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Qureshi N, Da Silva MLR, Abdul-Hamid H, Weng SF, Kai J, Leonardi-Bee J.
Strategies for screening for familial hypercholesterolaemia in primary care and other community settings.
Cochrane Database of Systematic Reviews 2021, Issue 10. Art. No.: CD012985.
DOI: [10.1002/14651858.CD012985.pub2](https://doi.org/10.1002/14651858.CD012985.pub2).

www.cochranelibrary.com

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[Intervention Review]

Strategies for screening for familial hypercholesterolaemia in primary care and other community settings

Nadeem Qureshi¹, Maria Luisa R Da Silva¹, Hasidah Abdul-Hamid^{1,2}, Stephen F Weng³, Joe Kai¹, Jo Leonardi-Bee⁴

¹Division of Primary Care, School of Medicine, University of Nottingham, Nottingham, UK. ²Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Malaysia. ³Cardiovascular and Metabolism, Janssen Research & Development, High Wycombe, UK. ⁴Centre for Evidence Based Healthcare, Division of Epidemiology and Public Health, Clinical Sciences Building Phase 2, University of Nottingham, Nottingham, UK

Contact address: Hasidah Abdul-Hamid, hasidah.abdulhamid@nottingham.ac.uk.**Editorial group:** Cochrane Cystic Fibrosis and Genetic Disorders Group.**Publication status and date:** New, published in Issue 10, 2021.**Citation:** Qureshi N, Da Silva MLR, Abdul-Hamid H, Weng SF, Kai J, Leonardi-Bee J. Strategies for screening for familial hypercholesterolaemia in primary care and other community settings. *Cochrane Database of Systematic Reviews* 2021, Issue 10. Art. No.: CD012985. DOI: [10.1002/14651858.CD012985.pub2](https://doi.org/10.1002/14651858.CD012985.pub2).

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ABSTRACT

Background

Familial hypercholesterolaemia is a common inherited condition that is associated with premature cardiovascular disease. The increased cardiovascular morbidity and mortality, resulting from high levels of cholesterol since birth, can be prevented by starting lipid-lowering therapy. However, the majority of patients in the UK and worldwide remain undiagnosed. Established diagnostic criteria in current clinical practice are the Simon-Broome and Dutch Lipid Clinical network criteria and patients are classified as having probable, possible or definite familial hypercholesterolaemia.

Objectives

To assess the effectiveness of healthcare interventions strategies to systematically improve identification of familial hypercholesterolaemia in primary care and other community settings compared to usual care (incidental approaches to identify familial hypercholesterolaemia in primary care and other community settings).

Search methods

We searched the Cochrane Inborn Errors of Metabolism Trials Register. Date of last search: 13 September 2021.

We also searched databases (Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, PubMed, Embase, CINAHL, Web of Science, and SCOPUS) as well as handsearching relevant conference proceedings, reference lists of included articles, and the grey literature. Date of last searches: 05 March 2020.

Selection criteria

As per the Effective Practice and Organisation of Care (EPOC) Group guidelines, we planned to include randomised controlled trials (RCTs), cluster-RCTs and non-randomised studies of interventions (NRSI). Eligible NRSI were non-randomised controlled trials, prospective cohort studies, controlled before-and-after studies, and interrupted-time-series studies.

We planned to selected studies with healthcare interventions strategies that aimed to systematically identify people with possible or definite clinical familial hypercholesterolaemia, in primary care and other community settings. These strategies would be compared with usual care or no intervention.

We considered participants of any age from the general population who access primary care and other community settings.

Strategies for screening for familial hypercholesterolaemia in primary care and other community settings (Review)

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Data collection and analysis

Two authors planned to independently select studies according to the inclusion criteria, to extract data and assess for risk of bias and the certainty of the evidence (according to the GRADE criteria). We contacted corresponding study authors in order to obtain further information for all the studies considered in the review.

Main results

No eligible RCTs or NRSIs were identified for inclusion, however, we excluded 28 studies.

Authors' conclusions

Currently, there are no RCTs or controlled NRSI evidence to determine the most appropriate healthcare strategy to systematically identify possible or definite clinical familial hypercholesterolaemia in primary care or other community settings. Uncontrolled before-and-after studies were identified, but were not eligible for inclusion. Further studies assessing healthcare strategies of systematic identification of familial hypercholesterolaemia need to be conducted with diagnosis confirmed by genetic testing or validated through clinical phenotype (or both).

PLAIN LANGUAGE SUMMARY

Healthcare strategies for identifying possible or definite clinical familial hypercholesterolaemia in primary care and other community settings

Background

One of the most common inherited conditions is familial hypercholesterolaemia, people with this condition have raised cholesterol from birth. This condition can result in the arteries being narrowed by excess cholesterol sticking to their walls and can lead to heart disease at an early age. However, treatment with cholesterol-lowering tablets markedly reduces this risk.

As well as raised cholesterol in the blood, family history of heart disease and the presence of fatty lumps under the skin could indicate familial hypercholesterolaemia.

