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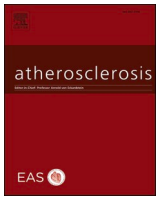

Cardiovascular disease morbidity is associated with social deprivation in subjects with familial hypercholesterolaemia (FH): A retrospective cohort study of individuals with FH in UK primary care and the UK Simon Broome register, linked with national hospital records

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ABSTRACT

Background: Social deprivation is associated with higher cardiovascular disease (CVD) morbidity and mortality. We examined whether this is also observed in people with Familial Hypercholesterolaemia (FH).
Methods: Subjects with FH and linked secondary care records in Hospital Episode Statistics (HES) were identified from UK Clinical Practice Research Datalink (CPRD) and the Simon Broome (SB) adult FH register. Cox proportional hazards regression estimated hazard ratios (HR) for composite CVD outcomes (first HES outcome of coronary heart disease, myocardial infarction, angina, stroke, transient ischaemic attack, peripheral vascular disease, heart failure, coronary revascularisation interventions (PCI and CABG)) in Index of Multiple Deprivation (IMD) quintiles.
Results: We identified 4309 patients with FH in CPRD (1988–2020) and 2956 in the SB register. Both cohorts had considerably fewer subjects in the most deprived compared to the least deprived quintile (60 % lower in CPRD and 52 % lower in SB). In CPRD, the most deprived individuals had higher unadjusted HRs for composite CVD (HR 1.71 [CI 1.22–2.40]), coronary heart disease (HR 1.63 [1.11–2.40]) and mortality (HR 1.58 [1.02–2.47]) compared to the least deprived but these became insignificant after adjusting for age, sex, smoking and alcohol consumption. In the SB register, hazard ratios for composite CVD increased with increasing deprivation quintiles and remained significant after adjustment for age, sex, smoking and alcohol consumption (adjusted HR in quintile 5 vs quintile 1 = 1.83 [1.54–2.17]).
Conclusions: Strikingly fewer individuals with FH are identified from lower socioeconomic groups, though the most deprived FH patients have the highest risk of CVD and mortality. In CPRD, this risk was largely explained by smoking and alcohol consumption, but not in the SB register. More effective strategies to detect FH and optimise risk factor management, are needed in lower socioeconomic groups.

1. Introduction

While it is well known that measures of social deprivation are associated with higher cardiovascular diseases (CVD) morbidity and mortality [1,2], we are unaware of similar analyses to determine if there is a socioeconomic gradient in CVD incidence in subjects with Familial

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Hypercholesterolaemia (FH). FH is a genetic disease, inherited in an autosomal dominant fashion [3] with a prevalence in the UK of around 1 per 250 [4]. Patients with FH have high cholesterol from birth. Their CVD risk is determined by their "LDL-C-burden" [5], which is the sum of their untreated LDL-cholesterol level and the duration it has been high (i.e. their age). Studies from the UK have shown that, if untreated, around 50 % of men with FH will have developed heart disease by the age of 50 years and about 30 % of women by the age of 60 years [6]. However, FH can be managed successfully by taking one of several different cholesterol lowering medications, most commonly a statin. On average, people with FH who are under the management of a lipid clinic have been shown to have the same life expectancy as men and women in the general population [7]. In fact, since people with FH are all advised to have a healthy diet and lifestyle and supported in smoking cessation, they actually have lower rates of certain cancers and fewer other co-morbidities [7].

The 2021 CVD Prevent Audit reported that overall, 0.2 % of the General Practice (GP) population in England has a coded diagnosis of FH [8]. They also noted a 40 % higher prevalence of GP recorded FH in the least deprived quintile compared to the most deprived quintile of the population. While there will be several contributing factors explaining this difference, it is likely that individuals from deprived backgrounds are less likely to attend for the UK National Health Checks programme [9], which for many individuals is the first opportunity for them to have a blood lipid profile measurement. In the current work we have examined CVD morbidity in patients in the UK CPRD primary care database and the UK Simon Broome (SB) adult FH register using linkage to the UK secondary care Hospital Episodes Statistics (HES), in individuals of different socioeconomic status as estimated using the English Index of Multiple Deprivation (IMD) [10].

2. Materials and methods

2.1. Data source and baseline measures

The Simon Broome register includes individuals with FH recruited from 21 participating specialist lipid clinics in the United Kingdom. Recruitment of patients into the register began in 1980, and methods have been described previously [7,11,12]. A fasting blood specimen taken at the registration visit determined serum total cholesterol, triglycerides and high-density lipoprotein cholesterol [7,11,12]. Serum low density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald equation [13]. For the current analysis, patients' records have been linked to Hospital Episodes Statistics (HES) for ascertainment of secondary care inpatient morbidity data including admissions for cardiovascular disease. All patients were followed up from the date of their SB registration until their first hospitalisation for cardiovascular disease, date of death, emigration/loss to follow-up or last date of data collection, whichever occurred first. All patients gave informed consent for inclusion in the Simon Broome register. The study received approval from the local ethics committee of each participating centre, and approvals for obtaining the linked hospital data was approved by NHS digital (DARS ref: NIC-115405) and Confidentiality Advisory Committee (CAG ref: 18/CAG/0007). The overall study obtained ethical approval from NHS Health Research Authority (IRAS ref: 214,219).

The Clinical Practice Research Datalink (CPRD) is a nationally representative database of routine primary care electronic healthcare records of patients in the UK [14]. The database contains data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours and referrals to secondary care. It has a coverage of approximately 15 % of the UK population (approximately 11.3 million patients in CPRD GOLD, June 2020 release) and patients are broadly representative of the UK general population in terms of age, sex and ethnicity [14]. Patients' primary care records from CPRD were linked with their secondary care records from hospital episode statistics (HES) and death registration records from the Office of National Statistics (ONS). Data access and ethical approval was granted by the CPRD Independent Scientific Advisory Committee (Protocol number 20_093) in June 2020.

