Atherosclerosis
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Abstract:
Background: Differences in the perceived prevalence of familial hypercholesterolemia (FH) by ethnicity are unclear.

Objective: To study the prevalence, determinants and management of diagnostically-coded FH in an ethnically diverse population in South London.

Methods: A cross-sectional analysis of 40 practices in 332,357 adult patients in Lambeth was undertaken. Factors affecting a (clinically coded) diagnosis of FH were investigated by multi-level logistic regression adjusted for socio-demographic and lifestyle factors, co-morbidities, and medications.

Results: The age-adjusted FH % prevalence rate (OR, 95%CI) ranged from 0.10-1.11, 0.00-1.31. Lower rates of FH coding were associated with age (0.96, 0.96-0.97) and male gender (0.75, 0.65-0.87), p<0.001. Compared to a White British reference group, a higher likelihood of coded FH was noted in Other Asians (1.33, 1.01-1.76), p=0.05, with lower rates in Black Africans (0.50, 0.37-0.68), p<0.001, Indians (0.55, 0.34-0.89) p=0.02, and in Black Caribbeans (0.60, 0.44-0.81), p=0.001. The overall prevalence using Simon Broome criteria was 0.1%, we were unable to provide ethnic specific estimates due to low numbers.

Lower likelihoods of FH coding (OR, 95%CI) were seen in: non-native English speakers (0.66, 0.53-0.81), most deprived income quintile (0.68, 0.52-0.88), smokers (0.68,0.55-0.85), hypertension (0.62, 0.52-0.74), chronic kidney disease (0.64, 0.41-0.99), obesity, (0.80, 0.67-0.95), diabetes (0.31, 0.25-0.39) and CVD (0.47, 0.36-0.63). 20% of FH coded patients were not prescribed lipid-lowering medications, p<0.001.

Conclusions: Inequalities in diagnostic coding of FH patients exist. Lower likelihoods of diagnosed FH were seen in Black African, Indian and Caribbean ethnic groups, in contrast to higher diagnoses in Other Asian ethnic groups. Hypercholesterolaemia requiring statin therapy was associated with FH diagnosis, however the presence of cardiovascular disease (CVD) risk factors lowered the diagnosis rate for FH.

Mariam Molokhia¹, Anthony S. Wierzbicki², Helen Williams³
Arushan Kirubakaran,¹ Rohan Devani¹, Stevo Durbaba¹, Salma Ayis¹, Nadeem Qureshi⁴

Research:
-We examined prevalence FH by ethnicity, coding and CVD risk management

Findings:
-We found inequalities in diagnostic coding of FH patients
-Compared with White ethnicity, lower likelihoods of diagnosed FH were seen in Black African, Black Caribbean and Indian ethnic groups, in contrast to higher levels in other Asian ethnic groups

Impact:
-This study identified health inequalities, with lower levels of diagnosis in areas of greater deprivation; non-native English speakers, Black African, Black Caribbean, and Indian ethnic groups, smokers and individuals with comorbidities
Age-adjusted FH prevalence was highest in the Other Asian ethnic group, with lowest rates in the Chinese, Missing and Black African/Black Caribbean ethnic groups.

Black African, Black Caribbean and Indian ethnic groups were less likely to be coded with FH after adjusting for ethnicity, gender, lifestyle and medical factors.
Assessment of ethnic inequalities in diagnostic coding of familial hypercholesterolaemia (FH): A cross-sectional database study in Lambeth, South London

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ABSTRACT

**Background and aims:** Differences in the perceived prevalence of familial hypercholesterolemia (FH) by ethnicity are unclear. We aimed to study the prevalence, determinants and management of diagnostically-coded FH in an ethnically diverse population in South London.

**Methods:** A cross-sectional analysis of 40 practices in 332,357 adult patients in Lambeth was undertaken. Factors affecting a (clinically coded) diagnosis of FH were investigated by multi-level logistic regression adjusted for socio-demographic and lifestyle factors, co-morbidities, and medications.

**Results:** The age-adjusted FH % prevalence rate (OR, 95%CI) ranged from 0.10-1.11, 0.00-1.31. Lower rates of FH coding were associated with age (0.96, 0.96-0.97) and male gender (0.75, 0.65-0.87), p<0.001. Compared to a White British reference group, a higher likelihood of coded FH was noted in Other Asians (1.33, 1.01-1.76), p=0.05, with lower rates in Black Africans (0.50, 0.37-0.68), p<0.001, Indians (0.55, 0.34-0.89) p=0.02, and in Black Caribbeans (0.60, 0.44-0.81), p=0.001. The overall prevalence using Simon Broome criteria was 0.1%, we were unable to provide ethnic specific estimates due to low numbers.

Lower likelihoods of FH coding (OR, 95%CI) were seen in: non-native English speakers (0.66, 0.53-0.81), most deprived income quintile (0.68, 0.52-0.88), smokers (0.68,0.55-0.85), hypertension (0.62, 0.52-0.74), chronic kidney disease (0.64, 0.41-0.99), obesity, (0.80, 0.67-0.95), diabetes (0.31, 0.25-0.39) and CVD (0.47, 0.36-0.63). 20% of FH coded patients were not prescribed lipid-lowering medications, p<0.001.

**Conclusions:** Inequalities in diagnostic coding of FH patients exist. Lower likelihoods of diagnosed FH were seen in Black African, Black Caribbean and Indian ethnic groups, in contrast to higher diagnoses in White and Other Asian ethnic groups. Hypercholesterolaemia requiring statin therapy was associated with FH diagnosis, however the presence of cardiovascular disease (CVD) risk factors lowered the diagnosis rate for FH.

Keywords: Familial hypercholesterolaemia, ethnicity, inequalities, coding
1. Introduction

Familial hypercholesterolemia (FH) is associated with high levels of low-density lipoprotein cholesterol disease (LDL-C) leading to development of cardiovascular CVD at younger ages, with highest relative risk at age <40 years (1-3). Increased levels of LDL-C from birth lead to increased coronary artery disease (4, 5). Mutations in one of 3 genes (LDLR, APOB and PCKS9) cause most monogenic FH, although most cases of raised cholesterol are polygenic (1-3). Diagnostic algorithms for FH advise that either the Simon Broome criteria or Dutch Lipid Clinic Network (DLCN) scores can be used to diagnose patients with FH (1-3, 6, 7) although a modified DLCN has higher specificity for FH diagnosis (8). Currently only 7% of FH patients have been identified in the UK (9) as worldwide (5). The NHS Long Term Plan aims to increase FH detection to at least 25% in the next 5 years supported by the NHS genomics programme (10).

The prevalence of monogenic FH is thought to be 1 in 250-350 (1-3). Though inequalities in ascertainment and management of CVD are well established, little data exists on FH. In the UK determinants associated with FH diagnoses in primary care include male gender, age, statin prescribing and family history of CVD (11, 12). Lower socioeconomic level is linked to premature coronary heart disease (CHD), (13) but few studies have examined effects of deprivation in FH. The risk of premature CVD in FH can be dramatically improved by early introduction of high potency statins (14). International and UK The National Institute for Health and Care Excellence (NICE) guidelines recommend reducing LDL-C by greater than 50% from baseline in FH individuals (1-3, 6).

This study aimed to examine the prevalence of primary care coded FH and according to Simon Broome Criteria, by ethnicity, the determinants of coding and extent of CVD risk management in an ethnically diverse population.

1.1 Objectives

(1) To ascertain diagnosed FH age-adjusted prevalence by ethnic group. (2) To describe sociodemographic and clinical characteristics associated with FH diagnostic coding. (3) To examine CVD risk factor management in individuals diagnosed with FH-

2. Materials and methods

2.1 Study design

A cross-sectional database study was undertaken using a primary care electronic health record database in Lambeth, South London- Lambeth DataNet (LDN), and involved a cross-sectional survey of people with a Read diagnostic code for FH [Table S1] on the health record held by their GP. We determined coding status, risk factors, and measures of FH diagnosis and management.

