Original research

Sex disparity in subsequent outcomes in survivors of coronary heart disease

Ralph Kwame Akyea ,[1] Evangelos Kontopantelis ,[2] Joe Kai,[1] Stephen F Weng,[1] Riyaz S Patel,[3,4] Folkert W Asselbergs,[3,4,5] Nadeem Qureshi [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2021-319566).

For numbered affiliations see end of article.

Correspondence to
Dr Ralph Kwame Akyea, Primary Care Stratified Medicine, School of Medicine, University of Nottingham, Nottingham, NG7 2RD, UK; Ralph.Akyea1@nottingham.ac.uk

FWA and NQ contributed equally.

Received 22 April 2021
Accepted 3 August 2021
Published Online First 24 August 2021

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.

Linked

► http://dx.doi.org/10.1136/heartjnl-2021-320031

Check for updates

To cite: Akyea RK, Kontopantelis E, Kai J, *et al*. *Heart* 2022;**108**:37–45.

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

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,

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

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);

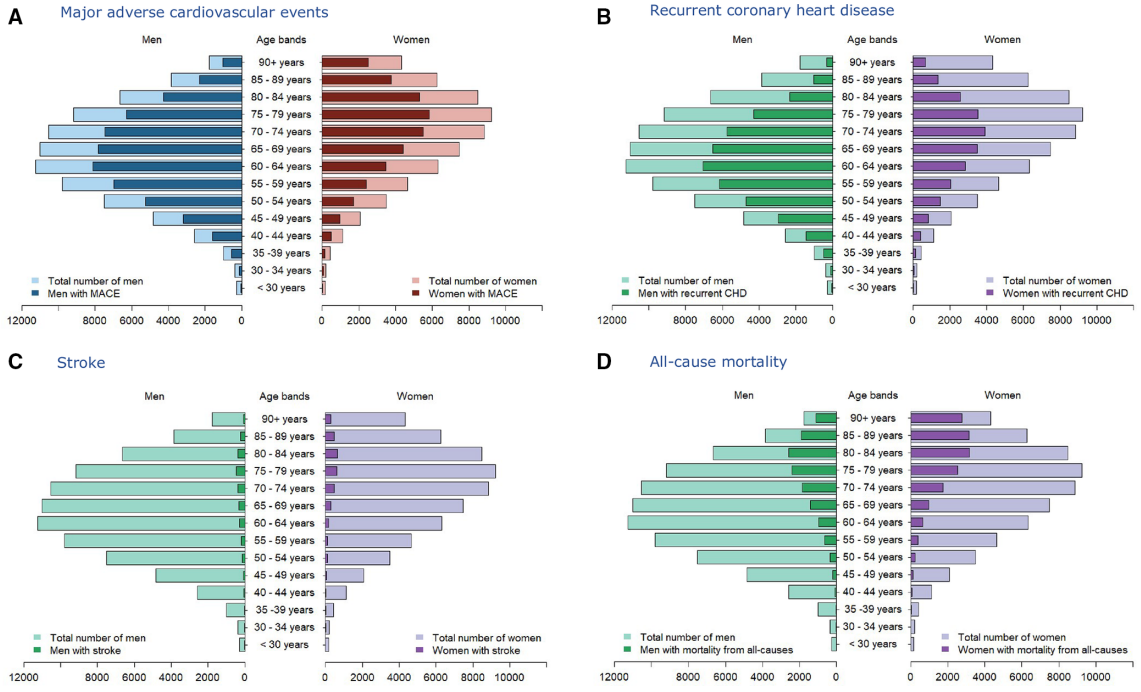

Figure 1 Distribution of first subsequent major adverse outcomes by sex and 5-year age group for patients with incident CHD. CHD, coronary heart disease; MACE, major adverse cardiovascular events.