We identified all individuals aged 18 years or older in CPRD, with a coded diagnosis of FH in their primary care record, and linked secondary care records in HES. Follow-up of these individuals started only after they had contributed one year of records in general practice. All individuals with records of pre-existing cardiovascular disease (defined as recorded diagnoses of coronary heart disease (CHD), myocardial infarction (MI), unstable and stable angina, stroke, transient ischaemic attack (TIA), peripheral vascular disease, heart failure, or any coronary revascularisation procedure - percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)) before the start of the study follow-up, were excluded. Individuals were followed up until first diagnosis of cardiovascular disease (CVD) in secondary care (using HES records). Those who did not develop CVD were followed up until death, transfer out of the practice or study end date, whichever occurred first.

2.2. Measure of socioeconomic deprivation

The measure of socioeconomic status/deprivation used was the English Index of Multiple Deprivation (IMD). The IMD is an area-level weighted composite measure derived from indicators covering different domains of material deprivation – housing, employment, income, access to services, education and skills, crime and living environment [15]. IMD classifies areas into five quintiles based on relative deprivation, with quintile 1 being the least deprived, and quintile 5 being the most deprived.

2.3. Outcome measures

The main outcomes of interest in the study cohort were cardiovascular disease (CVD) and all-cause mortality. Incident CVD events were defined as first hospital admission recorded in HES for coronary heart disease (CHD), stroke, transient ischaemic attack (TIA), peripheral vascular disease, heart failure and coronary revascularisation procedures - percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). CVD was analysed as a composite measure as well as subtypes of CVD, and outcomes were identified from HES using the relevant International Classification of Diseases, 10th revision (ICD-10) and OPCS codes (codes are shown in the supplementary online file). Mortality records were ascertained from the ONS death registry.

2.4. Statistical analyses

Baseline characteristics of patients in the CPRD database and Simon Broome register were reported as counts (percentages), mean (standard deviation) and median (interquartile range) for categorical, continuous normally-distributed and continuous non-normally distributed variables respectively. Within the cohorts studied, the chi-squared test of significance was used to assess differences between categorical variables, while the analysis of variance (ANOVA) and the Kruskal-Willis test were used to assess differences between continuous variables with normal distribution and non-normal distributions respectively. Using time to event analyses, the crude incidence rates of composite CVD, CVD subtypes, and all-cause mortality outcomes were determined in the Simon Broome and CPRD FH cohorts, over the study period. In both study cohorts, Cox proportional hazards regression estimated the hazards ratios for CVD outcomes and mortality in more deprived socioeconomic groups compared to the least deprived group.

As there is a likelihood that certain patients with a clinical coded diagnosis of FH in primary care (CPRD) may not fulfil the Simon Broome FH-diagnostic criteria, and may not have monogenic FH, sensitivity analyses were conducted to assess the incidence rates and hazards ratios for CVD in different CPRD FH patient subgroups defined using more

stringent diagnostic thresholds of total cholesterol at baseline.

All analyses were conducted using Stata SE version 16 statistical package and significance was defined at the $p \leq 0.05$ level.

3. Results

3.1. Characteristics of subjects with FH, by level of socioeconomic deprivation

3.1.1. UK CPRD primary care database

The CPRD database had 4309 patients with a coded diagnosis of FH who were free from CVD at the start of follow-up, and linked with HES admission data over a follow-up period from 1988 to 2020. The baseline characteristics of these subjects by IMD quintiles is shown in Table 1. The proportion of individuals with clinical code for FH decreased with increasing levels of deprivation, such that there were 60.5 % fewer FH patients in the most deprived quintile (IMD-5) than the least deprived quintile (IMD-1) (Table 1 and Fig. 1). Ethnicity was unknown for 37 % of individuals in the CPRD database; Whites comprised 57 %, while Black and Asian ethnic groups accounted for 1.3 % and 3.5 % of individuals, respectively. There was a notably higher proportion of Whites compared to other ethnic groups across all IMD quintiles. Total cholesterol and triglyceride measures at baseline did not differ significantly between the IMD quintiles but mean LDL-C and HDL-C measures were lowest in the most deprived quintile. At baseline, CPRD patients in the most deprived quintile (IMD-5) had the highest prevalence of obesity and significantly more of these patients were current-smokers compared to patients from IMD quintiles 1,2,3 and 4 (p-value for trend, <0.001). As expected, the proportion of subjects with hypertension and type 2 diabetes were significantly different between quintiles, being higher in the most deprived quintile. Age at FH diagnosis, prevalence of chronic kidney disease and atrial fibrillation did not differ between the IMD quintiles (Table 1), nor did age at first statin treatment, statin potency, the use of corticosteroid medications or coronary interventions (Supplementary Table 1).

3.1.2. UK Simon Broome FH register

From this FH register, a total of 2956 subjects had data linkage with HES-Admitted patient care records and IMD measures of deprivation. HES-linked data were available from April 1997 to March 2018. The characteristics of these subjects at initial registration into the register are shown in Table 2 by IMD quintiles. Fig. 1 shows that similar to findings in CPRD, the number of individuals with FH decreased with increasing levels of deprivation such that there were 52 % fewer FH patients in the most deprived quintile (IMD 5) compared to the least deprived quintile 1. Table 2 shows that at the time of registration in the SB register, there were no significant differences in age, body mass index, pre-treatment total cholesterol concentration and pre-treatment triglyceride levels between the different IMD quintiles. SB individuals in the most deprived quintiles reported significantly higher prevalence of current smoking. In the SB cohort, 82 % of individuals were White, while Black and Asian ethnic groups accounted for 0.2 % and 2.5 % of individuals, respectively. Higher proportions of individuals from Black and Asian ethnic groups were observed in the most deprived IMD quintiles (IMD 4 and 5)

Table 1
Characteristics of CPRD individuals with FH, by socio-economic deprivation IMD class (n = 4309 individuals with IMD records).

