

Improving identification and management of familial hypercholesterolaemia in primary care: Pre- and post-intervention study



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ABSTRACT

Background and aims: Familial hypercholesterolaemia (FH) is a major cause of premature heart disease but remains unrecognised in most patients. This study investigated if a systematic primary care-based approach to identify and manage possible FH improves recommended best clinical practice.

Methods: Pre- and post-intervention study in six UK general practices (population 45,033), which invited patients with total cholesterol >7.5 mmol/L to be assessed for possible FH. Compliance with national guideline recommendations to identify and manage possible FH (repeat cholesterol; assess family history of heart disease; identify secondary causes and clinical features; reduce total & LDL-cholesterol; statin prescribing; lifestyle advice) was assessed by calculating the absolute difference in measures of care pre- and six months post-intervention.

Results: The intervention improved best clinical practice in 118 patients consenting to assessment (of 831 eligible patients): repeat cholesterol test (+75.4%, 95% CI 66.9–82.3); family history of heart disease assessed (+35.6%, 95% CI 27.0–44.2); diagnosis of secondary causes (+7.7%, 95% CI 4.1–13.9), examining clinical features (+6.0%, 95% CI 2.9–11.7). For 32 patients diagnosed with possible FH using Simon-Broome criteria, statin prescription significantly improved (18.8%, 95% CI 8.9–35.3), with non-significant mean reductions in cholesterol post-intervention (total: −0.16 mmol/L, 95% CI −0.78–0.46; LDL: −0.12 mmol/L, 95% CI −0.81–0.57).

Conclusions: Within six months, this simple primary care intervention improved both identification and management of patients with possible FH, in line with national evidence-based guidelines. Replicating and sustaining this approach across the country could lead to substantial improvement in health outcomes for these individuals with very high cardiovascular risk.

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1. Introduction

Familial hypercholesterolaemia (FH) is the most common autosomal dominant disorder with at least 1 in 500 individuals affected in the general population [1]. Over 80% of an estimated 120,000 individuals in the United Kingdom remain undiagnosed, with similar rates of under-diagnosis across Europe, which results in major lost opportunities to prevent premature heart disease and death [2]. Left untreated, coronary heart disease (CHD) will develop in approximately 50% of men with FH by the age of 50 and 30% of

women with FH by the age of 60 [3]. This results in a 100-fold increase in mortality risk compared to the general population [4,5]. This can be very effectively reduced by high intensity lipid lowering treatment, resulting in a 48% reduction in CHD mortality [6].

Despite established national clinical guidelines in several countries [7–9], people with raised cholesterol are not recognised as having FH. In the UK, cholesterol levels are well captured in primary care electronic health records, offering the opportunity to improve recognition and quality of care of this condition. The English National Institute for Health and Care Excellence (NICE) guidelines introduced in 2008 [8], recommend general practitioners (GPs) use Simon-Broome diagnostic criteria to identify FH [10]. These state individuals with cholesterol levels over 7.5 mmol/L and a relevant family history of premature CHD be diagnosed as

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“possible FH” and be referred for specialist assessment and confirmation of diagnosis.

Combining a search of general practice electronic medical records for patients with elevated cholesterol and systematic collection of family history may improve identification of possible FH [11–13]. This should be accompanied by better recording of clinical features of FH and excluding secondary causes of raised cholesterol [8]. Further, proactive case ascertainment should also improve lipid management. This study aimed to assess whether such a proactive approach to identify possible familial hypercholesterolaemia (FH) in primary care improves best practice in accord with national guideline recommendations on identifying and managing FH [8].

2. Materials and methods

2.1. Study design

This was a pre- and post-intervention study over 17 months, which ended in Aug 2015. Ethical approval granted by the NRES Committee West Midlands – Solihull (Reference 12/WM/0322).

