Sex differences in cardiovascular morbidity associated with familial hypercholesterolaemia: A retrospective cohort study of the UK Simon Broome register linked to national hospital records

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1. Introduction

Familial hypercholesterolaemia is an autosomal dominant disorder characterised by lifelong elevated plasma levels of low-density lipoprotein (LDL) cholesterol, which when untreated, leads to increased risk of coronary heart disease (CHD) and premature death [1]. More recently, individuals with FH phenotype in primary care have been shown to have a greatly increased risk of not only CHD, but also stroke and peripheral vascular disease (PVD) [2]. Heterozygous FH affects 1 in 250 to 1 in 300 of the general population but the majority of these
individuals are undiagnosed [3,4]. If untreated, men with FH have a 50% risk of fatal or non-fatal CHD by age 50 years and women have a 30% risk by age 60 years [5].

In early studies of FH in the pre-statin era, CHD mortality was shown to be highest in the 20–39 year age group and reduced with increasing age [6]. Previous studies of the UK Simon Broome register examined changes in CHD mortality in FH patients both before and after the routine use of statins, and found that while there was a significant reduction in CHD mortality in men over time, excess mortality persisted in women [7], such that excess CHD mortality was 3-fold higher in women than men in the period from 2009 to 2015 [7]. These previous studies were limited to only coronary disease mortality outcomes in this patient population. As individuals with FH are now living longer due to effective lipid lowering therapies and coronary interventions [8], morbidity across a range of CVD outcomes now need to be examined. By linking records of Simon Broome register participants with their secondary care records from hospital episode statistics, we have now created the longest prospective cohort of FH patients known internationally.

This study evaluated the long-term CVD outcomes of individuals with heterozygous FH, and investigated any potential sex differences in cardiovascular disease morbidity associated with FH.

2. Materials and methods

2.1. Data source and baseline measures

The Simon Broome register includes individuals with FH recruited from 21 participating lipid clinics in the United Kingdom, to which they had been referred by either their general practitioners or hospital specialists. Recruitment of patients into the register began in 1980, and methods have been described previously [5,7,9]. Information recorded on registration into the Simon Broome register include individuals’ baseline demographic and clinical characteristics such as age, smoking status, alcohol consumption, past medical history, medication history including use of lipid-lowering, antihypertensive and diabetic treatments, family history as well as clinical examination findings such as blood pressure, body mass index, tendon xanthomas, xanthelasma and arcus cornealis. A fasting blood specimen taken at the registration visit determined serum total cholesterol, triglycerides and high density lipoprotein [5,6,7]. Serum low density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald equation [10]. Lipoprotein (a) (Lp(a)) concentration was measured in a single laboratory using a previously described method [11]. Patients were classified as having either Simion Broome Definite FH or Possible FH using previously published criteria [5,7,9]. Registered patients in the Simon Broome register were linked with the National Health Service Central Registry, which is part of the Office for National Statistics, for ascertainment of death records including underlying cause and date of death. 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 obtained by the NHS digital (DARS ref: NIC-115465) and Confidentiality Advisory Committee (CAG ref: 18/CAG/0007). The overall study obtained ethical approval from the NHS Health Research Authority (IRAS ref: 214219).

2.2. Cardiovascular disease outcome measures

Incident cardiovascular disease (CVD) was defined as the first hospital admission recorded in HES for coronary heart disease (CHD), myocardial infarction (MI), angina (stable or unstable), stroke, transient ischaemic attack (TIA), peripheral vascular disease (PVD), heart failure, or coronary revascularisation interventions such as percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG). Cardiovascular disease outcomes were identified from HES using the relevant ICD-10 and OPCS codes (shown in Supplementary Data).

