Sex disparity in subsequent outcomes in survivors of coronary heart disease

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Short title: Sex disparities in subsequent outcomes after first CHD

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Total word count: Abstract – 250; Main text – 3,000

Number of Figures: 3; number of Tables: 3

This article has been accepted for publication in [Heart, 2021] following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/heartjnl-2021-319566

ABSTRACT

Objective: Evidence on sex differences in outcomes after developing 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 1-1-1998 and 31-12-2017 with no prior history of MACE. MACE outcome was a composite of recurrent CHD, stroke, peripheral vascular disease (PVD), 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 for MACE [hazard ratio (HR), 0.68 (95% CI 0.67-0.69); sub-hazard ratio (HRsd), 0.71 (0.70-0.72), respectively] and recurrent CHD (n=66,543, 46.3%), [HR, 0.60 (0.59-0.61); HRsd, 0.62 (0.61-0.63)] when compared with men after incident CHD. However, women had a significantly higher risk of stroke (n=5,740, 4.0%), [HR, 1.26 (1.19-1.33); HRsd, 1.32 (1.25-1.39)], heart

failure (n=7,905, 5.5%), [HR, 1.09 (1.04-1.15); HRsd, 1.13 (1.07-1.18)], and all-cause mortality (n=29,503, 20.5%), [HR,1.05 (1.02-1.07); HRsd, 1.11 (1.08-1.13)].

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.

Keywords: Coronary heart disease; major adverse cardiovascular events; secondary prevention; sex difference; competing risks

RESEARCH IN CONTEXT

What is already known about this subject?

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

What does this study add?

- Evidence on sex differences in first subsequent, composite major adverse cardiovascular events (MACE) 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.

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 sub-types, 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 MACE (recurrent CHD, stroke, peripheral vascular disease, heart failure, and cardiovascular-related mortality) after incident CHD.

In this population-based cohort study we used multiple databases of electronic health records from primary care consultations, secondary care (hospital admissions and procedure-level data), and the national death registry, 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 CPRD GOLD database of anonymised longitudinal primary care electronic health records,[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 (Index of Multiple Deprivation (IMD) 2015).[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. This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (Protocol number 19_023R).

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 12 months of their current registration period[16], the practice was deemed to be contributing 'up-to-standard' data – 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] – Supplemental Table I for codes used in identifying both incident and outcome events. Individuals with a prior history of any stroke, peripheral vascular disease (PVD) or heart failure before incident CHD were excluded. The study flow diagram is presented in Supplemental Figure I.

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 International Classification of Diseases, tenth revision (ICD-10) codes and Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) 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, the English Index of Multiple Deprivation 2015[15] linked to the individual's residential postcode was used. IMD is a weighted mean across the seven domains, hence offers a single score to describe the concept of deprivation; categorised into quintiles (quintile 1 – least deprived group to quintile 5 – most deprived group). Medication prescriptions (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 chi-squared 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 to 62.7% for LDL-C. Details on the proportion of missingness and differences in characteristics between those with and without missing data are provided in the Supplemental Tables II and III. To estimate missing values for BMI, systolic and diastolic blood pressures, HDL-C, LDL-C and total cholesterol levels, multiple imputation by chained equations was used to generate 10 imputed datasets using all the other available patient variables, and all the outcomes.[20] The imputed datasets were pooled into a single dataset 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% confidence intervals (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 hazard ratios from Cox proportional hazard regression models were used to analyse the time-to-event outcomes. Competing-risk analysis, which provides the cause-specific (or sub-) hazard ratio, was used to calculate the cumulative incidence of the outcomes. The method proposed by Fine and Gray[22] was used to estimate association of sex with the sub-hazard 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, socioeconomic status (SES), smoking status, BMI,

blood pressure (diastolic and systolic), total cholesterol level, history of alcohol problem, diabetes mellitus (DM), dyslipidaemia, cancer, chronic kidney disease (CKD), hypertension, atrial fibrillation (AF), depression and a family history of cardiovascular disease (Model 2). The composite MACE outcome was further analysed using a win-ratio approach,[23] first described by Finkelstein and Schoenfeld,[24] which prioritizes fatal outcome(s) (that is, cardiovascular-related death) over less severe or non-fatal outcomes (that is, 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 version 16.1 (StataCorp LP) and R version 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 was 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. 22,366 of these individuals 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 (interquartile range (IQR): 8.4-17.7 years). The cohort comprised 63,078 (43.9%) women and were older than the men (median age of 73 vs 66 years, $p \leq 0.001$). Detailed descriptive characteristics for the study cohort presented by sex are presented in Table 1.