It is important that community-based health professionals, such as general practitioners and community pharmacists, can identify those at risk of possible or probable familial hypercholesterolaemia and refer them to a specialist. Specialists can confirm a diagnosis of familial hypercholesterolaemia through examination and a genetic test.

This review explores the impact of these healthcare strategies in primary care and other community settings to systematically identify people with possible and definite clinical familial hypercholesterolaemia.

Search date

13 September 2021.

Study characteristics

We did not find any studies that we could include in this review.

Key results

There were no studies eligible for inclusion in the review.

Quality of evidence

There were no studies included in the review.

Conclusions

Currently, there is a lack of evidence regarding the most appropriate healthcare strategy to identify possible or definite clinical familial hypercholesterolaemia in primary care and other community settings. Better-designed studies, with diagnosis of definite familial hypercholesterolaemia confirmed by genetic tests, are needed to clearly answer this question.

BACKGROUND

Description of the condition

Familial hypercholesterolaemia (FH) is an autosomal-dominant disease and has long been recognised as a cause of premature coronary heart disease (CHD) (Nordestgaard 2013). In the majority of people with FH, the disorder is caused by a mutation of the low-density lipoprotein (LDL) receptor gene which impairs the proper function of the receptor, thus resulting in very high levels of plasma cholesterol. This leads to early onset atherosclerosis, causing excess morbidity and mortality from CHD (Goldstein 1995).

It has been reported that the majority of people with FH have the heterozygous form, with an estimated one in 500 people affected (Baumer 2009; Foody 2014). However, more contemporary data suggest that prevalence may be as high as one in 200, with over 30 million individuals affected worldwide (Benn 2012; Hu 2020; Nordestgaard 2012; Nordestgaard 2013; Weigman 2015). Based on predicted prevalence and the number of people currently diagnosed, it is reported that the majority of affected individuals remain undiagnosed (Demott 2008; Nordestgaard 2013). The importance of early identification is to allow treatment prior to the appearance of CHD symptoms, since affected individuals have an estimated 100-fold increase in CHD mortality compared to unaffected adults (Demott 2008; Nordestgaard 2013; Simon Broome Register Group 1991). It is estimated that half of the men with heterozygote FH will have developed CHD by 55 years of age and one third of women by 60 years of age (Marks 2003).

Several national guidelines on identifying and managing FH have been published (Goldberg 2011; Haralambos 2016; Harada-Shiba 2012; Hata 2002; Knowles 2015; NICE 2008; Nordestgaard 2013; Simon Broome Register Group 1991; Sullivan 2013; Williams 1993). In these guidelines, confirmation of FH diagnosis involves assessment against one or more specified diagnostic criteria which include:

- Simon Broome criteria (Simon Broome Register Group 1991). The criteria identify individuals with possible or definite FH as adults with total cholesterol > 7.5 mmol/L (LDL > 4.9 mmol/L) or children (less than 16 years of age) with total cholesterol over 6.7 mmol/L (LDL > 4.0 mmol/L), combined with a family history of premature heart disease or raised cholesterol or presence of tendinous xanthomata (or a combination of these) (NICE 2008; Qureshi 2009). This has been adopted in England and Wales following recommendations by the National Institute for Health and Care Excellence (NICE), following a review of non-randomised studies (NICE 2017).
- US MedPed criteria (Williams 1993) only use age-specific total cholesterol thresholds and do not incorporate family history or clinical signs during an examination (Watts 2015).
- Dutch Lipid Clinic Network (DLCN) criteria (Defesche 2004; Reiner 2011; Watts 2011). In Europe, the European Atherosclerosis Society and the European Society of Cardiology recommend using the DLCN criteria (Reiner 2015; Nordestgaard 2013). The DLCN criteria combine five domains: family history; clinical history; physical examination (presence of tendinous xanthomata or arcus cornealis (or both)); and LDL-cholesterol levels. A scoring system then identifies individuals with a diagnosis of possible, probable or definite FH based on a scoring criteria (Austin 2004; Haase 2012; Nordestgaard 2013; Watts

2011). Wales has adopted a modified version of the DLCN criteria that includes triglyceride concentrations (Haralambos 2016).

- Japanese criteria (Harada-Shiba 2012). These criteria combine LDL levels (180 mg/dL or more), physical examination (presence of tendinous xanthoma or nodule xanthoma and family history (relatives in the 1st and 2nd degree) of FH or premature CAD (males younger than 55 years and females younger than 65 years). Individuals meeting two criteria are regarded as having FH, with the recommendation for further genetic testing. These supersede previous guidelines developed by the Japanese Atherosclerosis Society (Hata 2002).

Furthermore, most guidelines recommend that once individuals with FH have been diagnosed, they commence high-intensity statin therapy and identify other relatives with the condition (Gidding 2015; Goldberg 2011; NICE 2017; Nordestgaard 2013; Sullivan 2013).