2.3. Statistical analyses

Baseline characteristics of patients in the Simon Broome register were assessed, and these were reported as proportions, mean (standard deviation) and median (interquartile range) for categorical and continuous variables, respectively. Appropriate statistical tests such as chi-squared, t-tests and Mann-Whitney U tests were used to assess differences in categorical and continuous variables, between males and females. Incidence rates of composite CVD outcomes were assessed for all SB patients as well as within pre-defined patient subgroups, and Cox-proportional hazard models estimated hazards ratios for CVD. We determined the observed number of incident CVD events per person-years of follow-up, stratified by sex and age-groups (<30 years, 30 to >50 years and in the over 50 year age-groups). Standardised morbidity ratios (SMbR) were calculated using indirect standardisation, with age and sex-specific CVD incidence rates of the UK primary care non-FH population, as reference rates [2]. We calculated the expected number of CVD events as the number of person-years of follow-up in the SB cohort multiplied by the incidence rate for the comparable age-group and sex in the reference population. Standardised morbidity ratios (SMbR) were computed as the observed number of CVD events divided by the expected number of events:

$$\text{SMbR} = \frac{\text{observed number of CVD events in the SB population}}{\text{expected number of CVD events if the age – sex specific rates were the same as the reference population}}$$

The 95% confidence intervals of the SMbR were derived using an error factor (EF), with the equation: 95% CI = SMbR / EF to SMbR × EF, where EF = exp (1.96 / √di).

SMbR was estimated for both composite CVD and constituent CVD outcomes. We conducted the primary analyses on all eligible individuals in the Simon Broome register, with or without a history of CVD. To evaluate the impact of having a previous history of CVD, we conducted sensitivity analyses by restricting the population to a subset of patients who had no history of previous CVD at the time of registration. Considering that secondary care records in HES only became available after 1 April 1997, a further sensitivity analysis was done with analyses restricted to only those individuals with registration dates in Simon Broome on or after 1 April 1997. All analyses were conducted using Stata SE version 15 statistical package.
and although low overall, was similar to the prevalence of type 2 diabetes in the UK general population during the period of recruitment of the patient cohort [12]. Only 21.8% of the SB cohort had measures of Lp(a) at registration, but there was no statistically significant difference between these measures in males and females. Genetic test results were only available for 599 patients (20% of the study population) and an FH-causing variant was identified in 399 (67% of those tested), with no significant difference between males and females. Overall, women on the SB register had a better CVD risk factor profile, but a later age at FH diagnosis and commencement of LLT.

