Original research

Application of a risk stratification tool for familial hypercholesterolaemia in primary care: an observational cross-sectional study in an unselected urban population

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ABSTRACT

Objective The Familial Hypercholesterolaemia Case Ascertainment Tool (FAMCAT) has been proposed to enhance case finding in primary care. In this study, we test application of the FAMCAT algorithm to describe risks of familial hypercholesterolaemia (FH) in a large unselected and ethnically diverse primary care cohort.

Method We studied patients aged 18–65 years from three contiguous areas in inner London. We retrospectively applied the FAMCAT algorithm to routine primary care data and estimated the numbers of possible cases of FH and the potential service implications of subsequent investigation and management.

Results Of the 777 128 patients studied, the FAMCAT score estimated between 11 736 and 23 798 (1.5%–3.1%) individuals were likely to have FH, depending on an assumed FH prevalence of 1 in 250 or 1 in 500, respectively. There was over-representation of individuals of South Asian ethnicity among those likely to have FH, with this cohort making up 41.9%–45.1% of the total estimated cases, a proportion which significantly exceeded their 26% representation in the study population.

Conclusions We have demonstrated feasibility of application of the FAMCAT as an aid to case finding for FH using routinely recorded primary care data. Further research is needed on validity of the tool in different ethnic groups and more refined consideration of family history should be explored. While FAMCAT may aid case finding, implementation requires information on the cost-effectiveness of additional health services to investigate, diagnose and manage case ascertainment in those identified as likely to have FH.

INTRODUCTION

The National Health Service (NHS) Long Term Plan is committed to reducing cardiovascular disease with an ambition to prevent 150 000 strokes, heart attacks and dementia cases over 10 years by detecting and treating risk factors including hypercholesterolaemia.[1] Ischaemic heart disease (IHD) and strokes are among the most common causes of death in the UK[2] with particularly high risks where the median age-standardised prevalence of hypercholesterolaemia (>6.2 mmol/L) exceeds 20%.[3] The Global Burden of Disease Study and the WHO Global Action Plan highlight that reduction of premature cardiovascular mortality is an international priority.[4 5]

Familial hypercholesterolaemia (FH) is a genetic disorder characterised by elevated serum low-density lipoprotein cholesterol (LDL-C).[6 7] In individuals of European descent, FH is associated with a 10-fold greater lifetime risk of IHD and early death.[8] Diagnosis is through clinical evaluation with validated diagnostic criteria (Simon Broome (SB) or Dutch Lipid Clinic Network (DLCN)) and consideration of genetic testing.[9] Global cardiovascular risk scores are not applicable to patients with FH as they are already at high risk of IHD.[8 10] Evidence supports early treatment in substantially reducing the risk of FH-related IHD and mortality. For patients with an inadequate response to standard therapies, there are expanded options from secondary care including PCSK9 inhibitors and new-in-class drugs.[11–14] However, over 75% of estimated FH cases are undiagnosed[15 16] representing a missed opportunity to reduce the burden of cardiovascular disease.

Existing approaches to case finding of FH in primary care are suboptimal. The National Institute of Clinical Excellence advises assessment of people considered at high risk of FH based on total cholesterol levels or reported family history.[10] Time and resource constraints in primary care precludes application of the SB and DLCN assessment consistently and completely in large numbers of patients. Therefore, current approaches to case finding are associated with significant inaccuracies and have the potential for underdiagnosis of FH and referral of high numbers of false positives.

The FH Case Ascertainment Tool (FAMCAT) is an externally validated case finding tool to identify individuals likely to have FH through systematic searching of routine primary care records for lipid profiles and other contributory variables.[17 18] Subsequent targeting of detailed clinical assessments to those at highest risk could enable more appropriate use of limited clinical resources, greater accuracy in identification of cases and improvement in case finding coverage.[19 20] Estimates of the cohort size allow for service planning and commissioning intentions, including primary care workload, demand for genetic testing and development of specialist clinics.

OBJECTIVE

In this study, we retrospectively applied the FAMCAT to an unselected population of over 770 000 primary care patients aged 18–65 years in East London, UK, using routinely collected primary care data. We report on the risk stratification of the population by FAMCAT and the number of cases identified as likely to have FH, requiring further clinical assessment.

METHODS

Study setting

The analysis dataset included all primary care patients aged 18–65 years registered with general practitioners within three Clinical Commissioning Groups (CCGs) in East London. This comprised 127 practices (City and Hackney, n=42; Newham, n=50; Tower Hamlets, n=35), which use the Egton Medical Information Systems (EMIS) electronic health record. Compared with UK averages, this inner urban population has a greater proportion of individuals from black, South Asian and minority ethnic groups, younger average age, and higher levels of socioeconomic deprivation. In these CCGs, implementation of primary and secondary cardiovascular disease prevention strategies is higher than the national average. However, local levels of cardiovascular morbidities, in particular, premature cardiovascular disease, are ranked in the top 10% in the UK.[21]

Defining the study population

We included men and women aged 18–65 years old registered with a participating practice at the time of data extraction (01 July 2019). As FH is associated with premature IHD, we set the upper age limit as 65 years old. De-identified data based on Read codes in EMIS records were extracted centrally by the Clinical Effectiveness Group, Queen Mary University of London, including age, sex, ethnicity, clinical conditions (online supplemental table 1) and social deprivation. Deprivation was defined by national 2015 Index of Multiple Deprivation (IMD) quintiles derived from a geographical area comprising approximately 150 households. Blood pressure (BP) and smoking status were defined based on their most recent records. Ethnic group is self-reported and recorded in the health records and then categorised as black ethnicity including black African, Caribbean and black British; South Asian including Bangladeshi, Pakistani, Indian and other Indian subcontinent; white including white British and European; and other ethnic group including missing or not stated.

Definition of the FAMCAT variables

The FAMCAT score was devised and externally validated by Weng *et al*.[17] In this study, we matched our definitions of the FAMCAT variables as closely as possible with that of the original (online supplemental table 2). For cholesterol, we considered the highest ever recorded value and if both total cholesterol and LDL-C were available, we gave preference to LDL-C. The highest triglyceride measured within 5 years of the highest cholesterol was used. In cases of missing triglyceride and/or cholesterol data, we used the mean value of the analysis sample based on patient's sex, age group of either <40 years or ≥40 years and the IHD status. In alignment with Weng *et al*,[17] outlying observations of cholesterol and triglyceride levels and data entry errors were excluded. We classed levels as 'untreated' if there was no record of prescription for lipid-lowering drugs (statin, fibrate, bile acid sequestrant, nicotinic acid) in the 90 days prior to cholesterol measurement. We categorised potency of lipid-lowering therapy into low (fluvastatin or pravastatin ≤40 mg/day; simvastatin ≤

Table 1 Characteristics of the study population aged 18–65 years and the characteristics of the FAMCAT derivation cohort aged 16 years or above

	Study population	Derivation cohort (Weng *et al*)[17]
	n (%) or mean (SD)	n (%) or mean (SD)*
Total	777 128	2 228 562
Age (years), mean (SD)†	37.2 (11.6)	49.5 (16.7)
Age during cholesterol measurement (years), mean (SD)‡§	35.7 (10.8)	57 (16.3)
Gender, n (%)		
Male	372 471 (47.9)	1 083 539 (48.6)
Female	404 657 (52.1)	1 145 023 (51.4)
Ethnicity, n (%)		Not available
White	308 694 (39.7)	
South Asian	201 957 (26.0)	
Black	104 138 (13.4)	
Other	60 601 (7.8)	
Unknown¶	101 738 (13.1)	
IMD (national quintiles), n (%)		Not available
Quintile 1 (least deprived)	5555 (0.7)	
Quintile 2	16 318 (2.1)	
Quintile 3	50 812 (6.5)	
Quintile 4	323 883 (41.7)	
Quintile 5 (most deprived)	379 446 (48.8)	
Lipid profile, mean (SD)		
Highest total cholesterol recorded, mmol/L**	5.3 (1.2)	5.8 (1.3)
Highest LDL cholesterol recorded, mmol/L††	3.5 (1.1)	3.6 (1.1)
Triglycerides during cholesterol measurement, mmol/L‡‡[§§]	1.7 (1.3)	1.7 (1.2)
Lipid-lowering drug usage at time of cholesterol measurement, n (%)		
Prescribed fibrate, bile acid sequestrant or nicotinic acid	730 (0.1)	9817 (0.4)
Prescribed low-potency statin	754 (0.1)	37 799 (1.7)
Prescribed medium-potency statin	21 344 (2.8)	125 315 (5.6)
Prescribed high-potency statin	33 034 (4.3)	35 582 (1.6)
Family history, n (%)		
Family history of familial hypercholesterolaemia	3440 (0.4)	12 985 (0.6)
Family history of raised cholesterol	10 176 (1.3)	8796 (0.4)
Family history of myocardial infarction	152 155 (19.6)	71 596 (3.2)
Pre-existing coronary heart disease, n (%)	7950 (1.0)	Not available
Premature onset coronary heart disease (<60 years), n (%)	6444 (0.8)	Not available
Current smoker, n (%)	157 549 (20.3)	Not available
Diabetes, n (%)	42 844 (5.5)	285 765 (12.8)
Hypertension, n (%)	59 215 (7.6)	Not available
Familial hypercholesterolaemia, n (%)	16 573 (2.1)	Not available
Stroke TIA, n (%)	3500 (0.5)	Not available
Kidney disease, n (%)	11 629 (1.5)	261 458 (11.7)

*Clinical characteristics presented in the derivation cohort for men and women were combined using the formula for combining summary statistics across two groups in Cochrane Handbook for Systematic Reviews of interventions.[24]
†Median (IQR): 35.0 (28.0–45.0).
‡Median (IQR): 34.0 (28.0–42.0).
§Patient's age at the time of data extraction was used where cholesterol is missing.
¶Unknown ethnic group=not stated code or missing.
**Data missing/outlying for 467 007 (60.1%) of 777 128 patients.
††Data missing/outlying for 514 876 (66.3%) of 777 128 patients.
‡‡Data missing/outlying for 521 584 (67.1) of 777 128 patients.
§§Median (IQR): 1.3 (0.9–3.1).
FAMCAT, Familial Hypercholesterolaemia Case Ascertainment Tool; IMD, Index of Multiple Deprivation; LDL, low-density lipoprotein; TIA, transient ischaemic attack.

