Original research

Sex disparity in subsequent outcomes in survivors of coronary heart disease

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ABSTRACT

Objective Evidence on sex differences in outcomes after developing coronary heart disease (CHD) has focused on recurrent CHD, all-cause mortality or revascularisation. We assessed sex disparities in subsequent major adverse cardiovascular events (MACE) in adults surviving their first-time CHD.

Methods Using a population-based cohort obtained from the Clinical Practice Research Datalink (CPRD GOLD) linked to hospitalisation and death records in the UK, we identified 143 702 adults (aged ≥18 years) between 1 January 1998 and 31 December 2017 with no prior history of MACE. MACE outcome was a composite of recurrent CHD, stroke, peripheral vascular disease, heart failure and cardiovascular-related mortality. Multivariable models (Cox and competing risks regressions) were used to assess differences between sexes.

Results There were 143 702 adults with any incident CHD (either angina, myocardial infarction or coronary revascularisation). Women (n=63 078, 43.9%) were older than men (median age, 73 vs 66 years). First subsequent MACE outcome was observed in 91 706 (63.8%). Women had a significantly lower risk of MACE (hazard ratio (HR), 0.68 (95% CI 0.67 to 0.69); sub-hazard ratio (HRsd), 0.71 (0.70 to 0.72), respectively) and recurrent CHD (n=66 543, 46.3%) (HR, 0.60 (0.59 to 0.61); HRsd, 0.62 (0.61 to 0.63)) when compared with men after incident CHD. However, women had a significantly higher risk of stroke (n=5740, 4.0%) (HR, 1.26 (1.19 to 1.33); HRsd, 1.32 (1.25 to 1.39)), heart failure (n=7905, 5.5%) (HR, 1.09 (1.04 to 1.15); HRsd, 1.13 (1.07 to 1.18)) and all-cause mortality (n=29 503, 20.5%) (HR, 1.05 (1.02 to 1.07); HRsd, 1.11 (1.08 to 1.13)).

Conclusions After incident CHD, women have lower risk of composite MACE and recurrent CHD outcomes but higher risk of stroke, heart failure, and all-cause mortality compared with men.

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INTRODUCTION

Coronary heart disease (CHD) is a global public health problem[1] and remains a major cause of early morbidity and mortality despite advances in treatment and public health.[2] With many individuals surviving their initial CHD presentation, there is a growing population with established CHD with a substantially high risk of subsequent cardiovascular events or death.[3] The residual high risk in these individuals persists despite optimal therapy.[4] Greater and more nuanced understanding of their risk of subsequent events is needed to enable more targeted secondary prevention strategies.

A large body of evidence has outlined differences in the clinical presentation,[5 6] diagnosis[7] and management/treatment[8–10] between men and women with an established diagnosis of CHD. Women with established CHD may have a lower probability of coronary revascularisation procedures[9] and a higher mortality outcome compared with men.[9] Most research examining sex differences in patients' outcomes with CHD or CHD subtypes has focused primarily on recurrent CHD or CHD subtypes, all-cause mortality, revascularisation or outcomes in the first year after CHD.[9 11] However there remains considerable uncertainty about wider experience of composite cardiovascular outcomes such as major adverse cardiovascular events (MACE) (recurrent CHD, stroke, peripheral vascular disease (PVD), heart failure and cardiovascular-related mortality) after incident CHD.

In this population-based cohort study we used multiple databases of electronic health records (EHRs) from primary care consultations, secondary care (hospital admissions and procedure-level data), and the national death registry, known to be representative of the UK population. We sought to estimate sex disparities in first subsequent MACE outcome in adults with any incident CHD.

METHODS

Data source

This prospective population-based cohort study used the UK Clinical Practice Research Datalink (CPRD GOLD) database of anonymised longitudinal primary care EHRs,[12] linked to secondary care hospitalisation data (Hospital Episode Statistics (HES)),[13] national mortality data (Office for National Statistics (ONS))[14] and social deprivation data (2015 Index of Multiple Deprivation (IMD)).[15] Individuals included in the CPRD GOLD database, from a network of general practices across the UK, are representative of the UK general population in terms of sex, age and ethnicity,[12] thereby validating CPRD GOLD for epidemiological research.

Study population

We identified a cohort of individuals with any incident non-fatal CHD in either primary care (CPRD GOLD) or secondary care (HES) data between 1 January 1998 and 31 December 2017, so long as the patient has at least 12 months of registration at the practice, the diagnosis was made after the first

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12 months of their current registration period,[16] the practice was deemed to be contributing 'up-to-standard' data (online supplemental methods), and the patient's CPRD record had linkage to HES. CHD was defined as angina, myocardial infarction (MI) or coronary revascularisation (coronary bypass surgery or coronary angioplasty)[17] (online supplemental table 1 for codes used in identifying both incident and outcome events). Individuals with a history of any stroke, PVD or heart failure before incident CHD were excluded. The study flow diagram is presented in online supplemental figure 1.

Outcome measures

First subsequent MACE after incident CHD was the primary outcome. MACE was defined as a composite of recurrent CHD, any stroke, PVD, heart failure or cardiovascular-related mortality, based on record from across the linked data sources (CPRD, HES or ONS registry). All-cause mortality was considered as a secondary outcome.

The study cohort and outcomes were identified from CPRD using Read codes, from HES using the International Classification of Diseases, Tenth Revision codes, and the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures revision 4.6 for procedure codes. All code lists used are available for download from https://portal.caliberresearch.org.[18]

Cohort demographics and baseline characteristics

Age was defined at the time of incident CHD. Ethnicity was categorised into six groups: Asian, Black, Mixed, Other, White and unknown.[19] To describe socioeconomic status (SES), the 2015 English IMD[15] linked to the individual's residential postcode was used. IMD is a weighted mean across seven domains, hence offers a single score to describe the concept of deprivation, categorised into quintiles (from quintile 1 (least deprived group) to quintile 5 (most deprived group)). Medication prescription (issue of prescription) at baseline was defined as a prescription within 12 months before incident CHD. For cholesterol (low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total), body mass index (BMI) and blood pressure measures (diastolic and systolic), the most recent values/measures within 24 months before incident CHD were used. All other comorbidities were defined based on the latest record before incident CHD.

Statistical analysis

The Shapiro-Wilk test was used to assess normality of distribution for continuous variables. Mann-Whitney U test for continuous data and χ^2 test for categorical data were used to compare baseline characteristics between men and women. The level of missing values ranged between 17.5% for blood pressure measures and 62.7% for LDL cholesterol. Details on the proportion of missingness and differences in characteristics between those with and without missing data are provided in online supplemental tables 2 and 3. To estimate missing values for BMI, systolic and diastolic blood pressures, HDL cholesterol, LDL cholesterol and total cholesterol levels, multiple imputation by chained equations was used to generate 10 imputed data sets using all the other available patient variables and all the outcomes.[20] The imputed data sets were pooled into a single data set using Rubin's rules.[21] Age-standardised prevalence for comorbidities and prescribed medications at baseline were obtained by using the study population to standardise the prevalence across men and women.

Incidence rates with 95% CI for first subsequent MACE, its individual constituents and all-cause mortality end points were calculated by dividing the number of incident outcomes by the total person-years at risk. Kaplan-Meier curves accompanied by HRs from Cox proportional hazard regression models were used to analyse the time-to-event outcomes. Competing risk analysis, which provides the cause-specific HR (or sub-HR), was used to calculate the cumulative incidence of the outcomes. The method proposed by Fine and Gray[22] was used to estimate the association of sex with the subhazard of MACE (or the specific individual constituent of MACE) and all-cause mortality. Non-cardiovascular-related mortality was considered a competing risk for MACE outcome. For both Cox and competing risks models, results are presented for models adjusted for age (model 1) and models adjusted for age, SES, smoking status, BMI, blood pressure (diastolic and systolic), total cholesterol level, history of alcohol problem, diabetes mellitus, dyslipidaemia, cancer, chronic kidney disease (CKD), hypertension, atrial fibrillation (AF), depression and a family history of cardiovascular disease (CVD) (model 2). The composite MACE outcome was further analysed using a win ratio approach,[23] first described by Finkelstein and Schoenfeld,[24] which prioritises fatal outcome(s) (ie, cardiovascular-related death) over less severe or non-fatal outcomes (ie, recurrent CHD, stroke, PVD and heart failure) for composite outcome. The R package, WWR, was used for the win ratio analysis. In a sensitivity analysis, subsequent outcomes within 30 days were considered as representing or relating to the same incident CHD event.[25] Analyses were, therefore, restricted to subsequent outcomes occurring after 30 days of incident CHD. All statistical analyses were performed using Stata SE V.16.1 and R V.4.0.3. An alpha level of 0.05 was used for all analyses.

Patient and public involvement

Patients or the public were not involved in the design, conduct or reporting. We plan on involving patient groups in the dissemination of our research findings.

RESULTS

There were a total of 166 068 individuals aged 18 years and over with any incident CHD between 1998 and 2017 in either CPRD GOLD or HES. Of these individuals 22 366 with a record of a major adverse event prior to their incident CHD event were excluded from the analysis. The study, therefore, included a cohort of 143 702 individuals 18 years and over with incident CHD and no prior record of MACE.

Baseline characteristics

The median follow-up time was 13.4 years (IQR: 8.4–17.7 years). The cohort comprised 63 078 (43.9%) women, who were older than men (median age of 73 vs 66 years, $p \leq 0.001$). Detailed descriptive characteristics of the study cohort presented by sex are shown in table 1.

After adjustment for age, women had a higher prevalence of the following comorbidities and known risk factors at the time of incident CHD when compared with men: CKD (9.3% vs 8.2%), depression (25.6% vs 13.0%), dyslipidaemia (12.9% vs 11.2%), family history of CVD (27.7% vs 21.0%), hypertension (46.9% vs 40.6%), hypothyroidism (10.9% vs 2.8%), migraine (9.1% vs 3.2%) and rheumatoid arthritis (2.5% vs 1.2%). Within 12 months prior to the incident CHD, women had a higher number of prescriptions for antiarrhythmic, antidepressant, antiepileptic, antihypertensive, antiplatelet, beta-blockers, corticosteroid,

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Table 1 Descriptive characteristics of the study population

