and clinical risk factors on CAD recurrence.

Methods and results Data were from 7024 UK Biobank middle-aged adults with established CAD at enrolment. Cox proportional hazards regressions modelled associations of age at enrolment, age at first CAD diagnosis, sex, cigarette smoking, physical activity, diet, sleep, Townsend Deprivation Index, body mass index, blood pressure, blood lipids, glucose, lipoprotein(a), C reactive protein, estimated glomerular filtration rate (eGFR), statin prescription, and CAD polygenic risk score (PRS) with first post-enrolment CAD recurrence. Over a median [interquartile range] follow-up of 11.6 [7.2–12.7] years, 2003 (28.5%) recurrent CAD events occurred. The hazard ratio (95% confidence interval [CI]) for CAD recurrence was the most pronounced with current smoking (1.35, 1.13–1.61) and per standard deviation increase in age at first CAD (0.74, 0.67–0.82). Additionally, age at enrolment, CAD PRS, C-reactive protein, lipoprotein(a), glucose, low-density lipoprotein cholesterol, deprivation, sleep quality, eGFR, and high-density lipoprotein (HDL) cholesterol also significantly associated with recurrence risk. Based on C indices (95% CI), the strongest predictors were CAD PRS (0.58, 0.57–0.59), HDL cholesterol (0.57, 0.57–0.58), and age at initial CAD event (0.57, 0.56–0.57). In addition to traditional risk factors, a comprehensive model improved the C index from 0.644 (0.632–0.654) to 0.676 (0.667–0.686).

Conclusion Sociodemographic, clinical, and laboratory factors are each associated with CAD recurrence with genetic risk, age at first CAD event, and HDL cholesterol concentration explaining the most.

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Structured Graphical Abstract

Key Question

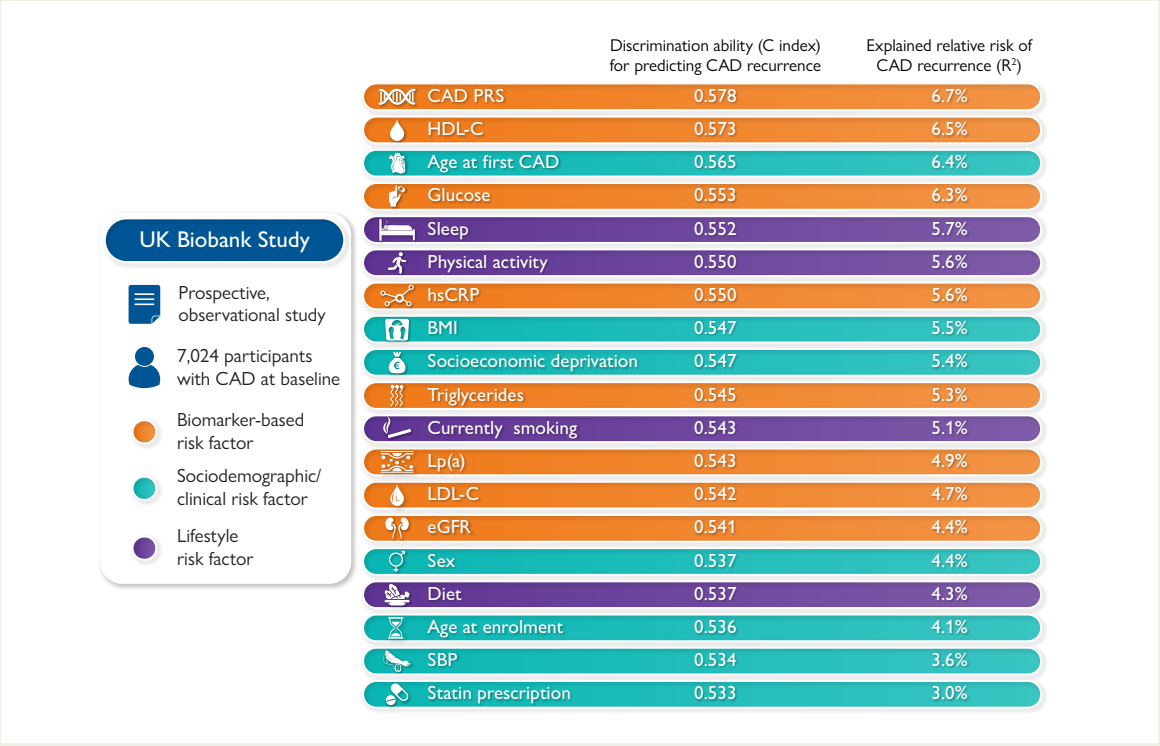
To what extent do genetic, sociodemographic, lifestyle, and clinical risk factors predict coronary artery disease (CAD) recurrence?

Key Finding

In a middle-aged UK population with established CAD, the strongest predictors of recurrent CAD event were polygenic risk, high-density lipoprotein cholesterol, and age at first diagnosis. Age, lipoprotein(a), glucose, low density lipoprotein cholesterol, socioeconomic deprivation, sleep, and renal function were also significantly associated with recurrence risk.

Take Home Message

Comprehensive assessment of genetic, sociodemographic, lifestyle, and clinical risk factors improves prediction of recurrent CAD risk. Nevertheless, the majority of CAD recurrence risk remains unexplained, potentially contributing to persistence of premature death.



BMI body mass index; CAD coronary artery disease; eGFR estimated glomerular filtration rate; HDLc high-density lipoprotein cholesterol; hsCRP high-sensitivity C-reactive protein; LDLc low-density lipoprotein cholesterol; Lp(a) lipoprotein(a); PRS polygenic risk score; SBP systolic blood pressure

Keywords Secondary prevention • Coronary artery disease • Risk prediction • Preventive cardiology • Epidemiology

Introduction

Among individuals with coronary artery disease (CAD), modern paradigms to prevent event recurrence ('secondary prevention') focus on risk factor optimization, particularly potent reduction of low-density lipoprotein (LDL) cholesterol, antiplatelets, and lifestyle modification.[1] Unfortunately, for the last two decades, complications of CAD represent the leading cause of death among adults globally.[2,3] Understanding the mechanisms contributing to residual risk of recurrent events may inform public health strategies as well as new trials.