10 mg/day), medium (fluvastatin or pravastatin 80 mg/day; simvastatin 20 mg/day or 40 mg/day; atorvastatin ≤10 mg/day; rosuvastatin 5 mg), or high (simvastatin 80 mg; atorvastatin ≥ 20 mg/day; rosuvastatin ≥10 mg/day) intensity.

Calculation of FAMCAT risk

FH risk was calculated through application of the FAMCAT regression equations to our study population with variables defined as outlined. Estimates were based on probability thresholds of both 1 in 250 and 1 in 500 population prevalence of FH.[16 22] We categorised risk stratification resulting from this analysis as unlikely, may or likely to have FH. A relative population risk of <1 indicated the individual was unlikely to have FH, a relative population risk from 1 to 5 indicated the individual may have FH, and a relative population risk of >5 indicated the individual is likely to have FH. We present these results for the whole cohort and separately for individuals with premature IHD (onset before age 65 years).

We performed a sensitivity analysis without imputations using the other variables to estimate the risk of FH where cholesterol and triglyceride were missing (see online supplemental table 3).

Patient and public involvement

Patients and the public were not involved in the design, conduct or outcome of this work.

RESULTS

Baseline population characteristics

The analysis sample comprised 404 657 women and 372 471 men with mean age (SD) of 37.2 (11.6) years (range 18–65 years). The population was ethnically diverse including white (308 694, 39.7%), South Asian (201 957, 26.0%), and black Caribbean and African (104 138, 13.4%) ethnic groups (table 1). Levels of deprivation were high relative to UK national averages with >90% of patients in the two most deprived IMD quintiles. The prevalence of smoking, diabetes, hypertension, chronic kidney disease (CKD) and stroke were 157 549 (20.3%), 42 844 (5.5%), 59 215 (7.6%), 11 629 (1.0%) and 3500 (0.5%), respectively. Prevalence of pre-existing IHD was 7950 (1.0%), with IHD recorded prior to the age 60 years in 6444 (81%) of these patients.

Level of recording of required data

Table 2 shows the level of data recording. Cholesterol was recorded for 82.5% (6558) of patients with IHD and 39.5% (303 921) of patients without IHD. Of the 16 573 with coded FH, 14.5% (2,397) did not have cholesterol recorded. Recording of cholesterol was more frequent for individuals aged 40 years and older.

FAMCAT risk applied to the whole cohort

Within the study population (777 128), 11 736–23 798 (1.5%–3.1%) patients were estimated to be likely to have FH, depending on the prevalence assumed (figure 1). A total of 36 630–80 372 (4.7%–10.3%) patients were estimated they may have FH (table 3). For individuals with IHD (7950), 552–938 (6.9%–11.8%) were likely to have FH and 1253–1842 (15.8%–23.2%) may have FH. For those without IHD (769 178), 11 184–22 860 (1.5%–3.0%) were likely to have FH. In total, between 48 366 and 104 170 people were estimated that they may or were likely to have FH who may need further investigation (between 6.2% and 13.4% of our total cohort). The computation of FAMCAT risk with and without missing data for both IHD and non-IHD resulted in changes of less than 1% in all categories of risk (online supplemental table 3).

Table 2 Completeness of data recording

	N	%
Age 18–65 years	777 128	
Cholesterol recorded*	310 436	40.1
BP recorded	676 855	87.1
IHD	7950	1.0
Age 18–39 years	490 482	
Cholesterol recorded*	106 404	21.7
BP recorded	399 078	81.4
IHD	252	0.1
Age 40–65 years	286 646	
Cholesterol recorded*	204 032	71.2
BP recorded	277 070	96.7
IHD	7698	2.7
With familial hypercholesterolaemia	16 573	
Cholesterol recorded*	14 173	85.5
BP recorded	16 522	99.7
IHD	1240	7.5
With IHD	7950	
Cholesterol recorded*	6556	82.5
BP recorded	7938	99.8
Without IHD	769 178	
Cholesterol recorded*	303 880	39.5
BP recorded	668 210	86.9

*Patients with non-missing or non-outlying LDL or total cholesterol values.
BP, blood pressure; IHD, ischaemic heart disease; LDL, low-density lipoprotein.

FAMCAT risk in ethnic groups

Table 4 describes risk of FH by ethnic group. A total of 39.7% of the study population were in white ethnic groups. Among individuals of white ethnicity who had IHD, 7.8%–13.2% were estimated they were likely to have FH, compared with 6.8%–11.6% of South Asians and 5.2%–9.9% of black African/Caribbean individuals. In white ethnic groups without IHD, 1.2%–2.5% were likely to have FH compared with 2.5%–4.8% in South Asian and 1.1%–2.8% in black African/Caribbean groups.

DISCUSSION

In this large study of 777 128 primary care patients, we demonstrated the feasibility of application of the FAMCAT algorithm to aid case finding of FH using routinely recorded primary care data. Our analysis identified between 48 366 and 104 170 (6.2%–13.4%) people who may or were likely to have FH who would therefore warrant further assessment and potentially genetic testing and specialist services. These findings have important implications for care and service planning in primary and secondary care.

In our population, 1 in 30 to 1 in 100 were likely to have FH according to FAMCAT risk stratification, compared with estimates of disease prevalence from 1 in 250 to 1 in 500.[16 22] Among individuals with pre-existing IHD, this increased to 6.9%–11.8%, suggesting that targeting testing and treatment for FH in this latter group would have a higher positive case yield.[19 20]

A total of 2.1% of this population were found to have a code for FH, which is higher than previously reported estimates of FH prevalence. The prevalence in our study may be inflated due to coding errors where patients with high cholesterol and/or family history of high cholesterol were incorrectly coded as 'FH'

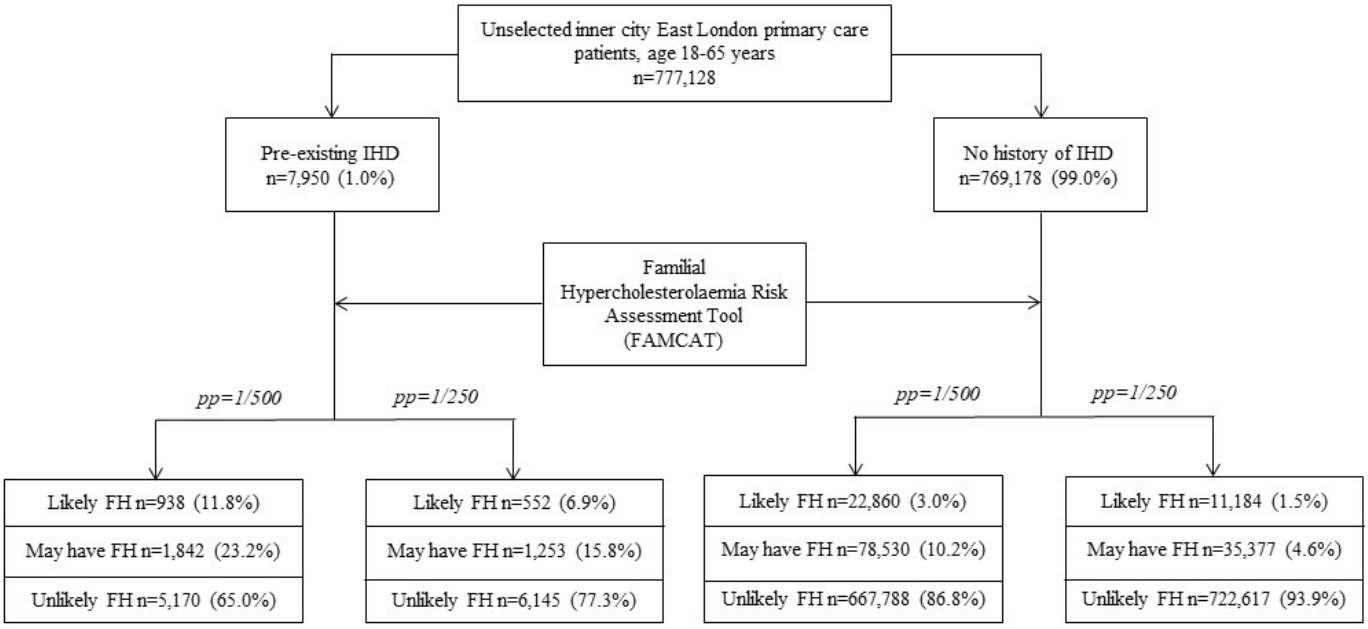

Figure 1 Risk of familial hypercholesterolaemia (FH) in inner East London calculated using FAMCAT algorithm, assuming population prevalence of 1 in 500 and 1 in 250. IHD, ischaemic heart disease; PP, population prevalence.

without further scrutiny to determine a correct diagnosis. Of those coded as having FH, 47.5% were identified by FAMCAT as unlikely to have FH (online supplemental table 4). Further clarification on the accuracy of these diagnoses is needed. This would require a case note review, which was not available in this study.