Characteristics	Total n (%) 143 702 (100)	Men n (%) 80 624 (56.1)	Women n (%) 63 078 (43.9)	P value
Follow-up (years), median (IQR)	13.4 (8.4–17.4)	13.5 (8.7–17.5)	13.0 (8.1–17.2)	
Age (years)	69 (59–78)	66 (56–75)	73 (63–81)	0.0001
Ethnicity				<0.001
Asian	3550 (2.5)	2202 (2.7)	1348 (2.1)	
Black	959 (0.7)	504 (0.6)	455 (0.7)	
Mixed	361 (0.3)	209 (0.3)	152 (0.2)	
Other	1174 (0.8)	727 (0.9)	447 (0.7)	
White	130 236 (90.6)	72 844 (90.4)	57 392 (91.0)	
Unknown	7422 (5.2)	4138 (5.1)	3284 (5.2)	
Socioeconomic status				<0.001
1 (least deprived)	30 273 (21.1)	17 962 (22.3)	12 311 (19.5)	
2	31 412 (21.9)	17 963 (22.3)	13 449 (21.3)	
3	30 259 (21.1)	16 963 (21.0)	13 296 (21.1)	
4	26 808 (18.7)	14 507 (18.0)	12 301 (19.5)	
5 (most deprived)	24 754 (17.2)	13 122 (16.3)	11 632 (18.4)	
Unknown	196 (0.1)	107 (0.1)	89 (0.1)	
Current smokers	27 750 (19.3)	17 664 (21.9)	10 086 (16.0)	<0.001
Alcohol problem	3456 (2.4)	2600 (3.2)	856 (1.4)	<0.001
Body mass index (kg/m^2)	27.7 (25.8–30.1)	27.9 (26.0–30.1)	27.6 (25.5–30.0)	0.0001
Diastolic blood pressure (mm Hg)	80 (74–85)	80 (75–85)	80 (72–84)	0.0001
Systolic blood pressure (mm Hg)	140 (130–149)	140 (130–148)	140 (130–150)	0.0001
HDL cholesterol (mmol/L)	1.4 (1.2–1.6)	1.3 (1.1–1.5)	1.5 (1.3–1.7)	0.0001
LDL cholesterol (mmol/L)	3.1 (2.6–3.5)	3.1 (2.6–3.5)	3.1 (2.6–3.6)	0.0001
Total cholesterol (mmol/L)	5.2 (4.7–5.7)	5.1 (4.6–5.6)	5.3 (4.8–5.8)	0.0001
Comorbidities				
Atrial fibrillation	11 286 (7.9)	6022 (7.5)	5264 (8.4)	<0.001
Cancer	18 311 (12.7)	9954 (12.4)	8357 (13.3)	<0.001
Chronic kidney disease	12 344 (8.6)	5545 (6.9)	6799 (10.8)	<0.001
COPD	9442 (6.6)	5302 (6.6)	4140 (6.6)	0.922
Depression	25 967 (18.1)	11 045 (13.7)	14 922 (23.7)	<0.001
Diabetes mellitus	19 861 (13.8)	11 403 (14.1)	8458 (13.4)	<0.001
Type 1 diabetes	1615 (1.1)	898 (1.1)	717 (1.1)	0.683
Type 2 diabetes	16 238 (11.3)	9408 (11.7)	6830 (10.8)	<0.001
Dyslipidaemia	17 303 (12.0)	9336 (11.6)	7967 (12.6)	<0.001
Family history of coronary heart disease	26 528 (18.5)	14 017 (17.4)	12 511 (19.8)	<0.001
Family history of cardiovascular disease	34 213 (23.8)	17 952 (22.3)	16 261 (25.8)	<0.001
Hypertension	62 493 (43.5)	31 536 (39.1)	30 957 (49.1)	<0.001
Hypothyroidism	9154 (6.4)	2102 (2.6)	7052 (11.2)	<0.001
Lupus erythematosus	324 (0.2)	77 (0.1)	247 (0.4)	<0.001
Migraine	7797 (5.4)	2776 (3.4)	5021 (8.0)	<0.001
Moderate-severe liver disease	452 (0.3)	250 (0.3)	202 (0.3)	0.733
Rheumatoid arthritis	2576 (1.8)	963 (1.2)	1613 (2.6)	<0.001
Severe mental illness	1371 (1.0)	658 (0.8)	713 (1.1)	<0.001
Transient ischaemic attack	5159 (3.6)	2534 (3.1)	2625 (4.2)	<0.001
Drug prescription				
Antiarrhythmic	7346 (5.1)	3348 (4.2)	3998 (6.3)	<0.001
Anticoagulant	8429 (5.9)	4569 (5.7)	3860 (6.1)	<0.001
Antidepressant	30 139 (21.0)	12 245 (15.2)	17 894 (28.4)	<0.001
Antidiabetic	16 170 (11.3)	9271 (11.5)	6899 (10.9)	0.001
Antiepileptic	9746 (6.8)	4612 (5.7)	5134 (8.1)	<0.001
Antihypertensive	77 180 (53.7)	39 738 (49.3)	37 442 (59.4)	<0.001
Antiplatelets	47 799 (33.3)	25 365 (31.5)	22 434 (35.6)	<0.001
Beta-blockers	39 692 (27.6)	20 103 (24.9)	19 589 (31.1)	<0.001
Corticosteroid	16 541 (11.5)	7560 (9.4)	8981 (14.2)	<0.001

Continued

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Table 1 Continued

Characteristics	Total n (%) 143 702 (100)	Men n (%) 80 624 (56.1)	Women n (%) 63 078 (43.9)	P value
Diuretics	47 885 (33.3)	20 069 (24.9)	27 816 (44.1)	<0.001
Statin				<0.001
Low intensity	5810 (4.0)	2978 (3.7)	2832 (4.5)	
Moderate intensity	29 331 (20.4)	16 946 (21.0)	12 385 (19.6)	
High intensity	8030 (5.6)	4537 (5.6)	3493 (5.5)	
Intervention				
Percutaneous coronary intervention	1969 (1.4)	1488 (1.9)	481 (0.8)	<0.001

%, percentage/proportion; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n, total number.

diuretics, and both low-intensity and high-intensity statins, after adjusting for age. Online supplemental table 4 details the age-adjusted prevalence for comorbidities, risk factors and prescribed medications.

First subsequent MACE outcome

Most first subsequent major adverse outcomes occurred within 2 years of incident CHD, with the median time to outcome ranging from 0.11 years (IQR: 0.02–0.81) for recurrent CHD to 2.54 years (IQR: 0.63–5.83) for subsequent stroke event. Of the 143 702 individuals with incident CHD, 91 706 (63.8%) had a MACE (men: 55 087 (68.3%) vs women: 36 619 (58.1%)), 66 543 (46.3%) had a recurrent CHD, 5740 (4.0%) strokes, 1624 (1.1%) PVD, 7905 (5.5%) heart failure, 9894 (6.9%) cardiovascular death and 29 503 (20.5%) all-cause death, occurring after the incident CHD events. Figure 1 and online supplemental figure 2 show the distribution of individuals with major adverse outcomes, by sex and across 5-year age bands.

Incidence rate for clinical outcomes

The overall incidence rate for MACE was 25.18 per 100 person-years (95% CI 25.02 to 25.34), with a higher incidence rate in men compared with women (31.03 vs 19.62 per 100 person-years). Table 2 details the sex variation in the incidence of the constituent MACE outcomes. In comparing women with men, the age-adjusted and SES-adjusted sex-specific incidence rate ratio for MACE was 0.58 (0.57–0.59), for recurrent CHD 0.52 (0.51–0.53), for stroke 1.22 (1.16–1.29), for PVD 0.88 (0.80–0.97), for heart failure 1.00 (0.96–1.05), for CVD-related death 0.89 (0.85–0.93) and for all-cause mortality 0.92 (0.90–0.94).

Sex difference and clinical outcomes

After adjusting for age, socioeconomic and smoking status, BMI, blood pressure, total cholesterol, history of alcohol problem, diabetes, dyslipidaemia, cancer, CKD, hypertension, AF, depression and family history of CVD, in both Cox and competing risks models (table 3) women had a significantly lower risk of first subsequent MACE (HR, 0.68 (95% CI 0.67 to 0.69);

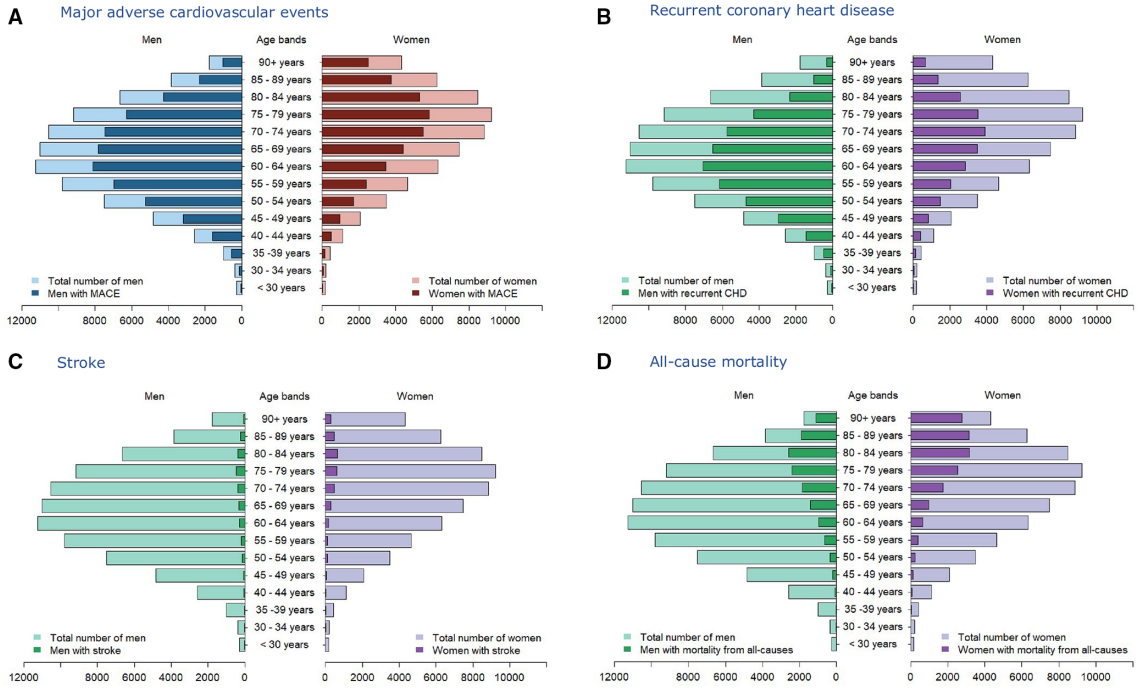

Figure 1 Distribution of first subsequent major adverse outcomes by sex and 5-year age group for patients with incident CHD. CHD, coronary heart disease; MACE, major adverse cardiovascular events.

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Table 2 Incidence of first subsequent major adverse outcomes (N=143 702)

	Median time to outcome (years)	Cases	Person-years*	Incidence rate (per 100 person-years)	Adjusted incidence rate ratio†
MACE (all)	0.18 (0.03–1.59)	91 706	3600	25.18 (25.02–25.34)	
Men	0.13 (0.02–1.04)	55 087	1800	31.03 (30.77–31.29)	Reference
Women	0.31 (0.04–2.47)	36 619	1900	19.62 (19.42–19.82)	0.58 (0.57–0.59)
Coronary heart disease (all)	0.11 (0.02–0.81)	66 543	3900	16.87 (16.74–17.00)	
Men	0.09 (0.02–0.58)	43 238	1900	22.29 (22.08–22.50)	Reference
Women	0.17 (0.03–1.29)	23 305	2000	11.63 (11.48–11.78)	0.52 (0.51–0.53)
Stroke (all)	2.54 (0.63–5.83)	5740	7500	0.77 (0.75–0.79)	
Men	2.33 (0.52–5.56)	2546	4300	0.60 (0.57–0.61)	Reference
Women	2.75 (0.71–6.07)	3194	3200	1.00 (0.97–1.04)	1.22 (1.16–1.29)
Peripheral vascular disease (all)	1.83 (0.35–4.88)	1624	7500	0.22 (0.21–0.23)	
Men	1.71 (0.35–4.68)	901	4300	0.21 (0.19–0.22)	Reference
Women	1.95 (0.34–5.20)	723	3200	0.23 (0.21–0.24)	0.88 (0.80–0.97)
Heart failure (all)	0.95 (0.14–3.83)	7905	7400	1.07 (1.05–1.09)	
Men	0.73 (0.11–3.54)	3823	4300	0.90 (0.87–0.93)	Reference
Women	1.22 (0.19–4.11)	4082	3100	1.30 (1.26–1.34)	1.00 (0.96–1.05)
Cardiovascular mortality (all)	0.20 (0.02–3.13)	9894	7600	1.29 (1.27–1.32)	
Men	0.21 (0.02–3.06)	4579	4400	1.04 (1.02–1.08)	Reference
Women	0.19 (0.02–3.22)	5315	3300	1.63 (1.59–1.67)	0.89 (0.85–0.93)
All-cause mortality (all)	1.37 (0.08–5.07)	29 503	7800	3.77 (3.73–3.82)	
Men	1.20 (0.07–4.78)	13 668	4500	3.07 (3.02–3.12)	Reference
Women	1.54 (0.08–5.34)	15 835	3400	4.71 (4.63–4.78)	0.92 (0.90–0.94)

*100 person-years at risk; all: both men and women; follow-up time: median follow-up time in years reported with IQR.
†Incident rate ratio adjusted for age (continuous variable) and Index of Multiple Deprivation (socioeconomic status).
MACE, major adverse cardiovascular events.

sub-HR (HRsd), 0.71 (95% CI 0.70 to 0.72), respectively) and recurrent CHD (HR, 0.60 (95% CI 0.59 to 0.61); HRsd, 0.62 (95% CI 0.61 to 0.63)) when compared with men after incident CHD. Women, however, had a significantly higher risk of any stroke (HR, 1.26 (95% CI 1.19 to 1.33); HRsd, 1.32 (95% CI 1.25 to 1.39)), heart failure (HR, 1.09 (95% CI 1.04 to 1.15); HRsd, 1.13 (95% CI 1.07 to 1.18)) and all-cause mortality (HR, 1.05 (95% CI 1.02 to 1.07); HRsd, 1.11 (95% CI 1.08 to 1.13)).