Considering the possible assessment and referral pathway, individuals are initially assessed in primary care or another community setting. Primary care and other community settings could be a general or family practice, an ambulatory or outpatient care centre, or a community health centre. Subsequent referral may occur to a specialist, such as lipidologists, endocrinologists, cardiologists, clinical nurse specialists or geneticists, depending on the organisational infrastructure. The specialist would then confirm the diagnosis (including, in many cases, genetic testing), initiate management and offer cascade screening to other relatives (Bell 2012; Bell 2013; Troeung 2016).

Description of the intervention

In primary care and other community settings, the usual care most often involves incidental identification of those who may be at risk of FH, which may include the following strategies:

- assessment of FH opportunistically during an unrelated clinical consultation;
- assessment of FH as part of a routine health check or health screen;
- assessment of FH when an individual raises concerns about their cholesterol or family history of heart disease.

However, FH remains underdiagnosed and undertreated, with up to 80% of individuals affected and resulting in major lost opportunities to prevent premature heart disease (Nordestgaard 2013; Qureshi 2009).

It has been suggested that a more systematic approach may help to identify more individuals in the primary care and other community settings (Gidding 2015; Reiner 2015; Vallejo-Vaz 2015). These interventions could include: prospective population screening (Wald 2016); retrospective searches of health records (Gray 2008); proactive computer-generated reminders (Qureshi 2016); case-finding by healthcare practitioners and review of patient records (Green 2016); and pathology laboratories reporting back clinicians about individuals who might have FH (Troeung 2016).

How the intervention might work

Prospective population screening programmes have been a successful strategy to target specific demographics of the population more likely to have a condition. For example, the UK National Health Service faecal occult blood test screening program

for early detection of colorectal cancer targets the population by age (those aged 60 to 74 years) and has led to a 16% reduction in mortality from colorectal cancer (Hewitson 2007).

Systematic searching of medical records (either manually or electronically) or pathology laboratory databases (Bell 2012; Gray 2008; Green 2016; Kirke 2015; Weng 2015) could identify individuals with relevant risk factors for FH, such as a history of raised cholesterol, premature heart disease, significant family history of CHD, and clinical signs.

An alert could be added to the medical records of individuals at risk to remind their doctor to check their cholesterol level. These reminders are an example of changing clinician behaviour using antecedent cues (Michie 2004). Agreement could be reached with local pathology laboratories contacting the primary care physician by telephone when a very high cholesterol result is processed (Bell 2014a).

Why it is important to do this review

The WHO recognises the need to prevent and control cardiovascular disease (CVD), and that managing raised lipids is a key modifiable risk factor (WHO 2011). Internationally, it is recognised that a universal targeted approach to identify and manage heterozygote FH is a key priority to prevent CVD (Benn 2012; Nordestgaard 2013; Reiner 2015; Robinson 2013; Watts 2015). For successful identification of FH, case finding needs to extend beyond the specialist lipid clinic to primary care (NICE 2008) and other community non-health settings, such as occupational health services (Kirke 2015).

For people who are affected by FH, there is strong evidence for the benefits of early identification and treatment (Demott 2008; Marks 2003; NICE 2017). High-intensity lipid-lowering treatment is very effective with a 44% reduction in CHD mortality (Besseling 2016). However, evidence-based approaches to support guideline implementation are underdeveloped (Grimshaw 1993; Michie 2004). Improving the current low detection rate of FH is urgently needed.

Moreover, identification of index cases will lead to the detection of affected but asymptomatic relatives, especially those at a younger age, resulting in early initiation of statin treatment to lower cholesterol with the recognised reduction in premature mortality, and long-term morbidity. As 50% of first degree relatives of people with confirmed FH will also have the condition, cascade screening by specialists has been shown to be a cost-effective approach (Marks 2003; Nherera 2011). This has also improved quality of life in those family members identified (van Maarle 2003).

To overcome existing gaps in care and reduce the preventable global burden of disease arising from FH, dissemination of current evidence to healthcare providers and policy makers is needed. This can inform the development of the most effective evidence-based guidelines to deliver optimal care for people with FH, thus enabling clinicians to expedite diagnosis and initiate effective treatment. Evidence on which strategies are effective for improving the identification of FH is needed in order to prioritise primary healthcare resources and target those individuals at greater risk of developing premature CHD.

The review may also provide an exemplar for improving identification of other common monogenic disorders in

the primary care setting. Furthermore, the evidence may provide generic findings relevant to developing other pertinent interventions in this context.

OBJECTIVES

To assess the effectiveness of healthcare interventions strategies to systematically improve identification of familial hypercholesterolaemia in primary care and other community settings compared to usual care (incidental approaches to identify familial hypercholesterolaemia in primary care and other community settings).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), cluster-RCTs and non-randomised study interventions (NRSI). Eligible NRSIs were non-randomised controlled trials, prospective cohort studies, controlled before-and-after studies, and controlled interrupted-time-series (ITS) studies as per the Effective Practice and Organisation of Care guidelines (EPOC 2017).