FAMCAT in ethnic groups

The risk of FH varied by ethnicity. In those with IHD, FH likelihood was highest in white and lowest in black ethnic groups. In people without IHD, the FH likelihood was highest in South Asian and lowest in black groups. This may suggest that FH is a more important factor in development of IHD for white ethnicities. Alternatively, our observations may indicate lower sensitivity of FAMCAT in detecting FH in black and South Asian ethnic groups. Indeed, lower predictive accuracy of the FAMCAT in these groups has been previously highlighted.[18] Further research is needed on potential ethnicity differential disease patterns of FH and the performance of risk prediction tools including the FAMCAT for informed clinical application in ethnically diverse populations.

Comparison with FAMCAT validation population

The FAMCAT validation population[17] ran from 1999 to 2013, while our population was more contemporaneous comprising those currently registered in 2019. Our population was, on average, younger than that studied by Weng *et al*, with a mean age of 37.2 vs 49.5 years.[17] The average age at first cholesterol

Table 3 Predicted number of cases of familial hypercholesterolaemia assuming population prevalence of 1 in 500 and 1 in 250

	1/500		1/250	
	N	%	N	%
All patients	**777 128**		**777 128**	
Likely to have familial hypercholesterolaemia	23 798	3.1	11 736	1.5
May have familial hypercholesterolaemia	80 372	10.3	36 630	4.7
Unlikely to have familial hypercholesterolaemia	672 958	86.6	728 762	93.8
Patients with IHD	**7950**		**7950**	
Likely to have familial hypercholesterolaemia	938	11.8	552	6.9
May have familial hypercholesterolaemia	1842	23.2	1253	15.8
Unlikely to have familial hypercholesterolaemia	5170	65.0	6145	77.3
Patients without IHD	**769 178**		**769 178**	
Likely to have familial hypercholesterolaemia	22 860	3.0	11 184	1.5
May have familial hypercholesterolaemia	78 530	10.2	35 377	4.6
Unlikely to have familial hypercholesterolaemia	667 788	86.8	722 617	93.9

IHD, ischaemic heart disease.

Table 4 Comparison of risk of FH estimated by FAMCAT by ethnicity

		FH 1/500		FH 1/250	
	Total	Number	%	Number	%
Patients with IHD	**7950**	**938**	11.8	**552**	6.9
White	2562	337	13.2	199	7.8
South Asian	3718	431	11.6	251	6.8
Black African/Caribbean	776	77	9.9	40	5.2
Other	438	45	10.3	32	7.3
Unknown*	456	48	10.5	30	6.6
Patients without IHD	**769 178**	**22 860**	3.0	**11 184**	1.5
White	306 132	7640	2.5	3591	1.2
South Asian	198 239	9571	4.8	5046	2.5
Black African/Caribbean	103 362	2850	2.8	1157	1.1
Other	60 163	1309	2.2	642	1.1
Not stated/missing*	101 282	1490	1.5	748	0.7

*Unknown ethnic group=not stated code or missing.
FAMCAT, Familial Hypercholesterolaemia Case Ascertainment Tool; FH, familial hypercholesterolaemia; IHD, ischaemic heart disease.

measurement was higher in the Weng *et al* cohort (57 vs 35.7 years) as was the prevalence of diabetes and CKD (12.8% vs 5.5%, 11.7% vs 1.5%), which is likely to be due to older age of participants in their cohort. There is a difference in the mean total cholesterol, while the mean LDL is similar between our study populations. However, the standard deviations of the means overlap, indicating that this difference is not statistically significant. Our population had a higher proportion of people with a recorded family history of myocardial infarction: 19.6% vs 3.2% in the Weng *et al* cohort. Recording of family history is integral to the national NHS Health Check programme in East London which may be the main reason for high levels of documentation, though the accuracy of these recordings is unknown.[23] FAMCAT only considers family history of IHD as a binary score and does not consider kinship or prematurity of onset. The relevance of accurate family history of premature IHD is an outstanding issue for further research as it is an essential element of further case identification. A comparison cannot be made between ethnicity and deprivation as they were not reported in the Weng *et al* paper. In keeping with Weng *et al*, patients on ezetimibe alone had their levels classed as 'untreated'. We also observed less missingness in all variables of interest for individuals aged over 40 years, corresponding to the 40–74 years of eligibility threshold for the NHS Health Check since 2009 and the inclusion of BP in the national Quality and Outcomes Framework for people over 40 years since 2013.

Implications for clinical practice

The 23 798 patients who were likely to have FH represent a large group of patients within which FH cases may exist, and these have been relatively easily identified through a data-driven approach. Use of the FAMCAT algorithm could allow primary care practices to generate a list of patients who may have FH, where the diagnosis has not yet been considered or excluded, using routinely recorded data. These at-risk individuals could be reviewed in more detail to determine an up-to-date FAMCAT risk and, if appropriate, clinical evaluation using the DLCN or SB criteria and genetic testing to confirm their disease status.

FAMCAT has showed a high degree of discrimination (area under the receiver operating curve 0.832, 95% CI 0.820 to 0.845). Assuming a population frequency of 1 in 500, FAMCAT had a sensitivity of 84% (1028 predicted vs 1219 observed cases) and specificity of 60% (443 949 predicted vs 745 781 observed non-cases), with a positive predictive value of 0.84% and a negative predictive value of 99.2%.[18] In other words, for every 119 people likely to have FH, after further investigation, 1 person would be identified with FH and 118 would not have genetically confirmed FH but would nevertheless require clinical advice on whether further treatment was required based on the family history and clinical findings.

This study demonstrates that other localities could potentially use FAMCAT to aid FH case finding, though not all areas have the digital maturity to run algorithms across the entire local population. The application of FAMCAT is likely to generate substantial additional workload for primary and secondary care services. Therefore, it is imperative to consider infrastructure requirements to accommodate the expected increase in demand in both community and secondary care settings. For instance, development of dedicated community FH facilities may be of value to reduce the burden on existing hospital lipid clinics. Such large-scale changes to specialist investigations would require evidence of cost-effectiveness and substantial changes to current care pathways.

Those who have not had an ischaemic cardiac event but are deemed likely to have FH by FAMCAT represent a group who may not otherwise have been identified before an index myocardial infarction or stroke, and for whom testing and treatment would play an important part in positively altering their disease trajectory. An FH diagnosis will help ensure they have appropriate treatment, and is also important for their families and cascade testing. In those who have had a cardiac event, confirmation of FH would have similar implications including for first-degree relatives.

Limitations

FAMCAT is not diagnostic, it merely applies a risk estimate. As seen in this paper, this approach generates a large cohort who need further scrutiny, first in primary care with a detailed family history and examination, then in secondary care for genetic testing and clinical advice. The FAMCAT algorithm generates substantial numbers at high FH risk for further investigation and management, and this process has yet to be assessed for cost-effectiveness.

Calculating individual FH risks without cholesterol and triglyceride measurements assumes values that fall into the ideal category in the FAMCAT algorithm. This could lead to incorrect estimates. Hence, we imputed missing values using population means for IHD and non-IHD groups. This approach artificially reduces the overall variability of missing variables. In studies where the primary purpose is hypothesis testing, this approach to imputation may lower the threshold for achieving statistical significance. However, this limitation is less important for this study, as the purpose of our work is demonstration of feasibility and description of the FAMCAT.

Use of the FAMCAT relies on recording of coded data including BP, cholesterol and family history. There was less

Key messages

What is already known on this subject?

- Underdiagnosis of familial hypercholesterolaemia (FH) represents a significant missed opportunity for prevention of coronary artery disease and premature death. The FH Risk Ascertainment Tool (FAMCAT) is designed to improve case finding in primary care but has not been studied in unselected primary care settings.

What might this study add?

- The original FAMCAT Study used a national dataset of selected volunteer practices to estimate likelihood of FH from routine data in primary care electronic health records. Our study applies FAMCAT to a large, unselected and ethnically diverse urban population. We estimate the number of people with possible FH and their demographic and clinical characteristics.

How might this impact on clinical practice?

- We demonstrated that FAMCAT could be feasibly applied to routine primary care data to enhance identification of individuals with FH. This information informs planning of health service provision and highlights recording of family history and ethnicity as topics for further research and improvement.

missingness of these variables for individuals aged over 40 years old, notably of cholesterol. This is likely due to the NHS Health Check and suggests this could also be an opportunity to estimate the FAMCAT risk. A total of 60.5% of patients without IHD and 14.5% with IHD did not have a record of cholesterol measurement. A complete lipid profile is advisable for optimal accuracy of FAMCAT.