The baseline (pre-intervention period) was defined as the 6-month period from when a participants' total cholesterol was found to be ≥ 7.5 mmol/L after the release of the NICE FH guidelines in November 2008. The intervention was first introduced at various time points from March 2013 (first practice recruited) to January 2014 (last practice recruited). During this period, participants with total cholesterol levels ≥ 7.5 mmol/L were invited to complete a family history questionnaire. If the family history was positive, the patients was then offered further clinical assessment over a six month period (post-intervention period). This process is shown in Fig. 1.

2.2. Participants

All general practices in Nottingham (East Midlands, UK) were invited to participate in this study. We received initial expressions of interest from 18 general practices. Six of these practices responded (33.3%) following provision of further study information, and all these were recruited (four inner city, one suburban, one rural).

Patients from each of the six practices were eligible if they were aged 18 years or over, with a total cholesterol level greater than 7.5 mmol/L documented in their primary care electronic health records (EHRs). Participants with a confirmed diagnosis of familial

hypercholesterolaemia were excluded. Full details of participant recruitment are reported elsewhere [14]. Written informed consent was obtained from each patient included in the study as outlined in the study protocol which conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been prior approved by the Institution's ethics committee on research on humans.

2.3. Intervention and procedure

The intervention consisted of an educational session with general practitioners and practice nurses which lasted an hour on case-identification and assessment of FH using Simon-Broome diagnostic criteria recommended in the current NICE guidelines [8]. The computer-based reminder message that appears when they accessed eligible participants' records in patient consultations was also demonstrated.

A baseline data extraction from electronic health records (EHR) was then completed to identify eligible participants and their electronic health records were tagged with a reminder message whenever the record was accessed in a consultation. In line with NICE FH guidelines [8], this prompted their GP to opportunistically assess for secondary causes of raised cholesterol, ask participants to complete Family History and Symptom Questionnaires (FHSQ) and repeat lipid profile. Four months into the intervention, eligible participants not yet invited opportunistically by practitioners were contacted through postal invitation by their practice.

Postal invitations included requests to conduct a follow-up fasting lipid test and complete the FHSQ. After return of the FHSQ, a research assistant collated fasting lipid results, current family history information, statin therapy, and notified GPs and participants if there was any possibility of a FH diagnosis based on NICE Simon-Broome criteria [8]. Post-intervention, we then assessed GP compliance to national (NICE) guideline recommendations on best clinical practice for FH identification and management.

2.4. Outcome measures

Outcome measures for compliance to NICE guideline recommendations were assessed for all recruited participants at the end of the pre-intervention period (Fig. 1, Time 2) and at the end of the intervention period (post-intervention) (Fig. 1, Time 4), including: (i) Assessment for FH in patients with elevated cholesterol (ii) Management of patients who have been diagnosed with possible FH. (see Table 1; further detail is available in Supplementary Data).