2.2 Data sources and quality

This study utilised a dataset derived from general practice electronic health records (EHRs) for one inner-London borough, Lambeth DataNet (LDN), extracted in October 2020. LDN contains patient-level clinical data, prescribing data, laboratory data, and demographic information (including ethnicity, based on categories of the UK 2001 census), risk factors, and comorbidities. Demographic factors, comorbidities, and other quality-of-care measures were investigated in a multi-ethnic population identified as having FH based on their clinical diagnostic coding.

All coded data was extracted apart from narrative text (the GP consultation record) or the content of any letters/correspondence, free text on other medical documents or from the 3.2% of patients with an informed dissent code in their case-notes.
LDN data contains data from all routine service driven GP records, therefore if the GP does not code something, then the data is 'missing'. However, the GP incentivisation scheme, Quality Outcomes Framework (QOF) ensures high levels of coding. Patient registration data also ensures high levels of coding. All prescriptions issued by GPs are captured (unless handwritten or prescribed out of hours).

2.3 Participants
The study examined records from adult participants (332,357 adults aged ≥ 18 years). LDN contains anonymised patient data from all 40 practices in Lambeth, South London, extracted in 2020.

2.4 Identification of FH coding status
The diagnosis of FH was based on clinical coding in general practice (GP) electronic health records using the Read code classification system (Table S1). Validation of FH codes was undertaken using current Simon Broome criteria, age and total cholesterol (>7.5 mmol/L in under 30; and >9mmol/L ≥30 years) and excluding those with baseline triglyceride, (TG) 2.3 mmol/L or above and/or a diagnosis of non-alcoholic fatty liver disease (NAFLD).

2.5 Covariates
Demographic variables analysed included factors likely to influence CVD risk: age, gender, and ethnicity based on 2011 census categories. The Income Deprivation Domain of the Index of Multiple Deprivation was used as a measure of relative deprivation, together with English as a first language, lifestyle variables (smoking status, obesity) co-morbidities (history of hypertension, diabetes, chronic kidney disease (CKD), cardiovascular disease (CVD), and laboratory results: including lipid profiles cholesterol, LDL-C and triglyceride data where available. Prescribing data: lipid lowering medications (statins and fibrates), and frequency of general practice attendance, were identified using Read codes and QOF disease registers (15, 16).

Lipid lowering medication was divided into two categories: any statin or fibrate use and high efficacy statin use, based on the definition of high-intensity treatment by NICE (17, 18).

Self-reported ethnicity was divided into 11 groups: White, Black African, Black Caribbean, Bangladeshi, Pakistani, Indian, Other Asian, Chinese, Arab, Other (e.g. Mixed and Other Non-White ethnic groups) and 'Not stated/Unknown' which was given to individuals who did not wish to provide their ethnicity. For the sensitivity analyses 5 ethnic groups were considered due to low numbers: White, Black African, Black Caribbean, Other, and Unknown/Not stated. An additional category called ‘Missing’ was used to indicate unavailable patient ethnicity information. Pearson’s Chi Square test was applied to observe differences between variables and test significance across the different ethnic groups (using White ethnicity as a reference group).

2.6 Statistical analysis
Crude and age adjusted prevalence rates of FH were calculated by ethnic group. The figures showing age-adjusted FH prevalence rates by ethnicity were produced using Poisson regression estimates (19).

The logistic regression analysis followed a stepwise partially adjusted model to assess the association of risk factors associated with FH coding identified from the literature in diverse ethnic groups (11, 12). Multilevel multivariable logistic regression analysis was used to assess the determinants of FH coding by ethnic group whilst adjusting for confounding variables and practice effects, (OR, odds ratios, 95% confidence intervals (CI) and associated p-value). Interaction effects were tested for FH coding and ethnic groups, using interaction terms for age group, income quintile level and obesity in the fully adjusted multilevel models. Collinearity was tested by calculating variance inflation factors (VIF), (Table S2).
CVD risk factors and quality of care were examined including lipid-lowering pharmacotherapy, smoking, LDL-C levels, BMI measurements and blood pressure control in FH diagnosed individuals.

All analyses were conducted using STATA™ (version 16.0) (19). Results were reported using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist.

2.7 Ethics

Information Governance and ethical approval was provided by NHS South East London Clinical Commissioning Group (CCG) and NHS Lambeth CCG.

2.8 Patient and public involvement

Patients were involved in the review and evaluation of this research. During the feasibility stage, priority of the research question, and study design were informed by discussions with patients through a workshop on diagnosis of FH in primary care (Society for Academic Primary Care (SAPC). Madingley, Cambridge 2019) attended by patients, GPs and researchers. We have worked closely with a patient representative who has been advising on how we can raise awareness of FH in primary care. We intend to disseminate the main results to health care professionals and patients with PPI involvement. Some of the initial results from this work have been presented at the Heart UK annual conference, 2021 (to professional and public audiences) and to participating practices.

3. Results

3.1 Summary characteristics of study population update

The characteristics of 332,357 adult patients (aged ≥ 18 years) across ethnic groups are summarised in Table 1. The largest ethnic group was White (55%). The majority of the study population was in the 30-39 age group (29.1%) reflecting the young population demographic. The White ethnic group were the least deprived, (1<sup>st</sup>) income quintile (25.5%), and the Black African group had the highest percentage in the most deprived (5<sup>th</sup>) income quintile (33.2%), p<0.001. For lifestyle indicators (all p<0.001), obesity (BMI>30kg/m<sup>2</sup>) was highest in the Black African (27.3%) and Black Caribbean (27.1%) groups. Current reported smoking levels were highest in the Black Caribbean (25.3%) group, (18.6% BMI and 5.6% smoking data were missing). [Table 1] The Bangladeshis, accounted for the largest proportion with prescribed statins (11.9%) and high dose statins (12.5%). The Bangladeshi and Caribbean group also ranked highest for annual GP visit frequency (≥7 visits/year) (28.4% and 26.3% respectively), p<0.001 (not shown).

Income deprivation was associated with lower levels of FH diagnosis, p<0.001 (not shown).

3.2 Crude and adjusted FH prevalence

A diagnostic Read Code of FH coding was found in 801 patients. The crude overall % prevalence (95%CI) of FH was 0.24, 0.22-0.26 and highest in the Other Asian (1.11, 0.92-1.33), Bangladeshhi (0.45, 0.18-0.92) and Indian (0.39, 0.24-0.60) ethnic groups, p<0.001. (Figure 1, Table S3). The age-adjusted FH prevalence was highest in the Other Asian (1.11, 0.91-1.31), p<0.0001 and Bangladeshhi (0.45, 0.12-0.79), p=0.008 ethnic groups, with lowest rates in the Chinese (0.10, 0.00-0.20), p=0.046, Missing (0.11, 0.07-0.15), Black African (0.12, 0.08-0.15) Black Caribbean (0.14, 0.10-0.18) ethnic groups, both p<0.0001. (Figure 1, Table S3).

3.3 Intraclass correlation coefficient (ICC)

Initial analyses found an ICC value of 0.003 (0.002-0.005). The practice variation for likelihood of FH coded diagnosis was highly significant with 32% variance (0.19-0.54) (Model 6), therefore we adjusted for practice in the multi-level model.
3.4 Regression models

A summary of multilevel multivariable logistic regression models across eleven ethnic groups is provided in Table 2 (OR, 95%-CI). In the fully adjusted model for FH coding, compared with White ethnicity, excess prevalence of diagnosed FH was noted in the Other Asian ethnic group (OR 1.33, 1.01-1.76). In contrast, lower levels of FH coding were observed in Black African (OR 0.50, 0.37-0.68), p<0.001 Black Caribbean (OR 0.60, 0.44-0.81), p=0.001 and Indian (OR 0.55, 0.34-0.89), p=0.02 ethnic groups. Non-English speakers (OR 0.66, 0.53-0.81), p=0.001 and individuals in the 5th (most deprived) income quintile (OR 0.68, 0.52-0.88), p=0.003 were least likely to have coded FH compared to English speakers and those in the 1st income quintile (least deprived) respectively.