Table 3 Risk of first subsequent major adverse outcome for women compared with men (reference category)

	Cox model HR (95% CI)	Competing risks model* Sub-HR (95% CI)
Model 1†		
Major adverse cardiovascular event	0.68 (0.67 to 0.69)	0.71 (0.70 to 0.72)
Coronary heart disease	0.62 (0.61 to 0.63)	0.64 (0.63 to 0.65)
Stroke	1.25 (1.18 to 1.32)	1.33 (1.26 to 1.41)
Peripheral vascular disease	0.92 (0.83 to 1.02)	0.95 (0.86 to 1.06)
Heart failure	1.04 (1.00 to 1.09)	1.09 (1.04 to 1.14)
Cardiovascular-related death	0.94 (0.90 to 0.98)	0.99 (0.95 to 1.03)
All-cause mortality	0.96 (0.94 to 0.98)	1.02 (1.00 to 1.05)
Model 2‡		
Major adverse cardiovascular event	0.67 (0.66 to 0.68)	0.69 (0.68 to 0.70)
Coronary heart disease	0.60 (0.59 to 0.61)	0.62 (0.61 to 0.63)
Stroke	1.26 (1.19 to 1.33)	1.32 (1.25 to 1.39)
Peripheral vascular disease	0.92 (0.83 to 1.02)	0.95 (0.85 to 1.05)
Heart failure	1.09 (1.04 to 1.15)	1.13 (1.07 to 1.18)
Cardiovascular-related death	0.99 (0.95 to 1.03)	1.02 (0.98 to 1.06)
All-cause mortality	1.05 (1.02 to 1.07)	1.11 (1.08 to 1.13)

*Fine and Gray method for subdistribution regression with competing risks.[22]
†Model 1: adjusted for age (continuous variable).
‡Model 2: adjusted for age (continuous variable), socioeconomic status, smoking status, body mass index, blood pressure, total cholesterol level, history of alcohol problem, diabetes mellitus, dyslipidaemia, cancer, chronic kidney disease, hypertension, atrial fibrillation, depression and a family history of cardiovascular disease.

The cumulative incidence function (figure 2 and online supplemental figure 3) and Kaplan-Meier curves (figure 3 and online supplemental figure 4) as well as the adjusted Kaplan-Meier cumulative incidence curves (online supplemental figure 5) for MACE and its constituent outcomes illustrate women have a higher incidence of subsequent stroke, heart failure and all-cause mortality over a 10-year follow-up period.

To describe the effect of being a woman on the fatal outcome (cardiovascular-related death) in the composite MACE as compared with the non-fatal outcomes (recurrent CHD, stroke, PVD and heart failure), the win ratio was 1.331 (95% CI 1.329 to 1.331).

Sensitivity analysis

For the sensitivity analysis, 7566 (5.3%) individuals who died within 30 days of incident CHD were excluded. There were 76 571 subsequent MACE outcomes recorded after 30 days of incident CHD for the remaining 136 326 individuals. The median time from incident CHD to subsequent outcome after 30 days ranged from 0.58 years (IQR: 0.21–2.25) for recurrent CHD to 2.98 years (IQR: 0.85–6.59) for all-cause mortality (online supplemental table 5). After full adjustment, in both Cox and competing risks models (online supplemental table 6) women had a significantly lower risk of first subsequent MACE (HR, 0.70 (95% CI 0.69 to 0.71); HRsd, 0.71 (95% CI 0.70 to 0.72), respectively) and recurrent CHD (HR, 0.63 (95% CI 0.62 to 0.64); HRsd, 0.64 (95% CI 0.63 to 0.65)) when compared with men after incident CHD. Women, however,

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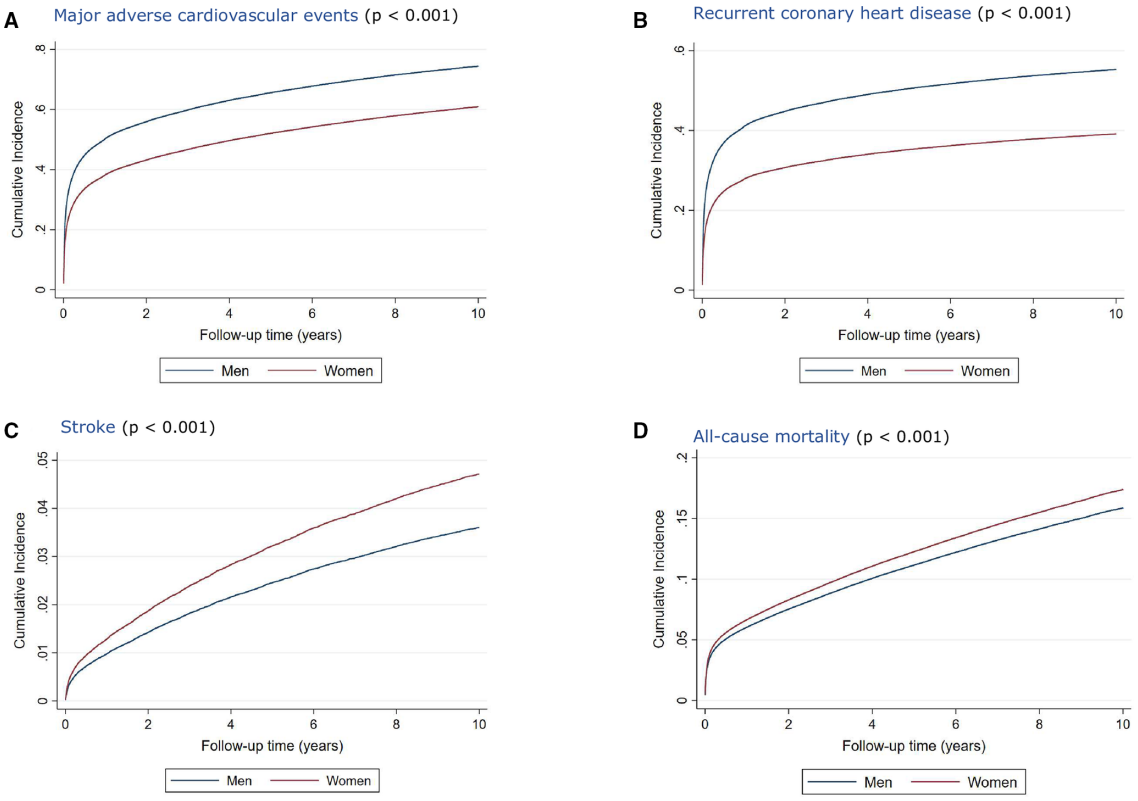

Figure 2 Cumulative incidence function plots for first subsequent major adverse outcomes.

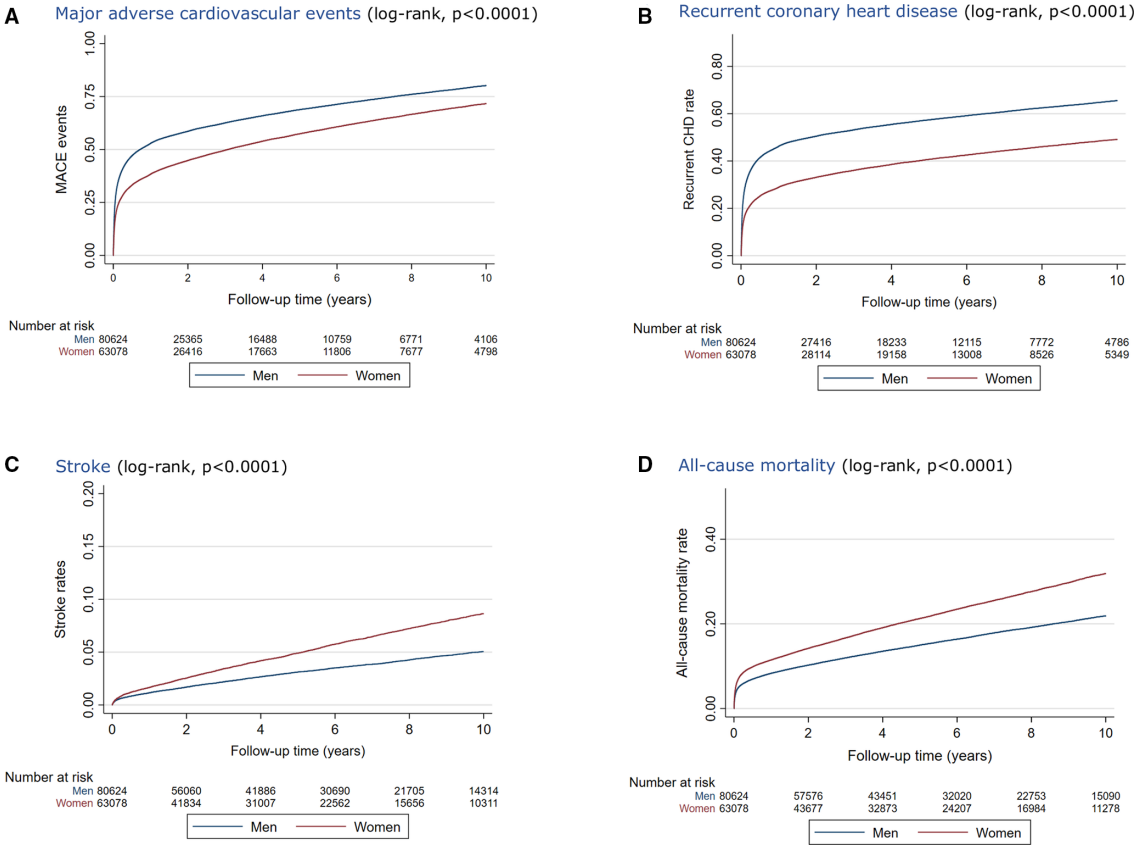

Figure 3 Kaplan-Meier plots for first subsequent major adverse outcomes. CHD, coronary heart disease; MACE, major adverse cardiovascular events.

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had a significantly higher risk of any stroke (HR, 1.21 (95% CI 1.15 to 1.28); HRsd, 1.27 (95% CI 1.20 to 1.34)) and all-cause mortality (HR, 1.01 (95% CI 0.98 to 1.04); HRsd, 1.08 (95% CI 1.05 to 1.11)). Similar sex differences were observed when the analysis was done by incident CHD time period (1998–2007 and 2008–2017) (online supplemental table 7) and when the analysis was restricted to 61 167 individuals with incident MI (online supplemental table 8).

DISCUSSION

Within a population-based cohort, we show there are sex disparities in the risk of developing first subsequent MACE and its individual constituent events in adults with any incident CHD. Women are less likely to have a MACE or recurrent CHD as a first subsequent event after incident CHD when compared with men. However, women are more likely to have stroke, heart failure or death from any cause after incident CHD.