After adjustment for age, women had a higher prevalence of the following comorbidities and known risk factors at time of incident CHD when compared to men: chronic kidney disease (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 incident CHD, women had a higher number of prescriptions for anti-arrhythmic, anti-depressant, anti-epileptic, anti-hypertensive, anti-platelet, beta-blockers, corticosteroid, diuretics, and both low- and high-intensity statins, after adjusting for age. Supplemental Table IV 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 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; 5,740 (4.0%) strokes; 1,624 (1.1%) PVD; 7,905 (5.5%) heart failure; 9,894 (6.9%) cardiovascular death; and 29,503 (20.5%) all-cause death, occurring after the incident CHD events. Figure 2 and Supplemental Figure II 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: 25.02–25.34), with a higher incidence rate in men compared to 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 to men, the age- and SES-adjusted sex-specific IRR for MACE was 0.58 (0.57–0.59), for recurrent CHD 0.52 (0.51–0.53), stroke: 1.22 (1.16–1.29), PVD: 0.88 (0.80–0.97), heart failure: 1.00 (0.96–1.05), CVD-related death: 0.89 (0.85–0.93), and 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 [hazard ratio (HR), 0.68 (95% CI 0.67-0.69); sub-hazard ratio (HRsd), 0.71 (95% CI 0.70-0.72), respectively] and recurrent CHD [HR, 0.60 (95% CI 0.59-0.61); HRsd, 0.62 (95% CI 0.61-0.63)] when compared with men after incident CHD. Women, however, had a significantly higher risk of any stroke [HR, 1.26 (95% CI 1.19-1.33); HRsd, 1.32 (95% CI 1.25-1.39)], heart failure [HR, 1.09 (95% CI 1.04-1.15); HRsd, 1.13 (95% CI 1.07-1.18)], and all-cause mortality [HR,1.05 (95% CI 1.02-1.07); HRsd, 1.11 (95% CI 1.08-1.13)].

The cumulative incidence function (CIF) [Figure 2 and Supplemental Figure III] and Kaplan-Meier curves (Figure 3 and Supplemental Figure IV) as well as the adjusted Kaplan-Meier cumulative incidence curves (Supplemental Figure V) 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 to the non-fatal outcomes (recurrent CHD, stroke, PVD, and heart failure), the win ratio was 1.331 (95% CI 1.329-1.331).

Sensitivity analysis

For the sensitivity analysis, 7,566 (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, Supplemental Table V. After full adjustment, in both Cox and competing risks models (Supplemental Table VI) women had a significantly lower risk of first subsequent MACE [HR, 0.70 (95% CI 0.69-0.71); sub-hazard ratio (HRsd), 0.71 (95% CI 0.70-0.72), respectively] and recurrent CHD [HR, 0.63 (95% CI 0.62-0.64); HRsd, 0.64 (95% CI 0.63-0.65)] when compared with men after incident CHD. Women, however, had a significantly higher risk of any stroke [HR, 1.21 (95% CI 1.15-1.28); HRsd, 1.27 (95% CI 1.20-1.34)] and all-cause mortality [HR,1.01 (95% CI 0.98-1.04); HRsd, 1.08 (95% CI 1.05-1.11)]. Similar sex differences were observed when the analysis was done by incident CHD time period (1998-2007 and 2008-2017) – Supplemental Table VII and when the analysis was restricted to 61,167 individuals with incident myocardial infarction – Supplemental Table VIII.