CONCLUSION

We were able to implement the FAMCAT algorithm across entire localities to estimate likely numbers of patients requiring investigation for FH and assist commissioners and health service providers to determine these approaches. However, further research on the external validity in different settings and populations is warranted for the tool to be applied more widely. The recording of key variables including first-degree family history of premature IHD and the missing data requires improvement for use in service settings. Such data-driven approaches have the potential to improve detection of FH in the general population and reduce cardiovascular morbidity and mortality, but evidence of cost-effectiveness for full implementation of such a pathway is currently lacking.

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Contributors JR and CC conceived the study. CW conducted the data extraction and the analysis. All authors contributed to the planning of the study and the manuscript.

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Competing interests RSP reports personal fees from SANOFI, grants from AMGEN, and personal fees from NOVARTIS, outside the submitted work.

Patient consent for publication Not required.

Ethics approval This study is based on de-identified information obtained from routinely compiled general practitioner electronic health records and did not require ethics committee approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplemental information. Data are extracted from patient record systems held by GP practices. Outputs of the data extracted are collated and in the format of tables within the paper or in supplemental information.

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Supplementary Table 1. List of Read Codes

Code List of all variables included in the FAMCAT model (ref….)

1) **Lipid Measurements**

Total Cholesterol

44OE	Plasma total cholesterol level
44P	Serum cholesterol
44P1	Serum cholesterol normal
44P2	Serum cholesterol borderline
44P3	Serum cholesterol raised
44P4	Serum cholesterol very high
44PH	Total cholesterol measurement
44PJ	Serum total cholesterol level
44PK	Serum fasting total cholesterol
44PZ	Serum cholesterol NOS
4I3O	Fluid sample cholesterol level
EGTON456	Fasting serum cholesterol

LDL Cholesterol

44d4	Plasma random LDL cholesterol level
44d5	Plasma fasting LDL cholesterol level
44dB	Plasma LDL cholesterol level
44P6	Serum LDL cholesterol level
44P7	Serum VLDL cholesterol level
44PD	Serum fasting LDL cholesterol level
44PE	Serum random LDL cholesterol level
44PI	Calculated LDL cholesterol level
44PL	Non HDL cholesterol level
44PL0	Serum non high density lipoprotein cholesterol level
44PL1	Estimated serum non-HDL cholesterol level
EGTONLD1	LDL cholesterol level

Triglycerides

44e	Plasma triglyceride level
44e0	Plasma random triglyceride level
44e1	Plasma fasting triglyceride level
44Q	Serum triglycerides
44Q1	Serum triglycerides normal
44Q2	Serum triglycerides borderline
44Q3	Serum triglycerides raised
44Q4	Serum fasting triglyceride level
44Q5	Serum random triglyceride level
44QZ	Serum triglycerides NOS
4I3W	Fluid sample triglyceride level

4QA1	Triglyceride level

EGTON457	Fasting triglycerides

2) Definite Familial Hypercholesterolaemia

C320-1	Familial hypercholesterolaemia
C3200	Familial hypercholesterolaemia

3) Family History of Familial Hypercholesterolaemia

1269	Family history of familial hypercholesterolaemia

4) Family History of Raised Cholesterol/Hypercholesterolaemia

122H	No FH of hypercholesterolaemia
1262	FH: Raised blood lipids
126B	FH: Hypercholesterolaemia in first degree relative

5) Family History of myocardial infarction

12C2-1	FH: Myocardial infarction < 60
12C2-2	FH: MI- Myocardial infarct <60
12C3-1	FH: Myocardial infarction > 60
12C3-2	FH: MI- myocardial infarct >60
12C5	FH: Myocardial infarction
12C5-2	FH: Ischaemic heart disease
12CA	FH myocardial infarction male first degree age known
12CB	FH myocardial infarction male first degree age unknown
12CC	FH myocardial infarction female first degree age known
12CD	FH myocardial infarction female first degree age unknown
12CI	FH: premature coronary heart disease
12CN	FH: Myocardial infarct in 1st degree female relative <65 yrs
12CP	FH: Myocardial infarct in 1st degree male relative <55 years
ZV173	[V]Family history of ischaemic heart disease
ZV173-1	[V]Family history of ischaemic heart disease (IHD)
ZV173-2	[V]Family history of myocardial infarction

6) Coronary Heart Disease

G3	Ischaemic heart disease
G3-1	Arteriosclerotic heart disease
G3-2	Atherosclerotic heart disease
G3-3	IHD - Ischaemic heart disease
G30	Acute myocardial infarction
G30-1	Attack - heart
G30-2	Coronary thrombosis

G30-3	Cardiac rupture following myocardial infarction (MI)
G30-4	Heart attack
G30-5	MI - acute myocardial infarction
G30-6	Thrombosis - coronary
G30-7	Silent myocardial infarction
G300	Acute anterolateral infarction
G301	Other specified anterior myocardial infarction
G3010	Acute anteroapical infarction
G3011	Acute anteroseptal infarction
G301z	Anterior myocardial infarction NOS
G302	Acute inferolateral infarction
G303	Acute inferoposterior infarction
G304	Posterior myocardial infarction NOS
G305	Lateral myocardial infarction NOS
G306	True posterior myocardial infarction
G307	Acute subendocardial infarction
G3070	Acute non-Q wave infarction
G3071	Acute non-ST segment elevation myocardial infarction
G308	Inferior myocardial infarction NOS
G309	Acute Q-wave infarct
G30B	Acute posterolateral myocardial infarction
G30X	Acute transmural myocardial infarction of unspecif site
G30X0	Acute ST segment elevation myocardial infarction
G30y	Other acute myocardial infarction
G30y0	Acute atrial infarction
G30y1	Acute papillary muscle infarction
G30y2	Acute septal infarction
G30yz	Other acute myocardial infarction NOS
G30z	Acute myocardial infarction NOS
G31	Other acute and subacute ischaemic heart disease
G310	Postmyocardial infarction syndrome
G310-1	Dressler's syndrome
G311	Preinfarction syndrome
G311-1	Crescendo angina
G311-2	Impending infarction
G311-3	Unstable angina
G311-4	Angina at rest
G3110	Myocardial infarction aborted
G3110-1	MI - myocardial infarction aborted
G3111	Unstable angina
G3112	Angina at rest
G3113	Refractory angina
G3114	Worsening angina
G3115	Acute coronary syndrome

G311z	Preinfarction syndrome NOS
G312	Coronary thrombosis not resulting in myocardial infarction
G31y	Other acute and subacute ischaemic heart disease
G31y0	Acute coronary insufficiency
G31y2	Subendocardial ischaemia
G31y3	Transient myocardial ischaemia
G31yz	Other acute and subacute ischaemic heart disease NOS
G32	Old myocardial infarction
G32-1	Healed myocardial infarction
G32-2	Personal history of myocardial infarction
G33	Angina pectoris
G330	Angina decubitus
G3300	Nocturnal angina
G330z	Angina decubitus NOS
G33z	Angina pectoris NOS
G33z0	Status anginosus
G33z1	Stenocardia
G33z2	Syncope anginosa
G33z3	Angina on effort
G33z4	Ischaemic chest pain
G33z5	Post infarct angina
G33z6	New onset angina
G33z7	Stable angina
G33zz	Angina pectoris NOS
G34	Other chronic ischaemic heart disease
G340	Coronary atherosclerosis
G340-1	Triple vessel disease of the heart
G340-2	Coronary artery disease
G3400	Single coronary vessel disease
G3401	Double coronary vessel disease
G342	Atherosclerotic cardiovascular disease
G344	Silent myocardial ischaemia
G34y	Other specified chronic ischaemic heart disease
G34y0	Chronic coronary insufficiency
G34y1	Chronic myocardial ischaemia
G34yz	Other specified chronic ischaemic heart disease NOS
G34z	Other chronic ischaemic heart disease NOS
G34z0	Asymptomatic coronary heart disease
G35	Subsequent myocardial infarction
G350	Subsequent myocardial infarction of anterior wall
G351	Subsequent myocardial infarction of inferior wall
G353	Subsequent myocardial infarction of other sites
G35X	Subsequent myocardial infarction of unspecified site
G36	Certain current complication follow acute myocardial infarct

G360	Haemopericardium/current comp folow acut myocard infarct
G361	Atrial septal defect/curr comp folow acut myocardal infarct
G362	Ventric septal defect/curr comp fol acut myocardal infarctn
G363	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365	Rupture papillary muscle/curr comp fol acute myocard infarct
G366	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G38	Postoperative myocardial infarction
G380	Postoperative transmural myocardial infarction anterior wall
G381	Postoperative transmural myocardial infarction inferior wall
G384	Postoperative subendocardial myocardial infarction
G38z	Postoperative myocardial infarction, unspecified

7) History of Diabetes

1JL	Suspected diabetes mellitus
66AJ-1	Unstable diabetes
66AJ1	Brittle diabetes
C10	Diabetes mellitus
C100	Diabetes mellitus with no mention of complication
C1000	Diabetes mellitus, juvenile type, no mention of complication
C1000-1	Insulin dependent diabetes mellitus
C1001	Diabetes mellitus, adult onset, no mention of complication
C1001-1	Maturity onset diabetes