The presence of many CVD risk factors (OR, 95%-CI) was associated with a lower likelihood of FH coding. Reduced coding was seen with age (OR 0.96, 0.96-0.97), male gender (OR 0.75, 0.65-0.87) and with current smokers (OR 0.68, 0.55-0.85) compared to non-smokers, presence of hypertension (OR 0.62, 0.52-0.74), CKD (OR 0.64, 0.41-0.99), obesity (BMI>30kg/m^2, OR 0.80, 0.67-0.95), diabetes (OR 0.31, 0.25-0.39) and established CVD (OR 0.47, 0.36-0.63). However, the presence of hypercholesterolaemia as indicated by any statin use (OR 132, 100-173) and use of high potency high dose statin therapy (OR 204, 158-263) were highly associated with coded FH coding, both p<0.001. Increased GP attendance was associated with lower likelihood of FH coding (OR 0.81, 0.67-0.97), p=0.02.

We found no interactions for ethnicity and age group, ethnicity and income or ethnicity and obesity for FH in a fully adjusted multilevel model. When stratified by age in sensitivity analyses (not shown), in those aged ≥40 years (but not in those <40 years) we found premature CVD was increased but not significantly associated with coding of FH in the fully adjusted model: OR 2.55, 95%-CI 0.32-20.28; p=0.38. No significant collinearity between any confounding variables was found as the variance inflation factor (VIF) was <5. [Table S2]

3.5 CVD risk factors and quality of care

Documentation of CVD risk factors specifically associated with FH such as LDL-C (19.6%) and family history of CVD (0.12%), were poor as was combined poor lipid and BP management (Table 3). Furthermore, these discrepancies are exacerbated by ethnicity (lowest recorded LDL-C % in White, Black African, Chinese and Arab ethnic groups, p<0.001) and the lowest 4th and 5th income quintiles were least likely to have LDL-C recorded (p=0.002). Despite a coded diagnosis of FH 20.1% of patients were not on any statin treatment. FH coded patients had a greater number of recorded blood pressure (BP) measurements (96.9% vs. 81.7%; p<0.001), but worse BP control (systolic BP ≥140 mmHg) (21.5% vs. 13.2%; diastolic BP≥90 mmHg 10.4 vs. 6.8% respectively, both p<0.001). Only 24/157 (15.3%) individuals had documented LDL-C reduced by recommended 50% from baseline values. Table 3.

3.6 Simon Broome (SB) criteria validated FH

48 adult patients (0.1%) were classified as likely to have FH using Simon Broome diagnostic criteria. We were unable to provide ethnic specific estimates due to low numbers (<10 in each ethnic group).

A summary of multilevel multivariable logistic regression models across five ethnic groups is provided in Table S4 (OR, 95%-CI). Reduced coding was seen with age (OR 0.88, 0.85-0.90), male gender (OR 0.51, 0.27-0.95). For those diagnosed according to SB criteria, use of regular and high potency high dose statin therapy were highly associated with FH diagnosis, (OR 855.4 303.8-2408.5) and (OR 3347.6, 1350.0-8300.9) respectively, both p<0.001. 17/48 (35%) individuals fulfilling SB criteria for FH had cholesterol values recorded and 3/48 (6%) had LDL-C values recorded; no individuals aged ≥30 years with cholesterol >9mmol/L; and one individual aged less than 30 with cholesterol >7.5mmol/L were coded as FH.
Of those with FH fulfilling SB criteria; available recorded cholesterol was >7.5mmol/L in 1/48 (2%) of those under 30; and none in those over 30.

There were no FH coded individuals with cholesterol over 9mmol/L and family history of CVD in those aged over 30 years. Similarly we found no FH coded individuals with cholesterol over 7.5mmol/L with family history of CVD in those younger than 30 years.

Out of 72 adults with coded family history of premature CHD, none fulfilled SB criteria for FH. [Table S5]

4. Discussion

4.1 FH prevalence and determinants of coding

This study found 801 patients had clinically coded diagnosis of FH. The age-adjusted FH prevalence rate was highest in the Other Asian and Bangladeshi ethnic groups, with lowest rates in the Chinese, Missing and Black African/Black Caribbean ethnic groups.

In partially adjusted models, older age was significantly associated with increased likelihood of FH coding, however this association was reversed in the fully adjusted model, after adjusting for lifestyle factors, co-morbidities, lipid lowering drugs and GP consultation frequency.

In the fully adjusted model adjusted for practice, Black African, Black Caribbean and Indian ethnic groups were less likely to have FH coding and Other Asians were likely to have higher levels of FH coding. Males, non-English speakers, and individuals in the most deprived income quintile were least likely to have a FH coding compared to females, English speakers, and those in the least deprived income quintile, respectively. A lower likelihood of FH coding was associated with the presence of other CVD risk factors such as smoking, obesity, hypertension, CKD, diabetes, or established CVD. A graphical overview of the study findings is included (Graphical Abstract).

4.2 Risk factor management

The presence of hypercholesterolaemia as indicated by any statin use (OR 132,100-173) or the use of high-potency high-dose statin therapy (OR 204,158-263) was highly associated with coded FH coding as the prescription of statin therapy is common with total elevated cholesterol irrespective of calculated CVD risk (20). Despite a diagnosis of FH, 20% of coded patients were not on any lipid-lowering treatment. In this population, only 24/157 (15%) patients with recorded LDL-C measurements attained the recommended LDL-C reduction of 50% (6). If hypertension was present, ~20% of FH coded patients did not achieve NICE target BP guidance, despite having had a greater number of blood pressure (BP) measurements taken. Sensitivity analyses using FH diagnosed using Simon Broome criteria showed similar results, but was underpowered due to low numbers.

4.3 Comparison with existing literature

This study identified lower prevalence of coded FH in Black African, Black Caribbean and Indian ethnic groups and increased levels in Other Asian compared to White ethnic groups in South East London. A study in North East London found an over-representation of individuals of South Asian ethnicity (not seen in Black African or White individuals) identified using the FAMCAT tool (11) for FH risk stratification, although this, like this study, was not based on genetically confirmed cases (21). This effect is likely driven by the excess rate of premature CVD seen in Indian South Asian populations. As the worldwide prevalence of FH cases is 1 in 250-350 (0.3-0.4%), (1-3) this suggests health inequalities exist due to cases being missed in Black African and Black Caribbean ethnic groups.
Inequality in diagnosis of FH, an autosomal dominant disorder, by gender were seen in this study. Women are diagnosed with FH at an older age compared to men but men are commenced on lipid-lowering therapy at a younger age compared to females in the Simon Broome cohort study in the UK (22, 23). A cross-sectional study in 15,015 participants in Brazil found that prevalence of ascertained FH, based on DLCN specific scores varied significantly by ethnic group, with classifications of ‘Whites’, ‘Browns’ and ‘Blacks’ giving prevalence values of 1 in 417, 1 in 204 and 1 in 156 (p<0.001) respectively (24). Similar findings have previously been reported in the UK (22, 23), the CASCADE SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE-FH) registry in the USA (25) and in Canada (26). A recent systematic review and meta-analysis revealed variation across ethnicity in FH diagnoses using a range of diagnostic algorithms with and without genetic testing, ranging from 0.25% (1:400) to 0.52% (1:192), with the highest prevalence seen among the Black and Brown (from Brazil) and the lowest among the (SE) Asian individuals; however the White group showed highly heterogeneous results (I²=96) and numbers were low in the Brown ethnicity group (n=20). (27)

The findings of lower levels of FH coding amongst non-English speakers and ethnic groups with high levels of deprivation mirror those in non-FH populations and are of concern as deprivation is associated with a higher incidence of CVD and CVD mortality (28, 29), and access to genomic testing.(30) These variations may represent differential rates of access, coding, detection, or mis-diagnosis. The poor documentation of the key CVD risk factors associated with diagnosis of FH of recorded LDL-C (19.6%) and family history of CVD (0.12%) will limit FH ascertainment and diagnosis in this cohort and may limit the application of electronic health care record searches.