CAD is a complex disease whose lifelong management requires multifactorial strategies accounting for existing comorbidities, lifestyle, and underlying socioeconomic environment.[4–6] Despite contemporary clinical guidelines[7–10] recommending intensive lipid, blood pressure, and glucose control to patients with prior atherosclerotic cardiovascular disease (ASCVD), adherence is not uniform[11–13] and events remain high even when adherence is high.[14–16] Based on analyses limited to well-recognized risk factors in three clinical trials of cholesterol-lowering medicines,[14–17] contemporary guidelines recommend subsetting individuals with CAD to 'very high-risk' to identify individuals for whom further cholesterol-lowering is warranted.[7,8,18] Nevertheless, patients with established ASCVD exhibit a gradient of cardiovascular health, management, and residual risk for secondary events.[3,5,12]

In addition to well-established risk factors, lifestyle factors as well as novel biomarkers increasingly available in clinical practice have been linked to increased CAD risk. Adverse health behaviours, namely

cigarette smoking,[19] obesity,[20] physical inactivity,[21] and unfavourable diet,[22] independently magnify future cardiovascular disease risks. Furthermore, adding lipoprotein(a), inflammatory or kidney function measures yields modest prognostic information beyond traditional risk variables in multiethnic population-based cohorts and in higher-risk subsets of individuals such as those with chronic kidney disease.[23–25]

More recently, both monogenic variants and genome-wide polygenic risk score (PRS) have reliably predicted and refined CAD risk estimation and trajectories independent of conventional risk factors, implying opportunities for risk attenuation strategies earlier in life.[26–29] Beyond independent prognostic information, genetic predisposition and health behaviors each exert additive effects on future cardiovascular risks.[30]

Nevertheless, the influence of all the risk factors together for recurrent CAD events remains poorly understood particularly outside *post hoc* analyses from clinical trials with limited follow-up period. Better estimation of this risk gradient may enable more efficient allocation of therapeutic intensification and identify very high risk subgroups meriting new therapeutic strategies in trials. Therefore, we examined the independent associations and relative prognostic value of genetic, sociodemographic, lifestyle, and clinical risk factors on CAD recurrence in a contemporary population-based cohort.

Methods

Data source and study population

The UK Biobank is a prospective cohort study of approximately 500 000 adults aged 40 to 69 years at recruitment living in the UK.[31] Between 2006 and 2010, participants underwent anthropometric measurement, biospecimen collection, and questionnaires on demographics, health behaviours, and medical histories (see Supplementary data online, *Table S1*). Healthcare utilisation was linked to National Health Service records permitting the ascertainment of prevalent clinical conditions as well as incident events.

Based on physician diagnoses or procedural codes (see Supplementary data online, *Table S2*), 8234 participants had recognized CAD prior to UK Biobank enrolment, including those with either single or multiple episodes (*Figure 1*). We excluded 41 participants with mismatch between self-reported and genotypically-inferred sex, sex aneuploidy, missing genotype rates ≥1%, or excess genotypic heterozygosity reflecting poor genotype quality. We further excluded 948 closely related individuals (kinship index >0.088) using the KING software.[32] Lastly, 221 participants with incomplete covariates measurements were excluded. A final analytical sample of 7024 was studied (see Supplementary data online, *Figure S1*).

The UK Biobank study protocol was approved by the North West Multi-centre Research Ethics Committee (11/NW/0382) and the secondary data usage (UK Biobank application #7089) for the present analyses was approved by the Massachusetts General Hospital institutional review board (2021P002228). UK Biobank data are available to researchers by application (https://www.ukbiobank.ac.uk/). Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. All participants provided electronically signed consent.

Assessment of sociodemographic, lifestyle, and clinical risk factors

Variables were selected based on previously described ASCVD risk prediction models in the U.S. and Europe.[33,34] Sex was self-reported from fixed categories of female and male. Racial and ethnic background was self-identified from fixed categories of African, Bangladeshi, British, Caribbean, Chinese, Indian, Irish, Pakistani, White and Asian, White and Black African, White and Black Caribbean, Other Asian, Other Black, Other White, Other mixed, or Other/unknown. Single-inverse normalized Townsend Deprivation Index[35] was quantified based on employment, car ownership, home ownership, and household overcrowding. Current smoking was defined as lifetime smoking of at least 100 cigarettes and currently without cessation. Based on self-report and aligned with current recommendations,[36,37] regular physical activity was defined as engaging in >3 days or 150 min of moderate-to-vigorous physical per week. Dietary intake was assessed based on average annual intake of fruit, vegetable, whole grains, fish, dairy, vegetable oils, refined grains, meats, and sugar-sweetened beverages (see Supplementary data online, *Table S3*) in accordance with the Eatwell Guide.[38] Sleep behaviour was assessed based on modified apnea-hypopnea index,[39] which characterizes sleep duration, insomnia symptoms, snoring, and narcolepsy (see Supplementary data online, *Table S4*).

Body mass index was measured using Tanita BC-418MA body composition analyser (Tanita, Tokyo, Japan) and recorded as a ratio of weight in kilograms to height in squared meters. After 5 min of seated rest, blood pressure was measured on two consecutive occasions with 1 min interval using Omron 705 IT electronic blood pressure monitor (OMRON Healthcare Europe, Hoofddorp, Netherlands); the mean of the first and the second automated readings was adopted for the data analysis.[40] Blood biochemistry, including total, LDL, and high-density lipoprotein (HDL) cholesterols, triglycerides, glucose, glycated A1c, and creatinine, were assayed within 24 h of non-fasting sample collection. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[41] Lipoprotein(a) and high-sensitivity C-reactive protein (hsCRP) were measured by immunoturbidimetric assay using Beckman Coulter AU5800 analyser (Brea, CA, USA).

Hypertension was defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg, or prescription of an antihypertensive medication. Hypercholesterolemia was defined as total cholesterol ≥200 mg/dL or statin prescription. Diabetes mellitus was defined as glycated A1c ≥6.5% or prior physician diagnosis.