C1001-2	Non-insulin dependent diabetes mellitus
C100z	Diabetes mellitus NOS with no mention of complication
C101	Diabetes mellitus with ketoacidosis
C1010	Diabetes mellitus, juvenile type, with ketoacidosis
C1011	Diabetes mellitus, adult onset, with ketoacidosis
C101y	Other specified diabetes mellitus with ketoacidosis
C101z	Diabetes mellitus NOS with ketoacidosis
C102	Diabetes mellitus with hyperosmolar coma
C1020	Diabetes mellitus, juvenile type, with hyperosmolar coma
C1021	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z	Diabetes mellitus NOS with hyperosmolar coma
C103	Diabetes mellitus with ketoacidotic coma
C1030	Diabetes mellitus, juvenile type, with ketoacidotic coma
C1031	Diabetes mellitus, adult onset, with ketoacidotic coma
C103y	Other specified diabetes mellitus with coma
C103z	Diabetes mellitus NOS with ketoacidotic coma
C104	Diabetes mellitus with renal manifestation
C1040	Diabetes mellitus, juvenile type, with renal manifestation
C1041	Diabetes mellitus, adult onset, with renal manifestation
C104y	Other specified diabetes mellitus with renal complications
C104z	Diabetes mellitus with nephropathy NOS
C105	Diabetes mellitus with ophthalmic manifestation
C1050	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C1051	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y	Other specified diabetes mellitus with ophthalmic complicatn
C105z	Diabetes mellitus NOS with ophthalmic manifestation
C106	Diabetes mellitus with neurological manifestation
C106-2	Diabetes mellitus with neuropathy
C106-3	Diabetes mellitus with polyneuropathy
C1060	Diabetes mellitus, juvenile, + neurological manifestation
C1061	Diabetes mellitus, adult onset, + neurological manifestation
C106y	Other specified diabetes mellitus with neurological comps
C106z	Diabetes mellitus NOS with neurological manifestation
C107	Diabetes mellitus with peripheral circulatory disorder
C107-1	Diabetes mellitus with gangrene
C107-2	Diabetes with gangrene
C1070	Diabetes mellitus, juvenile +peripheral circulatory disorder
C1071	Diabetes mellitus, adult, + peripheral circulatory disorder
C1072	Diabetes mellitus, adult with gangrene
C107z	Diabetes mellitus NOS with peripheral circulatory disorder
C108	Insulin dependent diabetes mellitus
C108-1	IDDM-Insulin dependent diabetes mellitus
C108-2	Type 1 diabetes mellitus
C108-3	Type I diabetes mellitus

C1080	Insulin-dependent diabetes mellitus with renal complications
C1080-1	Type I diabetes mellitus with renal complications
C1080-2	Type 1 diabetes mellitus with renal complications
C1081	Insulin-dependent diabetes mellitus with ophthalmic comps
C1081-2	Type 1 diabetes mellitus with ophthalmic complications
C1082	Insulin-dependent diabetes mellitus with neurological comps
C1082-1	Type I diabetes mellitus with neurological complications
C1082-2	Type 1 diabetes mellitus with neurological complications
C1083	Insulin dependent diabetes mellitus with multiple complicatn
C1084	Unstable insulin dependent diabetes mellitus
C1084-1	Unstable type I diabetes mellitus
C1084-2	Unstable type 1 diabetes mellitus
C1085	Insulin dependent diabetes mellitus with ulcer
C1085-1	Type I diabetes mellitus with ulcer
C1085-2	Type 1 diabetes mellitus with ulcer
C1086	Insulin dependent diabetes mellitus with gangrene
C1087	Insulin dependent diabetes mellitus with retinopathy
C1087-1	Type I diabetes mellitus with retinopathy
C1087-2	Type 1 diabetes mellitus with retinopathy
C1088	Insulin dependent diabetes mellitus - poor control
C1088-1	Type I diabetes mellitus - poor control
C1088-2	Type 1 diabetes mellitus - poor control
C1089	Insulin dependent diabetes maturity onset
C1089-1	Type I diabetes mellitus maturity onset
C1089-2	Type 1 diabetes mellitus maturity onset
C108A	Insulin-dependent diabetes without complication
C108A-1	Type I diabetes mellitus without complication
C108B	Insulin dependent diabetes mellitus with mononeuropathy
C108B-1	Type I diabetes mellitus with mononeuropathy
C108C	Insulin dependent diabetes mellitus with polyneuropathy
C108D	Insulin dependent diabetes mellitus with nephropathy
C108D-1	Type I diabetes mellitus with nephropathy
C108E	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E-1	Type I diabetes mellitus with hypoglycaemic coma
C108E-2	Type 1 diabetes mellitus with hypoglycaemic coma
C108F	Insulin dependent diabetes mellitus with diabetic cataract
C108F-1	Type I diabetes mellitus with diabetic cataract
C108H	Insulin dependent diabetes mellitus with arthropathy
C108H-1	Type I diabetes mellitus with arthropathy
C108J-1	Type I diabetes mellitus with neuropathic arthropathy
C108J-2	Type 1 diabetes mellitus with neuropathic arthropathy
C108y	Other specified diabetes mellitus with multiple comps
C108z	Unspecified diabetes mellitus with multiple complications
C109	Non-insulin dependent diabetes mellitus

C109-1	NIDDM - Non-insulin dependent diabetes mellitus
C109-2	Type 2 diabetes mellitus
C109-3	Type II diabetes mellitus
C1090	Non-insulin-dependent diabetes mellitus with renal comps
C1090-1	Type II diabetes mellitus with renal complications
C1090-2	Type 2 diabetes mellitus with renal complications
C1091	Non-insulin-dependent diabetes mellitus with ophthalm comps
C1091-1	Type II diabetes mellitus with ophthalmic complications
C1091-2	Type 2 diabetes mellitus with ophthalmic complications
C1092	Non-insulin-dependent diabetes mellitus with neuro comps
C1092-1	Type II diabetes mellitus with neurological complications
C1092-2	Type 2 diabetes mellitus with neurological complications
C1093	Non-insulin-dependent diabetes mellitus with multiple comps
C1094	Non-insulin dependent diabetes mellitus with ulcer
C1094-1	Type II diabetes mellitus with ulcer
C1094-2	Type 2 diabetes mellitus with ulcer
C1095	Non-insulin dependent diabetes mellitus with gangrene
C1095-1	Type II diabetes mellitus with gangrene
C1095-2	Type 2 diabetes mellitus with gangrene
C1096	Non-insulin-dependent diabetes mellitus with retinopathy
C1096-1	Type II diabetes mellitus with retinopathy
C1096-2	Type 2 diabetes mellitus with retinopathy
C1097	Non-insulin dependent diabetes mellitus - poor control
C1097-1	Type II diabetes mellitus - poor control
C1097-2	Type 2 diabetes mellitus - poor control
C1099	Non-insulin-dependent diabetes mellitus without complication
C109A	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A-1	Type II diabetes mellitus with mononeuropathy
C109B	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B-1	Type II diabetes mellitus with polyneuropathy
C109C	Non-insulin dependent diabetes mellitus with nephropathy
C109C-1	Type II diabetes mellitus with nephropathy
C109C-2	Type 2 diabetes mellitus with nephropathy
C109D	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D-1	Type II diabetes mellitus with hypoglycaemic coma
C109D-2	Type 2 diabetes mellitus with hypoglycaemic coma
C109E	Non-insulin depend diabetes mellitus with diabetic cataract
C109E-1	Type II diabetes mellitus with diabetic cataract
C109E-2	Type 2 diabetes mellitus with diabetic cataract
C109F-1	Type II diabetes mellitus with peripheral angiopathy
C109F-2	Type 2 diabetes mellitus with peripheral angiopathy
C109G	Non-insulin dependent diabetes mellitus with arthropathy
C109G-1	Type II diabetes mellitus with arthropathy
C109G-2	Type 2 diabetes mellitus with arthropathy