The combination of raised cholesterol in FH with additional CVD risk factors such as smoking and obesity increase CVD risk. Our findings of lower FH coding in smokers and obese individuals are also likely to represent health inequality as these are higher risk groups for CVD but differ from other studies. A higher rate of suboptimal treatment has previously been reported in smokers in Israel, (31) which may reflect either patient attitudes to CVD risk or inequalities in access to health care. The prevalence of these risk factors combined with poor lipid and blood pressure management implies a high level of untreated CVD risk. Furthermore, these discrepancies are exacerbated in some ethnic groups (lowest recorded LDL-C % in White, Black African, Chinese, and ‘Other’ ethnic groups with FH, p<0.001), despite the fact that LDL-C was more likely to be recorded in the lowest 4 and 5th income quintiles in this study (p=0.002). Data from the CASCADE-FH registry in the USA also showed Asian and Black individuals were 40-50% less likely to achieve target LDL-C reduction than Whites (25) again suggesting major inequalities in knowledge and access.

Statin use was highly associated with FH coding and this could be attributed to reverse causality (a proxy for hypercholesterolaemia) or delayed FH diagnosis. A cohort study design could look at temporality of medication use in relation to FH coding although this was not possible with a cross-sectional design. In this study, only 80% of FH diagnosed patients were on statin management and the majority did not achieve LDL-C reduction of 50%.

Other studies have recognised sub-optimal knowledge and management with only a minority of patients with FH are started on high potency statins and modest reduction in cholesterol levels (32, 33). Inequalities associated with younger age, ethnicity and primary prevention status have also been documented in other studies (31) and likely reflect poor knowledge about FH and its management.

4.4 Strengths and limitations
A key strength of this study was the well characterised ethnically and socioeconomically diverse population studied. The data had a high representation of Black African, Black
Caribbean, Asian and “Other” ethnic groups which allows for thorough examination of these ethnicities and association with FH coding. These groups are at higher risk of CVD, independently due to co-morbidities such as hypertension which is substantially increased by the presence of FH. Another strength was the use of sequential multilevel modelling, allowing for practice effects.

Limitations included missing data which may result in bias in the exposures and outcomes reported. Another limitation was the inability to capture unmeasured confounders such as medication adherence and other lifestyle variables. Quantitative bias analysis could provide an estimate of uncertainty arising from systematic errors, here likely from FH misclassification (including misdiagnosis) and errors in recording of variables (smoking, obesity, ethnicity). The numbers of individuals with FH in some ethnic groups (apart from White, Black African and Black Caribbean groups) were small, which may result in low power. However, ethnicity recording is currently high in primary care records and could be triangulated with country of birth and mother language to obtain a more detailed picture. Genetic testing data was unavailable which may have resulted in misclassification of FH. Although we carried out a re-analysis using Simon Broome criteria; due to missing lipid data (total cholesterol (35%) and LDL-C (6%)) and low numbers our results were underpowered.

The data sampled for this study did not include links to Hospital Episode Statistics data on referrals for FH or genetic diagnosis (most individuals would be referred to a single local site for this). Though secondary care communications do provide data on FH diagnosis and any pathogenic changes found how well these are transcribed to primary care record is unclear. A survey of hospital data for the locality showed that 102 patients had been coded as likely FH by the centre of which 49 received a diagnosis of monogenic FH (A.S. Wierzbicki; personal communication).

4.5 Implications for the future practice
We have identified ethnic inequalities, with lower rates of FH coding for Black African, Black Caribbean and Indian ethnic groups and in individuals with known risk factors for CVD including male gender, obesity, smoking, comorbidities, non-English speakers, and lower income groups. Resources should be targeted to identify the potential under reporting of FH in these groups. We found suboptimal management of CVD risk across all ethnic groups with poor lipid and blood pressure management of FH patients. Appropriate disease management and pharmacotherapy should be in place for these patients who are at risk of premature morbidity and mortality to reduce avoidable inequalities.

4.6 Conclusion
The results from this study are clinically important as they highlight areas of unmet need in accurate diagnostic coding and management of FH. We identified health inequalities with lower level of FH coding in Black African, Black Caribbean and Indian ethnic groups, men, and individuals with existing CVD risk factors and co-morbidities which would benefit from targeted, culturally sensitive interventions to improve health outcomes. Specific focus should look at early reduction of risk factors which are easily modifiable, including improved cholesterol screening and treatment, assessment of smoking and long-term conditions. Future clinical research and guidelines should aim to improve recording and management of FH. With improved lipid management and reducing other modifiable CVD risk, the risk of CVD can be significantly reduced, thus improving patient quality of life and avoiding premature mortality.
**Table 1: Summary characteristics of 332, 357 adults ≥ 18 years* in Lambeth, South London**
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<td>Familial Hypercholesterolaemia Simon Broome criteria</td>
<td>34 (0.7)</td>
<td>2 (0.04)</td>
<td>2 (0.04)</td>
<td>7 (0.15)</td>
<td>1 (0.02)</td>
<td>2 (0.04)</td>
<td>46 (0.01)</td>
<td>p=0.18</td>
</tr>
<tr>
<td>Men</td>
<td>18 (0.72)</td>
<td>1 (0.04)</td>
<td>1 (0.04)</td>
<td>4 (0.16)</td>
<td>9 (0.0)</td>
<td>1 (0.04)</td>
<td>25 (0.02)</td>
<td>p=0.49</td>
</tr>
<tr>
<td>Women</td>
<td>16 (0.70)</td>
<td>1 (0.04)</td>
<td>1 (0.04)</td>
<td>3 (0.13)</td>
<td>1 (0.04)</td>
<td>1 (0.04)</td>
<td>23 (0.01)</td>
<td>p=0.52</td>
</tr>
<tr>
<td>Family History Premature CHD</td>
<td>35 (0.03)</td>
<td>3 (0.01)</td>
<td>4 (0.02)</td>
<td>7 (0.02)</td>
<td>2 (0.03)</td>
<td>1 (0.0)</td>
<td>72 (0.02)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15,111 (8.3)</td>
<td>7,894 (20.1)</td>
<td>6,670 (23.9)</td>
<td>4,220 (10.0)</td>
<td>458 (7.2)</td>
<td>1,869 (5.4)</td>
<td>36,218 (10.9)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1,243 (0.7)</td>
<td>438 (1.1)</td>
<td>527 (1.9)</td>
<td>276 (0.7)</td>
<td>35 (0.6)</td>
<td>147 (0.4)</td>
<td>2,666 (0.8)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>2,767 (1.5)</td>
<td>368 (0.9)</td>
<td>606 (2.2)</td>
<td>775 (1.3)</td>
<td>64 (1.0)</td>
<td>200 (0.6)</td>
<td>4,780 (1.4)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1,184 (0.7)</td>
<td>120 (0.3)</td>
<td>230 (0.7)</td>
<td>302 (0.7)</td>
<td>20 (0.3)</td>
<td>77 (0.3)</td>
<td>1,933 (0.6)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>405 (0.2)</td>
<td>104 (0.3)</td>
<td>127 (0.5)</td>
<td>82 (0.2)</td>
<td>9 (0.1)</td>
<td>38 (0.1)</td>
<td>765 (0.2)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>2,596 (1.4)</td>
<td>906 (2.3)</td>
<td>1,171 (4.2)</td>
<td>609 (1.5)</td>
<td>66 (1.0)</td>
<td>230 (0.7)</td>
<td>5,580 (1.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>5,436 (3.0)</td>
<td>3,788 (3.7)</td>
<td>3,471 (12.5)</td>
<td>3,353 (8.1)</td>
<td>210 (3.3)</td>
<td>755 (2.2)</td>
<td>17,023 (5.1)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