Construction of CAD PRS

Central quality control and imputation of UK Biobank genotypic data were previously described.[31]Briefly, genotypes were obtained using either UK Biobank Axiom or UK BiLEVE Axiom arrays (Affymetrix Research Service Laboratory, Santa Clara, California, USA). The Haplotype Reference Consortium (HRC) and the merged UK10K + 1000 Genomes were used as reference panels for imputation with preference for the HRC panel when single nucleotide variants (SNVs) were present in both panels. Principal component analysis was performed using fastPCA based on a pruned set of 147 604 common independent SNVs among unrelated individuals to delineate population structure.[42]

CAD PRS was derived from CARDIoGRAMplusC4D 1000 Genomes-based genome-wide significant association studies based on 184 305 individuals of European (77%), South Asian (13%), East Asian (6%), Hispanic, and African ancestry and imputed on the 1000 Genomes phase 1 v3 training set with 38 million variants.[43] We used a CAD PRS previously described using the AnnoPred framework—a Bayesian approach that leverages genomic and epigenomic functional annotations to quantify genetic risk through variant weights adjustment.[44–46] Briefly, the AnnoPred method partitions trait heritability and calculates posterior effect sizes by jointly modelling summary statistics and linkage disequilibrium matrix from a reference panel.[44]

Outcomes

To ascertain CAD prevalence and incidence, we relied on the HESIN master table that entails information on inpatient episodes of care, including diagnoses, admissions and discharge, operations, and procedures. The HESIN data do not account for information from participant self-report or other linked sources of data (i.e. hospital outpatient or primary care records), thereby minimizing information bias. The primary outcome was a first recurrent CAD that occurred after UK Biobank enrolment irrespective of the number of CAD events prior to enrolment. Specifically, International Classification of Diseases 9th and 10th revisions and Classification of

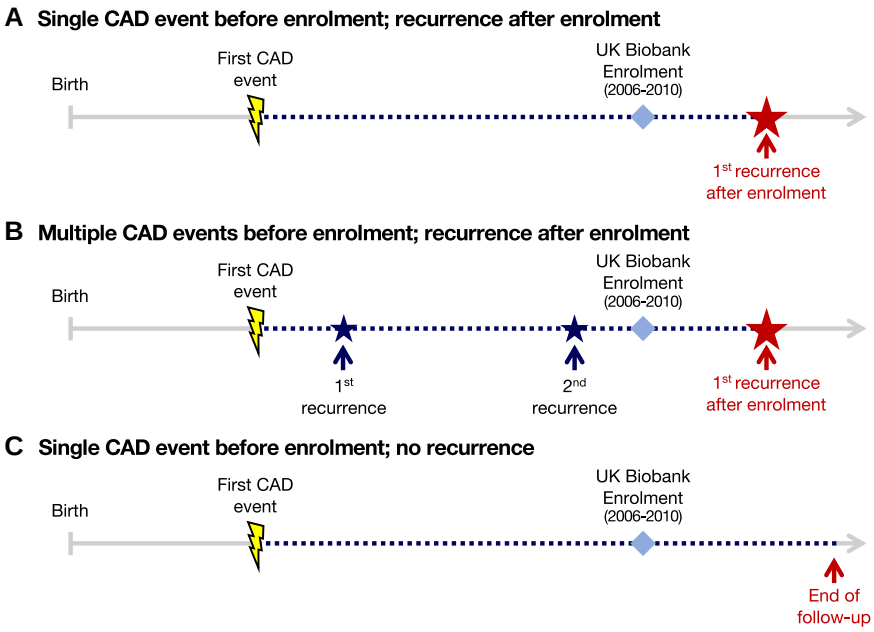


Figure 1 Possible timeline of recurrent CAD events included in the analysis. Scenario A describes participants with single CAD event prior to UK Biobank enrolment and first and only recurrence (denoted with red *) after enrolment. Scenario B describes participants with multiple CAD events prior to enrolment and one recurrence (red *) after enrolment. Scenarios *A* and *B* are considered recurrent CAD cases. However, scenario C describes participants with first and only CAD event prior to enrolment and without recurrence thereafter. Recurrence criteria within 28 days of the most recent event prior to enrolment is considered a bundled event from the same episode, thereby disregarded. Abbreviation: CAD, coronary artery disease.

Interventions and Procedures v4 indicating a diagnosis of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or death register indicating myocardial infarction and related sequelae as either a primary or secondary cause of death were captured. To distinguish independent incidence from bundled attributions of diagnoses and procedures from a single episode/hospitalization, we defined recurrence as a CAD event at least 28 days since the most recent CAD event prior to enrolment.[47] In secondary analyses, we separately assessed the first event of each component of the primary outcome.

Statistical analysis

Baseline characteristics between individuals without and with recurrent CAD were compared with the χ^2 test for categorical variables, independent *t*-test for continuous variables, and Mann–Whitney *U* test for continuous variables with nonparametric distributions. The treatment rates of prevalent cardiometabolic disorders, including hypertension, hypercholesterolemia, and diabetes mellitus, were compared with two-sample tests for equality of proportions.

We estimated CAD recurrence rates using the Kaplan–Meier method. Then, we tested the strengths of association for individual risk factors with CAD recurrence. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models adjusting for age at UK Biobank enrolment, age at first CAD event, sex, cigarette smoking, physical activity, diet, sleep, Townsend Deprivation Index, body mass index, systolic blood pressure, LDL and HDL cholesterols, triglycerides, glucose, lipoprotein(a), hsCRP, eGFR, statin prescription, the first 10 principal components, genotyping array, and CAD PRS. To confirm log-linearity between continuous predictors and the outcome, we compared the Akaike information criterions across logarithmic transformation, squared transformation, and restricted cubic spline models. The final model included log-transformed triglycerides, lipoprotein(a), and hsCRP given skewness of the distributions; squared transformations were applied to eGFR due to its nonlinearity. Satisfaction of the proportional hazards assumption was confirmed based on log-minus-log plot and Schoenfeld residuals. The end of the observation period was defined as the date of first post-enrolment recurrence, last follow-up, or 22 July 2021, whichever came first. To facilitate clinical utility of the present findings, we developed and internally validated the 10-year predicted risk score of recurrent CAD events (Supplementary data online, Methods S1).

The primary prognostic measure, the C index, estimates the probability of a model assigning a higher risk to participants who sustain CAD recurrence over a shorter period. The C index for individual risk factor was calculated from multivariable Cox regression model. From the conventional risk factors model (including age at enrolment, age at first CAD event, sex, body mass index, systolic blood pressure, lipids, glucose, statin prescription, and Townsend Deprivation Index), we compared improvements in model performance by sequentially adding (i) novel biomarkers [eGFR, hsCRP, and lipoprotein(a)]; (ii) lifestyle risk factors; and (iii) CAD PRS. Additionally, we derived estimated explained relative risks for each risk factor based on the entropy loss function and the Kullback–Leibler information gain, as previously described.[48] Briefly, we first constructed the *full* multivariate Cox proportional hazard model comprised of all aforementioned predictors. Then, we separately built *null* density models that represented the effect of excluding each covariate; the resultant entropy represents explained risk lost from permutation. Formulaically, the R^2 is derived from logarithmic mean of the *full* minus *null* model for each predictor. Bootstrapping was performed 1000 times to estimate the 95% CIs.