Due to the complex nature of the intervention and setting, we have included NRSIs as we anticipated potential limitations in the availability of RCTs.

Types of participants

Eligible participants of any age from the general population who access primary care or other community healthcare settings. We excluded participants who were selected from specialist settings with expertise in lipid disorders or those with a previous diagnosis of FH or other inherited lipid disorders. If the study contained both eligible and ineligible participants, we would have included the study if the data on eligible participants could be extracted (where at least 70% of the participants were eligible for our review).

Types of interventions

Intervention strategies that aimed to systematically identify people with possible or definite FH, in primary care and other community healthcare settings. Interventions which involved specialists delivering the interventions in these settings (e.g. FH nurse specialists performing case findings) were also appropriate for inclusion.

A systematic intervention strategy for identifying FH is defined as:

- prospective general population screening for FH using diagnostic criteria;
- retrospective electronic and manual health records search for participants who might have FH (i.e. based on elevated cholesterol levels, relevant family history, clinical characteristics, or combination of these factors);
- proactive computer-generated reminders for participants who might have FH (i.e. based on elevated cholesterol levels, past medical history, relevant family history, clinical characteristics, or combination of these factors);
- population based case-finding activities (i.e. healthcare practitioner reviewing patient records and contacting

individuals; pathology laboratories reporting back high cholesterol levels).

We planned to compare these systematic strategies to identify individuals with possible or definite clinical FH with usual care, where participants continued to receive their standard or current medical care (Reeves 2016). In this situation, usual care for FH identification in primary care and other community healthcare practice could include no activity to identify people with FH, or incidental and non-systematic strategies during routine consultations. An example of usual care could be noting a raised cholesterol during consultation with individuals presenting with concerns about their personal or family history. However, we excluded studies that used a comparator based on routinely available or historical data due to inherent biases associated with using this non-directly comparative design.

Where possible, we planned to compare interventions to each other if the usual care healthcare strategies were similar between or within the studies.

Types of outcome measures

Primary outcomes

1. Diagnosis of definite FH at the end of study follow-up, defined by a positive genetic mutation test or clinical phenotype typical of FH (as defined by diagnostic criteria)
2. Diagnosis of possible and probable FH (as defined by diagnostic criteria) at the end of study follow-up
3. Adverse events at the end of study follow-up (e.g. drug adverse events, hospitalisations, all-cause mortality)

Definition of the terms definite FH and possible FH can be found in an appendix (Appendix 1).

Secondary outcomes

1. Cholesterol levels in participants diagnosed with FH (total cholesterol, LDL cholesterol) at the end of study follow-up, and from the date of FH diagnosis
2. Cardiovascular mortality and morbidity of FH participants at end of study follow-up (minimum of one year follow-up)
3. Lipid-lowering treatment prescribed to people with FH (including stratification of statin prescribing by high, medium, low potency at end of study)
4. Referral of FH participants, at end of study follow-up, to a specialist service
5. Adverse self-reported psychological effects at end of study follow-up (e.g. worry, anxiety, depression with a validated instrument)
6. Management errors (e.g. misdiagnosis, inappropriate statin prescribing, inappropriate referrals to specialist)

Where multiple measurements of the same outcome are reported at different follow-up times, we would report all measurements as per the categories below:

1. short-term (outcome reported closest to three months of end of study follow-up (range can include one to four months));
2. medium-term (outcome reported closest to six months of end of study follow-up (range can include five to nine months));

3. long-term (outcome reported closest to 12 months of end of study follow-up (range can include over 10 months)).

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We identified relevant studies from the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register using the terms: (Hyperlipoproteinaemia:kw) AND (PCSK* OR proprotein OR evolocumab OR alirocumab OR IgG1 OR IgG2 OR antibod*:ti,ab,kw,mh,emt,misc1).

The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register: 13 September 2021.

In addition to the above, we have conducted a search of the following databases combining free-text terms and controlled vocabulary where applicable. For details of our search strategies, please see [Appendix 2](#).

- Cochrane Central Register of Controlled Trials (CENTRAL in the Cochrane Library (www.cochranelibrary.com); all years: searched 05 March 2020);
- PubMed (Epub Ahead of print, In process & Other non-Indexed Citations only) (www.ncbi.nlm.nih.gov/pubmed; 1946 to 05 March 2020);
- MEDLINE (OvidSP, EpubAhead of Print, In-process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (1946 to 05 March 2020);
- Embase (OvidSP) (1974 to 05 March 2020);
- CINAHL (EBSCOHost) (1937 to 05 March 2020);
- ProQuest Dissertations & Theses Global ProQuest (www.proquest.com/; 1861 to 05 March 2020);
- Web of Science (CPCI-S) (1898 to 05 March 2020);
- SCOPUS (Elsevier) (1823 to 05 March 2020).

