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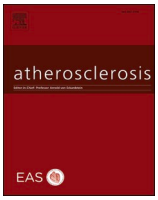

Assessment of ethnic inequalities in diagnostic coding of familial hypercholesterolaemia (FH): A cross-sectional database study in Lambeth, South London

Mariam Molokhia [a,b,*], Anthony S. Wierzbicki [c,d], Helen Williams [e], Arushan Kirubakaran [a,b], Rohan Devani [b], Stevo Durbaba [a,b], Salma Ayis [b], Nadeem Qureshi [f]

[a] School of Life Course and Population Sciences, United Kingdom
[b] King's College London, United Kingdom
[c] Department of Metabolic Medicine/Chemical Pathology, United Kingdom
[d] Guy's & St Thomas' Hospitals, United Kingdom
[e] Consultant Pharmacist for CVD, Medicines Use and Safety Team & South East London ICS, United Kingdom
[f] Department of Primary Care, University of Nottingham, United Kingdom

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ABSTRACT

Background and aims: Differences in the perceived prevalence of familial hypercholesterolemia (FH) by ethnicity are unclear. In this study, we aimed to assess 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 to 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.

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

* Corresponding author.
E-mail address: mariam.molokhia@kcl.ac.uk (M. Molokhia).

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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.

2. Patients 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 (Supplementary 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 (Supplementary 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 >9 mmol/L ≥ 30 years) and excluding those with baseline triglyceride, (TG) 2.3 mmo/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), (Supplementary 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

Table 1
Summary characteristics of 332, 357 adults ≥18 years* in Lambeth, South London.