The risk profiles of men and women have been shown to substantially differ when diagnosed with CHD[26] and fare much differently after incident CHD. The cause of disparities is multifaceted, relating to differences in baseline cardiovascular profile, access to care, use of resources and evidence-based guidelines, and social as well as environmental factors.[8 27] Previous studies have frequently been based on selected cohorts from trials, registries or individuals with specific type of CHD.[9 26] Consistent with our findings, a study of 3779 patients from the Euro Heart Survey of Stable Angina reported women have a higher risk of death even after multivariable adjustment.[9] However, in a study of 30 977 outpatients with stable coronary artery disease from the ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) register, similar event rates in men and women for the composite outcome of cardiovascular death, non-fatal MI or stroke at 1-year follow-up were observed after adjustment for baseline differences.[26] Although 22.6% of the CLARIFY study patients were women, women were more likely to have diabetes and hypertension, consistent with our findings.

Population-based studies, such as our study using data representative of the UK population, provide real-world evidence regarding sex differences in outcomes for patients with incident CHD.[28] It is by considering disparities across individuals from the whole spectrum of CHD that the full burden of subsequent MACE outcome can be captured and accurate distinctions made between men and women. Most studies have focused on sex differences in mortality outcome—differences in age, comorbidities and treatment use between men and women have largely explained the sex differences in mortality outcome.[11] Studies have also differed in the methodological approach used in assessing sex differences—logistic regression[26] as opposed to survival analysis.

The analysis of survival (time-to-event) data plays a key role in cardiovascular research and competing events are prevalent.[29] A competing event (eg, death from non-cardiovascular cause) hinders or changes the possibility of observing the outcome of interest (eg, death from cardiovascular-related death). Koller *et al*[29] found a large majority of clinical studies neglected the competing risks process despite the studies having populations susceptible to competing risks. Failure to account correctly for these competing events results in the overestimation of probabilities for the incidence of outcomes.[30] Our analyses illustrated the overestimation of the risk of first subsequent MACE and its constituents when using a standard Cox model. Our study demonstrates the importance of accounting for competing events. The impact of incorrectly treating competing events has practical importance as clinical decisions often rely on an individual's risk of a disease event or outcome.[31]

Combining multiple types of clinical outcomes into a single composite outcome is common in clinical research.[32] The usual analysis of time to first occurrence of any event in the composite outcome treats individual constituent outcomes as being equally important despite differences in clinical relevance and severity. The novel approach, win ratio,[23] provides a useful alternative for analyses of composite outcomes, addressing the limitations of usual first event analysis. Win ratio requires a ranking of outcomes by severity but does not require assigning a specific weight to each outcome. As shown in our study, women have more fatal outcome in composite MACE than men.

Strengths and limitations

This study has a number of strengths. First is the size and representativeness of the CPRD GOLD data set[12]; this large retrospective population-based study used primary care data linked to hospital and mortality records, allowing us to assess sex-related differences in major CVD events and mortality occurrence after incident CHD. Second, we used an incident cohort, which reflects current practice and avoids the distorting influences of bias present in cohorts with prevalent major adverse events. We acknowledge limitations generally inherent in studies using EHRs. These include missing data in EHRs, including CPRD GOLD. Potential ascertainment and information bias are acknowledged. The coded definitions of outcomes and CHD incident diagnosis used in this study are, however, well established due to the pay-for-performance scheme (Quality and Outcome Framework) which has improved documentation/coding for cardiovascular conditions and associated risk factors.[17 33] The potential for misclassification bias is, therefore, not likely. The subtyping of CHD in both primary care (CPRD GOLD) and secondary care (HES) databases is not reliable[34] and hence unable to assess differences for CHD subtypes. The use of 'softer' CHD codes in primary care data is yet to be validated.[35]

Key messages

What is already known on this subject?

- Sex differences exist in the presentation, treatment and outcomes of individuals with incident coronary heart disease (CHD).
- Most studies have focused on sex differences in recurrent CHD, all-cause mortality or revascularisation.

What might this study add?

- The study provides evidence on sex differences in the first subsequent composite major adverse cardiovascular events and constituent outcomes in individuals with any incident CHD using a large population-based cohort.

How might this impact on clinical practice?

- As more people are surviving their incident CHD events, further attention to all patients with incident CHD is needed to narrow this range of sex disparities in major subsequent clinical outcomes.
- Improving the standard and equity of care for women and men with incident CHD should recognise a 'one size fits all' approach may not hold.

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CONCLUSIONS

CHD remains the leading cause of mortality globally. Improved understanding of outcomes in patients with CHD is key to reduce the disease burden. In this large population-based cohort study of patients with any type of incident CHD, we identified after appropriate adjustments for confounders a lower risk of MACE and recurrent CHD in women when compared with men. However, there was a higher risk of stroke, heart failure and all-cause mortality in women. As more people are surviving their incident CHD events, further attention to all patients with incident CHD is needed to narrow this range of sex disparities in major subsequent clinical outcomes. Improving the standard and equity of care for women and men with incident CHD should recognise a 'one size fits all' approach may not hold.

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Contributors RKA, SW, FWA and NQ were involved in the design and planning of the study. RKA conducted the main statistical analysis and wrote the first draft of the manuscript. All authors contributed to the interpretation of the data, writing of the manuscript and critical revisions. RKA is the guarantor.

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Competing interests RKA currently holds an NIHR-SPCR funded studentship (2018-2021). SW is currently an employee of Janssen R&D. NQ was a member of the most recent NICE Familial Hypercholesterolaemia and Lipid Modification Guideline Development Groups (CG71 and CG181). NQ and SW have previously received honorarium from AMGEN. RSP has funding from the British Heart Foundation and the National Institute for Health Research. FWA is supported by UCL Hospitals NIHR Biomedical Research Centre. The remaining authors have no competing interests.

Patient consent for publication Not required.

Ethics approval This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol number 19_023R).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data supporting the findings of this study are available from the Clinical Practice Research Datalink (CPRD). Restrictions apply to the availability of these data, which were used under licence for the current study, hence are not publicly available.

Author note Additional references can be found in online supplemental file 1.

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SUPPLEMENTAL MATERIAL

Sex disparity in subsequent outcomes in survivors of coronary heart disease

Supplemental Methods	Glossary of Terms
Supplemental Figure 1	Distribution of all-cause mortality events by sex and 5-year age group for patients with incident CHD
Supplemental Figure II	Cumulative incidence function for all-cause mortality
Supplemental Table I	Clinical codes for identifying individuals with a diagnosis of coronary heart disease (Read, ICD-10 and OPCS 4.6 codes)
Supplemental Table II	Number (proportion) of people with missing data on risk factors, by sex
Supplemental Table III	Differences in characteristics between those with and without missing data by sex
Supplemental Table IV	Age-adjusted prevalence rate for comorbidities, risk factors and prescribed medications
Supplemental Table V	Incidence of first subsequent major adverse outcomes occurring after 30 days of incident coronary heart disease (n = 136,326)
Supplemental Table VI	Risk of first subsequent major adverse outcomes occurring after 30 days of incident coronary heart disease for women compared to men (reference category), n = 136,326
Supplemental Table VII	Risk of first subsequent major adverse outcomes by time of incident CHD diagnosis (1998-2007 vs 2008-2017), for women compared to men (reference category).

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Supplemental Table VIII	Risk of first subsequent major adverse outcomes in individuals with incident myocardial infarction diagnosis (n=61,167), for women compared to men (reference category)
Supplemental Reference	Additional references

Supplemental Methods Glossary of terms

Acceptable Patients

Patients are labelled as 'acceptable' for use in research by a process that identifies and excludes patients with non-continuous follow up or patients with poor data recording that raises suspicion as to the validity of the that patients record. Patient data is checked, for the following issues:

- An empty or invalid first registration date
- An empty or invalid current registration date
- Absence of a record for a year of birth
- A first registration date prior to their birth year
- A current registration date prior to their birth year
- A transferred-out reason with no transferred-out date
- A transferred-out date with no transferred-out reason
- A transferred-out date prior to their first registration date
- A transferred-out date prior to their current registration date
- A current registration date prior to their first registration date
- A gender other than Female/Male/Indeterminate
- An age of greater than 115 at end of follow up
- Recorded health care episodes in years prior to birth year
- All recorded health care episodes have empty or invalid event dates
- Registration status of temporary patients

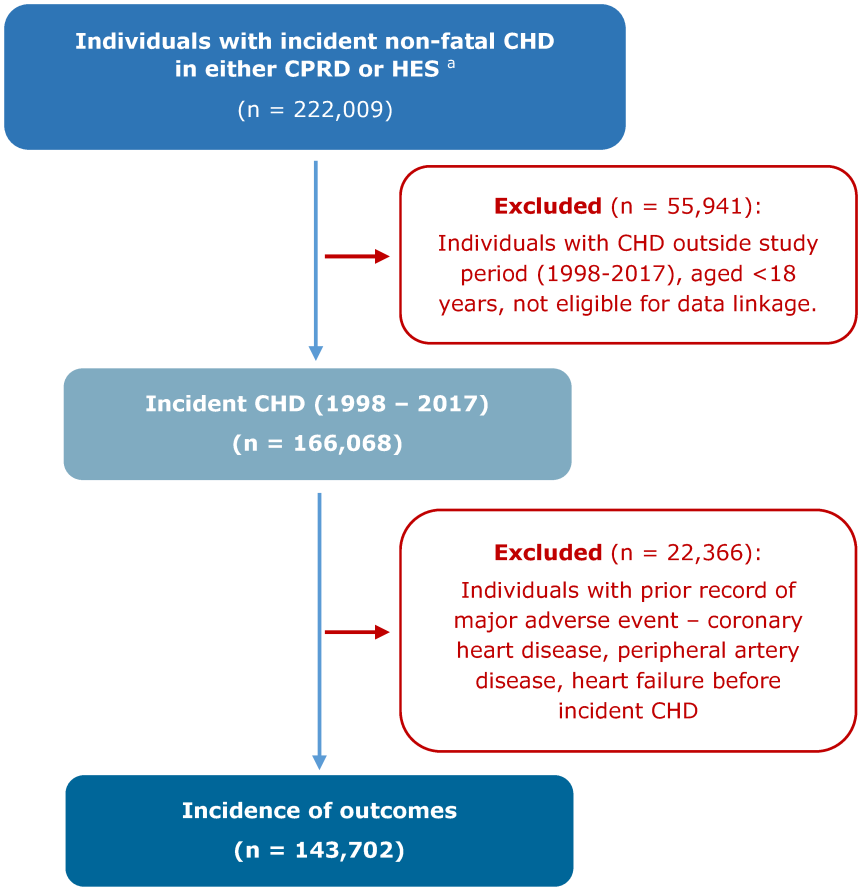
If any of these conditions are true, the patient is labelled unacceptable and is not recommended for use in research.

UTS date

The overall quality of data in practices is mediated by use of an 'up to standard' (UTS) date, which is deemed as the date at which data in the practice is considered to have continuous high-quality data fit for use in research. This is mediated by an analysis on the total data in the practice, which is refreshed every time a new collection for a practice is processed into the database. It is based on two central concepts: assurance of continuity in data recording (gap analysis), and avoidance of use of data for which transferred out and dead patients have been removed (death recording).

The UTS date is set to the latest of these dates for each practice. The CPRD recommend that analyses are performed on data following the practice UTS date.