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,

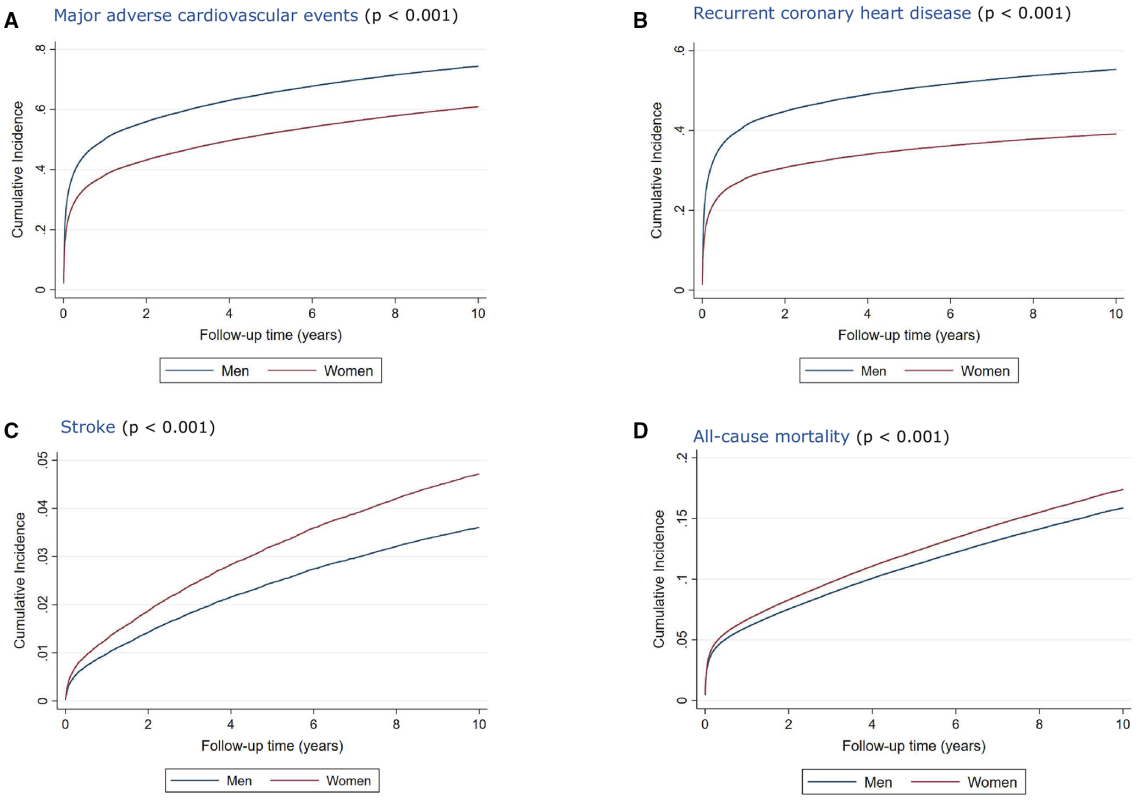

Figure 2 Cumulative incidence function plots for first subsequent major adverse outcomes.