C109H-1	Type II diabetes mellitus with neuropathic arthropathy
C109H-2	Type 2 diabetes mellitus with neuropathic arthropathy
C109J	Insulin treated Type 2 diabetes mellitus
C109J-1	Insulin treated non-insulin dependent diabetes mellitus
C109J-2	Insulin treated Type II diabetes mellitus
C10A5	Malnutritn-relat diabetes melitus wth periph circul complctn
C10B	Diabetes mellitus induced by steroids
C10B0	Steroid induced diabetes mellitus without complication
C10C	Diabetes mellitus autosomal dominant
C10C-1	Maturity onset diabetes in youth
C10C-2	Maturity onset diabetes in youth type 1
C10D	Diabetes mellitus autosomal dominant type 2
C10D-1	Maturity onset diabetes in youth type 2
C10E	Type 1 diabetes mellitus
C10E-1	Type I diabetes mellitus
C10E-2	Insulin dependent diabetes mellitus
C10E0	Type 1 diabetes mellitus with renal complications
C10E0-2	Insulin-dependent diabetes mellitus with renal complications
C10E1	Type 1 diabetes mellitus with ophthalmic complications
C10E1-1	Type I diabetes mellitus with ophthalmic complications
C10E1-2	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E2	Type 1 diabetes mellitus with neurological complications
C10E2-2	Insulin-dependent diabetes mellitus with neurological comps
C10E3	Type 1 diabetes mellitus with multiple complications
C10E3-1	Type I diabetes mellitus with multiple complications
C10E3-2	Insulin dependent diabetes mellitus with multiple complicat
C10E4	Unstable type 1 diabetes mellitus
C10E4-1	Unstable type I diabetes mellitus
C10E4-2	Unstable insulin dependent diabetes mellitus
C10E5	Type 1 diabetes mellitus with ulcer
C10E5-1	Type I diabetes mellitus with ulcer
C10E5-2	Insulin dependent diabetes mellitus with ulcer
C10E6	Type 1 diabetes mellitus with gangrene
C10E6-1	Type I diabetes mellitus with gangrene
C10E7	Type 1 diabetes mellitus with retinopathy
C10E7-1	Type I diabetes mellitus with retinopathy
C10E7-2	Insulin dependent diabetes mellitus with retinopathy
C10E8	Type 1 diabetes mellitus - poor control
C10E8-1	Type I diabetes mellitus - poor control
C10E8-2	Insulin dependent diabetes mellitus - poor control
C10E9	Type 1 diabetes mellitus maturity onset
C10E9-1	Type I diabetes mellitus maturity onset
C10EA	Type 1 diabetes mellitus without complication
C10EA-1	Type I diabetes mellitus without complication

C10EA-2	Insulin-dependent diabetes without complication
C10EB	Type 1 diabetes mellitus with mononeuropathy
C10EC	Type 1 diabetes mellitus with polyneuropathy
C10EC-1	Type I diabetes mellitus with polyneuropathy
C10EC-2	Insulin dependent diabetes mellitus with polyneuropathy
C10ED	Type 1 diabetes mellitus with nephropathy
C10ED-2	Insulin dependent diabetes mellitus with nephropathy
C10EE	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE-2	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EF	Type 1 diabetes mellitus with diabetic cataract
C10EF-2	Insulin dependent diabetes mellitus with diabetic cataract
C10EG	Type 1 diabetes mellitus with peripheral angiopathy
C10EH	Type 1 diabetes mellitus with arthropathy
C10EJ	Type 1 diabetes mellitus with neuropathic arthropathy
C10EK	Type 1 diabetes mellitus with persistent proteinuria
C10EL	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL-1	Type I diabetes mellitus with persistent microalbuminuria
C10EM	Type 1 diabetes mellitus with ketoacidosis
C10EM-1	Type I diabetes mellitus with ketoacidosis
C10EN	Type 1 diabetes mellitus with ketoacidotic coma
C10EN-1	Type I diabetes mellitus with ketoacidotic coma
C10EP	Type 1 diabetes mellitus with exudative maculopathy
C10EP-1	Type I diabetes mellitus with exudative maculopathy
C10EQ	Type 1 diabetes mellitus with gastroparesis
C10ER	Latent autoimmune diabetes mellitus in adult
C10F	Type 2 diabetes mellitus
C10F-1	Type II diabetes mellitus
C10F0	Type 2 diabetes mellitus with renal complications
C10F0-1	Type II diabetes mellitus with renal complications
C10F1	Type 2 diabetes mellitus with ophthalmic complications
C10F1-1	Type II diabetes mellitus with ophthalmic complications
C10F2	Type 2 diabetes mellitus with neurological complications
C10F2-1	Type II diabetes mellitus with neurological complications
C10F3	Type 2 diabetes mellitus with multiple complications
C10F4	Type 2 diabetes mellitus with ulcer
C10F4-1	Type II diabetes mellitus with ulcer
C10F5	Type 2 diabetes mellitus with gangrene
C10F5-1	Type II diabetes mellitus with gangrene
C10F6	Type 2 diabetes mellitus with retinopathy
C10F6-1	Type II diabetes mellitus with retinopathy
C10F7	Type 2 diabetes mellitus - poor control
C10F7-1	Type II diabetes mellitus - poor control
C10F9	Type 2 diabetes mellitus without complication
C10F9-1	Type II diabetes mellitus without complication

C10FA	Type 2 diabetes mellitus with mononeuropathy
C10FA-1	Type II diabetes mellitus with mononeuropathy
C10FB	Type 2 diabetes mellitus with polyneuropathy
C10FB-1	Type II diabetes mellitus with polyneuropathy
C10FC	Type 2 diabetes mellitus with nephropathy
C10FC-1	Type II diabetes mellitus with nephropathy
C10FD	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD-1	Type II diabetes mellitus with hypoglycaemic coma
C10FE	Type 2 diabetes mellitus with diabetic cataract
C10FE-1	Type II diabetes mellitus with diabetic cataract
C10FF	Type 2 diabetes mellitus with peripheral angiopathy
C10FF-1	Type II diabetes mellitus with peripheral angiopathy
C10FG	Type 2 diabetes mellitus with arthropathy
C10FG-1	Type II diabetes mellitus with arthropathy
C10FH	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ	Insulin treated Type 2 diabetes mellitus
C10FJ-1	Insulin treated Type II diabetes mellitus
C10FL	Type 2 diabetes mellitus with persistent proteinuria
C10FL-1	Type II diabetes mellitus with persistent proteinuria
C10FM	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM-1	Type II diabetes mellitus with persistent microalbuminuria
C10FN	Type 2 diabetes mellitus with ketoacidosis
C10FP	Type 2 diabetes mellitus with ketoacidotic coma
C10FQ	Type 2 diabetes mellitus with exudative maculopathy
C10FR	Type 2 diabetes mellitus with gastroparesis
C10G	Secondary pancreatic diabetes mellitus
C10G0	Secondary pancreatic diabetes mellitus without complication
C10H	Diabetes mellitus induced by non-steroid drugs
C10M	Lipoatrophic diabetes mellitus
C10N	Secondary diabetes mellitus
C10N0	Secondary diabetes mellitus without complication
C10y	Diabetes mellitus with other specified manifestation
C10y1	Diabetes mellitus, adult, + other specified manifestation
C10yy	Other specified diabetes mellitus with other spec comps
C10yz	Diabetes mellitus NOS with other specified manifestation
C10z	Diabetes mellitus with unspecified complication
C10z0	Diabetes mellitus, juvenile type, + unspecified complication
C10z1	Diabetes mellitus, adult onset, + unspecified complication
C10zy	Other specified diabetes mellitus with unspecified comps
C10zz	Diabetes mellitus NOS with unspecified complication
C11y0	Steroid induced diabetes
C314-1	Renal diabetes
C3500-1	Bronzed diabetes
Cyu2	[X]Diabetes mellitus

Cyu20	[X]Other specified diabetes mellitus
Cyu23	[X]Unspecified diabetes mellitus with renal complications
K01x1	Nephrotic syndrome in diabetes mellitus
K081	Nephrogenic diabetes insipidus
L1808-1	Gestational diabetes mellitus
L180X	Pre-existing diabetes mellitus, unspecified

8) History of Kidney Disease

1Z1	Chronic renal impairment
1Z10	Chronic kidney disease stage 1
1Z11	Chronic kidney disease stage 2
1Z12	Chronic kidney disease stage 3
1Z13	Chronic kidney disease stage 4
1Z14	Chronic kidney disease stage 5
1Z15	Chronic kidney disease stage 3A
1Z16	Chronic kidney disease stage 3B
1Z17	Chronic kidney disease stage 1 with proteinuria
1Z18	Chronic kidney disease stage 1 without proteinuria
1Z19	Chronic kidney disease stage 2 with proteinuria
1Z1A	Chronic kidney disease stage 2 without proteinuria
1Z1B	Chronic kidney disease stage 3 with proteinuria
1Z1C	Chronic kidney disease stage 3 without proteinuria
1Z1D	Chronic kidney disease stage 3A with proteinuria
1Z1E	Chronic kidney disease stage 3A without proteinuria
1Z1F	Chronic kidney disease stage 3B with proteinuria
1Z1G	Chronic kidney disease stage 3B without proteinuria
1Z1H	Chronic kidney disease stage 4 with proteinuria
1Z1J	Chronic kidney disease stage 4 without proteinuria
1Z1K	Chronic kidney disease stage 5 with proteinuria
1Z1L	Chronic kidney disease stage 5 without proteinuria
7A312	Open embolisation of renal artery
9Ot5	Predicted stage chronic kidney disease
D2150	Anaemia secondary to chronic renal failure
D4104	Renal polycythaemia
G22	Hypertensive renal disease
G222	Hypertensive renal disease with renal failure
G233	Hypertensive heart and renal disease with renal failure
G23z	Hypertensive heart and renal disease NOS
G701	Renal artery atherosclerosis
G721	Aneurysm of renal artery
G763	Hyperplasia of renal artery
K0	Nephritis, nephrosis and nephrotic syndrome
K01	Nephrotic syndrome
K010	Nephrotic syndrome with proliferative glomerulonephritis