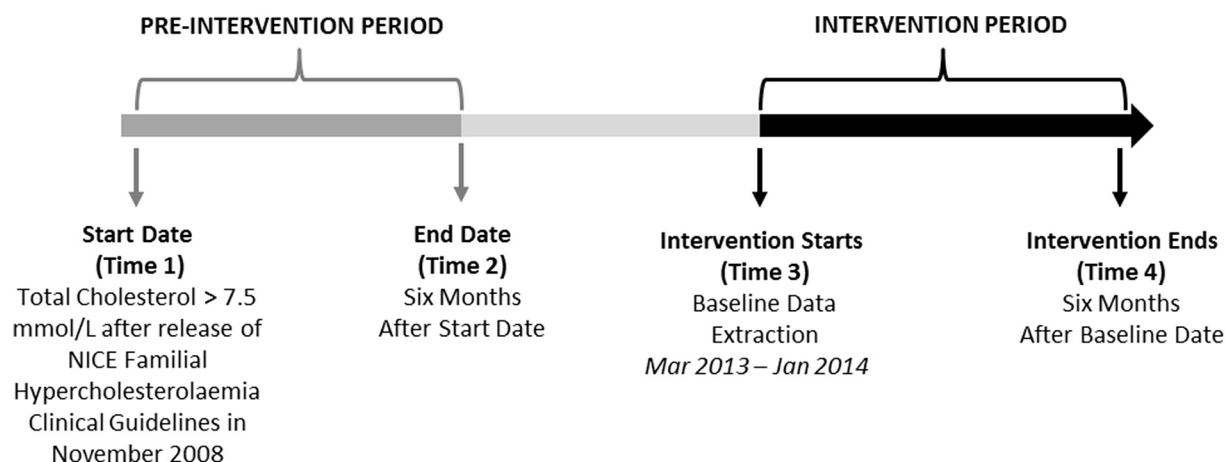


Fig. 1. Study process: pre- and during intervention periods.

These outcome measures were also extracted from general practice EHRs at the end of each six month period. Extraction from EHRs was performed using automated data extraction via medical codes and manual clinical record review for free-text entries and hospital correspondence.

For the assessment of FH in patients with elevated cholesterol, the primary outcome measure was defined as the difference in the proportion of patients with any family history of coronary heart disease (CHD) documented in their EHRs between pre- and post-intervention periods. Other outcome measures related to diagnostic assessment include the difference; between pre- and post-intervention periods in proportions of: patients with repeated cholesterol tests, diagnoses of secondary causes, biomarkers for secondary causes measured (TSH, HbA1c, serum creatinine, liver function tests), diagnoses of arcus senilis or xanthlasma. GPs in the study were advised to specifically assess for arcus cornealis and tendon xanthoma but code in the electronic health records as arcus senilis and generic xanthlasma due to limited availability of relevant NHS read codes.

For the management of those diagnosed with possible FH, the outcomes were change in total cholesterol, LDL cholesterol, as well as, difference in proportions of patients taking statin treatment (any and high potency), given advice for managing diet and weight, and given advice to stop smoking.

2.5. Sample size calculation

For the primary outcome measure, a sample size of 118 patients from the six practices would allow an absolute increase of 10% in the proportion of patients with family history of CHD recorded in EHRs to be determined with 95% confidence intervals to within $\pm 7\%$ (i.e. 95% CI 3%–17%), assuming a baseline of 3.7% from a previous study [15].

2.6. Statistical analysis

A descriptive analysis was conducted presenting numbers and percentages for all categorical outcome variables, with continuous variables of total cholesterol and LDL-cholesterol presented as mean and standard deviation, stratified by gender. To evaluate effects of the intervention on compliance to NICE guideline recommendations, we calculated the change in absolute difference for proportions with 95% confidence intervals (Wald's method based on normal approximation) [16] for categorical outcomes and mean difference with 95% confidence intervals [17] for continuous

cholesterol outcomes, between pre- and post-intervention periods. Continuous cholesterol variables were investigated for normality and if needed, were log-transformed for better fit. All analyses were conducted in STATA 14 MP4.

2.7. Ethical approval

Approved by NRES Committee West Midlands – Solihull (Reference 12/WM/0322).

3. Results

3.1. Study participants

In the six participating practices, there were 45,033 total patients registered on the baseline date. Baseline searches identified a total of 831 eligible patients who were at least 18 years of age who had total cholesterol greater than 7.5 mmol/L, and without a previous diagnosis of FH (1.84% of practice population). Six patients were excluded at baseline as they had a previous diagnosis of FH. During the 6 month intervention period, 127 of the 831 eligible patients (15.3%) consented to participate, two were excluded (one declined lipid test, one had a previous diagnosis of FH). Of the 125 eligible patients, 118 patients' medical records could be accessed (7 left the practice during study period). Thirty-two (27.1%) of the remaining 118 eligible patients met NICE Simon-Broome diagnostic criteria for possible FH, with two patients confirmed with definite FH. Further study details on participants with possible FH are provided elsewhere [14].