Ethnicity								
Variables N (%)	White N (%)	Black African N (%)	Black Caribbean N (%)	Other N (%)	Unknown N (%)	Missing N (%)	Total N (%) * total population 328, 948	p-values **
All	1,81,923	38,712	27,535	20,814	6,257	33,530	3,28,948	$p <$ 0.001
Men	90,473 (49.7)	19.099 (49.3)	12,577 (45.7)	20,177 (49.2)	3, 340 (53.4)	20,443 (61.0)	166,109 (50.5)	$p <$ 0.001
Women	91,450 (50.3)	19,613 (50.7)	14,958 (54.3)	20,814 (50.8)	2,917 (46.6)	13,087 (39.0)	162,839 (49.5)	$p <$ 0.001
18–29	46,936 (25.7)	7,953 (20.2)	5,566 (20.0)	10,736 (25.9)	1,892 (29.6)	11,452 (33.2)	84,535 (25.4)	$p <$ 0.001
30–39	59,814 (32.7)	8,794 (22.4)	5,268 (18.9)	12,335 (29.7)	1,974 (30.9)	8,497 (24.6)	96,682 (29.1)	$p <$ 0.001
40–49	31,048 (17.0)	9,061 (23.0)	4,819 (17.3)	8,220 (19.8)	1,170 (18.3)	5,828 (16.9)	60,146 (18.1)	$p <$ 0.001
50–59	21,194 (11.6)	8,085 (20.6)	5,956 (21.4)	5,067 (12.2)	737 (11.5)	5,017 (14.5)	46,056 (13.9)	$p <$ 0.001
60–69	12,164 (6.7)	3,313 (8.4)	2,975 (10.7)	2,800 (6.8)	346 (5.4)	2,386 (6.9)	23,984 (7.2)	$p <$ 0.001
70+	11,603 (6.4)	2,120 (5.4)	3,305 (11.9)	2,315 (5.6)	276 (4.3)	1,335 (3.9)	20,954 (6.3)	$p <$ 0.001
Country of birth England	49,641 (24.7)	4,791 (12.2)	7,712 (27.7)	4,411 (10.6)	751 (11.7)	733 (2.1)	68,039 (20.5)	$p <$ 0.001
Not born in England	45,051 (24.7)	15,821 (40.2)	8,167 (29.3)	16,836 (40.6)	1,332 (20.8)	1,984 (5.8)	89,191 (26.8)	$p <$ 0.001
Missing country of birth	88,067 (48.2)	18,714 (47.6)	12,010 (43.1)	20,226 (48.8)	4,312 (67.4)	31,798 (92.1)	175,127 (52.7)	$p <$ 0.001
Co-morbidities								
Cardiovascular Disease ICD-10	5,575 (3.1)	1,021 (2.6)	1,373 (4.9)	1,173 (2.8)	135 (2.1)	485 (1.4)	9,762 (2.9)	$p <$ 0.001
Familial Hypercholesterolaemia	459 (0.3)	53 (0.1)	51 (0.2)	190 (0.5)	12 (0.2)	36 (0.1)	801 (0.3)	$p <$ 0.001
Men	233 (0.3)	30 (0.2)	20 (0.2)	99 (0.5)	5 (0.2)	20 (0.1)	407 (0.3)	$p <$ 0.001
Women	226 (0.3)	23 (0.1)	31 (0.2)	91 (0.5)	7 (0.3)	16 (0.1)	394 (0.3)	$p <$ 0.001
Familial Hypercholesterolaemia Simon Broome criteria	34 (0.71)	2 (0.04)	2 (0.04)	7 (0.15)	1 (0.02)	2 (0.04)	48 (0.01)	$p <$ 0.18
Men	18 (0.72)	1 (0.04)	1 (0.04)	4 (0.16)	0 (0.0)	1 (0.04)	25 (0.02)	$p <$ 0.49
Women	16 (0.70)	1 (0.04)	1 (0.04)	3 (0.13)	1 (0.04)	1 (0.04)	23 (0.01)	$p <$ 0.52
Family History premature CHD	55 (0.03)	3 (0.01)	4 (0.02)	7 (0.02)	2 (0.03)	1 (0.0)	72 (0.02)	$p <$ 0.001
Hypertension	15,111 (8.3)	7,894 (20.1)	6,670 (23.9)	4,220 (10.2)	458 (7.2)	1,865 (5.4)	36,218 (10.9)	$p <$ 0.001
Stroke	1,243 (0.7)	438 (1.1)	527 (1.9)	276 (0.7)	35 (0.6)	147 (0.4)	2,666 (0.8)	$p <$ 0.001
Coronary Heart Disease	2,767 (1.5)	368 (0.9)	606 (2.2)	775 (1.9)	64 (1.0)	200 (0.6)	4,780 (1.4)	$p <$ 0.001
Myocardial Infarction	1,184 (0.7)	120 (0.3)	230 (0.8)	302 (0.7)	20 (0.3)	77 (0.2)	1,933 (0.6)	$p <$ 0.001
Heart Failure	405 (0.2)	104 (0.3)	127 (0.5)	82 (0.2)	9 (0.1)	38 (0.1)	765 (0.2)	$p <$ 0.001
Chronic Kidney Disease	2,598 (1.4)	906 (2.3)	1,171 (4.2)	609 (1.5)	66 (1.0)	230 (0.7)	5,580 (1.7)	$p <$ 0.001
Type 2 Diabetes	5,436 (3.0)	3,798 (9.7)	3,471 (12.5)	3,353 (8.1)	210 (3.3)	755 (2.2)	17,023 (5.1)	$p <$ 0.001
Socio-economic indicators								
IMD income quintiles								
1 (least deprived)	46,647 (25.8)	3,575 (9.2)	3,599 (13.0)	9,036 (22.1)	1,502 (23.6)	6,761 (19.8)	71,120 (21.6)	$p <$ 0.001
2	38,184 (21.1)	5,030 (12.9)	4,259 (15.3)	8,468 (20.7)	1,248 (19.6)	6,579 (19.3)	63,768 (19.4)	$p <$ 0.001
3	37,656 (20.9)	6,937 (17.8)	5,294 (19.1)	8,331 (20.4)	1,253 (19.7)	6,525 (19.1)	66,096 (20.1)	$p <$ 0.001
4	32,814 (18.2)	10,402 (26.7)	6,374 (22.9)	8,211 (20.1)	1,189 (18.7)	7,106 (20.8)	66,096 (20.1)	$p <$ 0.001
5 (most deprived)	25,439 (14.1)	13,064 (33.5)	8,257 (29.7)	6,870 (16.8)	1,161 (18.3)	7,198 (21.1)	61,989 (18.8)	$p <$ 0.001
Lifestyle indicators								
BMI								
Not Overweight (BMI <25 kg/m2)	92,982 (50.9)	11,265 (28.7)	8,833 (31.7)	18,469 (44.5)	2,480 (38.8)	9,162 (26.5)	143,191 (43.1)	$p <$ 0.001