## Socio-economic indicators

### IMD income quintiles

<table>
<thead>
<tr>
<th>quintile</th>
<th>1 (least deprived)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (most deprived)</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (least deprived)</td>
<td>46,647 (25.8)</td>
<td>3,575 (9.2)</td>
<td>3,599 (13.0)</td>
<td>9,062 (22.1)</td>
<td>1,502 (23.6)</td>
<td>6,761 (19.8)</td>
</tr>
<tr>
<td>2</td>
<td>38,164 (21.1)</td>
<td>5,030 (12.9)</td>
<td>4,259 (15.3)</td>
<td>8,468 (20.7)</td>
<td>1,248 (19.6)</td>
<td>6,579 (19.3)</td>
</tr>
<tr>
<td>3</td>
<td>37,656 (20.3)</td>
<td>6,937 (17.9)</td>
<td>6,294 (19.1)</td>
<td>8,331 (20.4)</td>
<td>1,253 (19.7)</td>
<td>6,525 (19.1)</td>
</tr>
<tr>
<td>4</td>
<td>32,814 (18.2)</td>
<td>10,402 (26.7)</td>
<td>8,374 (22.9)</td>
<td>8,211 (20.1)</td>
<td>1,189 (18.7)</td>
<td>7,106 (20.8)</td>
</tr>
<tr>
<td>5 (most deprived)</td>
<td>25,439 (14.1)</td>
<td>13,064 (33.5)</td>
<td>8,257 (23.7)</td>
<td>6,870 (16.8)</td>
<td>1,161 (18.3)</td>
<td>7,198 (21.1)</td>
</tr>
</tbody>
</table>

### Lifestyle indicators

#### BMI

<table>
<thead>
<tr>
<th>BMI</th>
<th>Not Overweight (BMI &lt; 25 kg/m²)</th>
<th>Overweight (BMI 25-29 kg/m²)</th>
<th>Obese (BMI &gt;30 kg/m²)</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>92,982 (50.9)</td>
<td>11,265 (28.7)</td>
<td>8,833 (31.7)</td>
<td>18,469 (44.5)</td>
</tr>
<tr>
<td>No</td>
<td>139,173 (76.1)</td>
<td>33,086 (84.2)</td>
<td>28,223 (89.1)</td>
<td>13,467 (35.7)</td>
</tr>
</tbody>
</table>

#### Smoking

| Smoking missing | 5,436 (3.0) | 1,589 (4.5) | 817 (2.3) | 1,855 (4.4) | 436 (6.8) | 8,510 (24.7) | 0 (0.0) | p<0.001 |
| High dose statin * *** | 6,390 (3.5) | 1,722 (4.4) | 1,705 (6.1) | 1,891 (4.6) | 178 (2.6) | 606 (1.8) | 12,491 (3.8) | p<0.001 |
| Frequency of GP Attendance in Last Year

#### Frequency of GP Attendance in Last Year

<table>
<thead>
<tr>
<th>Frequency</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 visits</td>
<td>129,952 (71.1)</td>
</tr>
<tr>
<td>4-6 visits</td>
<td>37,971 (14.4)</td>
</tr>
</tbody>
</table>

#### GP Practice Size

<table>
<thead>
<tr>
<th>Practice Size</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5,000</td>
<td>47,319 (25.9)</td>
</tr>
<tr>
<td>5,000-10,000</td>
<td>117,290 (64.2)</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>18,150 (9.9)</td>
</tr>
</tbody>
</table>

* p-value indicates significant difference from groups within category (e.g. Ethnicity – reference group is White ethnic) p<0.001. 100% is age and col specific by ethnicity, e.g. % of White ethnic group with FH

** Statin grouping: See Figure 4. *Any statin* also includes other lipid lowering drugs such as fibrates

---

**Notes:**
- BMI: Body Mass Index
- CHD: Coronary Heart Disease
- FH: Family History
- GP: General Practitioner
- IMD: Index of Multiple Deprivation
- P: Probability
- p<0.001 indicates statistical significance at the p=0.001 level.
**p-value indicates significant difference from groups within category (e.g. Ethnicity – reference group is White ethnicity) \( p<0.001 \).

100% is age and column specific by ethnicity, e.g., % of White ethnic group with FH.
**Table 2: Multilevel multivariable logistic regression models for diagnosed FH in 332, 357 adults aged ≥18 years, in Lambeth, South London**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ethnicity</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Caribbean</td>
<td></td>
<td>0.51 (0.38-0.69) (b)</td>
<td>0.48 (0.36-0.64) (b)</td>
<td>0.48 (0.36-0.64) (b)</td>
<td>0.51 (0.38-0.69) (b)</td>
<td>0.50 (0.37-0.67) (b)</td>
<td>0.50 (0.37-0.68) (b)</td>
</tr>
<tr>
<td>Bangladeshi</td>
<td></td>
<td>1.68 (0.79-3.56)</td>
<td>1.62 (0.76-3.44)</td>
<td>1.62 (0.76-3.44)</td>
<td>1.85 (0.87-3.94)</td>
<td>1.83 (0.86-3.90)</td>
<td>1.00 (0.46-2.17)</td>
</tr>
<tr>
<td>Pakistani</td>
<td></td>
<td>0.92 (0.49-1.74)</td>
<td>0.92 (0.49-1.73)</td>
<td>0.92 (0.49-1.73)</td>
<td>0.97 (0.52-1.84)</td>
<td>0.97 (0.51-1.84)</td>
<td>0.63 (0.33-1.20)</td>
</tr>
<tr>
<td>Indian</td>
<td></td>
<td>0.93 (0.59-1.47)</td>
<td>0.67 (0.42-1.07)</td>
<td>0.67 (0.42-1.07)</td>
<td>0.71 (0.44-1.13)</td>
<td>0.73 (0.46-1.17)</td>
<td>0.55 (0.34-0.89)</td>
</tr>
<tr>
<td>Asian Other</td>
<td></td>
<td>1.93 (1.51-2.46)</td>
<td>1.96 (1.53-2.50)</td>
<td>1.96 (1.53-2.50)</td>
<td>2.11 (1.64-2.70)</td>
<td>2.11 (1.64-2.71)</td>
<td>1.34 (1.01-1.76)</td>
</tr>
<tr>
<td>Chinese</td>
<td></td>
<td>0.38 (0.14-1.02)</td>
<td>0.38 (0.14-1.01)</td>
<td>0.38 (0.14-1.01)</td>
<td>0.43 (0.16-1.25)</td>
<td>0.45 (0.17-1.22)</td>
<td>0.45 (0.17-1.22)</td>
</tr>
<tr>
<td>Arab</td>
<td></td>
<td>1.33 (0.19-9.57)</td>
<td>1.44 (0.20-10.37)</td>
<td>1.44 (0.20-10.38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>0.81 (0.57-1.15)</td>
<td>0.89 (0.63-1.27)</td>
<td>0.89 (0.63-1.27)</td>
<td>0.94 (0.65-1.36)</td>
<td>0.97 (0.67-1.40)</td>
<td>0.85 (0.59-1.23)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>0.78 (0.44-1.40)</td>
<td>0.88 (0.49-1.57)</td>
<td>0.88 (0.49-1.57)</td>
<td>0.95 (0.53-1.71)</td>
<td>1.03 (0.58-1.84)</td>
<td>1.10 (0.61-1.98)</td>
</tr>
<tr>
<td>Variable</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Socio-deprivation quintiles</td>
<td>1 (least deprived)</td>
<td>1.04 (1.04-1.04)</td>
<td>1.04 (1.04-1.04)</td>
<td>1.04 (1.04-1.04)</td>
<td>1.04 (1.03-1.04)</td>
<td>0.96 (0.96-0.97)</td>
<td>0.75 (0.65-0.87)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.99 (0.86-1.14)</td>
<td>0.99 (0.86-1.14)</td>
<td>0.99 (0.86-1.14)</td>
<td>1.04 (0.90-1.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>English speaker</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Non English speaker</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>0.75 (0.58-0.97)</td>
<td>0.74 (0.57-0.95)</td>
<td>0.74 (0.57-0.95)</td>
<td>0.68 (0.52-0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle indicators</td>
<td>Obese (BMI &gt;30 kg/m²) vs non obese</td>
<td>1.25 (1.04-1.48)</td>
<td>1.25 (1.04-1.48)</td>
<td>1.25 (1.04-1.48)</td>
<td>1.25 (1.04-1.48)</td>
<td>0.80 (0.67-0.95)</td>
<td>0.80 (0.67-0.95)</td>
</tr>
<tr>
<td>Smoking Status</td>
<td>Non-smoker</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Current smoker</td>
<td></td>
<td>0.84 (0.68-1.04)</td>
<td>0.84 (0.68-1.04)</td>
<td>0.84 (0.68-1.04)</td>
<td>0.84 (0.68-1.04)</td>
<td>0.68 (0.55-0.85)</td>
<td>0.68 (0.55-0.85)</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td>0.27 (0.10-0.75)</td>
<td>0.27 (0.10-0.75)</td>
<td>0.27 (0.10-0.75)</td>
<td>0.27 (0.10-0.75)</td>
<td>0.32 (0.11-0.88)</td>
<td>0.32 (0.11-0.88)</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>Hypertension</td>
<td>0.62 (0.52-0.74)</td>
<td>0.62 (0.52-0.74)</td>
<td>0.62 (0.52-0.74)</td>
<td>0.62 (0.52-0.74)</td>
<td>0.62 (0.52-0.74)</td>
<td>0.62 (0.52-0.74)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>0.31 (0.25-0.39)</td>
<td>0.31 (0.25-0.39)</td>
<td>0.31 (0.25-0.39)</td>
<td>0.31 (0.25-0.39)</td>
<td>0.31 (0.25-0.39)</td>
<td>0.31 (0.25-0.39)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td></td>
<td>0.64 (0.41-0.99)</td>
<td>0.64 (0.41-0.99)</td>
<td>0.64 (0.41-0.99)</td>
<td>0.64 (0.41-0.99)</td>
<td>0.64 (0.41-0.99)</td>
<td>0.64 (0.41-0.99)</td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td>0.47 (0.36-0.63)</td>
<td>0.47 (0.36-0.63)</td>
<td>0.47 (0.36-0.63)</td>
<td>0.47 (0.36-0.63)</td>
<td>0.47 (0.36-0.63)</td>
<td>0.47 (0.36-0.63)</td>
</tr>
<tr>
<td>Medications</td>
<td>No statin</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Regular statin</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>High dose statin</td>
<td></td>
<td>131.81 (100.49-172.89)</td>
<td>131.81 (100.49-172.89)</td>
<td>131.81 (100.49-172.89)</td>
<td>131.81 (100.49-172.89)</td>
<td>203.71 (157.54-263.41)</td>
<td>203.71 (157.54-263.41)</td>
</tr>
<tr>
<td>GP consultation frequency in last 12 months</td>
<td>0-3 visits</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>4-6 visits</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>7+ visits</td>
<td></td>
<td>0.94 (0.78-1.14)</td>
<td>0.94 (0.78-1.14)</td>
<td>0.94 (0.78-1.14)</td>
<td>0.94 (0.78-1.14)</td>
<td>0.81 (0.67-0.97)</td>
<td>0.81 (0.67-0.97)</td>
</tr>
<tr>
<td>GP Variance Effect</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