We searched the following trial databases and resources:

- ISRCTN registry (www.isrctn.com/); all years: searched to 05 March 2020);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); all years: searched to 05 March 2020);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp.en); all years: searched to 05 March 2020).

Searching other resources

Reference lists

We checked the bibliographies of identified studies and any relevant systematic reviews for further references to relevant studies. We contacted the lead authors of identified studies to identify any available unpublished material and missing data or information regarding ongoing studies.

Handsearching

We have conducted handsearching for the relevant resources up to 05 March 2020. Search strategies for handsearching the following journals can be found in the appendices ([Appendix 3](#)).

- *Heart* (all years: searched to 05 March 2020) (www.heart.bmj.com/)
- *Atherosclerosis* (all years: searched to 05 March 2020) (www.atherosclerosis-journal.com/)
- *Journal of Clinical Lipidology* (all years: searched to 05 March 2020) (www.lipidjournal.com/)
- *Current Opinion in Lipidology* (all years: searched to 05 March 2020) (www.ovid.com/site/catalog/journals/439.jsp)
- *Journal of Inherited Metabolic Disease* (all years: searched to 05 March 2020) (www.link.springer.com/journal/10545)

In addition, we searched the following relevant charitable foundation websites up to 05 March 2020.

- HEART UK (all years: searched to 05 March 2020) (www.heart.org.uk)
- FH Foundation (all years: searched to 05 March 2020) (www.thefhfoundation.org/)

We also searched the following relevant guideline developers up to 05 March 2020.

- National Institute for Health and Care Excellence (all years: searched to 05 March 2020) (www.nice.org.uk/)
- Scottish Intercollegiate Guidelines Network (all years: searched to 05 March 2020) (www.sign.ac.uk/)
- National Institute for Health and Care Excellence Clinical Knowledge Summaries (all years: searched to 05 March 2020) (www.cks.nice.org.uk/)

We tried to identify any unpublished work by searching the abstract books of the following major cholesterol conferences up to 05 March 2020.

- Heart UK Annual Scientific Conference (all years: searched to 05 March 2020) (www.heartuk.org.uk)
- British Cardiovascular Society Conference (all years: searched to 05 March 2020) (www.bcs.com)
- European Atherosclerosis Society Conference (all years: searched to 05 March 2020) (www.eas-society.org)

We complemented the searches by making contact with leaders and researchers known to be active in the field in order to identify additional trials, including unpublished and ongoing studies.

Data collection and analysis

Selection of studies

We selected studies according to chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Lefebvre 2021](#)). We saved the results from the searches in Endnote reference managing software ([EndNote X8](#)). Two authors (JT*, MLDS) independently screened the titles and abstracts of the identified studies to check for eligibility. We then retrieved the full texts (where available) of the potentially eligible studies and two authors (JT, MLDS) independently screened these. We resolved any disagreements through discussion, or where necessary, with the assistance of a third author (NQ or JLB).

To guard against potential duplicate publication, we linked multiple reports using the same study participants. We reached agreement in all cases. We recorded details of studies excluded at the full-text stage together with reasons for exclusion based on the inclusion criteria for the review.

* please refer to '[Acknowledgements](#)'.

Data extraction and management

Two review authors (MLDS, HA-H) would have independently extracted and recorded data from included studies following guidance in chapter 5 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Li 2021](#)). We would have used standard data extraction forms, based on the checklist from the Cystic Fibrosis and Genetics Disorders Review Group, which we would have modified to allow relevant data to be captured from all the study designs which were eligible for inclusion in this review.

The data extraction form would have included study characteristics such as study methodology, participant characteristics (including ethnic or cultural characteristics, geographical location), sample size, strategies and characteristics (including process and duration of intervention), primary and secondary outcome measures, FH diagnostic criteria and definitions of other outcomes, and analysis performed in the original trials.

For NRSIs, we would have extracted additional data on confounding factors, the comparability of groups on confounding factors, methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) ([Reeves 2021](#)). Confounding factors need to be associated with both the intervention and the outcomes, thus such factors would be those assessed at a population- or service-level. Therefore, studies which have adjusted for confounders at participant-level, e.g. gender, should not have been adjusted for in the analyses. Population- or service-level factors may include, but are not limited to:

- type of health professional(s) delivering the intervention;
- size of the population being assessed;
- workload of the health professional(s)
- introduction of clinical nurse specialists
- introduction of direct pathway to access genetic testing in primary care or other community settings

For future versions of the review, if studies are included, we plan to resolve any discrepancies that arise in data extraction through discussion with a third author (JLB).

Assessment of risk of bias in included studies

If studies are included in future updates of the review, two review authors (NQ and SW) will independently assess the risk of bias; if there is a disagreement, a third author (JLB) will check each assessment and we will discuss the outcome until consensus is achieved.

If we include RCTs in future updates of the review, we will assess the risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* according to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other sources of bias (Higgins 2017). We will assess each domain as low, unclear or high risk of bias.