| Variable                                         | Male n (%) | Female n (%) | p-value
|--------------------------------------------------|------------|--------------|---------|
| Age at registration (years)                      | 41.1 (15.0)| 46.1 (16.8)  | <0.0001|
| BMI at registration (Kg/m²)                      | 25.17 (4.1)| 24.78 (5.2)  | 0.0343 |
| Follow-up (years)                                | 17.93 (11.17–23.98) | 18.15 (11.59–23.73) | 0.5993 |
| FH diagnosis type                                | n = 1418  | n = 1570     |         |
| Definite FH                                      | 770 (54.3) | 814 (51.9)   | 0.179  |
| Possible FH                                      | 648 (45.7) | 756 (48.1)   |         |
| Age started on LLT (years)                       | 37.5 (14.7) | 42.3 (17.0)  | <0.0001|
| Pre-treatment cholesterol (mmol/l)               | 9.4 (2.8)  | 9.7 (2.7)    | 0.0136 |
| Pre-treatment triglyceride (mmol/l)              | 1.8 (1.2–2.7) | 1.4 (1.0–2.2) | <0.0001|
| Pre-treatment lipoprotein Lp(a) (mg/dl)          | 29 (10–63), n = 314 | 25 (11–70), n = 339 | 0.9927 |
| Alcohol consumption (units/week)                 | 10 (1–20) | 2 (0–9)      | 0.0001 |
| Cigarette smoke exposure                         | 638 (45.0%, n = 1418) | 605 (38.6%, n = 1568) | 0.091  |
| Ever smoked cigarette (yes)                      | 224 (16.0%, n = 1404) | 293 (18.8%, n = 1556) | 0.116  |
| History of previous cardiovascular disease       | 250 (17.8%, n = 1403) | 226 (14.5%, n = 1554) | 0.0001 |
| Angina                                           | 187 (13.2%, n = 1418) | 99 (6.31%, n = 1570) | 0.0001 |
| Myocardial infarction                            | 352 (24.8%, n = 1418) | 276 (17.6%, n = 1570) | 0.0001 |
| Coronary artery disease (yes)                    | 10 (0.7%, n = 1404) | 20 (1.3%, n = 1558) | 0.173  |
| Stroke (yes)                                     | 13 (1.3%, n = 1027) | 18 (1.5%, n = 1168) | 0.254  |
| Transient ischaemic attack                       | 38 (2.7%, n = 1402) | 49 (3.2%, n = 1556) | 0.790  |
| History of claudication                          | 174 (17.0%, n = 1025) | 96 (8.3%, n = 1161) | <0.0001|
| Previous revascularisation (Angioplasty/CABG)    | 43 (37.49) | 51 (44.58)   | 0.0001 |
| Age at first MI (years)                          | 111 (10.9%, n = 1021) | 196 (16.9%, n = 1162) | <0.0001|
| History of hypertension                          | 20 (1.4%, n = 1418) | 19 (1.2%, n = 1570) | 0.718  |
| Use of other medications                         | 117 (11.4%, n = 1028) | 148 (12.7%, n = 1168) | 0.644  |
| Beta-blockers                                    | 39 (6.6%, n = 587)  | 54 (7.8%, n = 697)  | 0.610  |
| Ace-inhibitors                                   | 257 (18.1%, n = 1418) | 234 (14.9%, n = 1570) | 0.010  |
| Anti-platelet medication                         | 9 (1.5%, n = 587)  | 10 (1.4%, n = 697)  | 0.830  |
| Anticoagulant medication                         | 49 (4.8%, n = 1027) | 74 (6.3%, n = 1168) | 0.274  |
| Other antithrombinial medications                | 178 (60.3%) | 193 (65.5%)   | 0.416  |
| LDL-receptor                                     | 10 (3.4%)  | 13 (4.3%)    |         |
| Apo-B                                           | 4 (1.4%)   | 1 (0.3%)     |         |
| PCSK9                                            | 103 (34.9%) | 97 (31.9%)   |         |

Tests of significance for categorical variables were derived using the Pearson’s χ² test.

3. Results

A total of 3553 subjects in the Simon Broome (SB) database were recruited from participating lipid clinics between 1 January 1980 and 20 December 2010. Of these, 2988 (84%) had linked HES admitted patient care records, and comprised the final study cohort. Individuals without linked HES records had comparable baseline demographic characteristics to those with linked data, but a higher proportion of them had records of previous history of CVD. A comparison of baseline characteristics between individuals with and without linked HES records is shown in Supplementary Table 1.

The characteristics of the study population, at the time of registration into the Simon Broome register, are shown in Table 1. Of the cohort, 1418 (47.5%) were male. Compared to men, women were 5 years older at registration and 4.8 years older at the time of commencing lipid lowering treatment (LLT). While women had a slightly lower BMI than men, their mean untreated total cholesterol concentration was significantly higher, but median triglyceride concentration was significantly lower. Consumption of alcohol was significantly higher in men than women but significantly fewer women reported ever smoking, while the prevalence of current smoking was similar in men and women. Fewer women reported a prior history of CVD than men, with significant difference in myocardial infarction (MI), CHD and previous revascularisation, and women having had their first MI 8 years later than men. While significantly more women than men had a history of hypertension, the prevalence of type 2 diabetes was similar in men and women, and although low overall, was similar to the prevalence of type 2 diabetes in the UK general population during the period of recruitment of the patient cohort [12]. Only 21.8% of the SB cohort had measures of Lp(a) at registration, but there was no statistically significant difference between these measures in males and females. Genetic test results were only available for 599 patients (20% of the study population) and an FH-causing variant was identified in 399 (67% of those tested), with no significant difference between males and females. Overall, women on the SB register had a better CVD risk factor profile, but a later age at FH diagnosis and commencement of LLT.