Patient characteristics	unit	IMD class 1 n(%) 1229 (100)	IMD class 2 n(%) 1069 (100)	IMD class 3 n(%) 824 (100)	IMD class 4 n(%) 701 (100)	IMD class 5 n(%) 486 (100)	p-value
Baseline characteristics							
Age (years) at FH diagnosis	mean (SD)	49.19 (13.92)	49.01 (13.15)	48.49 (13.37)	46.96 (13.26)	47.94 (12.97)	0.0455
Female	n (%)	693 (56.39)	602 (56.31)	500 (60.68)	382 (54.49)	278 (57.20)	0.150
Ethnicity n (%)							
White/White British		677 (55.1)	603 (56.4)	453 (55.0)	425 (60.6)	307 (63.2)	
Black/Black British		5 (0.4)	4 (0.4)	6 (0.7)	16 (2.3)	25 (5.1)	<0.0001
Asian/Asian British		34 (2.8)	31 (2.9)	32 (3.9)	27 (3.9)	28 (5.8)	
Mixed		7 (0.6)	7 (0.7)	6 (0.7)	3 (0.4)	3 (0.6)	
Other/unknown		506 (41.2)	424 (39.7)	327 (39.7)	230 (32.8)	123 (25.3)	
BMI at registration	mean (SD)	27.85 (5.14)	28.51 (5.42)	28.65 (5.68)	29.32 (6.02)	30.46 (6.38)	0.0015
Total cholesterol (mmol/l)	mean (SD)	6.91 (1.80)	6.76 (1.80)	6.95 (1.78)	6.79 (1.66)	6.69 (1.71)	0.8589
LDL-C at FH diagnosis	mean (SD)	4.68 (1.54)	4.58 (1.60)	4.83 (1.73)	4.52 (1.51)	4.50 (1.60)	0.0132
HDL-C at FH diagnosis	mean (SD)	1.53 (0.50)	1.48 (0.46)	1.47 (0.46)	1.40 (0.40)	1.36 (0.45)	0.0055
Triglyceride (mmol/l) at FH diagnosis	median (IQR)	1.60 (1.09–2.30)	1.62 (1.10–2.50)	1.70 (1.10–2.40)	1.70 (1.10–2.50)	1.77 (1.20–2.80)	0.1780
Alcohol misuse	n (%)	11 (0.90)	8 (0.75)	9 (1.09)	7 (1.00)	6 (1.23)	0.892
Cigarette smoking status	n (%)	(n = 543)	(n = 512)	(n = 399)	(n = 335)	(n = 259)	<0.0001
Current		122 (22.47)	130 (25.39)	124 (31.08)	120 (35.82)	123 (47.49)	
Ex		119 (21.92)	136 (26.56)	100 (25.06)	55 (16.42)	43 (16.60)	
Never		302 (55.62)	246 (48.05)	175 (43.86)	160 (47.76)	93 (35.91)	
Physical activity level	n (%)	(n = 89)	(n = 66)	(n = 69)	(n = 57)	(n = 39)	0.285
Extremely inactive		8 (8.99)	10 (15.15)	7 (7.25)	7 (12.28)	5 (12.82)	
Sedentary		8 (8.99)	3 (4.55)	1 (1.45)	3 (5.26)	5 (12.82)	
Moderately active		69 (77.53)	50 (75.76)	62 (89.86)	47 (82.46)	28 (71.79)	
Extremely active		4 (4.49)	3 (4.55)	1 (1.45)	0 (0.00)	1 (2.56)	
Co-morbidities							
Atrial fibrillation	n (%)	17 (1.38)	14 (1.31)	15 (1.82)	16 (2.28)	7 (1.44)	0.642
Chronic kidney disease	n (%)	60 (4.88)	42 (3.93)	32 (3.88)	42 (5.99)	34 (7.00)	0.062
Hypertension	n (%)	258 (20.99)	219 (20.49)	173 (21.00)	182 (25.96)	126 (25.93)	0.015
Type 2 Diabetes	n (%)	58 (4.72)	66 (6.17)	37 (4.49)	57 (8.13)	44 (9.05)	0.001
Obesity/overweight	n (%)	118 (9.60)	133 (12.44)	103 (12.50)	104 (14.84)	82 (16.87)	0.001

IMD class 1 = least deprived, Class 5 = most deprived.