Ten sensitivity analyses were conducted. First, Fine–Gray[49] models were fitted to calculate hazards for CAD events in the presence of a competing risk of death. Second, we analysed total CAD risks based on Andersen–Gill[50] model to account for multiple recurrences. Third, we reassessed the association after excluding 76 individuals with identical first and recurrent CAD diagnostic/procedural code to mitigate the possibility of records being falsely carried over from the primary event. Fourth, we extended the 'washout' period between the most recent CAD event prior to enrolment and the outcome to 90 and

365 days, respectively. Fifth, as risk factors may differentially predict overt cardiovascular outcomes vs. procedures, we assessed the associations restricting to myocardial infarction and CAD-related death. Sixth, we excluded individuals who had the first recurrent event within 28 days after enrolment to homogenize immortal time. Seventh, we restricted to CAD as a primary cause of death to account for variability in underlying vs. contributory causes of death. Eighth, we examined whether the predictability of individual risk factor is comparable by sex. Nineth, we employed a multiethnic CAD genetic risk score[51] to confirm whether the rankings and magnitude of risk factors discrimination ability remain comparable between individuals of White European ancestry vs. non-White, non-European ancestry. Lastly, we quantified the magnitude of index event bias by assessing the difference between the marginal and *true* counterfactual effect estimate of genetic risk on CAD recurrence (Supplementary data online, Methods S2).

All statistical tests were two-sided, and statistical significance was set at $P < 0.05$. All analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The study included 7024 participants (mean [standard deviation, SD] age at enrolment, 62.4 [6.0] years; 1267 [18.0%] female). Mean [SD] age of first CAD diagnosis was 57.1 [6.6] years. The median [interquartile range, IQR] follow-up after study enrolment among included participants was 11.6 [7.2–12.7] years, during which 2003 (28.5%) recurrent CAD events occurred (*Table 1*). Individuals who sustained recurrence had a median [IQR] of 2 [2–3] events across lifespan (see Supplementary data online, *Figure S2*).

Compared to those without recurrent CAD, individuals who sustained recurrent events during follow-up were younger at first CAD event (with recurrence, 57.0 years vs. without recurrence, 58.4 years; $P < 0.001$), less likely to be female (15.8% vs. 18.9%; $P = 0.003$), and less likely to have White European ancestry (91.3% vs. 95.0%; $P < 0.001$). The majority of participants were taking lipid-lowering medications (92.9%) (see Supplementary data online, *Table S5*). Among individuals with antihypertensive medication prescription, 70.6% were prescribed renin-angiotensin system inhibitors and 70.9% beta blockers.

Risk factors associated with CAD recurrence

Figures 2 and *3* and Supplementary data online, *Table S6* illustrate the associations of sociodemographic, lifestyle, clinical, and genetic risk factors with CAD recurrence. Based on time-to-event analysis, per SD increase in age at enrolment significantly associated with HR (95% CI) of 1.26 (1.13–1.40) for recurrence; in contrast, older age at first CAD event was associated with reduced recurrence (0.74, 0.67–0.82). Despite a numerically higher proportion of male participants sustaining recurrent events, male sex was not independently associated with CAD recurrence in multivariable model (1.18, 0.98–1.41). Meanwhile, greater socioeconomic deprivation was significantly associated with recurrence by HR of 1.06 (1.01–1.13). Among all risk factors studied, current smoking was most robustly associated with CAD recurrence (1.35, 1.13–1.61). Favourable sleep quality also associated with lower recurrence (0.93, 0.88–0.99), but neither regular physical activity nor healthy diet were significantly associated.

Both conventional and novel clinical risk factors also significantly associated recurrent events. Specifically, per SD increase in HDL and LDL cholesterols were significantly associated with CAD recurrence by hazard of 0.85 (0.79–0.92) and 1.08 (1.01–1.15), respectively. While glucose levels (1.10, 1.04–1.16) significantly associated with recurrence, systolic blood pressure (1.05, 1.00–1.12) was marginally associated. Furthermore, higher concentrations of hsCRP (1.11, 1.05–1.16), lipoprotein(a) (1.10, 1.03–1.16), and conversely, eGFR (0.89, 0.84–0.95) significantly associated with CAD recurrence. A CAD PRS was only associated with HDL cholesterol and lipoprotein(a) (see Supplementary data online, *Table S7*). The CAD PRS was independently associated with recurrent CAD events by HR of 1.12 (1.05–1.19). An example of CAD recurrence risk estimation for a 60 years old, female patient with first CAD at age 55 years is shown in Supplementary data online, *Figures S3* and *S4*.

In endpoint specific analyses, we observed consistent effect estimates (see Supplementary data online, *Tables S8–S10*). Notably, current smoking, older age at enrolment, younger age at initial CAD diagnosis, lower HDL cholesterol concentration, and greater genetic predisposition remained strongly associated with repeat myocardial infarction, percutaneous coronary intervention, and coronary artery bypass graft, separately. While current smoking and age at first CAD diagnosis remained robustly associated with CAD-related death, male sex, body mass index, and eGFR were now also associated with CAD death (see Supplementary data online, *Table S11*). Meanwhile, CAD PRS and HDL cholesterol were not associated with CAD-related death.

Predictability of risk factors on CAD recurrence

Figure 4 and Supplementary data online, *Figures S5–S8* illustrate the discrimination ability and relative importance of individual risk factor on recurrent CAD events in ascending order of greatest importance. The most important predictors of CAD recurrence were CAD PRS (C index [95% CI]: 0.58, 0.57–0.59), HDL cholesterol (0.57, 0.57–0.58), and age at initial CAD event (0.57, 0.56–0.57), respectively. CAD PRS was the top predictor for secondary myocardial infarction and percutaneous coronary intervention but third for secondary coronary artery bypass graft surgery.

The addition of non-traditional risk factors to currently recognized traditional risk factors further improved prediction as measured by C index from 0.64 (0.63–0.65) to 0.68 (0.67–0.69) (*Table 2* and Supplementary data online, *Table S12*). In addition to traditional risk factors, eGFR, hsCRP, and lipoprotein(a) improved C statistic by 0.015 (0.013–0.017). Lifestyle factors further improved the C statistic by 0.005 (0.004–0.007). And CAD PRS in addition to all of the aforementioned factors even further improved the C statistic by 0.012 (0.010–0.014). However, a large fraction of recurrent CAD remains unexplained by these risk factors. Only 10.9% (9.5%–12.3%) of variation in recurrent CAD risk is explained by traditional risk factors and the comprehensive model explained 18.7% (17.0%–20.3%).