K011	Nephrotic syndrome with membranous glomerulonephritis
K012	Nephrotic syndrome+membranoproliferative glomerulonephritis
K013	Nephrotic syndrome with minimal change glomerulonephritis
K013-2	Steroid sensitive nephrotic syndrome
K014	Nephrotic syndrome, minor glomerular abnormality
K015	Nephrotic syndrome, focal and segmental glomerular lesions
K016	Nephrotic syndrome, diffuse membranous glomerulonephritis
K017	Nephrotic syn difus mesangial prolifertiv glomerulonephritis
K018	Nephrotic syn,difus endocapilary proliftv glomerulonephritis
K01A	Nephrotic syndrome, dense deposit disease
K01B	Nephrotic syndrome, diffuse crescentic glomerulonephritis
K01w	Congenital nephrotic syndrome
K01x0	Nephrotic syndrome in amyloidosis
K01x1	Nephrotic syndrome in diabetes mellitus
K01x2	Nephrotic syndrome in malaria
K01x3	Nephrotic syndrome in polyarteritis nodosa
K01x4	Nephrotic syndrome in systemic lupus erythematosus
K01y	Nephrotic syndrome with other pathological kidney lesions
K01z	Nephrotic syndrome NOS
K034	Renal cortical necrosis unspecified
K035	Renal medullary necrosis unspecified
K04	Acute renal failure
K041	Acute renal cortical necrosis
K042	Acute renal medullary necrosis
K043	Acute drug-induced renal failure
K044	Acute renal failure due to urinary obstruction
K04y	Other acute renal failure
K05	Chronic renal failure
K05-2	End stage renal failure
K050	End stage renal failure
K06	Renal failure unspecified
K060	Renal impairment
K060-1	Impaired renal function
K071	Renal fibrosis
K07z	Renal sclerosis NOS
K08	Impaired renal function disorder
K080	Renal osteodystrophy
K08y	Other impaired renal function disorder
K08y4	Renal tubular acidosis
K08yz	Other impaired renal function disorder NOS
K08yz-1	Renal acidaemia
K08z	Impaired renal function disorder NOS
K0A07	Acute nephrotic syndrm diffuse crescentic glomerulonephritis
K0B	Renal tubulo-interstitial disorders in diseases EC

K0B40	Renal tubulo-interstitial disorder in SLE
K0D	End-stage renal disease
K0E	Acute-on-chronic renal failure
K0y	Other specified nephritis, nephrosis or nephrotic syndrome
K0z	Nephritis, nephrosis and nephrotic syndrome NOS
K138-1	Renal vascular disorders
K1380	Renal artery embolism
K1381	Renal artery haemorrhage
K1382	Renal artery thrombosis
K138z	Renal vascular disorders NOS
K138z-1	Renal infarction
Kyu1	[X]Renal tubulo-interstitial diseases
Kyu2	[X]Renal failure
Kyu20	[X]Other acute renal failure
Kyu21	[X]Other chronic renal failure
Kyu40	[X]Other disorders resulting/impaired renal tubular function
L0703	Unspecified abortion with renal failure
L093	Renal failure following abortive pregnancy
L162	Unspecified renal disease in pregnancy
L1620	Unspecified renal disease in pregnancy unspecified
L1621	Unspecified renal disease in pregnancy - delivered
L393	Acute renal failure following labour and delivery
L3930	Post-delivery acute renal failure unspecified
L3931	Post-delivery acute renal failure - delivered with p/n prob
L3932	Post-delivery acute renal failure with postnatal problem
P7690	Renal artery stenosis
PD0	Renal agenesis and dysgenesis
PD000	Bilateral renal agenesis
PD030	Bilateral renal hypoplasia
PD1	Congenital cystic kidney disease
PD1-1	Congenital cystic renal disease
PD11	Polycystic kidney disease
PD11z	Polycystic kidney disease NOS
PD11z-1	Cystic kidney disease NEC
PD13	Multicystic renal dysplasia
PD1y	Other specified congenital cystic kidney disease
PD1y0	Fibrocystic kidney disease
PD1y0-1	Fibrocystic renal degeneration
PD1yz	Other congenital cystic kidney disease NOS
PD1z	Congenital cystic kidney disease NOS
Pyu70	[X]Other cystic kidney diseases
Q48y0	Congenital renal failure
SK08	Acute renal failure due to rhabdomyolysis
SP154	Renal failure as a complication of care

SP154-1	Kidney failure as a complication of care
SP154-2	Post operative renal failure

9) Statins

ATCH52120NEMIS	Atorvastatin Chewable Tablets Sugar Free 10 mg
ATCH52123NEMIS	Atorvastatin Chewable Tablets Sugar Free 20 mg
ATOR21782NEMIS	Atorvastatin Oral suspension 20 mg/5 ml
ATOR45702NEMIS	Atorvastatin Oral suspension 10 mg/5 ml
ATOR45703NEMIS	Atorvastatin Oral solution 10 mg/5 ml
ATOR46710NEMIS	Atorvastatin Oral solution 20 mg/5 ml
ATTA30130EMIS	Atorvastatin Tablets 10 mg
ATTA30131EMIS	Atorvastatin Tablets 20 mg
ATTA30132EMIS	Atorvastatin Tablets 40 mg
ATTA6253NEMIS	Atorvastatin Tablets 80 mg
ATTA73968NEMIS	Atorvastatin Tablets 30 mg
ATTA73969NEMIS	Atorvastatin Tablets 60 mg
CATA41300NEMIS	Caduet Tablets 5 mg + 10 mg
CHTA111761NEMIS	Cholib Tablets 145 mg + 20 mg
CHTA111762NEMIS	Cholib Tablets 145 mg + 40 mg
CRTA15074NEMIS	Crestor Tablets 10 mg
CRTA15075NEMIS	Crestor Tablets 20 mg
CRTA15076NEMIS	Crestor Tablets 40 mg
CRTA21336NEMIS	Crestor Tablets 5 mg
DOM/43668NEMIS	Dorisin Xl M/R tablets 80 mg
EZTA20280NEMIS	Ezetimibe And Simvastatin Tablets 10 mg + 20 mg
EZTA20281NEMIS	Ezetimibe And Simvastatin Tablets 10 mg + 40 mg
EZTA20282NEMIS	Ezetimibe And Simvastatin Tablets 10 mg + 80 mg
FETA111758NEMIS	Fenofibrate And Simvastatin Tablets 145 mg + 20 mg
FETA111759NEMIS	Fenofibrate And Simvastatin Tablets 145 mg + 40 mg
FLCA24125EMIS	Fluvastatin Capsules 20 mg
FLCA24126EMIS	Fluvastatin Capsules 40 mg
FLTA5289NEMIS	Fluvastatin M/R tablets 80 mg
INTA20284NEMIS	Inegy Tablets 10 mg/20 mg
INTA20285NEMIS	Inegy Tablets 10 mg/40 mg
INTA20286NEMIS	Inegy Tablets 10 mg/80 mg
LECA24121EMIS	Lescol Capsules 20 mg
LECA24122EMIS	Lescol Capsules 40 mg
LETA5290NEMIS	Lescol Xl M/R tablets 80 mg
LICH52125NEMIS	Lipitor Chewable tablets 10 mg
LICH52126NEMIS	Lipitor Chewable tablets 20 mg
LITA10719BRIDL	Lipostat Tablets 10 mg
LITA10721BRIDL	Lipostat Tablets 20 mg
LITA1910NEMIS	Lipobay Tablets 400 micrograms
LITA30124EMIS	Lipitor Tablets 10 mg

LITA30125EMIS	Lipitor Tablets 20 mg
LITA30126EMIS	Lipitor Tablets 40 mg
LITA30703EMIS	Lipostat Tablets 40 mg
LITA30759EMIS	Lipobay Tablets 100 micrograms
LITA30760EMIS	Lipobay Tablets 200 micrograms
LITA30761EMIS	Lipobay Tablets 300 micrograms
LITA6254NEMIS	Lipitor Tablets 80 mg
LITA6646NEMIS	Lipobay Tablets 800 micrograms
LUM/35734NEMIS	Luvinsta Xl M/R tablets 80 mg
NAM/86955NEMIS	Nandovar Xl M/R tablets 80 mg
PIM/42037NEMIS	Pinmactil M/R tablets 80 mg
PROR105037NEMIS	Pravastatin Oral suspension 5 mg/5 ml
PROR43659NEMIS	Pravastatin Oral suspension 40 mg/5 ml
PROR81506NEMIS	Pravastatin Oral solution 5 mg/5 ml
PRTA10455HILLI	Pravastatin Tablets 10 mg
PRTA10456HILLI	Pravastatin Tablets 20 mg
PRTA30705EMIS	Pravastatin Tablets 40 mg
RATA18271NEMIS	Ranzolont Tablets 10 mg
RATA18272NEMIS	Ranzolont Tablets 20 mg
RATA18273NEMIS	Ranzolont Tablets 40 mg
ROTA15069NEMIS	Rosuvastatin Tablets 10 mg
ROTA15071NEMIS	Rosuvastatin Tablets 20 mg
ROTA15072NEMIS	Rosuvastatin Tablets 40 mg
ROTA21335NEMIS	Rosuvastatin Tablets 5 mg
SIOR20422NEMIS	Simvastatin Oral suspension 20 mg/5 ml
SIOR25476NEMIS	Simvastatin Oral suspension 40 mg/5 ml
SIOR44785NEMIS	Simvastatin Oral Suspension (Sugar-Free) 20 mg/5 ml
SIOR44786NEMIS	Simvastatin Oral Suspension (Sugar-Free) 40 mg/5 ml
SIOR45597NEMIS	Simvastatin Oral solution 20 mg/5 ml
SIOR45598NEMIS	Simvastatin Oral solution 40 mg/5 ml
SITA10076BRIDL	Simvastatin Tablets 10 mg
SITA10078BRIDL	Simvastatin Tablets 20 mg
SITA16195NEMIS	Simvador Tablets 10 mg
SITA16196NEMIS	Simvador Tablets 20 mg
SITA16197NEMIS	Simvador Tablets 40 mg
SITA29406EMIS	Simvastatin Tablets 40 mg
SITA34996NEMIS	Simvador Tablets 80 mg
SITA3663NEMIS	Simvastatin Tablets 80 mg
STM/44675NEMIS	Stefluvin Xl M/R tablets 80 mg
ZOTA29404EMIS	Zocor Tablets 40 mg
ZOTA3664NEMIS	Zocor Tablets 80 mg
ZOTA8622EGTON	Zocor Tablets 10 mg
ZOTA8623EGTON	Zocor Tablets 20 mg