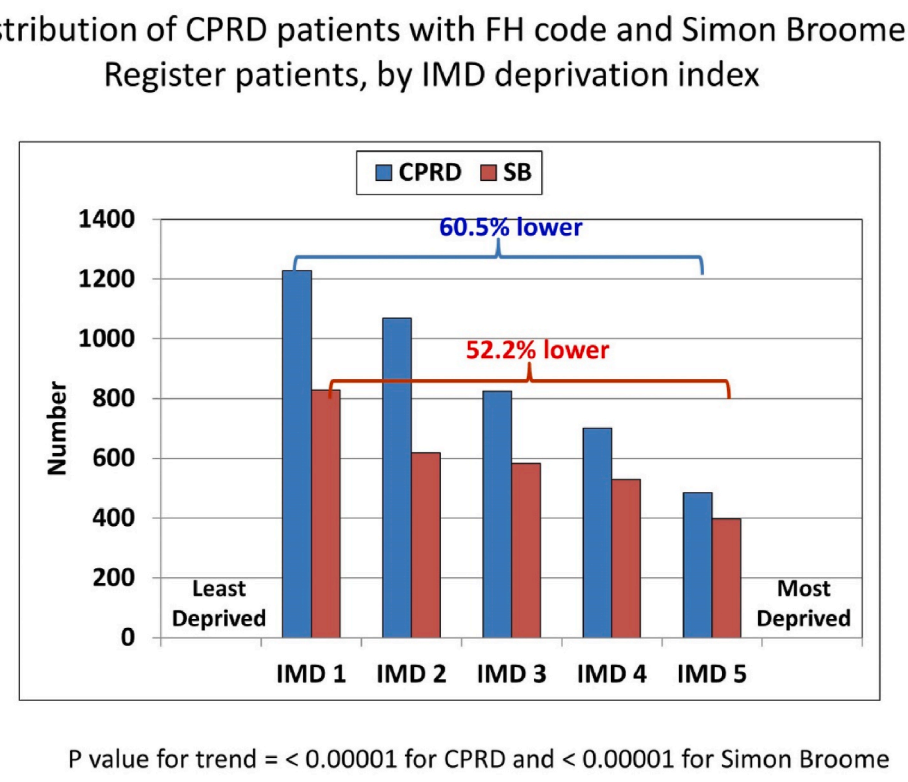

Fig. 1. Distribution of CPRD FH patients and Simon Broome FH patients by IMD score (IMD class 1 = least deprived, Class 5 = most deprived).

compared to the less deprived quintiles (IMD 1 and 2).

Unlike patients in CPRD, subjects with FH in the Simon Broome register included those who had a history of CVD at time of registration, and the prevalence of previous CVD was significantly higher in those from the most deprived IMD quintiles compared to the least deprived quintile. There was no significant difference in prevalence of hypertension between the IMD quintiles at time of SB registration but renal disease was most prevalent and diabetes was least prevalent in the least deprived IMD quintile compared to the most deprived IMD quintile.

3.2. Cardiovascular and mortality outcomes

3.2.1. UK CPRD primary care database

As shown in Table 3, the incidence rate (95 % CI) of composite CVD, per 1000 person years was 41 % lower in those in the least deprived quintile (14.70 (95 % CI 11.94–18.09) compared to the most deprived quintile (24.77 (95 % CI 19.02–32.26). Compared to those in the least deprived IMD quintile, the unadjusted hazards ratios (95 % CI) for composite CVD among those in quintiles 4 and 5 were 1.39 (95 % CI 1.01–1.91) and 1.71 (1.22–2.40) respectively. Higher unadjusted hazards ratios were also observed for coronary heart disease (HR 1.63 (1.11–2.40)) and all-cause mortality (HR 1.58 (1.02–2.47)), in the most deprived compared to the least deprived quintile (Supplementary Table 2). However, on adjustment for age, sex, smoking and alcohol consumption, there were no statistical differences in CVD and mortality risk between the IMD quintiles among individuals with coded diagnosis of FH in CPRD. (Table 3, Fig. 3 and Supplementary Table 2). Adjusted hazard ratio estimates for CVD remained consistent after including ethnicity in the multivariable analyses alongside age, sex, smoking, and alcohol (Table 3).

3.2.1.1. CPRD subgroup analyses. Subgroup analyses restricted to only the CPRD patients with baseline recorded total cholesterol concentration of ≥7.5 mmol/l, ≥8.0 mmol/l, ≥8.5mmol/and ≥9.0 mmol/l (Supplementary Table 3), showed a similar gradient of decreasing FH patient proportions with increasing levels of deprivation. Similar to the findings from the main analyses, the incidence and unadjusted hazards ratios for CVD increased with higher levels of deprivation. Also as previously shown, in all the CPRD patient subgroups, there were no longer significant differences in CVD risk between the different IMD groups after adjustment for age, sex, smoking and alcohol consumption.

3.2.2. UK Simon Broome FH register

Table 3 shows that among individuals with FH in the SB register, the incidence rate (95 % CI) of composite CVD was 40 % lower in the least compared to the most deprived quintile (21.59 [19.34–24.10] vs 35.95 [31.54–40.98] per 1000 person years at risk). Compared to subjects in the least deprived IMD quintile, the unadjusted hazards ratio (95 % CI) for composite CVD among those in quintiles 3, 4 and 5 were 1.31 (1.11–1.53), 1.34 (1.13–1.58) and 1.80 (1.51–2.13) respectively. After adjustment for age, sex, smoking and alcohol consumption, these HR estimates were not materially altered and there remained a significant gradient across quintiles (p value for trend <0.001) (see Fig. 3). These findings in the SB register persisted despite further adjustment for ethnicity in the multivariable analyses (Table 3). The Kaplan Meier event-free survival plot shown in Fig. 2 shows that individuals in the most deprived IMD quintile 5 have a significantly higher event rate than those in IMD quintile 1.

As the SB register included individuals who had prior CVD at time of registration, further analyses determined the baseline characteristics, incidence rate and hazards ratios for composite CVD among individuals in SB register who had no history of CVD at time of registration. Baseline characteristics of these individuals were similar to those of the entire SB cohort (shown in Supplementary Table 4). Incidence rates for CVD were lower among those with no history of CVD compared to the overall SB cohort but there remained a steep gradient of increasing CVD incidence with increasing quintiles of deprivation. Compared to the least deprived IMD quintile, the unadjusted hazards ratio (95 % CI) for composite CVD

Table 2
Characteristics of Simon Broome FH patients, by socio-economic deprivation (n = 2956 individuals with linked HES records and IMD measures).