Sensitivity analyses

As an alternative approach to account for competing risk of death, we reassessed CAD recurrence using Fine–Gray subdistribution hazards model. For all risk factors, the associations were minimally attenuated (see Supplementary data online, *Tables S6, S8–S10*). In addition, risk factors similarly predicted total recurrent events. Next, the results remained consistent (i) among participants who underwent different types of primary and secondary CAD, and (ii) when extending the period between the latest CAD event prior to enrolment and the first recurrence post-enrolment to 90 and 365 days, respectively (see Supplementary data online, *Tables S13* and *S14*). Analogously, the findings were consistent after excluding 20 individuals who underwent recurrent CAD event within 28 days since enrolment (see Supplementary

Table 1 Baseline characteristics of UK Biobank participants with CAD prior to enrolment

Characteristics	Without recurrent CAD	With recurrent CAD	*P* value[a]
Total, No.	5021	2003	
Age at enrolment, mean (SD), years	62.60 (5.86)	62.03 (6.21)	<0.001
Age at first CAD, median [IQR] years	58.39 [53.71–57.50]	57.02 [51.95–61.14]	<0.001
Female sex	950 (18.92)	317 (15.83)	0.003
Self-reported race/ethnicity			<0.001
White	4765 (94.96%)	1829 (91.31%)	
South Asian	153 (3.05%)	128 (6.39%)	
Black	39 (0.78%)	18 (0.90%)	
Chinese	5 (0.10%)	3 (0.15%)	
Other incl. multiracial	59 (1.18%)	25 (1.25%)	
Current smoker	564 (11.23%)	297 (14.83%)	<0.001
Regular physical activity	3213 (63.99%)	1178 (58.81%)	<0.001
Healthy diet score, mean (SD)	4.04 (1.61)	3.93 (1.63)	0.008
Favourable sleep score, mean (SD)	2.01 (1.00)	1.87 (1.03)	<0.001
Townsend Deprivation Index, median [IQR]	−1.85 [−3.43–1.18]	−1.44 [−3.22–1.93]	<0.001
Body mass index, mean (SD), kg/m^2	28.93 (4.53)	29.57 (4.75)	<0.001
Systolic blood pressure, mean (SD), mmHg	135.31 (18.91)	136.39 (19.94)	0.040
Diastolic blood pressure, mean (SD), mmHg	78.16 (10.16)	78.26 (10.78)	0.728
Hypertension	4776 (95.12%)	1914 (95.56%)	0.436
Antihypertensive medication	4283 (85.30%)	1733 (86.52%)	0.202
HDL cholesterol, mean (SD), mg/dL	46.11 (11.33)	43.94 (11.17)	<0.001
LDL cholesterol, mean (SD), mg/dL	100.52 (25.82)	103.20 (27.48)	<0.001
Triglycerides, median [IQR], mg/dL	62.72 [44.05–89.02]	66.59 [47.18–94.28]	<0.001
Hypercholesterolemia	4814 (95.88%)	1933 (96.51%)	0.219
Lipid-lowering medication	4655 (92.71%)	1873 (93.51%)	0.259
Glucose, mean (SD), mg/dL	99.34 (33.36)	105.64 (43.46)	<0.001
Hemoglobin A1c, mean (SD), %	5.82 (0.86)	6.04 (1.10)	<0.001
Type 2 diabetes mellitus	788 (15.69%)	471 (23.51%)	<0.001
Lipoprotein(a), median [IQR], nmol/L	26.39 [10.30–79.08]	33.55 [11.12–96.91]	<0.001
hsCRP, mean (SD), mg/L	2.74 (5.01)	3.37 (6.11)	<0.001
eGFR, median [IQR], mL/min/1.73m^2	90.74 [78.29–98.39]	90.79 [77.33–98.56]	0.038
Normalized CAD PRS, mean (SD)	−0.06 (1.00)	0.15 (0.98)	<0.001

Data are presented as mean (SD), median [IQR], or count (percent).
[a]Baseline characteristics between individuals without and with recurrent CAD were compared with the χ^2 test for categorical variables, independent *t*-test for continuous variables, and Mann–Whitney *U* test for continuous variables with nonparametric distributions. Abbreviations: CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; PRS, polygenic risk score; SD, standard deviation.

data online, *Table S15*). When restricting to diagnosis-based outcomes, CAD PRS, age at first CAD, and body mass index largely described combined recurrent myocardial infarction and CAD-related death (see Supplementary data online, *Table S16*). We also restricted the analysis to CAD as a primary (underlying) cause of death (see Supplementary data online, *Table S17*). Whereas the effect estimates remained largely comparable, the mortality risk associated with male sex (2.56, 1.15–5.73) was greater than risk based on CAD as either primary or secondary (contributory) cause of death. In the sex-stratified model, genetic risk (*P* for interaction$_{sex}$ = 0.399), HDL cholesterol (*P* for interaction$_{sex}$ = 0.369), and age at first CAD (*P* for interaction$_{sex}$ = 0.222) remained the most predictive of CAD recurrence (see Supplementary