3.2. Characteristics of study participants in the pre-intervention period

Comparing males and females (Table 2), in the 118 patients with baseline data, there were more females than males (61% vs. 39%), and the males were slightly older. The mean total cholesterol was also slightly higher in females, as was mean LDL-cholesterol and proportion with elevated cholesterol (total or LDL).

Considering potential opportunities for diagnosis of FH, after the release of NICE FH guidelines (CG71) in November 2008, median date when a total cholesterol ≥ 7.5 mmol/L was documented was 10 May 2009 for men and 8 February 2010 for women. During the pre-intervention period, cholesterol testing was repeated in only 1 man (2%) and 11 women (15%), whilst the proportion with family history documented (both complete and any family history of CHD was

Table 1
Outcome measures for compliance to NICE Familial Hypercholesterolaemia Guideline (CG71) recommendations.

Assessment for diagnosing familial hypercholesterolaemia (NICE CG71 Section 1.1)
Proportion of patients with any family history of coronary heart disease assessed
Proportion of patients with complete family history (age, condition, degree of relation) of coronary heart disease assessed
Proportion of patients with repeat cholesterol test
Proportion of patients diagnosed with secondary cause (diabetes, hypothyroidism, chronic kidney disease, liver disease)
Proportion of patients with TSH assessment (proxy for hypothyroidism investigations)
Proportion of patients with HbA1c assessment (proxy for diabetes investigation)
Proportion of patients with serum creatinine assessment (proxy for chronic kidney disease investigations)
Proportion of patients with bilirubin, ALP, or gamma GT assessment (proxy for liver disease)
Proportion of patients with arcus senilis or xanthlasma diagnosed
Management of diagnosed possible familial hypercholesterolaemia (NICE CG71 Section 1.3)
Total cholesterol levels (mmol/L)
LDL cholesterol levels (mmol/L)
Proportion of patients prescribed any statin treatment
Proportion of patients prescribed high potency statin treatment (Simvastatin ≥ 80 mg/day; Atorvastatin ≥ 20 mg/day; Rosuvastatin ≥ 10 mg/day)
Proportion of patients given dietary or weight management advice
Proportion of patients given smoking cessation advice

Table 2

Descriptive characteristics of recruited patients in pre-intervention period, extracted from electronic health records (EHRs) and manual review. Variables are means and standard deviations unless otherwise specified.

Patient characteristics	Male (n = 46)	Female (n = 72)
Age (years)	58 (9.0)	56 (7.5)
Family history of coronary heart disease assessed (%)	3 (6.5)	4 (5.6)
Complete family history ^a of coronary heart disease assessed (%)	1 (2.2)	2 (2.7)
Repeat cholesterol test (%)	1 (2.2)	11 (15)
Diagnosed with secondary cause ^b (%)	3 (6.5)	2 (2.7)
TSH assessed ^c (%)	28 (61)	37 (51)
HbA1c assessed ^d (%)	16 (35)	23 (32)
Serum creatinine assessed ^e (%)	38 (83)	65 (90)
Bilirubin, ALP, or gamma GT assessed ^f (%)	37 (80)	62 (86)
Arcus senilis or xanthelasma diagnosed (%)	0 (0.0)	1 (2.2)
Mean total cholesterol (mmol/L)	6.1 (1.6)	6.6 (1.5)
Mean LDL cholesterol (mmol/L)	3.8 (1.7)	4.0 (1.5)
Prescribed statins (%)	8 (17)	10 (14)
Prescribed high potency statins ^g (%)	2 (4.3)	4 (5.6)
Given dietary or weight management advice (%)	22 (48)	34 (47)
Given smoking cessation advice (%)	4 (8.7)	8 (11)

^a Complete family history is defined when age, condition, and degree of relation to patient is documented.

^b Diabetes, hypothyroidism, chronic kidney disease, liver disease.

^c Proxy for secondary investigations for hypothyroidism.