Patient characteristics Mean (SD)	IMD class 1 n(%) 828 (100)	IMD class 2 n(%) 618 (100)	IMD class 3 n(%) 584 (100)	IMD class 4 n(%) 529 (100)	IMD class 5 n(%) 397 (100)	p-value
Baseline characteristics (at registration)						
Age (years) at SB registration (mean (SD))	43.5 (15.6)	43.8 (16.3)	43.9 (16.2)	43.2 (16.5)	45.0 (16.8)	0.401
Female n (%)	389 (47.0)	324 (52.4))	299 (51.2)	293 (55.4)	244 (61.5)	<0.0001
Ethnicity n (%)						
White/White British	672 (81.2)	511 (82.7)	492 (84.3)	434 (82.0)	325 (81.9)	
Black/Black British	1 (0.1)	0 (0.0)	2 (0.3)	1 (0.2)	2 (0.5)	<0.0001
Asian/Asian British	7 (0.9)	12 (1.9)	15 (2.6)	25 (4.7)	15 (3.8)	
Mixed	0 (0.0)	1 (0.2)	2 (0.3)	3 (0.6)	1 (0.3)	
Other/unknown	148 (17.9)	94 (15.2)	73 (12.5)	66 (12.5)	54 (13.6)	
BMI (Kg/m2) at registration (mean (SD))	24.7 (4.6)	24.7 (4.6)	24.9 (4.5)	25.6 (4.9)	25.2 (4.9)	0.268
Pre-treatment cholesterol (mmol/l) mean(SD)	9.6 (1.9)	9.5 (3.6)	9.4 (1.9)	9.5 (2.0)	9.9 (2.3)	0.0667
Age started on lipid-lowering treatment (mean(SD))	39.6 (15.5)	40.2 (15.8)	39.6 (16.5)	40.0 (16.5)	41.6 (16.7)	0.3529
Pre-treatment cholesterol (mmol/l) mean(SD)	9.6 (1.9)	9.5 (3.6)	9.4 (1.9)	9.5 (2.0)	9.9 (2.3)	0.0667
Pre-treatment triglyceride (mmol/l) median (IQR)	1.6 (1.1–2.4)	1.5 (1.1–2.4)	1.6 (1.1–2.5)	1.7 (1.0–2.6)	1.7 (1.1–2.6)	0.3735
Alcohol units/week (median(IQR))	6 (1–14)	6 (1–12)	4 (0–10)	3 (0–12)	2 (0–10)	<0.0001
Cigarette smoking exposure n (%)						
Ever smoked cigarette (yes)	285 (34.4)	247 (40.1)	246 (42.1)	259 (49.0)	190 (47.9)	<0.0001
Current cigarette smoker (yes)	100 (12.2)	92 (15.0)	97 (16.7)	122 (23.3)	100 (25.7)	<0.0001
Co-morbidities (n (%) History of previous CVD						
Angina (yes)	112 (13.6)	79 (12.9)	96 (16.6)	103 (19.7)	81 (20.9)	0.006
Myocardial infarction (yes)	68 (8.2)	49 (7.9)	60 (10.3)	55 (10.4)	51 (12.9)	<0.0001
Coronary heart disease (yes)	156 (18.8)	108 (17.5)	132 (22.6)	119 (22.5)	106 (26.7)	0.003
Stroke (yes)	4 (0.5)	4 (0.7)	8 (1.4)	9 (1.7)	5 (1.3)	0.101
History of claudication	18 (2.2)	17 (2.8)	20 (3.5)	11 (2.1)	20 (5.2)	0.042
Previous revascularisation (Angioplasty/CABG)	76 (9.2)	38 (6.2)	55 (9.4)	58 (11.0)	40 (10.1)	0.001
History of renal disease	7 (0.9)	3 (0.5)	3 (0.5)	0 (0.0)	1 (0.3)	0.007
History of Diabetes	3 (0.4)	13 (2.1)	7 (1.2)	12 (2.3)	4 (1.0)	<0.0001
History of hypertension	73 (12.7)	53 (11.9)	68 (15.9)	68 (16.1)	44 (14.9)	0.256

(IMD quintile 1 = least deprived, quintile 5 = most deprived).

was 1.88 (1.49–2.38) among those in the most deprived IMD quintile, and there remained a significant increase in hazards ratios for CVD with increasing deprivation even after adjusting for age, sex, smoking and alcohol consumption (Table 4).

4. Discussion

This comparative cohort study found that in both primary care and specialist lipid registers, fewer patients were diagnosed with FH in the most deprived groups than in the least deprived groups (60 % lower in CPRD and 52 % lower in SB). We have confirmed that, as expected, among individuals with clinical FH diagnosis in primary care as well as those in the Simon Broome FH register, the incidence of cardiovascular disease increased with increasing socioeconomic deprivation. Reassuringly, in both groups of FH patients, there were no socioeconomic disparities in level of total cholesterol at baseline and age at first lipid-lowering treatment, and cigarette smoking was more prevalent in the lower socioeconomic quintiles.

Although it is unclear why fewer individuals with FH were from more deprived socioeconomic groups, several possible explanations exist. Individuals from deprived populations may be less likely to attend routine health checks or seek preventative care [16] and may also be less likely to report relevant family history [17], leading to missed opportunities for early identification or detection of FH. Additionally, the higher prevalence of comorbid conditions such as obesity, diabetes, or hypertension in socioeconomically deprived groups may complicate the clinical recognition of FH due to overlapping risk factors.