3.1. Cardiovascular disease outcomes

Admitted patient care records from HES were available from April 1997 to March 2018. The median follow-up for patients in the SB register was 18.1 years (IQR 11.4–23.9), constituting 52,000 person-years of follow-up. Over this period, there were 1327 CVD-related hospital admissions. As shown in Table 2, the overall incidence rate for any CVD event in the SB patients was 25.47 (95% CI 24.14–26.88) per 1000 person-years follow-up. Incidence rates were lower in women, and compared to men, women had an adjusted hazard ratio (HR) of 0.65 (0.58–0.73). As expected, incidence rates and hazards ratio for CVD increased steeply with increasing age, with incidence rates ranging from 6.31 (5.12–7.77) in those less than 30 years at registration to 77.6 (95% CI 72.5–82.7) in those over 70 years. The median age at first CVD-related hospital admission for CVD was 60.6 years (IQR 51.5–69.5) in men, and 70.0 years (IQR 60.0–77.6) in women. There were very few individuals with FH genetic test results, so statistically significant difference in hazard
observed to have larger excess CVD morbidity than men (7.55 years, and the lowest was in those over 50 years. Women with FH were that the highest excess CVD morbidity was in those younger than 30 years.

| FH diagnosis type       | Number of subjects | Person-years of follow-up | Sex                                | Person-years of follow-up |
|-------------------------|--------------------|---------------------------|-----------------------------------|---------------------------|
| Total                   | 2988               | 52,090                    | Sex                               | 25.47 (24.14–26.88)      |
| Male                    | 1418               | 24,630                    | Male                              | 25.71 (25.12–29.30)      |
| Female                  | 1570               | 27,470                    | Female                            | 23.96 (22.19–25.86)      |

Previous CVD includes previous CHD, MI, coronary revascularisation interventions (coronary angioplasty or CABG), stroke, TIA, intermittent claudication.

### Table 3

| Observed number of CVD events in men and women with FH in the Simon Broome register. |
|---------------------------------|----------------------------------|
| Person-years of follow-up       | Observed CVD events |
|                                  | Incidence rate/1000 person years (95% CI) | Expected CVD events | Standardised morbidity ratio (95% CI) |
|---------------------------------|-----------------------|---------------------|-----------------------------------|
| Males                           |                       |                      |                                   |
| <30 years                       | 614                   | 8.14                 | 25.79 (23.99–27.74)               |
| 30 to <50 years                 | 560                   | 8.68                 | 25.10 (23.17–27.18)               |
| ≥50 years                       | 674                   | 8.44                 | 26.88 (24.66–29.07)               |
| Total (men)                     | 2290                  | 8.48                 | 16.10 (15.25–17.64)               |
| Females                         |                       |                      |                                   |
| <30 years                       | 422                   | 7.26                 | 28.15 (26.30–30.28)               |
| 30 to <50 years                 | 57                    | 7.57                 | 23.95 (22.19–25.86)               |
| ≥50 years                       | 87                    | 7.40                 | 27.74 (25.18–30.28)               |
| Total (women)                   | 768                   | 7.26                 | 28.15 (26.30–30.28)               |

### Table 2

Incidence rate and hazards ratios for composite CVD outcomes among SB patient population.