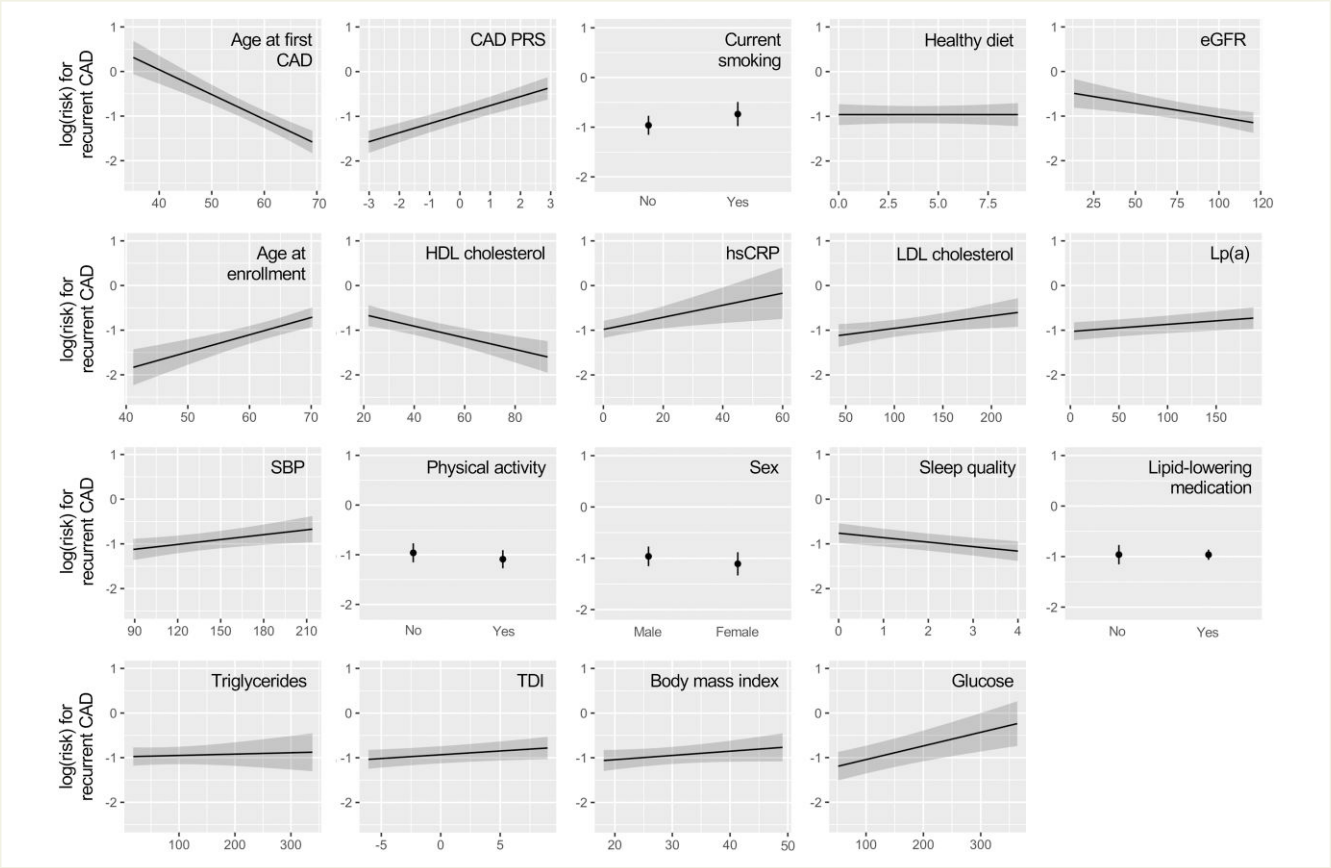


Figure 2 Predicted effect of individual risk factor on CAD recurrence risk. Categorical predictors are computed as binary variable. All models are based on Cox proportional hazards model adjusting for age at UK Biobank enrolment, age at first CAD event, cigarette smoking, physical activity, diet, sleep, Townsend Deprivation Index, body mass index, systolic blood pressure, LDL and HDL cholesterols, triglycerides, glucose, lipoprotein(a), hsCRP, eGFR, statin prescription, the first 10 principal components, genotyping array, and CAD PRS. Abbreviations: CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PRS, polygenic risk score; TDI, Townsend Deprivation Index.

data online, *Tables S18* and *S19*). We also examined whether the discrimination ability of risk factors rank analogously between individuals of White European vs. non-White, non-European ancestry. CAD PRS, HDL cholesterol, and age at first CAD remained the top three predictors of primary outcome; however, physical activity, cigarette smoking, and sex better explained recurrence in White European subgroups compared to their non-White, non-European counterparts (see Supplementary data online, *Table S20*, Supplementary data online, *Figure S9*). With all genetic, sociodemographic, lifestyle, and clinical risk factors modestly contributing to CAD recurrence, index event bias nominally (3.63%) underestimated the primary findings.

Discussion

Our analysis of UK prospective cohort data showed that CAD recurrence is associated with a range of genetic, sociodemographic, lifestyle, and clinical risk factors, and the association strengths and relative contributions differ from primary prevention settings. Notably, we observed that greater genetic predisposition to CAD is the strongest predictor of its recurrence, accompanied by HDL cholesterol and age at first CAD event (*Structured Graphical Abstract*). Furthermore, CAD recurrence also significantly associated with age at enrolment, socioeconomic deprivation, current smoking, sleep quality, hypercholesterolemia, hyperglycaemia, and renal function. These results suggest that simultaneous consideration of multilevel risk factors may improve estimation of residual risk after a first clinical ASCVD event and help to guide management decisions and future investigative opportunities to address recurrent risk. Our findings build on previous efforts to quantify discrimination of traditional and emerging risk factors with potential implications for secondary prevention of CAD.

First, we observed that both history of a premature first CAD event and elevated CAD PRS are the strongest and complementary risk factors for recurrence. Prior studies have shown that paternal and sibling histories of premature CAD events are independently associated with first CAD events.[52–54] Such empiric familial aggregation observations have theorized the importance of genetics for first CAD event risk in the population.[55,56] However, self-reported family history of cardiovascular disease and genetic predisposition as estimated by a CAD PRS are only mildly to moderately correlated yet both independently associate with first CAD event risk.[29,57,58] Analogously, age at a first event and a CAD PRS are both independently predictive of secondary events.[59] Our observations and these prior studies indicate the possibility of undiscovered familial risks promoting premature and recurrent CAD