If we include NRSIs in future updates of the review, we will assess the risk of bias for each outcome of interest in each study using the ROBINS-I tool developed by the Cochrane Non-Randomised Studies Methods Group (Sterne 2016). The tool considers seven domains: two domains of bias pre-intervention (bias due to confounding at population- or service-level (examples are described in 'Data extraction and management section') and bias in selection of participants into the study); one domain of bias at intervention (bias in the measurement of interventions); and four domains of bias post-intervention (bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. We will assess each domain as low, moderate, serious, or critical risk of bias or no information.

For controlled ITS designs, we will use the EPOC Risk of Bias tool which is based on assessing seven standard domains:

- intervention independent of other changes;
- shape of the intervention pre-specified;
- intervention unlikely to affect data collection;
- knowledge of the allocated interventions adequately prevented during the study;
- incomplete outcome data adequately reported;
- selective outcome reporting; and
- other risk of bias.

We will assess each domain as low, unclear or high risk of bias.

Measures of treatment effect

If we include studies in future updates of this review, where possible, we will report dichotomous outcomes using risk ratios (RR) together with 95% confidence intervals (95% CIs). For studies which have used randomisation, we will extract 2x2 data and estimate crude RRs; however, for studies without randomisation, we will extract RRs which would have been adjusted for baseline differences or the ratio of the RR post-intervention compared to the RR for pre-intervention. Where studies report other adjusted measures of effect, e.g. odds ratios, we will extract these and report them separately.

Where possible, we will report continuous outcomes using mean differences (MD) together with 95% CIs. For studies which have used randomisation, we will extract raw data and estimate crude MDs; however, for studies without randomisation, we will extract MDs for

the absolute change or the relative change, which will have been adjusted for baseline differences.

For studies with a non-randomised study design, we will consider additional analysis on adjusting for baseline group differences, with appropriate regression analysis based on the form of the outcome variables (continuous or binary).

For studies which have used a controlled ITS design, we will extract quantitative results from either a regression analysis with time trends before and after the intervention, adjusted for autocorrelation and any periodic changes, or from an ARIMA analysis. We will present the results for the outcomes as the change in level (immediate effect of the intervention) and the change in slope (longer-term effect of the intervention). If the results from a study using a controlled ITS design are only reported as data points in a scanable graph or in a table, we will attempt to re-analyse the data by contacting study authors for permission to use their raw study data (Ramsay 2003).

Unit of analysis issues

For future updates, if we include studies, we will consider whether any unit of analysis errors were made in the reported analysis for each study. For cluster-randomised studies, where the analysis may not adjust for the effect of clustering, if we identify a unit-of-analysis issue, we will attempt to correct the analysis by re-analysing the presented data. Or if there is insufficient information presented, we will contact the authors to obtain the necessary information or raw data. If we are not able to re-analyse the data taking into account clustering, we will report the uncorrected estimates without a measure of uncertainty (e.g. 95% CI) and analyse the results separately from non-clustered studies. For future updates, if we include studies with multiple-arm groups, we will only include intervention and comparator groups which are relevant to the systematic review. Since we anticipate that studies will include different comparator groups, where it is appropriate, we will combine different comparator groups together and compare this to the active intervention group in the meta-analysis. For studies which include multiple intervention groups, we will combine these together and compare this to the comparator group in the meta-analysis. For further unit of analysis issues, we will analyse these following the recommendation in chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

For studies that have accounted for repeated measures we aim to report their study measures.

Dealing with missing data

For future updates of this review, if we include studies and where important data are missing (e.g. standard deviations), we will contact the authors of studies published less than 10 years ago to request additional data. If we are unable to retrieve missing data, we will conduct a sensitivity analysis to compare study outcomes grouped by the amount of missing data: large amount (more than 30%); moderate amount (10% to 30%); low amount (less than 10%). We will then discuss the potential impact of the missing data on the findings of the review.

Assessment of heterogeneity

For future updates of this review, if we include studies, we plan to assess any heterogeneity we identify as follows.

Clinical heterogeneity

We will consider clinical heterogeneity which can result from differences between studies in the characteristics of the populations, interventions and outcomes. We will fully discuss the influence of clinical heterogeneity on the observed effects.

Methodological heterogeneity

It is likely that we will identify heterogeneity as a result of bias from the different study designs included in the review. We will fully discuss the influence of methodological heterogeneity on the observed effects.

Statistical heterogeneity

We will quantify the proportion of variation in the meta-analyses due to clinical and methodological heterogeneity using I^2 (Higgins 2002). We will also visually examine the inconsistency of the 95% CIs within each meta-analysis. We will describe the proportion of variability due to heterogeneity using the following values described in chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021):

- 0% to 40%: might not be important;
- 30% to 60% may represent substantial heterogeneity;
- 75% to 100% considerable heterogeneity.

Due to the different designs of any included studies, we anticipate that we will identify moderate to high levels of heterogeneity within each meta-analysis; therefore, we will conduct a thorough examination of the heterogeneity to try to describe reasons for its presence.