| Number of subjects | CVD events | Person-years of follow-up | Incidence rate (95% CI) of CVD | Unadjusted hazards ratio for CVD | Adjusted HR for age and sexa |
|--------------------|------------|---------------------------|-------------------------------|-------------------------------|-------------------------------|
| All subjects in SB register | 2988       | 52,090                    | 25.47 (24.14–26.88)            | 1.00                          | 1.00                          |
| Sex                |            |                           |                               |                               |                               |
| Male               | 1418       | 24,630                    | 27.17 (25.12–29.30)            | 1.00                          | 1.00                          |
| Female             | 1570       | 27,470                    | 23.96 (22.19–25.86)            | 0.89 (0.80–0.99)              | 0.65 (0.58–0.73)              |
| Age at registration (years) |          |                           |                               |                               |                               |
| <30                 | 614        | 89                       | 6.21 (5.12–7.77)               | 1.00                          | 1.00                          |
| 30 to <40           | 560        | 204                      | 10.95 (8.64–13.21)             | 3.38 (2.63–4.34)              | 3.32 (2.59–4.26)              |
| 40 to <50           | 620        | 305                      | 10.77 (8.18–13.36)             | 5.50 (4.34–6.98)              | 5.44 (4.29–6.98)              |
| 50 to <60           | 674        | 379                      | 10.44 (8.23–12.81)             | 8.09 (6.40–10.25)             | 8.54 (6.75–10.88)             |
| 60 to <70           | 425        | 293                      | 9.00 (7.09–11.04)              | 16.21 (12.68–20.74)           | 17.88 (13.96–22.91)           |
| ≥70                 | 87         | 74                       | 7.35 (5.96–9.00)               | 26.16 (18.58–36.84)           | 29.90 (21.18–42.20)           |
| FH diagnosis type   |            |                           |                               |                               |                               |
| Definite FH         | 1584       | 726                      | 25.79 (23.99–27.74)            | 1.00                          | 1.00                          |
| Possible FH         | 1404       | 601                      | 25.10 (23.17–27.18)            | 1.00 (0.90–1.12)              | 0.84 (0.75–0.93)              |
| No past history of CVD |          |                           |                               |                               |                               |
| Total (men)         | 2290       | 720                      | 16.40 (15.25–17.64)            | 1.00                          | 1.00                          |
| Past history of CVD | 698        | 607                      | 74.10 (68.44–80.24)            | 5.90 (5.27–6.60)              | 4.35 (3.06–3.89)              |

## Supplementary Table 2

On separate analyses of subtypes of the first CVD event, the SMbR for all subtypes were found to be higher in women than men (Fig. 2). The SMbR (95% CI) for CHD was substantially higher in women than men in the 30–50 year age group (19.66 (16.78–23.04) vs 12.54 (11.22–14.01)) and those over 50 years (7.65 (6.90–8.48) vs 5.82 (5.14–6.59)). Similarly, women had higher SMbR for PVD than men in the 30–50 year age group (16.16 (11.85–22.03) vs 8.18 (6.26–10.68)) and in the over 50 year age group (8.44 (7.02–10.14) vs 4.67 (3.68–5.93)). Higher SMbR for stroke was observed for women than men, but this was only in those aged over 50 years (5.66 (4.78–6.69) vs 2.83 (2.17–3.69)). In all CVD subtypes, the SMbR did not differ markedly between men and women with FH who were aged younger than 30 years. (data are shown in Supplementary Table 2).

### 3.2. Sensitivity analyses

On restricting all analyses to only the subset of FH patients who had no history of previous CVD at the time of registration into the Simon Broome register, as expected, SMbR for men and women of all age groups were lower than estimates from the whole cohort. There were however similar findings of higher SMbR for CVD in women than men in the 30–50 year group (10.68 (8.88–12.86) vs 7.06 (6.12–8.14)) and in those aged 50 years and over (4.11 (3.61–4.68) vs 2.73 (2.26–3.31) (Supplementary Table 4).

Further sensitivity analyses, which included only individuals who registered in the Simon Broome on or after the 1 April 1997, when
secondary care records in HES were available, found that similar to results of analyses of the whole cohort, SMbR for CVD was higher in women than men. Unlike findings from the whole cohort, the higher SMbR in women compared to men was most marked in those younger than 30 years. Due to the small sample size and few observed number of CVD events in this subgroup of patients, there was insufficient power to detect statistically significant measures of effect, and so the 95% confidence intervals for these estimates were very wide (Supplementary Table 5).

4. Discussion

4.1. Main findings

This study of the 36 year prospective cohort of patients with FH has shown that patients living with FH had excess rates of hospitalisations for CVD across all age groups, compared to the general population of individuals without FH. As expected, the incidence rate of CVD was lowest in those who were under 30 years at time of registration, and this increased with increasing age. However, compared to the general non-FH population, excess CVD morbidity due to FH, was highest in the youngest age group and decreased with increasing age. Overall, SMbR was 16-fold higher in FH patients than the general population in those under 30 years, and was 5-fold higher in those over 50 years. At registration, men with FH had higher prevalence of CVD risk factors, and were diagnosed and commenced on lipid-lowering treatment earlier than women with FH. Although the absolute incidence rate of CVD associated with FH was higher in men than women across all age groups, excess CVD morbidity compared to the general population without FH was substantially higher in women than men aged 30 years and over, and this was most marked in those aged 30–50 years at time of registration in Simon Broome.