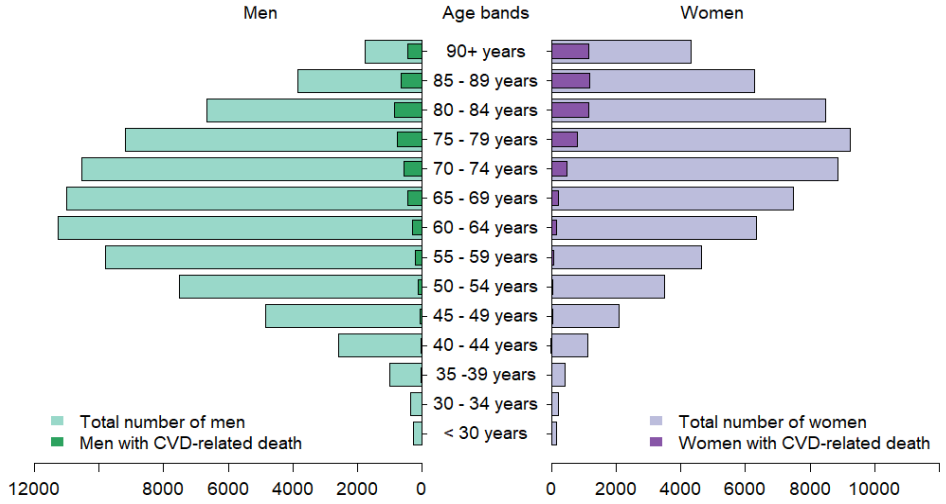
Supplemental Figure I Study flow diagram



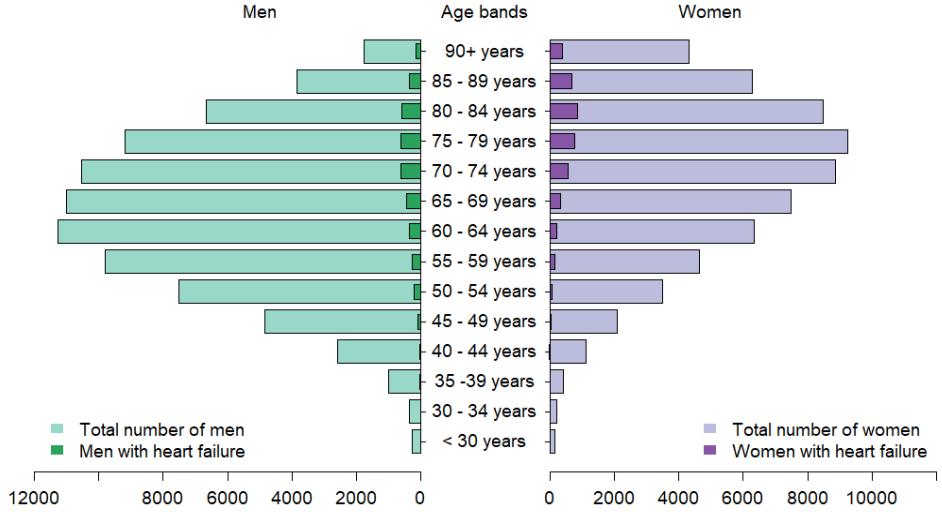
a. Incident non-fatal coronary heart disease (CHD) recorded between 1 January 1998 and 31 December 2017 in individuals 18 years and over with at least 12 months of registration with the practice. Practices contributing up-to-standard data and patient primary care record has linkage to HES.

Supplemental Figure II Distribution of cause mortality events by sex and 5-year age group for patients with incident CHD

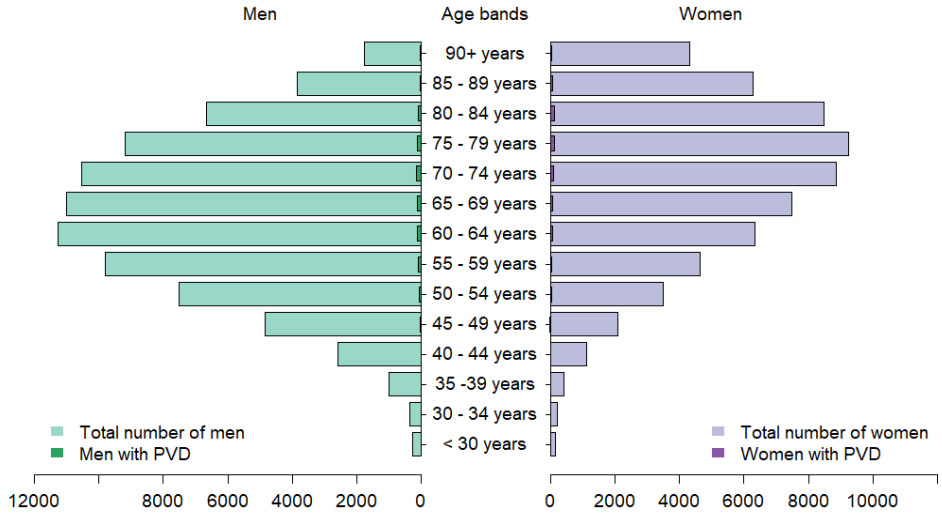
(a) Cardiovascular-related mortality



(b) Heart failure

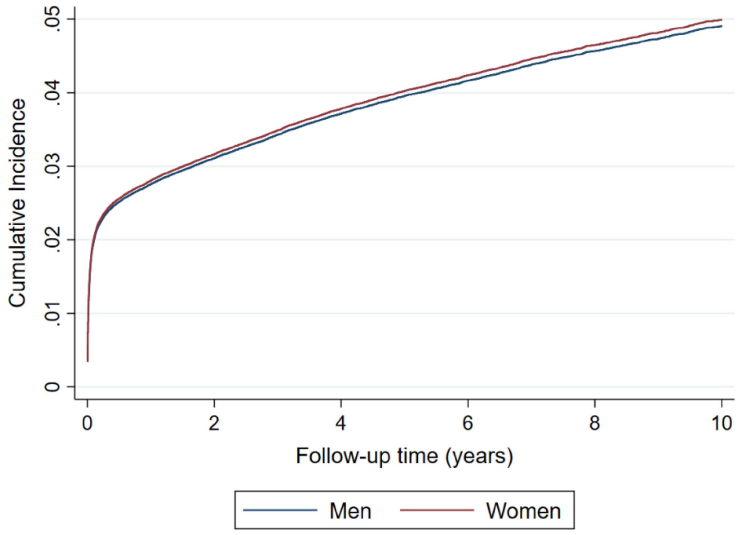


(c) Peripheral vascular disease

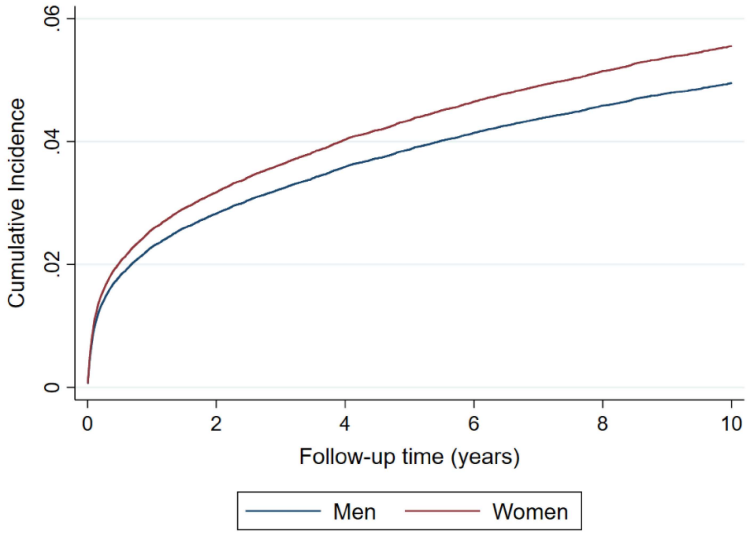


Supplemental Figure III Cumulative incidence function plots for cardiovascular-related mortality, heart failure, and peripheral vascular disease by sex

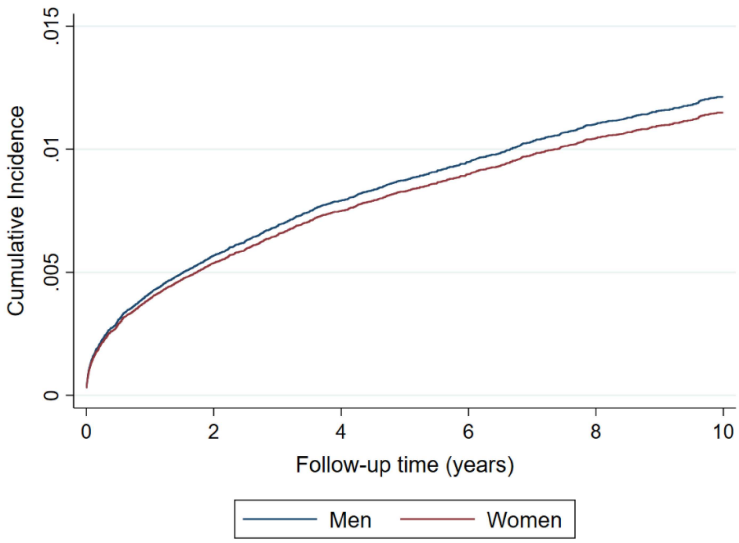
(a) Cardiovascular-related mortality (p = 0.410)



(b) Heart failure (p < 0.001)

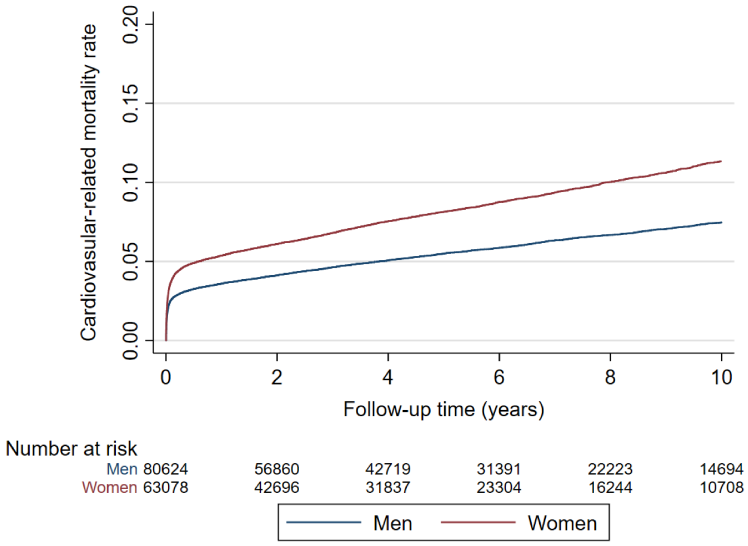


(c) Peripheral vascular disease (p = 0.318)

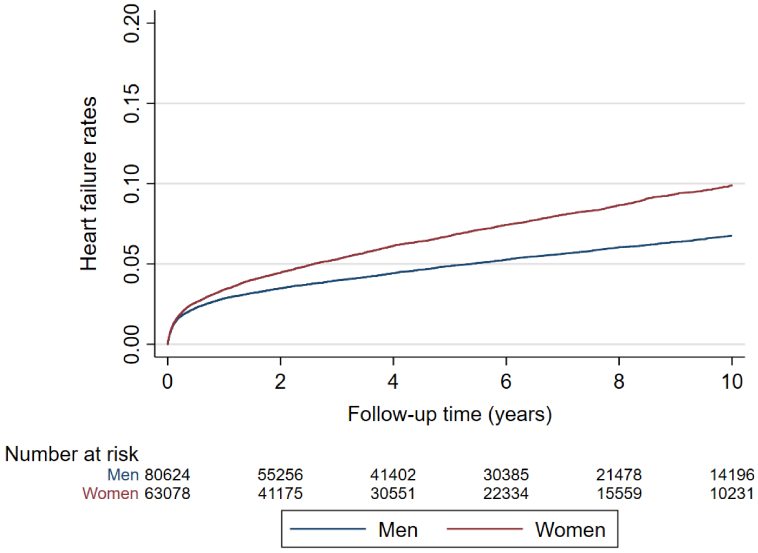


Supplemental Figure IV Kaplan-Meier plots for cardiovascular-related mortality, heart failure, and peripheral vascular disease by sex