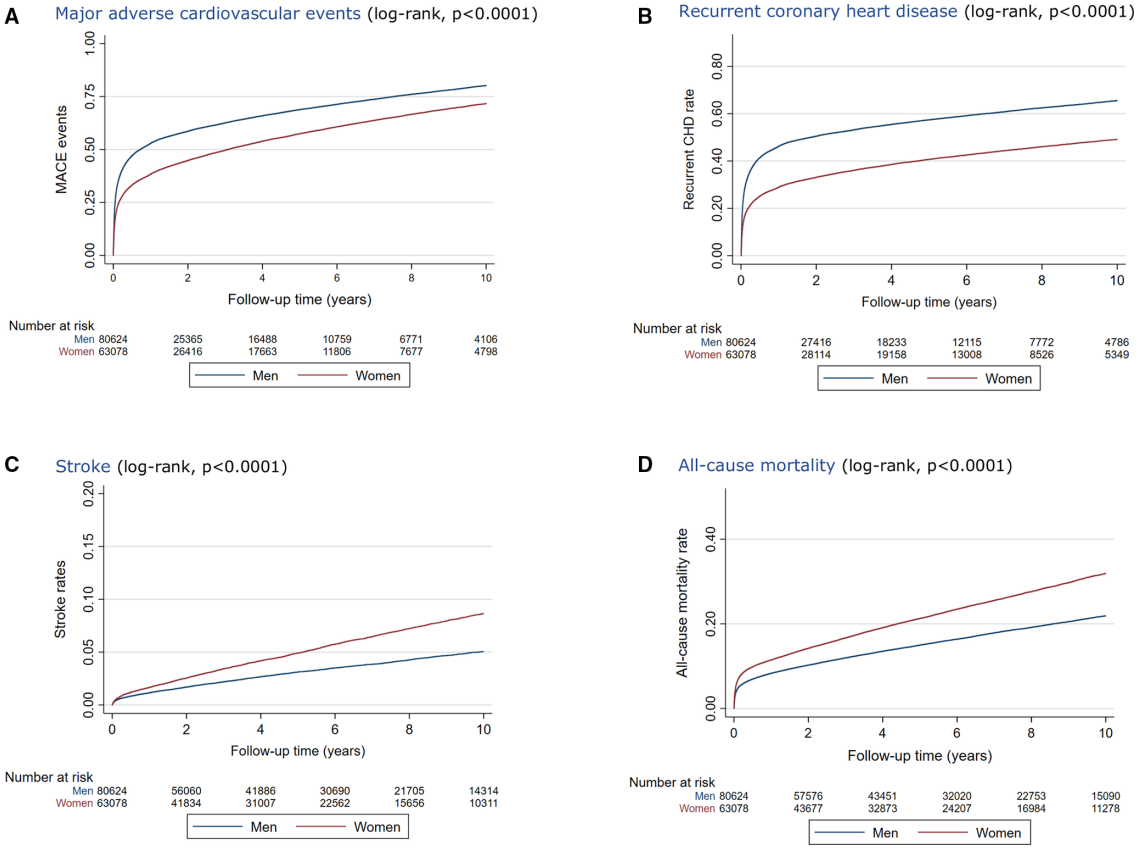

Figure 3 Kaplan-Meier plots for first subsequent major adverse outcomes. CHD, coronary heart disease; MACE, major adverse cardiovascular events.

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.

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.

Author affiliations
[1]Primary Care Stratified Medicine, School of Medicine, University of Nottingham, Nottingham, UK
[2]Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre (MAHSC), The University of Manchester, Manchester, UK
[3]Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, UK
[4]Health Data Research UK and Institute of Health Informatics, University College London, London, UK
[5]Department of Cardiology, Division of Heart and Lungs, University Medical Centre Utrecht, Utrecht, The Netherlands

Twitter Ralph Kwame Akyea @rkakyea, Evangelos Kontopantelis @dataevan, Stephen F Weng @StephenFWeng, Riyaz S Patel @DrRiyazPatel and Folkert W Asselbergs @fwasselbergs

Acknowledgements We thank the practices that contributed to CPRD GOLD.

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.

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.

Disclaimer 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.

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.

ORCID iDs
Ralph Kwame Akyea http://orcid.org/0000-0003-4529-8237
Evangelos Kontopantelis http://orcid.org/0000-0001-6450-5815
Nadeem Qureshi http://orcid.org/0000-0003-4909-0644