\(a\) OR, \(b\) 95% confidence interval.
Table 2 Key:
Model 1 examines ethnicity and FH coded diagnosis;
Model 2 examines ethnicity, age and FH coded diagnosis.
Model 3 examines ethnicity, gender and FH coded diagnosis.
Model 4 examines ethnicity, age, gender, income quintile rankings, language and FH coded diagnosis.
Model 5 examines ethnicity, age, gender, income quintile rankings, lifestyle factors and FH coded diagnosis.
Model 6 (fully adjusted model) examines ethnicity, age, gender, income quintile rankings, English as a first language, lifestyle factors, medications, co-morbidities, GP attendance frequency and FH coded diagnosis.

* $p<0.05$

$^b p<0.001$
Table 3: Quality of care measures by FH status in adults aged 18 years and over in Lambeth, South London

<table>
<thead>
<tr>
<th>Variables</th>
<th>FH not diagnosed N (%)</th>
<th>FH diagnosed N (%)</th>
<th>TOTALN (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recorded FH CVD</td>
<td>71 (0.02)</td>
<td>1 (0.12)</td>
<td>72 (0.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>No statin or fibrate</td>
<td>297,475 (90.1)</td>
<td>161 (20.1)</td>
<td>297,636 (89.6)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Regular statin or fibrate</td>
<td>12,279 (3.7)</td>
<td>212 (26.5)</td>
<td>12,491 (3.8)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>High dose statin(^{19})</td>
<td>20,435 (6.2)</td>
<td>428 (53.4)</td>
<td>20,863 (6.3)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Recorded LDL-C</td>
<td>5,147 (1.65)</td>
<td>157 (19.6)</td>
<td>5,304 (1.70)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>50% reduction in LDL-C not achieved</td>
<td>4,918 (96.7)</td>
<td>133 (84.7)</td>
<td>5,051 (96.3)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>50% reduction in LDL-C achieved</td>
<td>169 (3.3)</td>
<td>24 (15.3)</td>
<td>193 (3.7)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Non or Ex-smoker</td>
<td>249,886 (79.9)</td>
<td>682 (85.6)</td>
<td>250,568 (79.9)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>63,058 (20.2)</td>
<td>115 (14.4)</td>
<td>63,173 (20.1)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>BMI &lt;30kg/m(^2)</td>
<td>220,920 (66.6)</td>
<td>583 (72.8)</td>
<td>221,503 (66.7)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>BMI ≥30kg/m(^2)</td>
<td>48,860 (14.7)</td>
<td>185 (23.1)</td>
<td>49,045 (14.8)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Missing BMI</td>
<td>61,776 (18.6)</td>
<td>33 (4.1)</td>
<td>61,809 (18.6)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>BP never measured</td>
<td>60,568 (18.3)</td>
<td>25 (3.1)</td>
<td>60,593 (18.2)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>BP measured</td>
<td>270,988 (81.7)</td>
<td>776 (96.9)</td>
<td>271,764 (81.8)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Systolic BP ≥ 140mm Hg</td>
<td>35,761 (13.2)</td>
<td>167 (21.5)</td>
<td>35,928 (13.2)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Systolic BP &lt; 140mm Hg</td>
<td>235,227 (86.8)</td>
<td>609 (78.5)</td>
<td>235,836 (86.8)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Diastolic BP ≥ 90mm Hg</td>
<td>18,341 (6.8)</td>
<td>81 (10.4)</td>
<td>18,422 (6.8)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Diastolic BP &lt; 90mm Hg</td>
<td>252,647 (93.2)</td>
<td>695 (89.6)</td>
<td>253,342 (93.2)</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>
Figure 1: Crude and age-adjusted coded FH prevalence in adults aged 18 years and over by ethnicity in Lambeth, South London

Crude prevalence of coded FH in adults aged ≥ 18 years by ethnicity

Age-adjusted prevalence of coded FH in adults aged ≥ 18 years by ethnicity
Acknowledgements:

Declaration of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions: MM and NQ contributed to the idea generation and protocol development. AK and MM prepared the data for analysis, and performed the statistical analyses with support from SA. All authors interpreted study results. AK and MM had primary responsibility in writing the manuscript. AW and NQ also contributed to manuscript writing. All authors critically reviewed the manuscript.

Acknowledgments: This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London and The NHS Race & Health Observatory. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

References:


**Reviewers' comments:**

Reviewer #1: There is evidence that people of various races and ethnicities are more prone to be impacted by FH. Emerging evidence from United States, for example, discovered that FH was more common in people of African, Hispanic, and Asian heritage than in people of European descent, and yet people from racial and ethnic minority groups may face delays in diagnosis and treatment for FH, which can result in poor health outcomes. However, whether similar disparities based on racial and social divide in other countries are not yet well studied. In this manuscript, the authors detail the prevalence and determinants of diagnosing and documenting FH via ICD codes in a large diverse primary care population in the UK of >300K patients over a 10 year period.

1.1 *Please provide more details on how the EMR based registry was created on criteria, data pull mechanism, quality measures, addressing gaps in labs/medications and other factors. These details will be much appreciated by the wide readership of Atherosclerosis.*

We have provided detail as requested see Methods P.4 para 1-2.