(*continued on next page*)

Table 1 (*continued*)

Ethnicity								
Variables N (%)	White N (%)	Black African N (%)	Black Caribbean N (%)	Other N (%)	Unknown N (%)	Missing N (%)	Total N (%) * total population 328, 948	p-values **
Overweight (BMI >25 kg/m2)	42,623 (23.3)	11,570 (29.4)	7,815 (28.0)	10,207 (24.6)	1,258 (19.7)	4,839 (14.0)	78,312 (23.6)	$p <$ 0.001
Obese (BMI >30 kg/m2)	21,550 (11.8)	10,751 (27.3)	7,564 (27.1)	5,074 (12.2)	780 (12.2)	3,326 (9.6)	49,045 (14.8)	$p <$ 0.001
BMI missing	25,604 (14.0)	5,740 (14.6)	3,677 (13.2)	7,723 (18.6)	1,877 (29.4)	17,199 (49.8)	61,809 (18.6)	$p <$ 0.001
Current smoker								
Yes	38,156 (20.9)	4,652 (11.8)	7,054 (25.3)	6,141 (14.8)	1,333 (20.8)	5,837 (16.9)	63,173 (19.5)	$p <$ 0.001
No	139,173 (76.1)	33,086 (84.2)	20,018 (71.8)	33,497 (80.8)	4,626 (72.4)	20,168 (58.4)	250,568 (74.9)	$p <$ 0.001
Smoking missing	5,430 (3.0)	1,588 (4.0)	817 (2.9)	1,835 (4.4)	436 (6.8)	8,510 (24.7)	18,616 (5.6)	$p <$ 0.001
Medications								
Any statin	6,390 (3.5)	1,722 (4.4)	1,705 (6.1)	1,891 (4.6)	178 (2.8)	605 (1.8)	12,491 (3.8)	$p <$ 0.001
High dose statin***	9,910 (5.4)	3,208 (8.2)	3,167 (11.4)	3,291 (7.9)	258 (4.0)	1,029 (3.0)	20,863 (6.3)	$p <$ 0.001
Frequency of GP attendance in last year								
0-3 visits	129,952 (71.1)	24,550 (62.4)	15,502 (55.6)	28,990 (69.9)	4,734 (74.0)	27950 (81.0)	231,678 (69.7)	$p <$ 0.001
4 - 6 visits	26,287 (14.4)	6,840 (17.4)	5,040 (18.1)	5,961 (14.4)	811 (12.7)	3,460 (10.0)	48,399 (14.6)	$p <$ 0.001
7 + visits	25,520 (14.5)	7,936 (20.2)	7,347 (26.3)	6,522 (15.7)	850 (13.3)	3,105 (9.0)	52,280 (15.7)	$p <$ 0.001
GP Practice Size								
<5,000	47,319 (25.9)	13,158 (33.5)	9,535 (34.2)	11,671 (28.1)	2,182 (34.1)	7,540 (21.9)	91,405 (27.5)	$p <$ 0.001
5-10,000	117,290 (64.2)	23,822 (60.6)	16,357 (58.7)	27,451 (66.2)	3,925 (61.4)	22,640 (65.6)	211,485 (63.6)	$p <$ 0.001
>10, 000	18,150 (9.9)	2,346 (6.0)	1,997 (7.2)	2,251 (5.7)	288 (4.5)	4,335 (12.6)	29,467 (8.9)	$p <$ 0.001

***p*-value indicates significant difference from groups within category (e.g. Ethnicity – reference group is White ethnicity) p < 0.001.100 % is age and col specific by ethnicity, e.g. % of White ethnic group with FH.