REFERENCES

1 Go AS, Mozaffarian D, Roger VL, *et al*. Executive summary: heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 2014;129:399–410.
2 Ford ES, Capewell S. Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. *Annu Rev Public Health* 2011;32:5–22.
3 Benjamin EJ, Blaha MJ, Chiuve SE, *et al*. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 2017;135:e146–603.
4 Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol* 2005;46:1225–8.
5 Canto JG, Rogers WJ, Goldberg RJ, *et al*. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;307:813–22.
6 Khan NA, Daskalopoulou SS, Karp I, *et al*. Sex differences in acute coronary syndrome symptom presentation in young patients. *JAMA Intern Med* 2013;173:1863–71.
7 Hemal K, Pagidipati NJ, Coles A, *et al*. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE trial. *JACC Cardiovasc Imaging* 2016;9:337–46.
8 Steingart RM, Packer M, Hamm P, *et al*. Sex differences in the management of coronary artery disease. *N Engl J Med Overseas Ed* 1991;325:226–30.
9 Daly C, Clemens F, Lopez Sendon JL, *et al*. Gender differences in the management and clinical outcome of stable angina. *Circulation* 2006;113:490–8.
10 Gudnadottir GS, Andersen K, Thrainsdottir IS, *et al*. Gender differences in coronary angiography, subsequent interventions, and outcomes among patients with acute coronary syndromes. *Am Heart J* 2017;191:65–74.
11 Bucholz EM, Butala NM, Rathore SS, *et al*. Sex differences in long-term mortality after myocardial infarction: a systematic review. *Circulation* 2014;130:757–67.
12 Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: clinical practice research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.
13 NHS Digital. Hospital episode statistics (Hes), 2019. Available: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics [Accessed 21 Jun 2019].
14 Office for National Statistics. Deaths registration data. ONS, 2018. Available: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths [Accessed 21 Jun 2019].
15 Department of Communities and Local Government. English indices of deprivation 2015, 2015. Available: https://nottinghaminsight.org.uk/insight/key-datasets/indices-of-multiple-deprivation-2015.aspx [Accessed 10 Jul 2016].
16 Lewis JD, Bilker WB, Weinstein RB, *et al*. The relationship between time since registration and measured incidence rates in the general practice research database. *Pharmacoepidemiol Drug Saf* 2005;14:443–51.
17 Sundaram V, Bloom C, Zakeri R, *et al*. Temporal trends in the incidence, treatment patterns, and outcomes of coronary artery disease and peripheral artery disease in the UK, 2006-2015. *Eur Heart J* 2020;41:1636–49.
18 Kuan V, Denaxas S, Gonzalez-Izquierdo A, *et al*. A chronological map of 308 physical and mental health conditions from 4 million individuals in the English National Health Service. *Lancet Digit Health* 2019;1:e63–77.
19 Mathur R, Bhaskaran K, Chaturvedi N, *et al*. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health* 2014;36:684–92.
20 Royston P. Multiple imputation of missing values: update of ice. *Stata J* 2005;5:527–36.
21 Rubin DB. *Multiple imputation for nonresponse in surveys*. Wiley, 1987.
22 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
23 Pocock SJ, Ariti CA, Collier TJ, *et al*. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J* 2012;33:176–82.
24 Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med* 1999;18:1341–54.
25 Herrett E, Shah AD, Boggon R, *et al*. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ* 2013;346:f2350.
26 Steg PG, Greenlaw N, Tardif J-C, *et al*. Women and men with stable coronary artery disease have similar clinical outcomes: insights from the international prospective CLARIFY registry. *Eur Heart J* 2012;33:2831–40.
27 Aggarwal NR, Patel HN, Mehta LS, *et al*. Sex differences in ischemic heart disease: advances, obstacles, and next steps. *Circ Cardiovasc Qual Outcomes* 2018;11:e004437.

28 Asleh R, Manemann SM, Weston SA, *et al*. Sex differences in outcomes after myocardial infarction in the community. *Am J Med* 2021;134:114–21.
29 Koller MT, Raatz H, Steyerberg EW, *et al*. Competing risks and the clinical community: irrelevance or ignorance? *Stat Med* 2012;31:1089–97.
30 Wolbers M, Koller MT, Witteman JCM, *et al*. Prognostic models with competing risks. *Epidemiology* 2009;20:555–61.
31 Jackson R, Lawes CMM, Bennett DA, *et al*. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet* 2005;365:434–41.
32 Lim E, Brown A, Helmy A, *et al*. Composite outcomes in cardiovascular research: a survey of randomized trials. *Ann Intern Med* 2008;149:612–7.
33 Lester H, Campbell S. Developing Quality and Outcomes Framework (QOF) indicators and the concept of 'QOFability'. *Qual Prim Care* 2010;18:103–9.
34 Alexandrescu R, Bottle A, Jarman B, *et al*. Current ICD10 codes are insufficient to clearly distinguish acute myocardial infarction type: a descriptive study. *BMC Health Serv Res* 2013;13:1–8.
35 Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the general practice research database: a systematic review. *Br J Gen Pract* 2010;60:e128–36.