^d Proxy for secondary investigations for diabetes.

^e Proxy for secondary investigations for chronic kidney disease.

^f Proxy for secondary investigations for liver disease.

^g Simvastatin ≥ 80 mg/day, atorvastatin ≥ 20 mg/day, rosuvastatin ≥ 10 mg/day.

small in both genders, with similar levels of documentation in men and women (any family history assessed: 6.5% of men compared to 5.6% of women; complete family history assessed: 2.2% of men compared to 2.7% of women). Considering workup of patients, during six months pre-intervention period, clinical features of FH (arcus or xanthelasma) and diagnosis of secondary cause were uncommon, whilst investigation of secondary causes was better recorded. Further, during this pre-intervention period, statins were only prescribed for 8 men (17%) and 10 women (14%); of which 2 men (4%) and 4 women (6%) were prescribed high potency statins. Considering lifestyle advice, dietary or weight management advice was given to around 47% of both genders, with smoking cessation advice offered to around 10% of patients.

3.3. Guideline compliance in assessing individuals for familial hypercholesterolaemia

Compliance to guideline recommendations for assessing FH at the end of the pre-intervention and intervention periods (post-intervention) are shown in Table 3. First, considering identification of FH, over a third of the 118 patients (35.6%, 95% CI 27.0 to 44.2) had a family history of coronary heart disease documented. There was also a smaller but significant increase (6.8%, 95% CI 3.5 to 12.8) in documenting a complete family history (age, coronary heart disease, and degree of relation). There was a much greater increase in the proportion of patients receiving repeat cholesterol tests (75.4%, 95% CI 66.9 to 82.3), whilst there was a small but significant increase in examination for clinical features: with 7 more patients (6.0%, 95% CI 2.9 to 11.7) having arcus senilis or xanthelasma documented in records. There were similar levels of increasing diagnosis of secondary causes (7.7%, 95% CI 4.1 to 13.9) and investigating causes of raised cholesterol (from 6.8% for liver function tests to 12.7% for serum creatinine).

3.4. Guideline compliance in managing possible familial hypercholesterolaemia

Compliance to guideline recommendations for managing patients diagnosed with possible FH at the end of the pre-intervention and intervention periods (post-intervention) are

shown in Table 4.

Considering the possible impact of intervention on cholesterol management, compared to pre-intervention period, total cholesterol and LDL cholesterol at the end of the intervention period was not significantly reduced in these 32 patients with possible FH (total cholesterol: mean difference: -0.16 mmol/L, 95% CI -0.78 to 0.46 ; LDL cholesterol: mean difference: -0.12 mmol/L, 95% CI -0.81 to 0.57). However, there was a large and significant increase in statin prescribing for these 32 patients (18.8%, 95% CI 8.9 to 35.3). This difference was smaller but remained significant for prescribing a high potency statin (9.4%, 95% CI 3.2 to 24.2). Lifestyle risk reducing advice for coronary heart disease, as indicated by diet or weight management and smoking cessation, showed little recorded improvement pre- and post-intervention.

4. Discussion

This study suggests that a simple intervention in primary care can improve assessment and identification of possible familial hypercholesterolaemia among patients with high cholesterol. These patients accounted for almost 2% of the whole general practice population, highlighting the scale and need for assessment. Despite short follow-up period, the study demonstrated some improvement in management of patients with possible FH. Sustaining this effort over a longer period of time could potentially yield even greater gains.

Considering compliance with national recommendations on assessing patients for FH, repeat cholesterol testing and family history recording improved considerably, with more modest improvements in recommended completeness of family history recording and assessment of clinical signs. The intervention had more limited impact on investigation and diagnosis of secondary causes of FH.

Considering management of possible FH, statin prescribing improved greatly, with more modest improvement in high potency statin prescribing. Together with the short (six month) follow-up period, this may explain the smaller than expected improvements in cholesterol levels. There was also room for improvement in lifestyle risk-reducing advice. However, the baseline lifestyle advice given was quite high.