4.2. Strengths and limitations

The Simon Broome register is a well-established FH register, and until now it had been only linked to the Office for National Statistics for ascertainment of death records. This study used a new national linkage of patient records in the register with their secondary care records in hospital episode statistics, providing an 18-year follow-up, and making this the longest prospective study of FH in the world. To our knowledge, this study is the first to investigate long-term secondary care outcomes in a registry cohort of patients with FH. Over 84% of patients in the Simon Broome register had linked secondary care records from HES, which enabled comprehensive and robust ascertainment of different CVD outcomes, as well as interventions such as coronary interventions. We were also able to quantify the rates of coronary revascularisations in FH patients, which to date, has largely been understudied [13].
Study limitations include the lack of data on lipid-lowering treat-
ments or more recent LDL-cholesterol concentrations beyond the time of
SB registration, which could potentially explain the observed differences in
CVD outcomes in men and women. It had however been shown in the
2010 survey of FH management in adults attending UK lipid clinics [14]
that 86% of patients were on statin treatment, with 40% additionally
being treated with Ezetimibe; which was associated with a median
LDL-cholesterol reduction of 47% from baseline, at patients’ third lipid
visit [14]. As patients in our SB register cohort were recruited from
UK lipid clinics, it is reasonable to assume that the proportion on
lipid-lowering treatments will be consistent with findings from the
audit, as well as more recent national guideline recommendations [15].
Over 50% of men and women in the SB register fulfilled the “definite
FH” criteria, as such there may be a degree of selection bias towards
those with more severe FH phenotype. We had no data on obstetric
outcomes of women in this study, and so were unable to ascertain
whether CVD outcomes differed between women with documented
obstetric admissions who may have discontinued statin therapy during
pregnancy and lactation, and those with fewer or no documented ob-
stetric admissions. Also, electronically linked hospital records were only
available from 1997 onwards, and therefore in participants who were
registered prior to this date, there is likely under-ascertainment of CVD
outcomes. Although our expectations are that any under-ascertainment of
CVD outcomes are conservative in nature and not likely to affect
males and females differently, we conducted a sensitivity analyses of
those individuals whose date of registration in SB register was after the
inception of HES on 1 April 1997. Although the finding of higher SMbR
for CVD in women compared to men was broadly similar to findings
from the main analyses, statistical significance could not be determined
due to the small sample size of this patient subgroup.

A final limitation of the study is that, because DNA testing is not
widespread in the UK, only 15% of the SB cohort had a DNA confirmed
diagnosis. Therefore, there were too few mutation carriers to enable a
statistically robust assessment of the relationship between mutation
positive status (gene mutation) and CVD morbidity. However, all pa-
tients in the SB register were from specialist clinics and have clearly
defined clinical phenotypes of FH.

4.3. Comparison with existing literature

Our study finding that excess CVD morbidity due to FH was highest
in those younger than 30 years, and declined with advancing age, builds
on previous research from the Simon Broome register, which reported
the highest excess mortality from CHD before the age of 40 [6]. Consistent with our study findings, individuals in a Norwegian FH reg-
istry had the highest excess risk of acute MI and CHD in those aged
25–39 years [16].