Assessment of reporting biases

Where any future meta-analysis contains more than 10 studies, we plan to use funnel plots to assess the potential effects of reporting biases. Where funnel plot asymmetry is apparent, we will consider possible sources of asymmetry other than publication bias, e.g. based on domains of methodological quality, and conduct appropriate sensitivity analyses.

Data synthesis

If studies are included in future updates of this review, we plan to initially summarise all included studies using narrative synthesis methods. This will involve the use of narrative text and tables to summarise data based on the type of intervention and according to setting, we will consider outcomes in the light of differences in study designs and address potential sources of bias, potential confounding factors and any further methodological limitations for each of the studies being reviewed, including how these may have impacted on the study findings. We plan then to provide a synthesised summary of the studies, including the range and size of any reported associations and important study characteristics.

We will conduct separate meta-analyses for RCTs and NRSIs. We will use random-effects models to conduct meta-analyses due to anticipated differences in the effectiveness of the intervention by type of intervention, comparator, setting, and populations. We will include all studies in the primary meta-analyses, irrespective of the risk of bias scores given for each domain.

We will not include the quantitative findings from studies deemed to have a critical risk of bias in the synthesis (Reeves 2021).

We will perform meta-analysis using the Review Manager (RevMan) software (RevMan 2020) or Stata version 16 (STATA 2019).

Subgroup analysis and investigation of heterogeneity

If we include studies in future updates of this review, for each meta-analysis which includes at least five studies, we will perform subgroup analyses based on study-level variables and report a P value relating to the statistical test for differences between subgroups, where appropriate. We will consider the following characteristics:

- mode of diagnosis for FH (genetic or clinical);
- age of participant (under 10 years of age or 10 years of age and above);
- type of systematic intervention (prospective population screen, retrospective computer search, proactive computer reminders, population-based case finding);
- type of comparator;
- type of setting (primary medical care, employer-based clinics, community pharmacists).

We will undertake subgroup analyses using RevMan (RevMan 2020) or Stata version 16 (STATA 2019). We anticipate that due to the complexity of the intervention that most studies would include complex interventions and therefore we grouped studies primarily based on similarities between outcome measures.

Sensitivity analysis

If studies are included in future updates of this review, we plan to assess the impact of methodological quality on the results of the meta-analyses. We will compare the pooled effect size from this sensitivity analysis to the pooled effect size from the original analyses. For RCTs, the sensitivity analysis would be based on only those studies with an overall low risk of bias; for NRSIs (including controlled ITS designs), the sensitivity analysis would be based on only those with an overall low or moderate risk of bias. We will report sensitivity analyses in table format within this review.

Summary of findings and assessment of the certainty of the evidence

If we include studies in future updates of this review, we will create summary of findings tables for the primary outcomes, following the GRADE approach suggested in chapter 14 of the *Cochrane Handbook for Systematic Review of Interventions* (Schünemann 2021). This will state the participant population setting, intervention, comparison, and main outcome measures. In addition, the tables would have presented the quality rating of the evidence as 'high', 'moderate', 'low', or 'very low' using the following five GRADE considerations:

- risk of bias (serious or very serious);
- inconsistency (serious or very serious);
- indirectness (serious or very serious);
- imprecision (serious or very serious);
- publication bias (likely or very likely).

For NRSIs we will also consider the following factors:

- size of effect (large or very large);
- confounding (either reduces the demonstrated effect or increases the effect if no effect was observed (yes or no)).

In GRADE, we will rate NRSIs initially as low quality and downgrade or upgrade according to GRADE guidelines, if appropriate. We will present outcomes for these studies in separate tables from outcomes for the results of RCTs.