1.2 *Please provide specific % of missing relevant data*

We have included details on missing covariates such as smoking (5.6%) and BMI (18.6%) in the Summary Table 1 and summarised in the text. P. 6, para 1.

1.3 *Are there any prior studies on the accuracy of the reported ethnicity/race within these likely EMR based registries?*

We confirm high completeness of ethnicity recording in similar datasets; 82.3% for currently registered acceptable patients had an ethnicity recorded, which increased to 84.4% for acceptable patients registered after 1 April 2011, and 92.9% when restricted to acceptable patients with a registration date in the GP Quality Outcome Framework (QOF) incentivisation period. We agree ethnicity data recording is incomplete, which is common to most routinely collected data. We also examined country of birth and mother language to obtain a more detailed picture. This approach has already been implemented by members of our team as part of an algorithm to identify migrants in routinely collected health data.

We have cited a recent publication addressing this in the discussion. P9, para 3:


1.4 *Only about 0.24% of the population over the 10 yr period were coded as FH, which is likely very low prevalence by current standards. While understandably this may likely reflect physician inertia in recognition and formal diagnosis, it will be worthwhile if the authors can provide some more details if the diagnosis rate improved over the last 10 years? Clearly many ethnic groups have been less likely to be identified or coded as FH on the temporal cohort with likely equity implications. At the same time whether these were missed (under diagnosed) is question that is not addressed by the authors. One suggestion is to undertake similar efforts by and assessing whether an EMR based diagnosis which is not tied to 'diagnostic codes' alone can help identify these FH patients using EMR modified DLCN criteria and then compare whether the under diagnosis based on coding is a more systemic issues vs minorities are more likely to be missed The sensitivity, specificity, positive predictive value, negative predictive value for identifying FH patients via ICD 10 codes vs several cut points of the DLNC score can be used.*

We thank the reviewer for their helpful comments and have cited work which shows initiatives to improve FH ascertainment in the UK. We have carried out a re-analysis using Simon Broome criteria (there were insufficient data to carry out DLCN assessment) which suggested potential inequity in ascertainment for Black African, Black Caribbean and Other ethnic groups however due to low numbers in ethnic groups and
missing lipid data (total cholesterol (35%) and LDL-C (6%)) our results were underpowered and did not reach statistical significance. [Appendix Table 2S]

See some references for your team
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6662375/
How well can familial hypercholesterolemia be identified in an electronic health record database? - PubMed (nih.gov)
Familial Hypercholesterolemia Identification Algorithm in Patients with Acute Cardiovascular Events in A Large Hospital Electronic Database in Bulgaria: A Call for Implementation - PubMed (nih.gov)
We thank the reviewer for these references and have included some of these in our article.

1.5 An important piece of the paper is that diagnosis of FH is inversely related to social risk by the proxy area deprivation factors. Please provide insights in a sub analysis whether these social factors are also independently related to lower FH diagnosis in each ethnic subgroups or may present with differential impact.
We thank the reviewer and agree with this comment, analyses shows that deprivation is associated with lower levels of FH diagnosis, noted in P.6 para 1, and have already adjusted for this in our multivariable analysis (using income quintiles) [Table 2]. However as stated, we found no evidence of statistical interaction. P.6 para 6.

Reviewer #2:
I carefully read the manuscript “Assessment of Ethnic Inequalities in diagnostic coding of Familial Hypercholesterolaemia (FH): A Cross-Sectional Database Study in Lambeth, South London”.
This manuscript is very well written and the investigated topic is absolutely interesting and hot! I am confident that -if published- it will attract a lot of readers and collect a number of citations.
2.1 - Methods should be described more carefully and a sub-title “Statistical analysis” should be included at the end of the paragraph.
The text has been revised and Statistical Analysis has been cited accordingly.

- 2.2 All the abbreviations present in the manuscript should be defined at their first occurrence.
We have defined all abbreviations accordingly.

- 2.3 Could the authors distinguish between HeFH and HoFH?
This has been corrected (typographical error).

-2.4 I guess the authors confused "sex" with "gender", throughout the manuscript. According to WHO definition, sex refers to biological differences between males and females (e.g. gonads, sexual organs, chromosomes, hormones). Gender is a social, psychological and cultural construct and it is developed in the process of socialisation.
We have revised the text accordingly.

- The limitations of the analysis should be further and more deeply discussed.
We have expanded the limitation section. P. 9, para 4.

- In the manuscript, the authors include information as regards SBP. Could they refer also to DBP, please?
We have included data on diastolic blood pressure (DBP) accordingly. P. 7 para 1 and Table 3.

- In the manuscript, the authors should consider to refer to
We thank the reviewer for these suggestions; our model includes IMD quintile as a measure of socioeconomic deprivation and we have referenced accordingly in the discussion. We have also added a reference concerning the ethnic variation in FH ascertainment from a recent systematic review.

Reviewer #3: This interesting manuscript reports on Ethics inequalities in the diagnostic coding of familial hypercholesterolaemia (FH) from a cross-sectional analysis of 332,357 adult patients from 40 practices in Lambeth, UK. Compared to White ethnicity, lower likelihood of diagnosed FH was seen in Black African, Black Caribbean and Indian ethnic groups in contrast to higher levels in other Asian ethnic groups.

The manuscript is of interest but there are a few points the authors should address:
1. The diagnosis of FH was based on clinical coding and not on genetic testing which is acknowledged by the Authors but which is a major flaw and needs to be mentioned in more detail under limitations.
2. The prevalence in Black African was perceived as being lower and was about half of that seen in the white Ethnic group. However, is this prevalence perhaps true and not perceived? As far as I am aware there is no data from the African continent to show the prevalence of FH in the Black African population. It may well be less that in the Western world. If there are studies, please reference. If not, please comment.
3. The White, Black African and Black Caribbean cohorts were large but numbers in the other 8 Ethnic groups were small so this also needs to be mentioned as a limitation of the study as one cannot extrapolate results from such small cohorts.

We have acknowledged this in the limitations section. Discussion P. 9.

Minor points.
1. “Adapted Simon Broom criteria under validation of FH codes needs to be explained more fully.
We have explained this in more detail. P. 4 “Identification of coding status”
2. In Table 1 the total number of FH patients in each of the Ethnic cohorts should be included and not just that of male/female. Totals should also be included as a N number under variables in Table 3.
We have updated Table 1 accordingly for both FH diagnostically coded individuals and those who fulfil FH Simon Broome Criteria.

Editorial Office comments:
When revising your manuscript, please follow carefully the recommendations of our Atherosclerosis Style Guide to be downloaded from the following link:
https://eur03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fcdn.elsevier.com%2Fpromis_misc%2F_Atherosclerosis_style_guide_checklist.docx&data=05%7C01%7Cmariam.molokhia%40kcl.ac.uk%7C9bbbe7c64863413c500708db24969811%7C8370cf1416f34c16bb3c724071654356%7C0%7C0%7C638144001718503868%7CUnknown%7CTWfpbGZsb3d8eyJWljoiMC4wLjAwMDAiLCJQIjoiV2luMzliLCJBTiI6IkJTlTlIiLCJXVCi6Mn0%3D%7C3000%7C%7C%7C&sdata=D%2B8LypzqKGITPdiwXewV노o3ZG7e5ILszxZExD84xc%3D&reserved=0
- Make sure to apply the formatting requirements to all figures and tables where necessary (e.g. style of p values, gene and protein nomenclature).
- Make sure to use uniform lettering and sizing of your original artwork, including letters to indicate panels, throughout all figures.
- Make sure to submit high resolution versions of each figure.
- A graphical abstract is required at revision.

We have addressed these points.
Professor Kronenberg
Atherosclerosis Editor

Re: Assessment of Ethnic Inequalities in diagnostic coding of Familial Hypercholesterolaemia (FH)

Authors: Mariam Molokhia, Anthony S. Wierzbicki, Helen Williams, Arushan Kirubakaran, Rohan Devani, Stevo Durbaba, Salma Ayis, Nadeem Qureshi

Dear Professor Kronenberg,

I hope this finds you well.