The low prevalence of non-White individuals with FH in both CPRD and the SB register is partly attributable to population demographic make-up [18]. However, the numbers identified as FH were considerably lower than expected from the 2021 UK census data where 4 % of the population were of African and 9.3 % of Asian ethnicity [18]. While it is possible that the prevalence of FH-causing variants is lower in individuals of African or South Asian origin, this can be ruled out because using UK Biobank data, we have recently reported that the prevalence of FH-causing variants is not significantly different between these three ancestry groups [19]. This lower prevalence is also likely to reflect disparities in healthcare access, variations in health literacy levels, and potential ethnic differences in cholesterol profiles and FH-diagnostic thresholds.

The unadjusted hazard ratios for CVD were higher in the most deprived compared to the least deprived quintiles among individuals

Table 3
Incidence and hazards ratios for composite CVD, by patient socioeconomic deprivation in CPRD and Simon Broome FH patients.

Socio-economic deprivation classification (IMD)	CVD events	Person-years at risk	Incidence rate (95 % CI), per 1000 p_yrs	Unadjusted CVD Hazards ratio	HR adjusted by age and sex	HR adjusted by age, sex, smoking, alcohol consumption	HR adjusted by age, sex, ethnicity, smoking, alcohol consumption
UK CPRD FH Patients (n = 4309)							
1 – least deprived	89	6056	14.70 (11.94–18.09)	1.00	1.00	1.00	1.00
2	80	5006	15.98 (12.84–19.90)	1.08 (0.80–1.46)	1.11 (0.82–1.51)	0.71 (0.43–1.19)	0.71 (0.42–1.81)
3	68	3557	19.12 (15.07–25.25)	1.31 (0.96–1.80)	1.37 (1.00–1.88)	1.00 (0.60–1.67)	0.99 (0.59–1.66)
4	66	3238	20.38 (16.01–25.94)	1.39 (1.01–1.91)	1.51 (1.10–2.08)	0.99 (0.58–1.68)	1.00 (0.59–1.71)
5 – most deprived	55	2221	24.77 (19.02–32.26)	1.71 (1.22–2.40)	1.84 (1.31–2.57)	1.31 (0.78–2.20)	1.32 (0.78–2.24)
UK Simon Broome FH Register Patients (n=2956)							
1 – least deprived	318	14,730	21.59 (19.34–24.10)	1.00	1.00	1.00	1.00
2	241	11,013	21.88 (19.29–24.83)	1.02 (0.86–1.20)	1.01 (0.85–1.19)	1.00 (0.84–1.18)	1.01 (0.85–1.19)
3	282	10,419	27.07 (24.09–30.42)	1.31 (1.11–1.53)	1.32 (1.12–1.55)	1.32 (1.12–1.55)	1.32 (1.12–1.55)
4	253	9118	27.75 (24.53–31.39)	1.34 (1.13–1.58)	1.43 (1.21–1.69)	1.42 (1.20–1.68)	1.40 (1.19–1.66)
5 – most deprived	224	6231	35.95 (31.54–40.98)	1.80 (1.51–2.13)	1.84 (1.55–2.19)	1.83 (1.54–2.17)	1.84 (1.55–2.20)

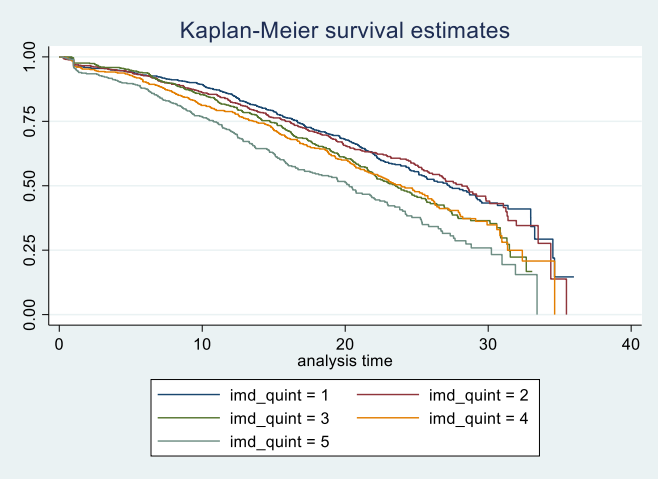

Fig. 2. Kaplan Meier survival estimates for CVD in Simon Broome FH patients by IMD quintile.

with FH in both primary care and the Simon Broome register. However, on adjusting for age, sex, smoking and alcohol consumption, there were no longer significant differences in the risk of CVD outcomes between primary care FH patients of different IMD socioeconomic groups, while the socioeconomic disparities persisted among individuals in the Simon Broome FH register. It is unclear why the SB and CPRD patients differed in the observed association between levels of deprivation and CVD after adjusting for lifestyle factors. This may be attributed in part to the greater generalisability of CPRD, which contains more current data on lifestyle variables, in contrast to SB, which relies on historical records. Perhaps the lifestyle variables captured at the time of registration into SB were not robustly reported, or do not accurately reflect the patients' status for the entirety of the study period. Also, subjects in the SB register were recruited from lipid clinics which are likely to provide more optimal management of FH.

Additionally, lifestyle factors such as diet and physical activity which are not routinely collected in CPRD or SB, may have also contributed to the observed increase in CVD risk (unadjusted hazard ratio) among more deprived IMD quintiles. Unhealthy dietary patterns and low levels of physical activity are well known risk factors for CVD [20]. Medication adherence to lipid-lowering treatments may also play a role in CVD outcomes. It is possible that more deprived subjects engaged less with their lipid-lowering treatments and lifestyle modification advice, contributing to the persistent socioeconomic disparities in CVD risk observed in the SB cohort.