10) Fibrates

ATCA239	Atromid-S Capsules 500 mg
BEM/34165EMIS	Bezagen Xl M/R tablets 400 mg
BETA362	Bezalip Tablets 200 mg
BETA363	Bezalip-Mono M/R tablets 400 mg
BETA4655	Bezafibrate Tablets 200 mg
BETA4656	Bezafibrate M/R tablets 400 mg
CITA21919EMIS	Ciprofibrate Tablets 100 mg
CLCA647	Clofibrate Capsules 500 mg
FECA1203NEMIS	Fenofibrate Capsules (Micronised) 267 mg
FECA13841NEMIS	Fenogal Capsules 200 mg
FECA18893NEMIS	Fenofibrate Capsules (Micronised) 200 mg
FECA24144EMIS	Fenofibrate Capsules 200 mg
FECA31990EMIS	Fenofibrate Capsules (Micronised) 67 mg
FECA9492HILLI	Fenofibrate Capsules 100 mg
FETA5643NEMIS	Fenofibrate Tablets (Micronised) 160 mg
FIM/51928NEMIS	Fibrazate Xl M/R tablets 400 mg
LICA1205NEMIS	Lipantil Micro 267 Capsules 267 mg
LICA1207NEMIS	Lipantil Micro 200 Capsules 200 mg
LICA22524NEMIS	Lipanthyl 300 Capsules
LICA24142EMIS	Lipantil Micro Capsules 200 mg
LICA9431BRIDL	Lipantil Capsules 100 mg
LIM/3539NEMIS	Liparol Xl M/R tablets 400 mg
LITA31988EMIS	Lipantil Micro 67 Capsules 67 mg
MOTA21917EMIS	Modalim Tablets 100 mg
SUTA5645NEMIS	Supralip Tablets 160 mg
ZIM/5338NEMIS	Zimbacol Xl M/R tablets 400 mg

11) Bile Acid Sequestrants

CHPO612	Cholestyramine Powder 4g
CHSU15277NEMIS	Cholestyramine Sugar Free Powder 4 grams/sachet
CHTA27652NEMIS	Cholestagel Tablets 625 mg
COGR4776	Colestipol Hydrochloride Sugar free granules 5 grams/sachet
COGR713	Colestid Granules Plain, 5 grams/sachet
COOR17597NEMIS	Colestyramine Oral Powder (sachets) 4 grams/sachet
COOR17598NEMIS	Colestyramine Oral Powder Sachets Sugar Free 4 grams/sachet
COSA21955EMIS	Colestid Orange Sachets 5 grams/sachet
COSA21957EMIS	Colestipol Hydrochloride Sachets (orange) 5 grams/sachet
MUTA3984	Muripsin Tablets
QUPO2421	Questran Powder 4g
QUPO9528BRIDL	Questran Light Powder 4 grams/sachet

12) Nicotinic Acid

BRTA395	Bradilan Tablets 250 mg

BRTA396	Bradilan Tablets 500 mg
NACA48437NEMIS	Nature's Bounty Time Released Niacin Capsules 250 mg
NIM/14469NEMIS	Nicotinic Acid M/R tablets 500 mg
NIM/16456NEMIS	Nicotinic Acid M/R tablets 750 mg
NIM/16457NEMIS	Nicotinic Acid M/R tablets 1 gram
NIM/16459NEMIS	Niaspan M/R tablets 500 mg
NIM/16460NEMIS	Niaspan M/R tablets 750 mg
NIM/16461NEMIS	Niaspan M/R tablets 1 gram
NIM/16463NEMIS	Nicotinic Acid Titration Starter Pack M/R tablets 7 x 375 mg, 7 x 500 mg, 7 x 750 mg
NIM/16465NEMIS	Niaspan Titration Starter Pack M/R tablets 7 x 375 mg, 7 x 500 mg, 7 x 750 mg
NIM/33335NEMIS	Nicotinic Acid And Laropiprant M/R tablets 1 gram + 20 mg
NITA1983	Nicotinic Acid Tablets 100 mg
NITA1984	Nicotinic Acid Tablets 25 mg
NITA1985	Nicotinic Acid Tablets 50 mg
NITA5202	Nicofuranose Tablets 250 mg
TRM/38503NEMIS	Tredaptive M/R tablets 1 gram + 20 mg

Supplementary Table 2. Definition of FAMCAT equation variables

FAMCAT equation variable	Definition in the original FAMCAT paper	Our definition
Highest total cholesterol or LDL	Total cholesterol of LDL measured during the study period, if both available, priority given to LDL. If multiple measurements available, then the highest value at any point was taken.	Highest ever level cholesterol measurement, preference given to LDL over total cholesterol if both available.
Age during cholesterol measurement (years)		Age at time of "highest ever cholesterol"
Triglycerides during cholesterol measurements	Triglycerides measured at the same time as cholesterol measurement (elevated triglycerides are negative indicator of FH)	Triglyceride at time of highest ever cholesterol or within 5 years of this measurement, if missing then imputed from age and sex.
Lipid-lowering drug usage during cholesterol measurement	Classified patients into treated vs treated – If the most recent prescription for lipid-lowering therapy overlapped with the date of the cholesterol measurement or ended within 30days of the measurement, the patient was classed as *treated* Otherwise classed as *untreated* The potency of lipid-lowering therapy was classified in the treated group into low, medium, or high potency: **Low:** Fluvastatin or Pravastatin ≤40 mg/day; Simvastatin ≤10 mg/day. **Medium:** Fluvastatin or Pravastatin 80 mg/day; Simvastatin 20 mg/day or 40 mg/day; Atorvastatin ≤10 mg/day; Rosuvastatin 5 mg. **High:** Simvastatin 80 mg; Atorvastatin ≥20 mg/day; Rosuvastatin ≥10 mg/day.	"treated" if record of prescription for lipid lowering drugs in the 90 days prior to the "highest ever cholesterol". Potency defined as per original paper.
Family history of FH	*If family history was not assessed, there was assumed to be no family history*	As per original definition
Family history of myocardial infarction	*If family history was not assessed, there was assumed to be no family history*	As per original definition
Family history of raised cholesterol	*If family history was not assessed, there was assumed to be no family history*	As per original definition
Diagnosis of diabetes		Defined using Read codes
Diagnosis of kidney disease		Defined using Read codes

Supplementary Table 2 footnote: eGFR: estimated glomerular filtration rate; FAMCAT: familial hypercholesterolaemia case ascertainment tool; FH: Familial hypercholesterolaemia; LDL: low density lipoprotein.

Supplementary Table 3. Predicted number of cases of Familial Hypercholesterolaemia assuming population prevalence of 1 in 500 and 1 in 250, calculated without imputations

	1/500		1/250	
	N	%	N	%
All patients	**777,128**		**777,128**	
Likely to have Familial Hypercholesterolemia	23,745	3.1	11,727	1.5
May Have Familial Hypercholesterolemia	74,667	9.6	36,185	4.7
Unlikely to have Familial Hypercholesterolemia	678,716	87.3	729,216	93.8
Patients with IHD	**7,950**		**7,950**	
Likely to have Familial Hypercholesterolemia	943	11.9	557	7.0
May Have Familial Hypercholesterolemia	1,833	23.1	1,249	15.7
Unlikely to have Familial Hypercholesterolemia	5,174	65.1	6,144	77.3
Patients without IHD	**769,178**		**769,178**	
Likely to have Familial Hypercholesterolemia	22,802	3.0	11,170	1.5
May Have Familial Hypercholesterolemia	72,834	9.5	34,936	4.5
Unlikely to have Familial Hypercholesterolemia	673,542	87.6	723,072	94.0

Supplementary Table 4. Predicted risk grouping using FAMCAT algorithm in patients coded as having Familial hypercholesterolaemia

	1/500		1/250	
	N	%	N	%
Patients coded as having Familial hypercholesterolaemia	**16,573**		**16,573**	
Likely to have Familial Hypercholesterolemia	4,013	24.2	2,276	13.7
May Have Familial Hypercholesterolemia	4,689	28.3	4,034	24.3
Unlikely to have Familial Hypercholesterolemia	7,871	47.5	10,263	61.9