Many thanks for your consideration of our paper “Assessment of Ethnic Inequalities in diagnostic coding of Familial Hypercholesterolaemia (FH)” for Atherosclerosis.

I confirm submission of our article to Atherosclerosis implies that the work described has not been published previously, except in the form of an abstract or as part of a published lecture or academic thesis.

I look forward to hearing from you in due course.

yours sincerely,

Mariam Molokhia

Reader in Epidemiology & Primary Care
https://kclpure.kcl.ac.uk/portal/mariam.molokhia.html
STROBE Checklist—all items completed.

STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

<table>
<thead>
<tr>
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(b) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** 2 | Explain the scientific background and rationale for the investigation being reported |
| **Objectives** 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** 4 | Present key elements of study design early in the paper |
| **Setting** 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| **Participants** 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants |
| **Variables** 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| **Data sources/measurement** 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| **Bias** 9 | Describe any efforts to address potential sources of bias |
| **Study size** 10 | Explain how the study size was arrived at |
| **Quantitative variables** 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| **Statistical methods** 12 | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) If applicable, describe analytical methods taking account of sampling strategy |
| **Results** 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
(b) Give reasons for non-participation at each stage  
(c) Consider use of a flow diagram |
| **Descriptive data** 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
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| **Outcome data** 15* | Report numbers of outcome events or summary measures |
| **Main results** 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
(b) Report category boundaries when continuous variables were categorized  
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| **Other analyses** 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** 18 | Summarise key results with reference to study objectives |
| **Limitations** 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| **Interpretation** 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| **Generalisability** 21 | Discuss the generalisability (external validity) of the study results |
| **Other information** 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for exposed and unexposed groups.
Monday, 13 February 2023

Professor Kronenberg
Atherosclerosis Editor

Re: Assessment of Ethnic Inequalities in diagnostic coding of Familial Hypercholesterolaemia (FH)

Authors: Mariam Molokhia, Anthony S. Wierzbicki, Helen Williams, Arushan Kirubakaran, Rohan Devani, Stevo Durbaba, Salma Ayis, Nadeem Qureshi

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Many thanks for your consideration of our paper “Assessment of Ethnic Inequalities in diagnostic coding of Familial Hypercholesterolaemia (FH)” for Atherosclerosis.

I look forward to hearing from you in due course.

yours sincerely,

Dr. Mariam Molokhia

Reader in Epidemiology & Primary Care

https://kclpure.kcl.ac.uk/portal/mariam.molokhia.html
STROBE Checklist—Checklist of items that should be included in reports of cross-sectional studies

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
Atherosclerosis style guide checklist

Atherosclerosis applies format guidelines to all accepted papers, with the aim of improving their readability.

Manuscripts that do not conform to the format guidelines of the Atherosclerosis Journal will be returned to the authors for reformatting.

Please find below a questionnaire to guide authors to comply with the formatting requirements for revised submissions. For more detailed information, visit our website.

Please note that when you answer “No” to a question, editing of your manuscript is required before submission to Atherosclerosis.

Manuscript structure and style

Does your manuscript contain all the below essential elements, in this order? Yes

- Title
- Authors, Affiliations, Contact Information
- Abstract in the Atherosclerosis format (Background and aims, Methods, Results, Conclusions)
- Introduction
- Materials and methods (or Patients and methods)
- Results
- Discussion
- Conflict of interest (mandatory)
- Financial support (if applicable)
- Author contributions (mandatory)
- Acknowledgements (if applicable)
- References
- Figures and Tables (with legends in the suitable style)

Abstract style

Is the Abstract structured in the below sections? Yes

- Background and aims
- Methods
- Results
- Conclusions

Figure and table legends

Are figure and table legends formatted as described below? Yes

Each figure and table legend should have a brief overarching title that describes the entire figure without citing specific panels, followed by a description of each panel, and all symbols used.

If a figure or table contains multiple panels, the letter describing each panel should be capitalized and surrounded by parenthesis: i.e. (A)(B)(C)(D).

Please make sure to apply the formatting requirements to figures and tables where necessary (e.g. style of p values, gene and protein nomenclature).

Footnotes to tables

Are footnotes to tables formatted as described below? Yes

Footnotes to tables should be listed with superscript lowercase letters, beginning with “a.” Footnotes must not be listed with numbers or symbols.

Abbreviations

Are abbreviations defined when first used in the text? Yes
Use of abbreviations should be kept at a minimum.

**Units**
Are units expressed following the international system of units (SI)?

Yes

If other units are mentioned, please provide conversion factors into SI units.

**DNA and protein sequences**
Are gene names italicized?

Yes

Gene names should be italicized; protein products of the loci are not italicized.

For murine models, the gene and protein names are lowercase except for the first letter.
(e.g., gene: Abcb4; protein: Abcb4)

For humans, the whole gene name is capitalized.
(e.g., gene: ABCB4; protein ABCB4)

**Mouse strains and cell lines**
Are knock-out or transgenic mouse strains and cell lines italicized and the symbol superscripted?

Yes

(e.g. ob/ob, p53+/+, p53+/−)

**p values**
Are p values consistently formatted according to the below style throughout the manuscript (including figures and tables)?

Yes

p <X
p >X
p=X

**Language**
Is your manuscript written in good English?

Yes

Please make sure that you consistently use either American or British English, but not a mixture of them.

Please make sure that words are written consistently in the same way throughout the manuscript.

e.g. non-significant or nonsignificant

e.g. down-regulation or downregulation

**Artwork**
Have you submitted high-resolution versions of your original artwork?

Yes

Please make sure to use uniform lettering and sizing in your original artwork, including letters to indicate panels, consistently throughout all figures.

**Atherosclerosis policy on the use of proper terminology when referring to intima-media thickness (IMT)**

Atherosclerosis has recently embraced a new editorial policy to clarify the use of proper terminology when referring to intima-media thickness (IMT):

**IMT should be referred to as “arterial injury” or “arteriopathy”, not atherosclerosis.**

For more details, please see the following letter to the editor and reply published in Atherosclerosis

“Carotid intima-media thickness should not be referred to as subclinical atherosclerosis: A recommended update to the editorial policy at Atherosclerosis”, Raggi and Stein 2020 (https://doi.org/10.1016/j.atherosclerosis.2020.09.015)

**Use of the terms “sex” vs. “gender”**

These terms should be used correctly, corresponding to the WHO definitions: [http://www.who.int/gender/whatisgender/](http://www.who.int/gender/whatisgender/)

“Sex” refers to the biological and physiological characteristics that define men and women. “Gender” refers to the socially constructed roles, behaviours, activities, and attributes that a given society considers appropriate for men and women.

**Graphical abstract**

The graphical abstract is mandatory at submission of the revised version of the paper.

**Technical requirements**

- **Size:** Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi
- **Font type and font size:** Calibri 18
- **Preferred file types:** TIFF, EPS, PDF or MS Office files
- **Content:** the abstract should consist of one single panel

**Content**

**Keep it simple**

The graphical abstract should:

- Have a clear start and end, "reading" from top-to-bottom or left-to-right
- Emphasize the new findings from the current paper without including excess details from previous literature
- Avoid the inclusion of features that are more speculative (unless the speculative nature can be made apparent visually)
- Not be too text-heavy; most of the content should be in a graphical form
- Use simple labels

Some examples of graphical abstracts:

Lahelma et al. 2022, Atherosclerosis; Volume 363 Pages 22-29 (December 2022)
Clarke et al., *Atherosclerosis*; Volume 354 Pages 15-22 (August 2022)

Katra et al. *Atherosclerosis*; Volume 366 Pages 1-7 (February 2023)

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Author contribution: MM and NQ contributed to the idea generation and protocol development. AK and MM prepared the data for analysis, and performed the statistical analyses with support from SA. All authors interpreted study results. AK and MM had primary responsibility in writing the manuscript. AW and NQ also contributed to manuscript writing. All authors critically reviewed the manuscript.