4.1. *Strengths and limitations of the study*

This is the first comparative study to assess CVD outcomes by socioeconomic groups among individuals with FH in primary care and those in a specialist FH register. The CPRD database is representative of the UK general practice population [14] and so, findings from the study of FH patients in this database are generalisable to the general population of individuals with FH. The Simon Broome register is a well-known and extensively studied FH register with a long prospective follow-up and new national linkage with subjects' secondary care records. Linkage of patient records in both datasets to secondary care records in HES enabled us to robustly ascertain and accurately quantify cardiovascular disease and mortality in the FH patients. While we cannot rule out some degree of overlap between the FH-Register and CPRD data sets we believe this is minimal. The CPRD consists of a self-selected subset of all general practices. In 2013, there were 8044 general practices in England [21], of which 674 (8.4 %) contributed pseudonymised patient data to the database [14]. By contrast, the 21 Simon Broome Register Lipid Clinics provided clinical services available to all the general practices in their hospital catchment areas and included 4 clinics that were tertiary referral centres also receiving referrals from outside their catchment areas. There was, therefore, likely to be only a small overlap between the SB Register and CPRD patients.

We acknowledge certain limitations inherently associated with the use of electronic health records [22]. Records of FH diagnosis in the CPRD database, as in all electronic primary care records, were dependent on entries made by the primary care practitioner during routine consultations, so it was not possible to determine whether FH diagnoses captured in the database were based solely on findings from primary care assessment of individuals with FH phenotype, or following more specialised assessment or genetic testing in secondary care. In the UK, until recently, genetic testing of FH has not been widely available, and the majority of diagnoses are made using clinical FH criteria [23]. It had been shown in a previous study of the Simon Broome register that only 13 % of individuals were genetically diagnosed [24], so it is reasonable to assume that the majority of individuals in both of our FH cohorts,

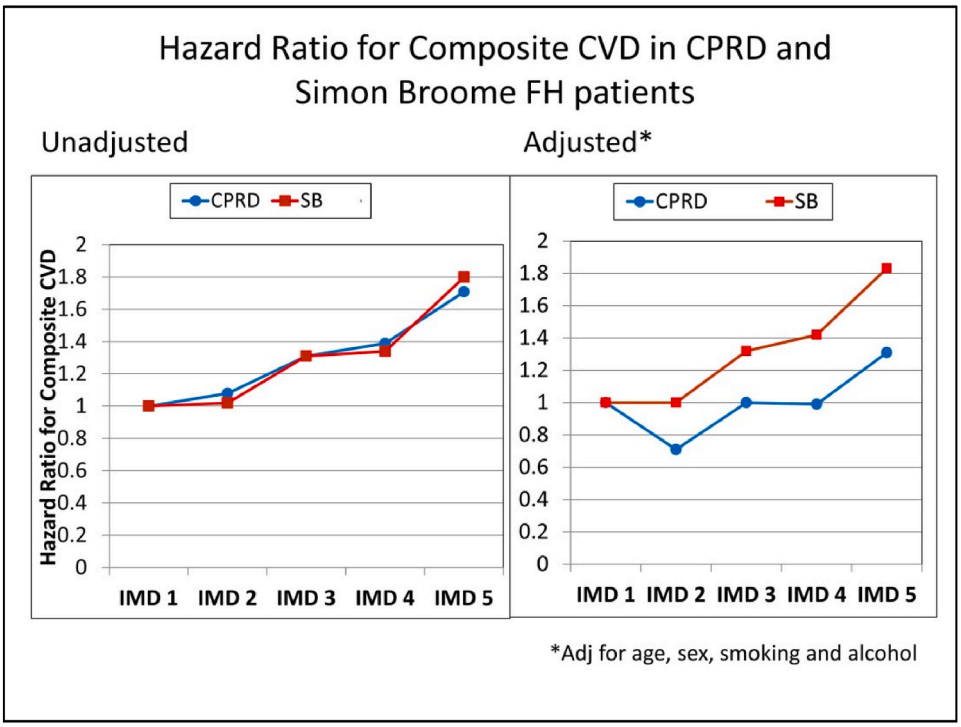

Fig. 3. Hazard ratios (unadjusted and adjusted) for composite CVD HES admissions in FH patients in CPRD and the Simon Broome Register.

Table 4
Incidence and hazards ratios for composite CVD, by patient socioeconomic deprivation in Simon Broome FH patients with no previous history of CVD (n = 2266).

Socio-economic deprivation classification (IMD)	CVD events	Person-years at risk	Incidence rate (95 % CI), per 1000 p_yrs	Unadjusted CVD Hazards ratio	HR adjusted by age and sex	HR adjusted by age, sex, smoking, alcohol consumption
1 – least deprived	172	12,604	13.65 (11.75–15.85)	1.00	1.00	1.00
2	134	9465	14.16 (11.95–16.77)	1.03 (0.82–1.29)	1.02 (0.82–1.28)	1.01 (0.81–1.27)
3	150	8477	17.69 (15.08–20.77)	1.38 (1.11–1.72)	1.43 (1.15–1.78)	1.44 (1.15–1.79)
4	139	7726	17.99 (15.24–21.25)	1.39 (1.11–1.74)	1.48 (1.18–1.86)	1.49 (1.19–1.87)
5 – most deprived	120	5140	23.35 (19.52–27.92)	1.88 (1.49–2.38)	1.99 (1.57–2.52)	2.00 (1.57–2.53)