DISCUSSION

Within a population-based cohort, we show there are sex disparities in the risk of developing first subsequent major adverse cardiovascular event (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 to 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 are multifaceted, relating to differences in baseline cardiovascular profile, access to care, use of resources and evidence-based guidelines, 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 3,779 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 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 was 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 (e.g., death from non-cardiovascular cause) hinders or changes the possibility of observing the outcome of interest (e.g., death from cardiovascular-related death). Koller et al, found a large majority of clinical studies neglected the competing risks process despite the studies having populations susceptible to competing risks.[29] 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, the size and representativeness of the CPRD GOLD dataset[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 electronic health records (EHRs). These including 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 sub-typing of CHD in both primary care (CPRD GOLD) and secondary care (HES) databases are not reliable;[34] hence unable to assess differences for CHD sub-types. The use of 'softer' CHD codes in primary care data is yet to be validated.[35]

Conclusions

Coronary heart disease 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 for women when compared with men. However, there was a higher risk for 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.

Acknowledgements

We thank the practices that contributed to the CPRD GOLD.

Source of funding

RKA is funded by a National Institute for Health Research School for Primary Care Research (NIHR SPCR) PhD Studentship award, supervised by JK, FWA, and NQ. The views expressed are those of the authors and not necessarily those of the NIHR, the NHS, or the Department of Health and Social Care.

Disclosures

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 & Lipid Modification Guideline Development Groups (CG71 & CG181). NQ and SW have previously received honorarium from AMGEN. RSP has funding from 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.

Contributions

RKA, SFW, 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 guarantor.

Data availability

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

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TABLES

Table 1. **Descriptive characteristics of study population**

Characteristics	**Total number** (%)	**Men** n (%)	**Women** n (%)	***p*-value**
	143,702 (100)	**80,624 (56.1)**	**63,078 (43.9)**	
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	3,550 (2.5)	2,202 (2.7)	1,348 (2.1)	
Black	959 (0.7)	504 (0.6)	455 (0.7)	
Mixed	361 (0.3)	209 (0.3)	152 (0.2)	
Other	1,174 (0.8)	727 (0.9)	447 (0.7)	
White	130,236 (90.6)	72,844 (90.4)	57,392 (91.0)	
Unknown	7,422 (5.2)	4,138 (5.1)	3,284 (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	3,456 (2.4)	2,600 (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 (mmHg)	80 (74 – 85)	80 (75 – 85)	80 (72 – 84)	0.0001
Systolic blood pressure (mmHg)	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)	6,022 (7.5)	5,264 (8.4)	<0.001
Cancer	18,311 (12.7)	9,954 (12.4)	8,357 (13.3)	<0.001
Chronic kidney disease	12,344 (8.6)	5,545 (6.9)	6,799 (10.8)	<0.001
COPD	9,442 (6.6)	5,302 (6.6)	4,140 (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)	8,458 (13.4)	<0.001
Type-1 diabetes	1,615 (1.1)	898 (1.1)	717 (1.1)	0.683
Type-2 diabetes	16,238 (11.3)	9,408 (11.7)	6,830 (10.8)	<0.001
Dyslipidaemia	17,303 (12.0)	9,336 (11.6)	7,967 (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	9,154 (6.4)	2,102 (2.6)	7,052 (11.2)	<0.001
Lupus erythematosus	324 (0.2)	77 (0.1)	247 (0.4)	<0.001
Migraine	7,797 (5.4)	2,776 (3.4)	5,021 (8.0)	<0.001
Moderate-severe liver disease	452 (0.3)	250 (0.3)	202 (0.3)	0.733
Rheumatoid arthritis	2,576 (1.8)	963 (1.2)	1,613 (2.6)	<0.001
Severe mental illness	1,371 (1.0)	658 (0.8)	713 (1.1)	<0.001
Transient ischaemic attack	5,159 (3.6)	2,534 (3.1)	2,625 (4.2)	<0.001
Drug prescription				
Anti-arrhythmic	7,346 (5.1)	3,348 (4.2)	3,998 (6.3)	<0.001
Anti-coagulant	8,429 (5.9)	4,569 (5.7)	3,860 (6.1)	<0.001
Anti-depressant	30,139 (21.0)	12,245 (15.2)	17,894 (28.4)	<0.001
Anti-diabetic	16,170 (11.3)	9,271 (11.5)	6,899 (10.9)	0.001
Anti-epileptic	9,746 (6.8)	4,612 (5.7)	5,134 (8.1)	<0.001
Anti-hypertensive	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)	7,560 (9.4)	8,981 (14.2)	<0.001
Diuretics	47,885 (33.3)	20,069 (24.9)	27,816 (44.1)	<0.001
Statin				<0.001
Low intensity	5,810 (4.0)	2,978 (3.7)	2,832 (4.5)	
Moderate intensity	29,331 (20.4)	16,946 (21.0)	12,385 (19.6)	
High intensity	8,030 (5.6)	4,537 (5.6)	3,493 (5.5)	
Intervention				
Percutaneous coronary intervention	1,969 (1.4)	1,488 (1.9)	481 (0.8)	<0.001