The substantially higher SMbR for composite CVD in women than
men, in the 30 to 50, and over 50 age groups, is a novel finding of
considerable clinical significance. Although a study of the general
population of adults with phenotypic FH in the United States had shown
that age-based acceleration of CHD risk was greater for women than men
[17], the study did not explore sex-differences in the increased risk of
composite CVD outcomes associated with FH. It had previously been
shown in the Simon Broome register that excess CHD deaths associated
with FH were 3-fold higher in women than men for the period 2009 to
2015 [7]. While excess CHD deaths declined in men comparing the
period before and after the routine use of statins, no corresponding
decline was observed over time in women [7]. There are several possible
explanations which may underlie our study finding of higher excess CVD
morbidity in women compared to men. We found that the mean ages for
commencing lipid-lowering treatment in men and women were 37.5
years and 42.3 years, respectively. While women typically develop CVD
at a later age than men, the risk of CVD is often underestimated in
women due to the misperception that females are ‘protected’ against
CVD before the menopause [18]. While premenopausal women have a
less pro-atherogenic plasma lipid profile than men, specifically greater
high-density lipoprotein (HDL) and lower LDL-cholesterol than men of the
same age [19], a study of children and adolescents with untreated
FH suggests that the cholesterol burden with untreated FH is signifi-
cantly higher in girls than boys [20]. These factors are likely to
contribute to the greater excess CVD burden in women with FH
compared to women without FH. Since statins are not recommended
during pregnancy and breastfeeding, women with children are also
likely to have experienced one or more interruptions of 2–3 years in
their lipid lowering therapy and thus to have accumulated a greater
“LDL-C burden” than men of the same age. Despite the greater CVD
burden observed in women with FH compared to non-FH women, the
incidence of CVD in individuals with FH remained lower in women than
men across all age groups, suggesting that women may still retain some
relative protection from CVD.

Statin prescribing rates have been shown to be lower in women than
men in the general population [21], with numerous studies reporting
that women in general are less likely to be prescribed evidence-based
guidelines, and less aggressively treated in cardiology care for both
primary [22] and secondary prevention [23]. Studies in the FH popu-
lation have also demonstrated greater prescribing of more potent
lipid-lowering therapy in men than women with FH, suggesting that FH
treatment may be suboptimal in women [24,25]. This is consistent with
findings from the survey of FH patients in UK lipid clinics, which showed
that more men than women attained the FH treatment target of 50% or
more reduction in baseline LDL-C [14]. In addition, gender was not
found to be associated with adherence to statin therapy in a study of
patients with FH [26].

4.4. Clinical implications and conclusion

This study finding of significantly higher risk of CVD in all age groups
of patients in this registry-based cohort, compared to the general pop-
ulation, emphasizes the importance of early diagnosis and treatment of
FH. Strategies to identify individuals with FH at a young age, before the
development of significant coronary atherosclerosis, would be particu-
larly helpful. Such strategies include cascade testing of relatives from
identified index cases [27], and universal screening for high cholesterol
in children, which would enable identification of parents with FH [28].
Our study provides confirmatory evidence of higher excess CVD
morbidity in younger age groups of patients with FH and, importantly,
provides novel insight into gender differences in the diagnosis and
management of FH, as well as substantial gender disparities in the excess
cardiovascular disease burden associated with FH. The finding that
higher CVD morbidity is markedly higher in women 30–50 year age group,
and also in those over 50 years, emphasizes the importance of early initiation of high intensity lipid-lowering treatment and highlights the need for optimisation of lipid-lowering and risk factor
management for all FH patients with particular attention to women with
FH.

Author contributions

BI conducted the analysis, and BI and SEH wrote the first draft and
subsequent revisions, led data management, and interpretation of
findings. SW developed the study design, obtained ethical and study
approvals to access the data, linked the SB-HES data, and cleaned the
data into an analysable form. NQ and JK conceptualised the study design
and methods, and provided primary care interpretation of findings. PR
adviced on refining study design,covarite selection. NQ and SEH pro-
vided overall supervision of the project. SEH, AN, PD, IFWM, NC and HS
provided expert interpretation of study findings and formulated ratio-
nale for additional analyses. SW verified all statistical analyses. NQ, SW,
JK, SEH, PR secured grant funding. All study authors have contributed to
interpretation, revising, writing and finalising the final submission.
version of the manuscript.

Declaration of competing interest

NQ has received honoraria and travel costs for lectures, meetings and survey from AMGEN. SW reports grants from National Institute for Health Research Health Technology Assessment Programme during the conduct of the study, personal fees from AMGEN, personal fees from Questph Ltd outside the submitted work and is a member of Clinical Practice Research DataLink Independent Scientific Advisory Committee (ISAC). 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

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