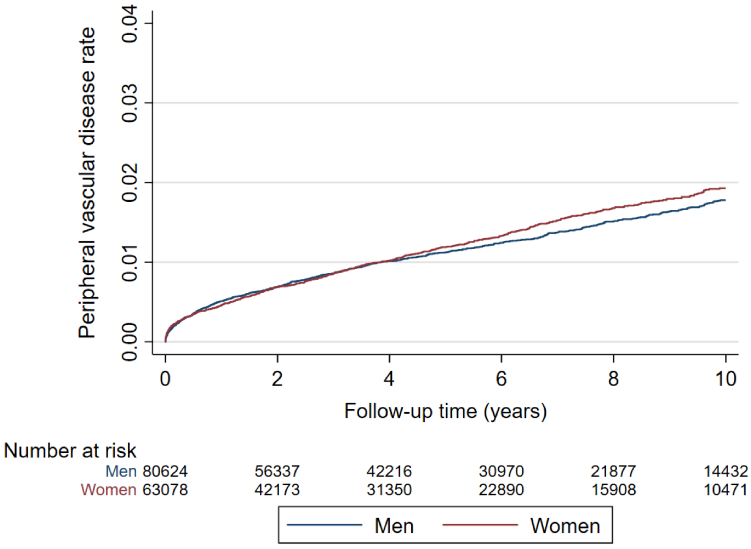
(a) Cardiovascular-related mortality (log-rank, p<0.0001)



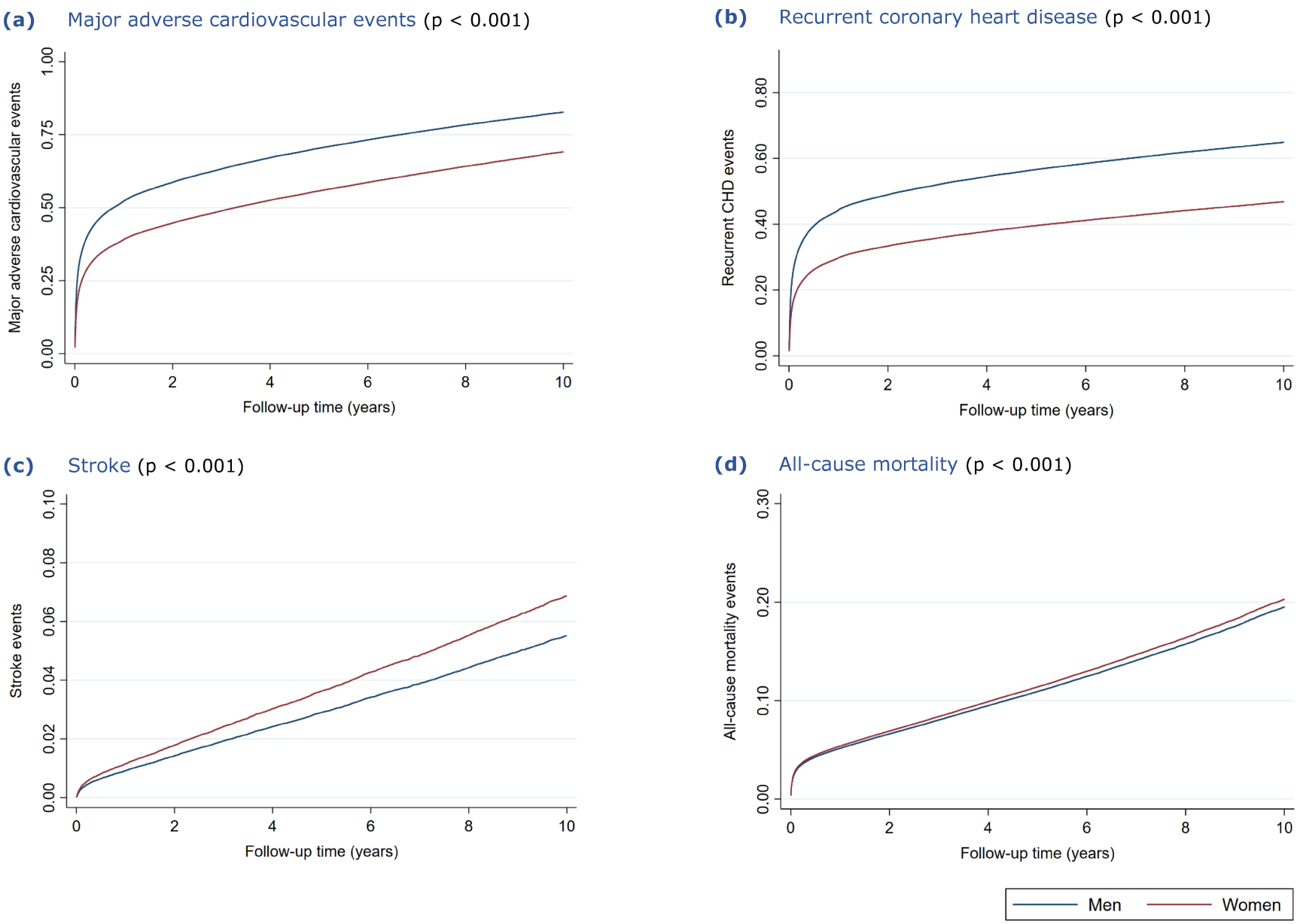
(b) Heart failure (log-rank, p<0.0001)



(c) Peripheral vascular disease (log-rank, p = 0.1662)

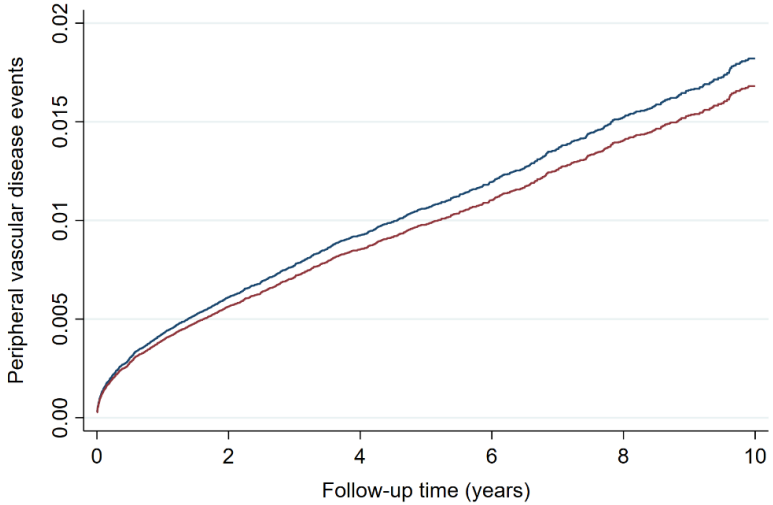


Supplemental Figure V Kaplan-Meier cumulative incidence plots for first subsequent major adverse outcomes by sex

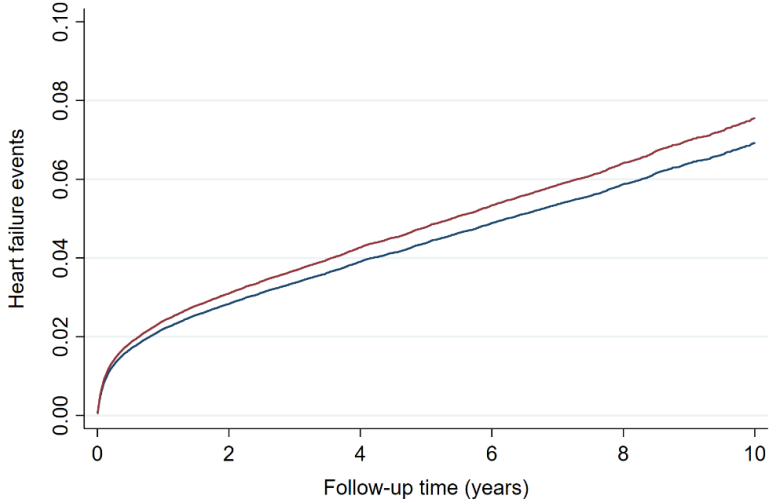


Supplemental Figure V *(continued …)*

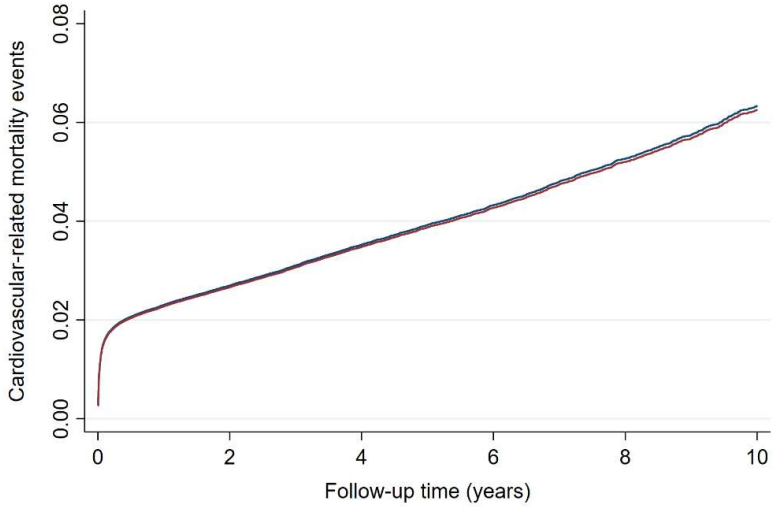
(e) Peripheral vascular disease (p=0.128)



(f) Heart failure (p < 0.001)



(g) Cardiovascular-related mortality (p = 0.550)



All Kaplan-Meier cumulative incidence plots have been adjusted for age, (continuous variable), socioeconomic status, smoking status, body mass index, blood pressure, total cholesterol level, history of alcohol problem, diabetes mellitus, dyslipidaemia, cancer, chronic kidney disease, hypertension, atrial fibrillation, depression, and a family history of cardiovascular disease.

Supplemental Table I Clinical codes for identifying individuals with a diagnosis of coronary heart disease (Read, ICD-10 and OPCS 4.6 codes)

CPRD diagnostic codes for identifying CHD in primary care data		
medcode	**Read code**	**Description**
240	G3...00	Ischaemic heart disease
241	G30..00	Acute myocardial infarction
1204	G30..14	Heart attack
1344	G340.12	Coronary artery disease
1414	G33z300	Angina on effort
1430	G33..00	Angina pectoris
1431	G311.13	Unstable angina
1676	G3z..00	Ischaemic heart disease NOS
1677	G30..15	MI - acute myocardial infarction
1678	G308.00	Inferior myocardial infarction NOS
1792	G3...13	IHD - Ischaemic heart disease
2491	G30..12	Coronary thrombosis
3704	G307.00	Acute subendocardial infarction
4017	G32..00	Old myocardial infarction
4656	G311.11	Crescendo angina
5387	G301.00	Other specified anterior myocardial infarction
5413	G340.00	Coronary atherosclerosis
6336	14A5.00	H/O: angina pectoris
7320	G343.00	Ischaemic cardiomyopathy
7347	G311100	Unstable angina
7696	G33z200	Syncope anginosa
7783	323..00	ECG: myocardial infarction
8568	G37..00	Cardiac syndrome X
8935	G302.00	Acute inferolateral infarction
9276	G31y000	Acute coronary insufficiency
9413	G31y.00	Other acute and subacute ischaemic heart disease
9507	G307000	Acute non-Q wave infarction
9555	G33z500	Post infarct angina
10260	6A4..00	Coronary heart disease review
10562	G307100	Acute non-ST segment elevation myocardial infarction
11048	G331.11	Variant angina pectoris
11648	8B3k.00	Coronary heart disease medication review
12139	G300.00	Acute anterolateral infarction
12229	G30X000	Acute ST segment elevation myocardial infarction
12804	G33z700	Stable angina
12986	G331.00	Prinzmetal's angina
13185	662K.00	Angina control