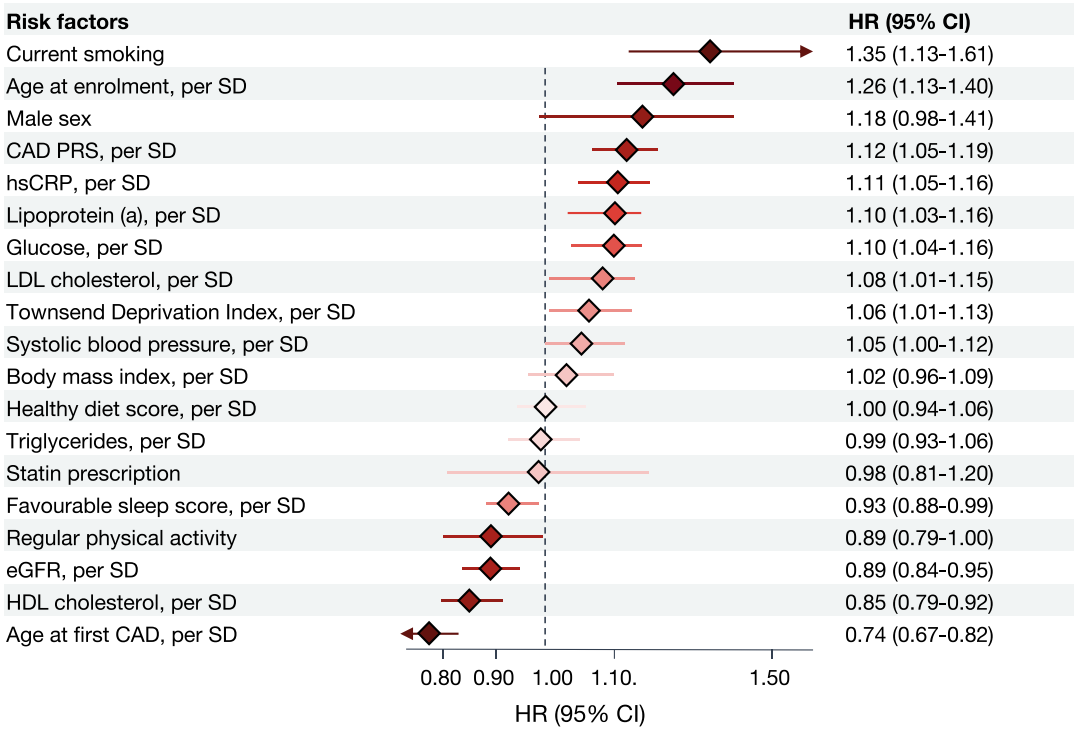


Figure 3 Association of sociodemographic, lifestyle, clinical, and genetic risk factors with risk of recurrent CAD events. Categorical predictors are computed as binary variable. HRs are adjusted for age at enrolment, age at first CAD event, sex, cigarette smoking, physical activity, diet, sleep, Townsend Deprivation Index, body mass index, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, glucose, lipoprotein(a), hsCRP, eGFR, statin prescription, the first 10 principal components, genotyping array, and CAD PRS. The colour gradient represents the magnitude of effect estimates. Abbreviations: CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; PRS, polygenic risk score.

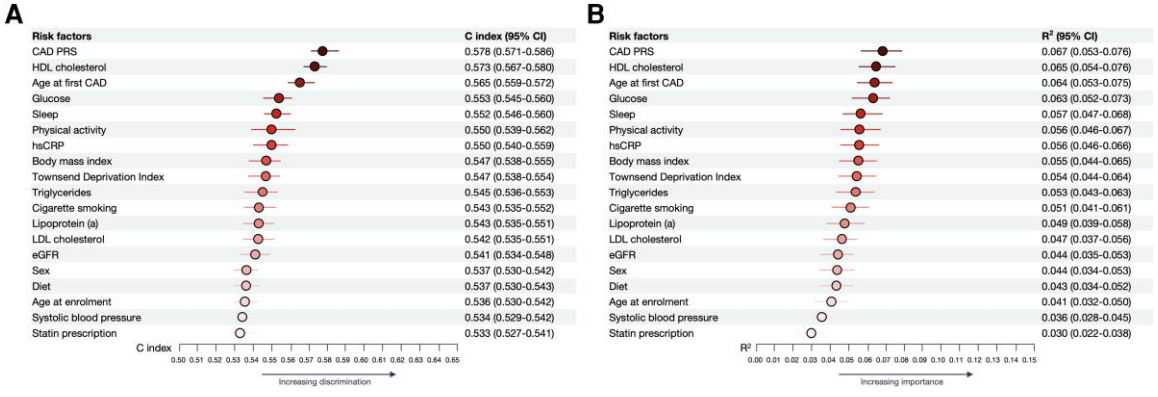


Figure 4 (*A*) Discrimination ability and (*B*) relative importance of individual genetic, sociodemographic, lifestyle, and clinical risk factors for predicting recurrent CAD events. The discrimination C index estimates the probability of a model assigning a higher risk to participants who undergoes CAD recurrence compared to those without recurrence. The estimated explained relative risk (R^2) reflects the strength of the association for risk factors for predicting CAD recurrence. R^2 was calculated based on the entropy loss function and the Kullback–Leibler information gain. All indexes are based on Cox proportional hazards model adjusting for age at UK Biobank enrolment, age at first CAD event, sex, cigarette smoking, physical activity, diet, sleep, Townsend Deprivation Index, body mass index, systolic blood pressure, LDL and HDL cholesterols, triglycerides, glucose, lipoprotein(a), hsCRP, eGFR, statin prescription, the first 10 principal components, genotyping array, and CAD PRS. Abbreviations: CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; PRS, polygenic risk score.

Table 2 Discrimination ability of genetic, sociodemographic, lifestyle, and clinical risk factors in combination for recurrent CAD events prediction

Model	C index (95% CI)				
	Composite CAD	Myocardial infarction	Percutaneous coronary intervention	Coronary artery bypass graft	CAD-related death
Conventional risk factors[a]	0.644 (0.632–0.654)	0.622 (0.602–0.642)	0.640 (0.624–0.655)	0.650 (0.632–0.669)	0.676 (0.659–0.695)
Conventional + eGFR + hsCRP + Lp(a)	0.659 (0.646–0.673)	0.633 (0.617–0.649)	0.647 (0.632–0.660)	0.662 (0.648–0.677)	0.691 (0.677–0.707)
Conventional + eGFR + hsCRP + Lp(a) +Lifestyle[b]	0.664 (0.652–0.677)	0.645 (0.630–0.659)	0.654 (0.640–0.670)	0.673 (0.658–0.786)	0.701 (0.689–0.713)
Conventional + eGFR + hsCRP + Lp(a) +Lifestyle + Genetics[c]	0.676 (0.667–0.686)	0.659 (0.648–0.669)	0.665 (0.652–0.678)	0.689 (0.679–0.700)	0.710 (0.697–0.724)

The discrimination C index estimates the probability of a model assigning a higher risk to participants who undergoes CAD recurrence compared to those without recurrence. The C index for individual risk factor was calculated from multivariable Cox regression model with age as time scale.
[a]Conventional risk factors include age at enrolment, age at first CAD event, sex, Townsend Deprivation Index, body mass index, systolic blood pressure, low- and high-density cholesterols, triglycerides, glucose, and statin prescription.
[b]Lifestyle risk factors include cigarette smoking, physical activity, diet, and sleep.
[c]Additionally adjusted for CAD PRS, the first 10 principal components, and genotyping array. Abbreviations: CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; hsCRP, high sensitivity C-reactive protein; Lp(a), lipoprotein(a); PRS, polygenic risk score.

events. Our study considered potentially shared lifestyle and sociodemographic factors implying novel genetic and non-genetic inheritance mechanisms. Such features may include unrecognized lifestyle and environmental factors as well as other mechanisms, including transgenerational epigenetic, cytoplasmic, and microbial inheritance.[60] Furthermore, current guideline-supported first-event risk calculators systematically underestimate risk in younger individuals and are thus unable to identify those at risk for premature CAD events. The identification of novel factors that promote premature CAD events may have important implications for recurrent CAD risk in the population.