Table 3

Change in compliance (absolute difference) to outcomes for assessing familial hypercholesterolaemia in 118 patients with elevated cholesterol.

NICE compliance outcomes for diagnosis of possible familial hypercholesterolaemia (n = 118)	Pre- intervention (Time 2)	Post- intervention (Time 4)	Absolute difference	95% confidence interval (%)
No. with any family history of coronary heart disease (%)	7 (5.9%)	49 (41.5%)	35.6%*	27.0, 44.2
No. with any complete family history ^a of coronary heart disease assessed (%)	3 (2.5%)	11 (9.3%)	6.8%*	3.5, 12.8
No. with repeat cholesterol test (%)	12 (10.2%)	101 (85.6%)	75.4%*	66.9, 82.3
No. diagnosed with secondary cause ^b (%)	5 (4.2%)	14 (11.9%)	7.7%*	4.1, 13.9
No. with TSH assessed ^c (%)	54 (45.8%)	69 (58.5%)	12.7%*	6.7, 18.7
No. with HbA1c assessed ^d (%)	39 (33.1%)	51 (43.2%)	10.1%*	5.9, 16.9
No. with serum creatinine ^e (%)	103 (87.3%)	113 (95.8%)	8.5%*	4.7, 14.9
No. with bilirubin, ALP, or gamma GT ^f (%)	99 (83.9%)	107 (90.7%)	6.8%*	3.5, 12.8
No. with arcus senilis or xanthlasma diagnosed (%)	1 (0.8%)	8 (6.8%)	6.0%*	2.9, 11.7

*Significant $p < 0.05$.^a Complete family history is defined when age, condition, and degree of relation to patient is documented.^b Diabetes, hypothyroidism, chronic kidney disease, liver disease.^c Proxy for secondary investigations for hypothyroidism.^d Proxy for secondary investigations for diabetes.^e Proxy for secondary investigations for chronic kidney disease.^f Proxy for secondary investigations for liver disease.**Table 4**

Change in compliance to outcomes (absolute difference) for management of 32 patients diagnosed with possible familial hypercholesterolaemia.

NICE compliance outcomes for management of familial hypercholesterolaemia (n = 32)	Pre- intervention (Time 2)	Post- intervention (Time 4)	Absolute difference	95% confidence interval (%)
No. prescribed any statins (%)	17 (53.1%)	23 (71.9%)	18.8% ^a	8.9, 35.3
No. prescribed high potency statins ^a (%)	3 (9.4%)	6 (18.8%)	9.4% ^a	3.2, 24.2
No. given dietary or weight management advice (%)	10 (31.3%)	11 (34.4%)	3.1%	0.01, 15.7
No. given smoking cessation advice (%)	11 (34.4%)	11 (34.4%)	0%	0, 10.7
	Pre- intervention (Time 2)	Post- intervention (Time 4)	Mean difference	95% confidence interval
Mean total cholesterol in mmol/L (SD)	7.23 (1.19)	7.07 (1.22)	-0.16	-0.78, 0.46
Mean LDL cholesterol in mmol/L (SD)	4.58 (1.32)	4.46 (1.36)	-0.12	-0.81, 0.57

* Significant $p < 0.05$.^a Simvastatin ≥ 80 mg/day, atorvastatin ≥ 20 mg/day, rosuvastatin ≥ 10 mg/day.

Whilst there are no randomised controlled trials for improving identification of possible FH using systematic approaches in primary care, there have been several observational studies [18–22]. These have used nurse review of patient records [19], telephone feedback from specialists [18], interpretative comments by specialists [23], and searches of family practice EHRs [20–22]. The latter similar to the approach used in this study. Although previous approaches have shown such strategies are feasible and promising, none has assessed intervention performance against national evidence-based guideline recommendations on the identification and initial management of FH.