13566	G30..11	Attack - heart
13571	G30..16	Thrombosis - coronary
14658	G30z.00	Acute myocardial infarction NOS
14782	662K200	Angina control - improving
14897	G301z00	Anterior myocardial infarction NOS
14898	G305.00	Lateral myocardial infarction NOS
15349	662Kz00	Angina control NOS
15373	662K100	Angina control - poor
15661	G310.11	Dressler's syndrome
15754	G34z.00	Other chronic ischaemic heart disease NOS
16408	G32..11	Healed myocardial infarction
17133	G30A.00	Mural thrombosis
17307	G311200	Angina at rest
17464	G32..12	Personal history of myocardial infarction
17689	G30..17	Silent myocardial infarction
17872	G301100	Acute anteroseptal infarction
18118	G311400	Worsening angina
18125	G330000	Nocturnal angina
18135	6A2..00	Coronary heart disease annual review
18842	G35..00	Subsequent myocardial infarction
18889	G34z000	Asymptomatic coronary heart disease
19542	662K000	Angina control - good
19655	G311.14	Angina at rest
20095	G330.00	Angina decubitus
20416	G3...12	Atherosclerotic heart disease
21844	G31y300	Transient myocardial ischaemia
22383	G3y..00	Other specified ischaemic heart disease
23078	G34y100	Chronic myocardial ischaemia
23579	G310.00	Post-myocardial infarction syndrome
23708	G361.00	Atrial septal defect/current complication following acute myocardial infarct
23892	G304.00	Posterior myocardial infarction NOS
24126	G360.00	Haemopericardium/current comp following acute myocardial infarct
24540	G34y000	Chronic coronary insufficiency
24783	G3...11	Arteriosclerotic heart disease
25842	G33z.00	Angina pectoris NOS
26863	G33z600	New onset angina
26972	3234.00	ECG: posterior/inferior infarct
26975	3233.00	ECG: antero-septal infarct.
27951	G31..00	Other acute and subacute ischaemic heart disease
27977	G31yz00	Other acute and subacute ischaemic heart disease NOS
28138	G34..00	Other chronic ischaemic heart disease
28554	G33zz00	Angina pectoris NOS
28736	G30y000	Acute atrial infarction

29300	662K300	Angina control - worsening
29421	G344.00	Silent myocardial ischaemia
29553	G366.00	Thrombosis atrium, auric append & vent/current comp following acute MI
29643	G303.00	Acute inferoposterior infarction
29758	G30X.00	Acute transmural myocardial infarction of unspecified site
29902	G330z00	Angina decubitus NOS
30330	G309.00	Acute Q-wave infarct
30421	G30..13	Cardiac rupture following myocardial infarction (MI)
32272	G38..00	Postoperative myocardial infarction
32854	G30B.00	Acute posterolateral myocardial infarction
34328	G311300	Refractory angina
34633	G34y.00	Other specified chronic ischaemic heart disease
34803	G30y.00	Other acute myocardial infarction
35119	G501.00	Post infarction pericarditis
35674	14A3.00	H/O: myocardial infarct <60
35713	G34yz00	Other specified chronic ischaemic heart disease NOS
36423	G36..00	Certain current complication following acute myocardial infarct
36523	G311.00	Pre-infarction syndrome
36854	G332.00	Coronary artery spasm
37657	G362.00	Ventricular septal defect/current comp for acute myocardial infarction
38609	G351.00	Subsequent myocardial infarction of inferior wall
39449	G312.00	Coronary thrombosis not resulting in myocardial infarction
39546	Gyu3000	[X]Other forms of angina pectoris
39655	G311.12	Impending infarction
39693	G31y200	Subendocardial ischaemia
40399	14A4.00	H/O: myocardial infarct >60
40429	G301000	Acute anteroapical infarction
41221	G30y200	Acute septal infarction
41835	G384.00	Postoperative subendocardial myocardial infarction
45809	G350.00	Subsequent myocardial infarction of anterior wall
45960	8B27.00	Antianginal therapy
46017	G30yz00	Other acute myocardial infarction NOS
46112	G380.00	Postoperative transmural myocardial infarction anterior wall
46166	G35X.00	Subsequent myocardial infarction of unspecified site
46276	G381.00	Postoperative transmural myocardial infarction inferior wall
47637	Gyu3300	[X]Other forms of chronic ischaemic heart disease
50372	14AH.00	H/O: Myocardial infarction in last year
52517	Gyu3.00	[X]Ischaemic heart diseases
52705	3236.00	ECG: lateral infarction
54251	G311z00	Pre-infarction syndrome NOS
54535	G33z100	Stenocardia
55137	G311011	MI - myocardial infarction aborted
55401	3235.00	ECG: subendocardial infarct

57062	14AJ.00	H/O: Angina in last year
59032	323Z.00	ECG: myocardial infarct NOS
59189	G363.00	Ruptured cardiac wall without haemopericard/cur comp fol ac MI
59940	G364.00	Ruptured chordae tendinae/curr comp fol acute myocardial infarct
61072	G311000	Myocardial infarction aborted
61670	889A.00	Diabetes mellitus insulin-glucose infus acute myocardial infarct
62626	G30y100	Acute papillary muscle infarction
63467	G306.00	True posterior myocardial infarction
66388	G33z000	Status anginosus
68357	G31y100	Microinfarction of heart
68401	Gyu3200	[X]Other forms of acute ischaemic heart disease
68748	G38z.00	Postoperative myocardial infarction, unspecified
69474	G365.00	Rupture papillary muscle/current comp following acute myocardial infarct
72562	G353.00	Subsequent myocardial infarction of other sites
95550	8H2V.00	Admit ischaemic heart disease emergency
96838	Gyu3400	[X]Acute transmural myocardial infarction of unspecified site

ICD-10 codes (HES) for identifying CHD from hospital admissions
I20, I21, I22, I23, I24, I25, Z95.5

OPCS 4.6 codes (HES) for identifying CHD from revascularization procedures
K40, K41, K42, K43, K44, K45, K46, K47.1, K49, K50, K75

Supplemental Table II Number (proportion) of people with missing data on risk factors, by sex

Variables	**All** n=143,702	**Men** [n=80,624 (56.1)]	**Women** [n=63,078 (43.9)]
Low density lipoprotein cholesterol (mmol/L)	90,116 (62.7)	50,108 (62.2)	40,008 (63.4)
High density lipoprotein cholesterol (mmol/L)	78,312 (54.5)	43,420 (53.9)	34,892 (55.3)
Body mass index (kg/m^2)	72,224 (50.3)	41,098 (51.0)	31,126 (49.4)
Total cholesterol (mmol/L)	62,517 (43.5)	34,655 (43.0)	27,862 (44.2)
Diastolic blood pressure (mmHg)	25,155 (17.5)	16,347 (20.3)	8,808 (14.0)
Systolic blood pressure (mmHg)	25,121 (17.5)	16,337 (20.3)	8,784 (13.9)

Supplemental Table III Differences in characteristics between those with and without missing data, by sex

	Men			Women		
	Without missing data	**With missing data** *	***p*-value**	**Without missing data**	**With missing data** *	***p*-value**
Number (proportion, %)	20,336 (25.2)	60,288 (74.8)		15,558 (24.7)	47,520 (75.3)	
Age (years)	65 (56 – 75)	67 (58 – 75)	0.0001	70 (62 – 78)	74 (63 – 82)	0.0001
Ethnicity			<0.001			<0.001
Asian	944 (4.6)	1,258 (2.1)		641 (4.1)	707 (1.5)	
Black	191 (0.9)	313 (0.5)		206 (1.3)	249 (0.5)	
Mixed	70 (0.3)	139 (0.2)		60 (0.4)	92 (0.2)	
Other	225 (1.1)	502 (0.8)		174 (1.1)	273 (0.6)	
White	18,193 (89.5)	54,651 (90.7)		14,058 (90.4)	43,334 (91.2)	
Unknown	713 (3.5)	3,425 (5.7)		419 (2.7)	2,865 (6.0)	
Index of Multiple Deprivation			<0.001			<0.001
1 (Least deprived)	4,781 (23.5)	13,181 (21.9)		3,093 (19.9)	9,218 (19.4)	
2	4,407 (21.7)	13,556 (22.5)		3,224 (20.7)	10,225 (21.5)	
3	4,066 (20.0)	12,897 (21.4)		3,080 (19.8)	10,216 (21.5)	
4	3,742 (18.4)	10,765 (17.9)		3,152 (20.3)	9,149 (19.3)	
5 (Most deprived)	3,319 (16.3)	9,803 (16.3)		3,000 (19.3)	8,632 (18.2)	
Unknown	21 (0.1)	86 (0.1)		9 (0.1)	80 (0.2)	
Current smokers	3,919 (19.3)	13,745 (22.8)	<0.001	2,569 (16.5)	7,517 (15.8)	0.04
Alcohol problem	759 (3.7)	1,841 (3.1)	<0.001	260 (1.7)	596 (1.3)	<0.001
Comorbidities						
Atrial fibrillation	1,875 (9.2)	4,147 (6.9)	<0.001	1,415 (9.1)	3,849 (8.1)	<0.001
Cancer	3,070 (15.1)	6,884 (11.4)	<0.001	2,303 (14.8)	6,054 (12.7)	<0.001
Chronic kidney disease	2,583 (12.7)	2,962 (4.9)	<0.001	2,823 (18.2)	3,976 (8.4)	<0.001
COPD	1,658 (8.2)	3,644 (6.0)	<0.001	1,219 (7.8)	2,921 (6.2)	<0.001
Depression	3,330 (16.4)	7,715 (12.8)	<0.001	4,356 (28.0)	10,566 (22.2)	<0.001
Diabetes mellitus	6,646 (32.7)	4,757 (7.9)	<0.001	4,667 (30.0)	3,791 (8.0)	<0.001
Type-1 diabetes	458 (2.3)	440 (0.7)	<0.001	327 (2.1)	390 (0.8)	<0.001
Type-2 diabetes	5,996 (29.5)	3,412 (5.7)	<0.001	4,201 (27.0)	2,629 (5.5)	<0.001

Dyslipidaemia	4,036 (19.9)	5,300 (8.8)	<0.001	3,527 (22.7)	4,440 (9.3)	<0.001
Family history of coronary heart disease	4,668 (23.0)	9,349 (15.5)	<0.001	4,203 (27.0)	8,308 (17.5)	<0.001
Family history of cardiovascular disease	5,995 (29.5)	11,957 (19.8)	<0.001	5,341 (34.3)	10,920 (23.0)	<0.001
Hypertension	11,778 (57.9)	19,758 (32.8)	<0.001	10,095 (64.9)	20,862 (43.9)	<0.001
Hypothyroidism	725 (3.6)	1,377 (2.3)	<0.001	2,283 (14.7)	4,769 (10.0)	<0.001
Lupus erythematosus	17 (0.1)	60 (0.1)	0.525	71 (0.5)	176 (0.4)	0.136
Migraine	804 (4.0)	1,972 (3.3)	<0.001	1,553 (10.0)	3,468 (7.3)	<0.001
Moderate-severe liver disease	96 (0.5)	154 (0.3)	<0.001	81 (0.5)	121 (0.3)	<0.001
Rheumatoid arthritis	248 (1.2)	715 (1.2)	0.703	389 (2.5)	1,224 (2.6)	0.605
Severe mental illness	244 (1.2)	414 (0.7)	<0.001	243 (1.6)	470 (1.0)	<0.001
Transient ischaemic attack	807 (4.0)	1,727 (2.9)	<0.001	792 (5.1)	1,833 93.9)	<0.001
Drug prescription						
Anti-arrhythmic	903 (4.4)	2,445 (4.1)	0.017	1,008 (6.5)	2,990 (6.3)	0.406
Anti-coagulant	1,424 (7.0)	3,145 (5.2)	<0.001	1,062 96.8)	2,798 (5.9)	<0.001
Anti-depressant	3,642 (17.9)	8,603 (14.3)	<0.001	4,997 (32.1)	12,897 (27.1)	<0.001
Anti-diabetic	5,462 (26.9)	3,809 (6.3)	<0.001	3,777 (24.3)	3,122 (6.6)	<0.001
Anti-epileptic	1,392 (6.9)	3,220 (5.3)	<0.001	1,566 (10.1)	3,568 (7.5)	<0.001
Anti-hypertensive	14,097 (69.3)	25,641 (42.5)	<0.001	11,689 (75.1)	25,753 (54.2)	<0.001
Antiplatelets	9,039 (44.5)	16,326 (27.1)	<0.001	7,140 (45.9)	15,294 (32.2)	<0.001
Beta-blockers	6,384 (31.4)	13,719 (22.8)	<0.001	5,662 (36.4)	13,927 (29.3)	<0.001
Corticosteroid	2,196 (10.8)	5,364 (8.9)	<0.001	2,489 (16.0)	6,492 (13.7)	<0.001
Diuretics	6,429 (31.6)	13,640 (22.6)	<0.001	7,421 (47.7)	20,395 (42.9)	<0.001
Statin			<0.001			<0.001
Low intensity	1,172 (5.8)	1,806 (3.0)		1,154 (7.4)	1,678 (3.5)	
Moderate intensity	7,992 (39.3)	8,954 (14.9)		5,743 (36.9)	6,642 (14.0)	
High intensity	2,365 (11.6)	2,172 (3.6)		1,851 (11.9)	1,642 (3.5)	