Second, socioeconomic deprivation is a central risk factor for CAD recurrence, particularly CAD-related death. Contemporary prediction models that exclude deprivation status have shown to significantly underpredict risk in the most deprived (SMART2[34]: observed, 6.4% vs. predicted, 4.6%; Pooled Cohort Equations[33]: 6.7% vs. 4.7%) and to overpredict risk in the most affluent group.[61] Socioeconomic status is a largely unrecognized risk factor reflecting intergenerational-, household- and individual-level wealth, employment, and education.[62] In fact, the differential associations of education and household income with cardiovascular outcomes are known to further vary across nationwide economic status.[63] Therefore, disaggregation of a composite socioeconomic index may better determine the extent to which each factor best contributes to secondary events.

Third, these results may inform the design of future CAD trials. Given trial cost and logistical considerations, contemporary event-driven CAD outcome trials are exclusively focused on preventing major adverse cardiovascular events among patients with prevalent CAD.[64] Given ease of screening based on clinical practice, current CAD trials generally maximize power for a given sample size based on an accumulation of clinical risk factors. This study shows that the explainability of recurrent CAD risk is nearly doubled when considering additional sociodemographic, lifestyle, biomarker, and genetic factors. The additional biomarkers [hsCRP, lipoprotein(a), and eGFR] are readily available and CAD PRS is increasingly readily available.[65] As such, ongoing clinical trials for lipoprotein(a)-lowering that target hepatic synthesis of apolipoprotein[66–68] are investigating the feasibility of lipoprotein(a) interventions in modifying secondary CAD risk. Furthermore, in secondary prevention trials, a high CAD PRS is enriched for recurrent events[69,70] and strongly predictive of pharmacological cholesterol-lowering clinical benefit, outsized the expectation from cholesterol-lowering in exploratory analyses.[65,69–71] When clinical trial participants are densely profiled and enriched for diverse factors promoting recurrent CAD risk, novel adaptable clinical trials may be able to rigorously isolate high-benefit groups more efficiently.[65,72]

Fourth, the vast majority of CAD recurrence risk remains unexplained. Despite prior studies indicating a high enrichment of standard modifiable risk factors among individuals with first events,[73,74] we find that such factors are not nearly as predictive for recurrent events. With current secondary prevention strategies aimed at appropriately aggressive management of modifiable risk factors (namely, LDL cholesterol and systolic blood pressure), such features naturally become less strongly predictive of subsequent events in the presence of high treatment rate. Such secular trends have important corresponding influences on evolving atherosclerosis biology.[75] Unsurprisingly, our analyses highlight risk contributors that are underappreciated or not addressed with current prevention paradigms. Nevertheless, with the substantial public health impact of CAD, the empiric observation that most recurrent CAD risk is unexplained highlights an urgent need for unbiased discovery research.

Strengths and limitations

Whereas the accumulated evidence on secondary prevention is primarily based on *post hoc* analyses from randomized controlled trials, our study simultaneously examined multidimensional risk factors on CAD recurrence based on nationwide observational study with broad systematic characterization across numerous putative risk factors. As UK Biobank represents a wide array of demographics and risk factor distributions reflective of the general population, our findings may be more generalizable compared to prior clinical trial studies. By leveraging a national biobank within a nationalized healthcare system, the sensitivity of clinically meaningful events is expected to be very high.

Despite the extensive characterization of exposures in the present dataset, potential limitations merit consideration. First, as all individuals inherently sustained first CAD events prior to enrolment, survival bias is an important consideration. We included age at first event and age at enrolment in analyses to account for this risk, and further considered total prior events in sensitivity analyses with robust results. Additionally, we only considered events after enrolment to mitigate the risks of reverse causation based on the exposures ascertained at enrolment. Second, individuals may have varying blood pressure or lipid-lowering medication concentrations and target risk factor goals after the initial CAD event. Furthermore, the duration between the first CAD incidence and cohort enrolment are not uniform across participants. Whether treatment up-titration and resultant intensive risk factors control reduce secondary events warrant further study among patients with homogeneous clinical history. Lastly, our results have limited generalizability to moderate- or high-risk regions with different risk factor burdens, incidence rates, and healthcare utilisations.[76] Similarly, as UK Biobank is predominantly comprised of middle-aged adults of White European ancestry, whether these findings extend to diverse populations requires further study. Nevertheless, the present study's recurrent rate aligns with that of prior secondary prevention study[77] and the estimates remained consistent after addressing the impact of competing risk of death, preventing age-differential overestimation of risk factors. Expanding the discovery to demographically diverse populations would enhance equitable cardiovascular management.

Conclusion

In a middle-aged UK population with established CAD, comprehensive consideration of clinical, sociodemographic, lifestyle, biomarker, and genetic factors improves prediction of recurrent CAD risk. Among the diverse risk factors investigated, high genetic predisposition to CAD, low HDL cholesterol, and younger age at first CAD event most strongly explained CAD recurrence risk. Nevertheless, the majority of CAD recurrence risk remains unexplained potentially contributing to its persistence as the world's leading cause of premature death among adults.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

M.C.H. reports consulting fees from CRISPR Therapeutics, advisory board service for Miga Health, and research support from Genetech; R.B. reports consulting fees from Casana Care, Inc., unrelated to current work; P.N. reports personal consulting fees from Allelica, Amgen, Apple, AstraZeneca, Blackstone Life Sciences, Foresite Labs, Genentech/Roche, Novartis, and TenSixteen Bio, investigator-initiated grants from Apple, AstraZeneca, Amgen, Novartis, and Boston Scientific, is a co-founder of TenSixteen Bio, is a scientific advisory board member of Esperion Therapeutics, TenSixteen Bio, and geneXwell, and spousal employment at Vertex, all unrelated to the present work. The remaining authors do not report any disclosures. No other relationships or activities that could appear to have influenced the submitted work.

Data Availability

UK Biobank data are available to researchers by application (https://www.ukbiobank.ac.uk/).

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Ethical Approval

The UK Biobank study protocol was approved by the North West Multi-centre Research Ethics Committee (11/NW/0382) and the secondary data usage (UK Biobank application #7089) for the present analyses was approved by the Massachusetts General Hospital institutional review board (2021P002228).

Pre-registered Clinical Trial Number

Not applicable.

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