would have been diagnosed using clinical FH diagnostic criteria. Another limitation of the use of routine primary care records in CPRD is the possibility of inaccurate coding or lack of data such as family history of CHD. The latter is included in several FH clinical diagnostic criteria [3]. Therefore, a proportion of the subjects in the CPRD database which were coded as FH would, for example, not fulfil the Simon Broome criteria for either Possible or Definite FH and therefore may not have monogenic FH. We addressed this limitation by conducting sensitivity analyses on subgroups of CPRD subjects with varying stringent thresholds of baseline total cholesterol. The findings – showing a decrease in FH proportions with increasing IMD deprivation quintiles, and no significant difference in hazards ratios for CVD across IMD quintiles after adjusting for age, sex, smoking, and alcohol use - were consistent with findings from the main CPRD analyses. In particular, 28 % (1216 out of 4309 patients) of the CPRD patient cohort had a baseline recorded total cholesterol of ≥9.0 mmol/l (the NICE recommended threshold to suspect FH in this age group [23]), and within this subgroup, compared to the least deprived quintile, those in the most deprived quintile had an unadjusted HR of 2.04 (1.14–3.62) which reduced to 1.01 (0.39–2.61) after adjustment for age, sex, alcohol and smoking.

The Simon Broome register captures self-reported information on alcohol consumption and smoking only at the time of registration, and no records of this information beyond registration. These baseline self-reported lifestyle data may be inaccurate and may also not be not a true reflection of patients' alcohol consumption and smoking over time. Also, the register has no records of lipid-lowering treatment or medication potency beyond registration. As a result, we were unable to assess whether lipid-lowering treatments or medication potencies differed between the different socioeconomic groups and whether any differences in treatment were associated with CVD outcomes. Individuals in Simon Broome register included those who had a history of previous CVD before enrolling into the register but the CPRD patients had no pre-existing CVD at the start of follow-up. By conducting sensitivity analyses of a subset of individuals in SB who had no record of CVD at time of registration, we were able to evaluate the robustness of our study findings and assess whether the disparities in our findings were influenced by history of previous CVD.

4.2. *Comparison with existing literature*

Our study finding confirms the finding of the UK wide-CVD Prevent audit of general practice patient notes [8]. The 2021 CVD Prevent Audit found a 40 % higher prevalence of GP recorded FH in the least deprived quintile compared to the most deprived quintile, which is very similar to our findings in the SB database where 28 % of participants were from the least deprived IMD quintile as compared to 13.4 % in the most deprived quintile, as well as in primary care where there were 28.5 % and 11.3 % of patients from the least compared to most deprived quintiles respectively. The reasons for this difference are unclear. While it may be possible that individuals in the socially deprived groups are less likely to attend general practice for health checks, such as the NHS health check programme [9] and so are less likely to have a cholesterol measurement

from which a GP suspicion of FH can be made, comparison of attendees and non-attendees suggests no major difference in deprivation index [25,26]. However, since there are fewer FH individuals from socially deprived groups identified in General Practice, fewer will be referred by GPs to lipid clinics, and consequently there will be fewer with a confirmed diagnosis of FH for recruitment to the Simon Broome Register.

The higher triglyceride, significantly lower LDL-C and HDL-C concentrations, and higher BMI observed with greater socio-economic deprivation in the CPRD cohort would be consistent with many of these patients being misdiagnosed as FH whereas, in fact, their dyslipidaemia may stem from non-genetic. This could explain why there is no increased hazard ratio after adjustment for age, sex, smoking and alcohol use. In contrast, the findings in the SB cohort may reflect the lifelong exposure to elevated LDL-C prior to initiating statin therapy. Additionally, very few FH patients continue to smoke after diagnosis, possibly due to the understanding that the excess CVD risk associated with smoking is largely mitigated after approximately 3–5 years of smoking cessation.

5. Clinical implications and conclusion

There appears to be inequality in the diagnosis of FH, with considerably fewer proportion of FH diagnosed in individuals from more socioeconomically deprived groups. In both CPRD and the SB Register the most deprived FH patients had the highest risk of CVD and mortality. In CPRD but not in the SB register this was largely explained by smoking and alcohol consumption. More effective clinical and health policy strategies are needed to detect FH in lower socio-economic groups, as well as support lifestyle changes, medication adherence and optimise risk factor management for this group.

CRediT authorship contribution statement

B. Iyen: Conceptualization, Funding acquisition, Formal analyses, Investigation, Writing – original draft, preparation, Writing – review & editing. **N. Qureshi:** Conceptualization, Funding acquisition, Writing – review & editing, Primary care interpretation of findings, Project administration, Supervision. **J. Kai:** Conceptualization, Writing – review & editing, Primary care interpretation of findings, Project administration. **N. Capps:** Writing – review & editing, Expert interpretation of findings. **P.N. Durrington:** Writing – review & editing, Expert interpretation of findings. **J. Cegla:** Writing – review & editing, Expert interpretation of findings. **H. Soran:** Writing – review & editing, Expert interpretation of findings. **J. Schofield:** Writing – review & editing, Expert interpretation of findings. **H.A.W. Neil:** Writing – review & editing, Expert interpretation of findings. **S.E. Humphries:** Writing – original draft, Visualization, Writing – review & editing, Expert interpretation of findings, Supervision.

Patient and Public Involvement

This study was co-designed with input from our Patient and Public Involvement (PPI) group as a means of ensuring that the research question was relevant to the needs of people with FH and other end users. This team of patient co-investigators fed into the design, delivery, and interpretation of our research findings.

Availability of data and materials

The CPRD data analysed during this study are available from the Clinical Practice Research Datalink (CPRD) (enquiries@cprd.com) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the CPRD Research Data Governance (RDG) team (enquiries@cprd.com).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NQ has received honoraria and travel costs for lectures, meetings and survey from AMGEN. SEH reports grants from British Heart Foundation during the conduct of the study. The remaining authors have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.119142.

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