4.1. Strengths

This study was successful in measuring outcomes for patients on all specified FH guideline recommendations, and is one of the first experimental studies to demonstrate changes in best practice within six months of intervention in primary care. This included significant increases in repeating cholesterol testing, assessing for family history of heart disease, diagnosing secondary causes, and examining for clinical features of FH, while also increasing statin prescribing for those diagnosed with possible FH. Although there was no significant decrease in mean total cholesterol or LDL-cholesterol within the brief follow up period, this simple intervention nevertheless identified individuals with possible FH who were previously unrecognised and who are benefiting from lipid lowering therapies.

The intervention was successfully implemented in general practices from populations with higher levels of socio-economic deprivation, with variation of uptake from 8 to 15% from the four inner city practices, 14% from the suburban practice, and 27% from the urban practice [14]. While lower rates of FH diagnosis, higher levels of premature coronary heart disease [24], and poorer management of patients with increased cardiovascular risk [25] are more common in this context, improvements in compliance to guideline recommendations were still demonstrated.

Finally, we were able to combine outcome data from both coded EHR searches and free text in manual review of the clinical records to enhance the completeness of the outcome measures. This process is consistent with previous studies on FH identification using both EHRs and manual review [20,22].

4.2. Limitations

Within the constraints of the short study period, a relatively modest number of eligible patients were engaged and agreed to assessment, but this was sufficient for the specified study sample size. The lower uptake of eligible patients with elevated cholesterol was also due to purposeful recruitment in areas of low deprivation (4/6 practices). It is recognised that patients from these deprived UK areas may face greater challenges in engaging with preventive and primary health care in the context of multiple morbidities and competing health and other life priorities [26].

The six-month follow-up period did not allow for full review and access to secondary care outcomes for the 32 patients who were diagnosed with possible FH. This includes confirming the diagnosis by genetic testing for the monogenic mutation.

The primary limitation of this exploratory study is its non-randomised and uncontrolled design; therefore the observed changes in compliance to NICE guideline recommendations must be interpreted with caution, as they may not be directly attributable to the intervention. Other potential external influences could include the recently introduced UK Department of Health vascular check (CVD risk assessment programmes) [27] or release of revised NICE lipid modification guidelines that briefly highlight the

importance of identifying FH [28,29], though there is no evidence of their major impact on routine primary care practice given continuous under-diagnosis of FH in primary care [2].

Finally, in line with NICE guideline recommendations, only those patients who have ever had a cholesterol above the threshold (>7.5 mmol) were assessed. However, from our search of EHRs, we observed some patients below this threshold were prescribed statins prior to their cholesterol result entry. These individuals could have had possible FH. Systematic approaches to account for treatment effects as well as other relevant clinical criteria are currently being developed. [22,30–33].

4.3. Conclusion

This study shows the promise of a simple intervention to improve identification and management of possible familial hypercholesterolaemia in line with clinical guideline recommendations. If this simple intervention was rolled out across primary care, this could lead to a substantial improvement in recognition of possible FH leading to improved health outcomes for these individuals through targeted specialist follow-up and management. Further testing of this intervention is merited, using a cluster-randomised controlled design, with a longer study period to improve patient engagement and assessment of longer-term outcomes.

Conflicts of interest

Nadeem Qureshi is a member of the National Institute for Health and Care Excellence (NICE) familial hypercholesterolaemia guideline development group (CG71). Stephen Weng is a member of the Clinical Practice Research Datalink Independent Scientific Advisory Committee under the UK Medicines and Health Regulatory Agency. The remaining authors have no conflicts of interest to disclose.

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Author contributions

SW wrote the first draft of the manuscript, conducted the primary analysis. NQ and JK conceived the study, developed the study design, and contributed to the analysis. JT recruited patients, extracted the data, and conducted the manual review of patient records. JLB contributed to the primary analysis and verified the statistical methods. All study authors have contributed to writing and finalising the final submission version of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.atherosclerosis.2018.04.037>.

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