CHD: coronary heart disease; n: total number; %: percentage/proportion; COPD: chronic obstructive pulmonary disease; HDL: high density lipoprotein; LDL: low density lipoprotein; MACE: major adverse cardiovascular event; NOS: not otherwise specified.

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	3,600	25.18 (25.02 – 25.34)	
Men	0.13 (0.02 – 1.04)	55,087	1,800	31.03 (30.77 – 31.29)	Reference
Women	0.31 (0.04 – 2.47)	36,619	1,900	19.62 (19.42 – 19.82)	0.58 (0.57 – 0.59)
Coronary heart disease (All)	0.11 (0.02 – 0.81)	66,543	3,900	16.87 (16.74 – 17.00)	
Men	0.09 (0.02 – 0.58)	43,238	1,900	22.29 (22.08 – 22.50)	Reference
Women	0.17 (0.03 – 1.29)	23,305	2,000	11.63 (11.48 -11.78)	0.52 (0.51 – 0.53)
Stroke (All)	2.54 (0.63 – 5.83)	5,740	7,500	0.77 (0.75 – 0.79)	
Men	2.33 (0.52 – 5.56)	2,546	4,300	0.60 (0.57 – 0.61)	Reference
Women	2.75 (0.71 – 6.07)	3,194	3,200	1.00 (0.97 – 1.04)	1.22 (1.16 – 1.29)
Peripheral arterial disease (All)	1.83 (0.35 – 4.88)	1,624	7,500	0.22 (0.21 – 0.23)	
Men	1.71 (0.35 – 4.68)	901	4,300	0.21 (0.19 – 0.22)	Reference
Women	1.95 (0.34 – 5.20)	723	3,200	0.23 (0.21 – 0.24)	0.88 (0.80 – 0.97)
Heart failure (All)	0.95 (0.14 – 3.83)	7,905	7,400	1.07 (1.05 – 1.09)	
Men	0.73 (0.11 – 3.54)	3,823	4,300	0.90 (0.87 – 0.93)	Reference
Women	1.22 (0.19 – 4.11)	4,082	3,100	1.30 (1.26 – 1.34)	1.00 (0.96 – 1.05)
Cardiovascular mortality (All)	0.20 (0.02 – 3.13)	9,894	7,600	1,29 (1.27 – 1.32)	
Men	0.21 (0.-2 – 3.06)	4,579	4,400	1.04 (1.02 – 1.08)	Reference
Women	0.19 (0.02 – 3.22)	5,315	3,300	1.63 (1.59 – 1.67)	0.89 (0.85 – 0.93)
All-cause mortality (All)	1.37 (0.08 – 5.07)	29,503	7,800	3.77 (3.73 – 3.82)	
Men	1.20 (0.07 – 4.78)	13,668	4,500	3.07 (3.02 – 3.12)	Reference
Women	1.54 (0.08 – 5.34)	15,835	3,400	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 interquartile range.

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

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

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

* Fine and Gray method for sub-distribution 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.

FIGURES