*** Statin grouping: See Fig. 4; 'any statin' also includes other lipid lowering drugs such as fibrates.

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 was the least deprived, (1st) income quintile (25.5%), and the Black African group had the highest percentage in the most deprived (5th) income quintile (33.2%), $p < 0.001$. For lifestyle indicators (all $p <$ 0.001), obesity (BMI>30 kg/m^2) 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), $p < 0.001$ (data 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), Bangladeshi (0.45, 0.18–0.92) and Indian (0.39, 0.24–0.60) ethnic groups, $p < 0.001$. (Fig. 1, Supplementary Table S3). The age-adjusted FH prevalence was highest in the Other Asian (1.11, 0.91–1.31), $p < 0.0001$ and Bangladeshi (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, $p < 0.0001$. (Fig. 1, Supplementary 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,

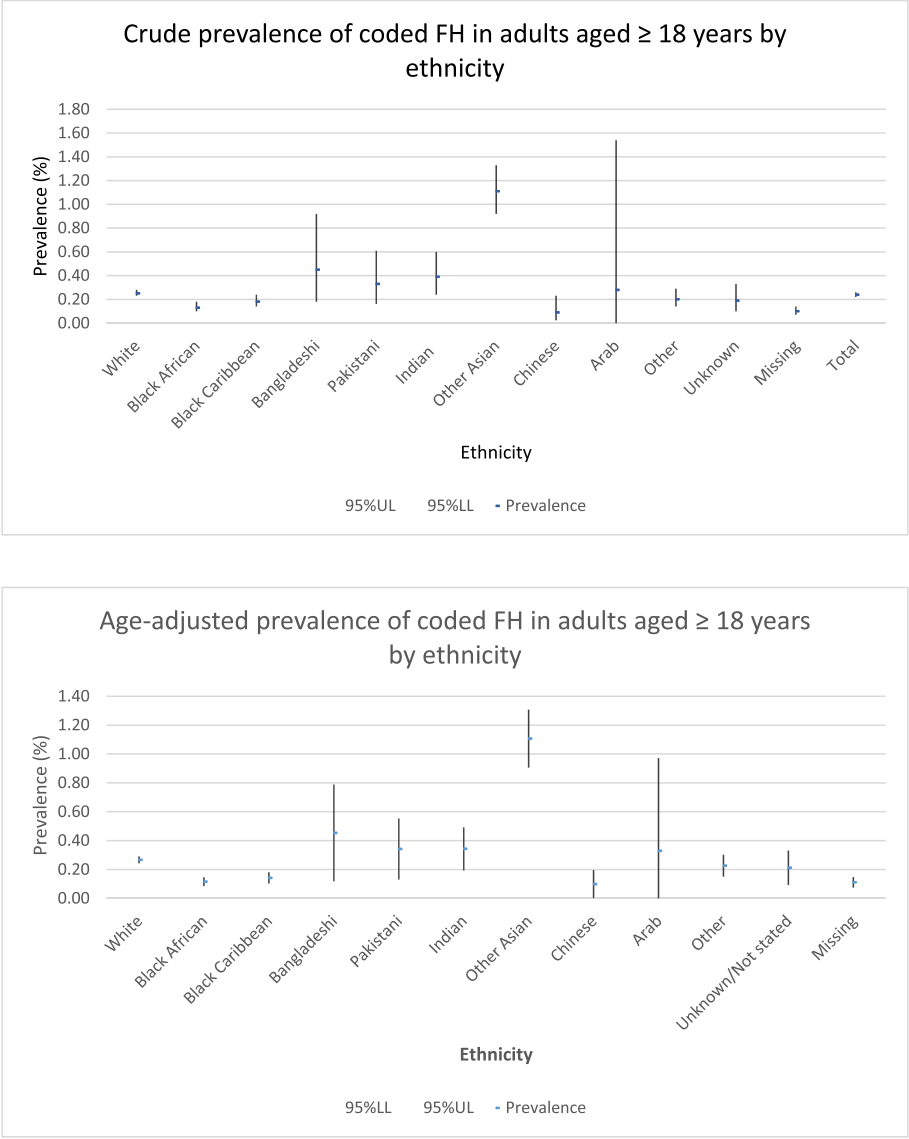

Fig. 1. Crude and age-adjusted coded FH prevalence in adults aged 18 years and over by ethnicity in Lambeth, South London.

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>30 kg/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 (Supplementary 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

Table 2
Multilevel multivariable logistic regression models for diagnosed FH in 332, 357 adults aged ≥18 years, in Lambeth, South London.