* Individuals included in the "with missing data" group had missing data on at least one of the risk factors: body mass index, systolic and diastolic blood pressures, HDL cholesterol, LDL cholesterol or total cholesterol

Supplemental Table IV Age-adjusted prevalence rate for comorbidities, risk factors and prescribed medications

Characteristics	**Men,** n (%) 80,624 (56.1)	**Women,** n (%) 63,078 (43.9)
Age (years), Median (IQR)	66 (56 – 75)	73 (63 – 81)
Age (years), Mean (SD)	65.6 (12.9)	71.4 (13.3)
Comorbidities and risk factors		
Atrial fibrillation	8.5 (8.3 – 8.7)	7.2 (7.0 – 7.4)
Cancer	14.1 (13.8 – 14.3)	12.1 (11.8 – 12.3)
Chronic kidney disease	8.2 (8.0 – 8.4)	9.3 (9.1 – 9.5)
COPD	7.2 (7.0 – 7.4)	6.3 (6.1 – 6.5)
Depression	13.0 (12.8 – 13.2)	25.6 (25.3 – 26.0)
Diabetes mellitus	14.4 (14.1 – 14.6)	13.5 (13.2 – 13.8)
Type-1 diabetes	1.1 (1.0 – 1.1)	1.3 (1.1 – 1.3)
Type-2 diabetes	11.9 (11.7 – 12.2)	10.8 (10.6 – 11.1)
Dyslipidaemia	11.2 (10.9 – 11.4)	12.9 (12.6 – 13.1)
Family history of coronary heart disease	16.3 (16.0 – 16.5)	21.7 (21.3 – 22.0)
Family history of cardiovascular disease	21.0 (20.8 – 21.3)	27.7 (27.4 – 28.1)
Hypertension	40.6 (40.3 – 40.9)	46.9 (46.5 – 47.3)
Hypothyroidism	2.8 (2.7 – 2.9)	10.9 (10.6 – 11.1)
Lupus erythematosus	0.1 (0.1 – 0.1)	0.4 (0.3 – 0.5)
Migraine	3.2 (3.1 – 3.3)	9.1 (8.8 – 9.3)
Moderate-severe liver disease	0.3 (0.2 – 0.3)	0.3 (0.3 – 0.4)
Rheumatoid arthritis	1.2 (1.2 – 1.3)	2.5 (2.4 – 2.6)
Severe mental illness	0.8 (0.7 – 0.8)	1.1 (1.1 – 1.3)
Transient ischaemic attack	3.6 (3.5 – 3.7)	3.6 (3.5 – 3.8)
Medication prescriptions		
Anti-arrhythmic	4.3 (4.1 – 4.4)	6.3 (6.1 – 6.5)
Anti-coagulant	6.2 (6.0 – 6.4)	5.6 (5.5 – 5.8)
Anti-depressant	15.0 (14.7 – 15.2)	29.6 (29.3 – 30.0)
Anti-diabetic	11.6 (11.4 – 11.8)	11.2 (10.9 – 11.5)
Anti-epileptic	5.6 (5.5 – 5.8)	8.7 (8.5 – 8.9)
Anti-hypertensive	50.4 (50.1 – 50.8)	58.1 (57.7 – 58.5)
Antiplatelets	33.0 (32.6 – 33.3)	34.1 (33.8 – 34.5)
Beta-blockers	25.2 (24.8 – 25.5)	30.8 (30.5 – 31.2)
Corticosteroid	9.9 (9.7 – 10.1)	14.2 (13.9 – 14.5)
Diuretics	27.4 (27.0 – 27.7)	40.7 (40.3 – 41.1)
Low-intensity statin	3.7 (3.6 – 3.9)	4.5 (4.3 – 4.7)
Moderate-intensity statin	20.8 (20.5 – 21.1)	20.0 (19.6 – 20.3)
High-intensity statin	5.4 (5.2 – 5.5)	5.9 (5.7 – 6.1)

Age-adjusted prevalence presented as proportion (%) with 95% confidence interval.

IQR: inter-quartile range; SD: standard deviation

Supplemental Table V Incidence of first subsequent major adverse outcomes occurring after 30 days of incident coronary heart disease (n = 136,326).

	Median time to outcome (years)	**Cases**	**Person-years** *	**Incidence rate** (per 100 person-years)	**Adjusted incidence rate ratio** †
MACE (All)	0.88 (0.24 – 3.28)	76,571	4,500	17.06 (16.94 – 17.18)	
Men	0.69 (0.22 – 2.83)	45,945	2,300	19.62 (19.44 – 19.80)	Reference
Women	1.20 (0.30 – 3.92)	30,626	2,100	14.26 (14.10 – 14.42)	0.66 (0.65 – 0.67)
Coronary heart disease (All)	0.58 (0.21 – 2.25)	52,946	4,800	11.03 (10.94 – 11.13)	
Men	0.51 (0.19 – 1.97)	34,434	2,500	13.70 (13.54 – 13.82)	Reference
Women	0.79 (0.24 – 2.75)	18,512	2,300	8.11 (8.00 – 8.23)	0.59 (0.58 – 0.60)
Stroke (All)	2.93 (1.02 – 6.18)	6,196	7,500	0.83 (0.81 – 0.85)	
Men	2.82 (0.95 – 6.04)	2,806	4,300	0.65 (0.63 – 0.68)	Reference
Women	3.03 (1.08 – 6.27)	3,390	3,200	1.07 (1.03 – 1.10)	1.20 (1.14 – 1.26)
Peripheral arterial disease (All)	2.22 (0.68 – 5.31)	1,864	7,500	0.25 (0.24 – 0.26)	
Men	2.12 (0.62 – 5.21)	1,084	4,300	0.25 (0.24 – 0.27)	Reference
Women	2.47 (0.77 – 5.42)	780	3,200	0.24 (0.23 – 0.26)	0.82 (0.74 – 0.90)
Heart failure (All)	1.32 (0.33 – 4.30)	8,791	7,400	1.19 (1.17 – 1.22)	
Men	1.09 (0.28 – 3.98)	4,415	4,200	1.04 (1.01 – 1.07)	Reference
Women	1.58 (0.38 – 4.65)	4,376	3,100	1.39 (1.35 – 1.44)	0.94 (0.90 – 0.98)
Cardiovascular mortality (All)	2.47 (0.57 – 5.93)	6,774	7,600	0.89 (0.86 – 0.91)	
Men	2.42 (0.60 – 5.89)	3,206	4,400	0.73 (0.71 – 0.76)	Reference
Women	2.52 (0.54 – 5.94)	3,568	3,300	1.08 (1.06 – 1.13)	0.89 (0.85 – 0.94)
All-cause mortality (All)	2.98 (0.85 – 6.59)	25,622	7,900	3.26 (3.22 – 3.30)	
Men	2.83 (0.81 – 6.40)	12,093	4,500	2.70 (2.65 – 2.75)	Reference
Women	3.12 (0.91 – 6.80)	13,529	3,400	4.00 (3.93 – 4.07)	0.92 (0.90 – 0.95)

* 100 person-years at risk; All – both men and women; Follow-up time: median follow-up time in years reported with interquartile range.

† Incident rate ratio adjusted for age (continuous variable) and index of multiple deprivation (socioeconomic status).

Supplemental Table VI Risk of first subsequent major adverse outcomes occurring after 30 days of incident coronary heart disease for women compared to men (reference category). n = 136,326

	Traditional Cox model Hazard ratio (95% CI)	**Competing risks model** * Sub-hazard ratio (95% CI)
Full adjusted models		
Major adverse cardiovascular event	0.70 (0.69 – 0.71)	0.71 (0.70 – 0.72)
Coronary heart disease	0.63 (0.62 – 0.64)	0.64 (0.63 – 0.65)
Stroke	1.21 (1.15 – 1.28)	1.27 (1.20 – 1.34)
Peripheral vascular disease	0.84 (0.77 – 0.93)	0.87 (0.78 – 0.96)
Heart failure	1.01 (0.96 – 1.05)	1.04 (0.99 – 1.08)
Cardiovascular-related death	0.94 (0.89 – 0.99)	0.99 (0.94 – 1.04)
All-cause mortality	1.01 (0.98 – 1.04)	1.08 (1.05 – 1.11)

* Fine and Gray method for sub-distribution regression with competing risks[26]

Models adjusted for age, (continuous variable), socioeconomic status, smoking status, body mass index, blood pressure, total cholesterol level, history of alcohol problem, diabetes mellitus, dyslipidaemia, cancer, chronic kidney disease, hypertension, atrial fibrillation, depression, and a family history of cardiovascular disease.

Supplemental Table VII Risk of first subsequent major adverse outcomes by time of incident CHD diagnosis (1998-2007 vs 2008-2017), for women compared to men (reference category).

	1998 – 2007 (n=77,586) Hazard ratio (95% CI)	**2008 – 2017** (n=66,116) Hazard ratio (95% CI)
Full adjusted Cox models		
Major adverse cardiovascular event	0.67 (0.66 – 0.69)	0.67 (0.65 – 0.68)
Coronary heart disease	0.61 (0.60 – 0.62)	0.60 (0.58 – 0.61)
Stroke	1.30 (1.21 – 1.40)	1.20 (1.09 – 1.31)
Peripheral vascular disease	0.94 (0.83 – 1.07)	0.88 (0.74 – 1.06)
Heart failure	1.10 (1.03 – 1.17)	1.09 (1.01 – 1.17)
Cardiovascular-related death	0.96 (0.91 – 1.01)	1.03 (0.96 – 1.11)
All-cause mortality	1.02 (0.99 – 1.05)	1.09 (1.05 – 1.13)

Models adjusted for age, (continuous variable), socioeconomic status, smoking status, body mass index, blood pressure, total cholesterol level, history of alcohol problem, diabetes mellitus, dyslipidaemia, cancer, chronic kidney disease, hypertension, atrial fibrillation, depression, and a family history of cardiovascular disease.

Supplemental Table VIII Risk of first subsequent major adverse outcomes in individuals with incident myocardial infarction diagnosis (n=61,167), for women compared to men (reference category).

	Traditional Cox model Hazard ratio (95% CI)
Major adverse cardiovascular event (n=49,127)	0.79 (0.77 – 0.80)
Coronary heart disease (n=38,904)	0.74 (0.72 – 0.76)
Stroke (n=1,706)	1.35 (1.22 – 1.50)
Peripheral vascular disease (n=534)	0.95 (0.79 – 1.14)
Heart failure (n=3,264)	1.21 (1.12 – 1.30)
Cardiovascular-related death (n=4,719)	1.10 (1.03 – 1.17)
All-cause mortality (n=10,284)	1.17 (1.12 – 1.22)