Variables	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Ethnicity						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black African	0.51 (0.38–0.69)[b]	0.48 (0.36–0.64)[b]	0.48 (0.36–0.64)[b]	0.51 (0.38–0.69)[b]	0.50 (0.37–0.67)[b]	0.50 (0.37–0.68)[b]
Black Caribbean	0.71 (0.53–0.96)[a]	0.55 (0.41–0.73)[b]	0.55 (0.41–0.73)[b]	0.55 (0.41–0.74)[b]	0.55 (0.41–0.74)[b]	0.60 (0.44–0.81)[b]
Bangladeshi	1.68 (0.79–3.56)	1.62 (0.76–3.44)	1.62 (0.76–3.44)	1.85 (0.87–3.94)	1.83 (0.86–3.90)	1.00 (0.46–2.17)
Pakistani	0.92 (0.49–1.74)	0.92 (0.49–1.73)	0.92 (0.49–1.73)	0.97 (0.52–1.84)	0.97 (0.51–1.84)	0.63 (0.33–1.20)
Indian	0.93 (0.59–1.47)	0.67 (0.42–1.07)	0.67 (0.42–1.07)	0.71 (0.44–1.13)	0.73 (0.46–1.17)	0.55 (0.34–0.89)[a]
Other Asian	1.93 (1.51–2.46)[b]	1.96 (1.53–2.50)[b]	1.96 (1.53–2.50)[b]	2.11 (1.64–2.70)[b]	2.11 (1.64–2.71)[b]	1.33 (1.01–1.76)[a]
Chinese	0.38 (0.14–1.02)	0.38 (0.14–1.01)	0.38 (0.14–1.01)	0.43 (0.16–1.15)	0.45 (0.17–1.22)	0.45 (0.17–1.22)
Arab	1.33 (0.19–9.57)	1.44 (0.20–10.37)	1.44 (0.20–10.38)	_	_	_
Other	0.81 (0.57–1.15)	0.89 (0.63–1.27)	0.89 (0.63–1.27)	0.94 (0.65–1.36)	0.97 (0.67–1.40)	0.85 (0.59–1.23)
Unknown/Not stated	0.78 (0.44–1.40)	0.88 (0.49–1.57)	0.88 (0.49–1.57)	0.95 (0.53–1.71)	1.03 (0.58–1.84)	1.10 (0.61–1.98)
Missing	0.40 (0.28–0.56)[b]	0.46 (0.33–0.65)[b]	0.46 (0.33–0.65)[b]	0.50 (0.35–0.73)[b]	0.70 (0.48–1.01)	0.85 (0.58–1.23)
Age		1.04 (1.04–1.04)[b]	1.04 (1.04–1.04)[b]	1.04 (1.04–1.04)[b]	1.04 (1.03–1.04)[b]	0.96 (0.96–0.97)[b]
Gender			0.99 (0.86–1.14)	0.99 (0.86–1.14)	1.04 (0.90–1.20)	0.75 (0.65–0.87)[b]
Socio-economic indicators						
Income deprivation quintiles						
1 (least deprived)	Ref	Ref	Ref	Ref	Ref	Ref
2				1.00 (0.81–1.23)	1.00 (0.81–1.22)	0.99 (0.80–1.22)
3				0.74 (0.60–0.93)[a]	0.73 (0.59–0.91)[a]	0.71 (0.56–0.89)[b]
4				0.89 (0.71–1.12)	0.88 (0.70–1.10)	0.82 (0.65–1.04)
5 (most deprived)				0.75 (0.58–0.97)[a]	0.74 (0.57–0.95)[a]	0.68 (0.52–0.88)[b]
Language						
English speaker	Ref	Ref	Ref	Ref	Ref	Ref
Non-English Speaker				0.75 (0.61–0.92)	0.77 (0.62–0.94)	0.66 (0.53–0.81)[b]
Missing				0.86 (0.71–1.05)	0.90 (0.74–1.10)	0.90 (0.74–1.10)
Lifestyle indicators						
Obese (BMI >30 kg/m^2) *vs* non obese					1.25 (1.04–1.48)[a]	0.80 (0.67–0.95)[a]
Missing					0.40 (0.28–0.58)[b]	0.67 (0.46–0.97)[a]
Smoking status						
Non-smoker	Ref	Ref	Ref	Ref	Ref	Ref
Ex-smoker					1.14 (0.96–1.34)	1.01 (0.85–1.21)
Current smoker					0.84 (0.68–1.04)	0.68 (0.55–0.85)[b]
Missing					0.27 (0.10–0.75)[a]	0.32 (0.11–0.88)[a]
Co-morbidities						
Hypertension						0.62 (0.52–0.74)[b]
Diabetes						0.31 (0.25–0.39)[b]
Chronic Kidney Disease						0.64 (0.41–0.99)[a]
CVD						0.47 (0.36–0.63)[b]
Medications						
No statin	Ref	Ref	Ref	Ref	Ref	Ref
Regular statin	Ref					131.81 (100.49–172.89)[b]
High dose statin[17]						203.71 (157.54–263.41)[b]
GP consultation frequency in last 12 months						
0-3 visits	Ref	Ref	Ref	Ref	Ref	Ref
4 - 6 visits						0.94 (0.78–1.14)
7 + visits						0.81 (0.67–0.97)[a]
GP Variance Effect						0.32 (0.19–0.54)

[a] $p < 0.05$.
[b] $p < 0.001$.
- Not included in this model.
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.

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 Supplementary 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, 4303.8–2408.5) 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 >9 mmol/L; and one individual aged less than 30 with cholesterol >7.5 mmol/L were coded as FH.

Of those with FH fulfilling SB criteria; available recorded cholesterol was >7.5 mmol/L in 1/48 (2%) of those under 30; and none in those over 30.

There were no FH coded individuals with cholesterol over 9 mmol/L and family history of CVD in those aged over 30 years. Similarly, we found no FH coded individuals with cholesterol over 7.5 mmol/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 (Supplementary Table S5).

Table 3
Quality of care measures by FH status in adults aged 18 years and over in Lambeth, South London.

Variables	FH not diagnosed N (%)	FH diagnosed N (%)	TOTAL N (%)	*p*-value
Recorded FH CVD	71 (0.02)	1 (0.12)	72 (0.02)	0.06
No statin or fibrate	297,475 (90.1)	161 (20.1)	297,636 (89.6)	$p < 0.001$
Regular statin or fibrate	12,279 (3.7)	212 (26.5)	12,491 (3.8)	
High dose statin	20,435 (6.2)	428 (53.4)	20,863 (6.3)	
Recorded LDL-C	5147 (1.65)	157 (19.6)	5304 (1.70)	$p < 0.001$
50% reduction in LDL-C not achieved	4918 (96.7)	133 (84.7)	5051 (96.3)	$p < 0.001$
50% reduction in LDL-C achieved	169 (3.3)	24 (15.3)	193 (3.7)	
Non or Ex-smoker	249,886 (79.9)	682 (85.6)	250,568 (79.9)	$p < 0.001$
Current smoker	63,058 (20.2)	115 (14.4)	63,173 (20.1)	
BMI <30 kg/m^2	220,920 (66.6)	583 (72.8)	221,503 (66.7)	$p < 0.001$
BMI ≥30 kg/m^2	48,860 (14.7)	185 (23.1)	49,045 (14.8)	
Missing BMI	61,776 (18.6)	33 (4.1)	61,809 (18.6)	
BP never measured	60,568 (18.3)	25 (3.1)	60,593 (18.2)	$p < 0.001$
BP measured	270,988 (81.7)	776 (96.9)	271,764 (81.8)	
Systolic BP ≥ 140 mm Hg	35,761 (13.2)	167 (21.5)	35,928 (13.2)	$p < 0.001$
Systolic BP < 140 mm Hg	235,227 (86.8)	609 (78.5)	235,836 (86.8)	
Diastolic BP ≥ 90 mm Hg	18,341 (6.8)	81 (10.4)	18,422 (6.8)	$p < 0.001$
Diastolic BP < 90 mm Hg	252,647 (93.2)	695 (89.6)	253,342 (93.2)	

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.

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 ($I^2 = 96$) 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 [34]. 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.

CRediT authorship contribution statement

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

Declaration of competing 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.

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Appendix A. Supplementary data

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