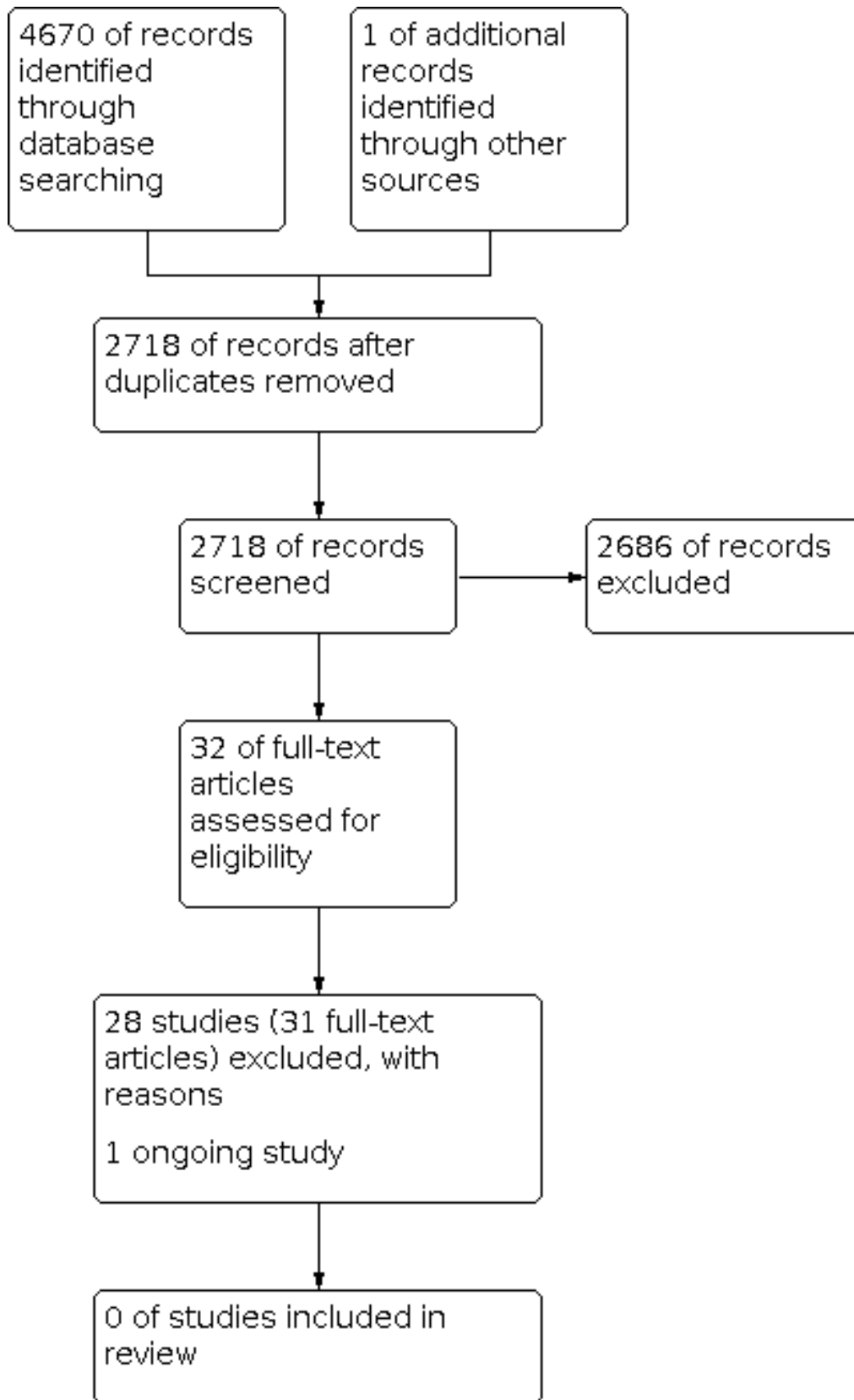
RESULTS

Description of studies

Results of the search

Please refer to [Figure 1](#).

Figure 1. Figure 1. Study flow diagram.



We found 4671 citations using the search strategy run on 05 March 2020 and 13 September 2021, from which we identified 32 citations (to 29 studies) as potentially relevant. Following review of the full-text articles, none of the studies were eligible for inclusion in this review. We excluded 28 studies (31 citations) for not fulfilling the inclusion criteria, for further information please refer to the relevant table ([Characteristics of excluded studies](#)). We assessed one study as ongoing ([Arnold-Reed 2017](#)).

Included studies

We found no studies that were eligible for inclusion in this review.

Excluded studies

We excluded 28 studies from the review, as described in 'Characteristics of excluded studies' table ([Amor-Salamanca 2017](#); [Aref-Eshghi 2017](#); [Bell 2012](#); [Bell 2013](#); [Bell 2014a](#); [Bell 2014b](#); [Bell 2015](#); [Bender 2016](#); [Benlian 2009](#); [Benn 2012](#); [Casula 2017](#); [Elis 2020](#); [Gray 2008](#); [Green 2016](#); [Jayne 2016](#); [Kirke 2015](#); [Nanthen 2015](#); [NCT03253432](#); [NCT03398954](#); [NCT03520140](#); [Qureshi 2016](#); [Safarova 2016](#); [Shipman 2014](#); [Steyn 1998](#); [Troeng 2016](#); [Vickery 2017](#); [Weng 2018](#); [Zamora 2017](#)). More than half of these studies were excluded because they did not have control group (n = 20) and another reason for exclusion were ineligible participants (n = 8).

Ongoing studies

We identified one study which is still ongoing ([Arnold-Reed 2017](#)). This study will use a pragmatic cluster pre-post intervention design to assess the effectiveness of a primary care-based model of care on detection and management of FH in adults in Australia.

Risk of bias in included studies

There were no studies included in this review.

Other potential sources of bias

There were no studies included in this review.

Effects of interventions

There were no studies included in this review.

DISCUSSION

Summary of main results

Identifying individuals with FH and starting lipid-lowering treatment will reduce the risk of premature CHD. However, there is no evidence from RCTs or eligible NRSIs for healthcare strategies to identify FH in primary care and other community settings (NRSIs as defined by EPOC guideline (non-RCTs, prospective cohort studies, controlled before-and-after studies, and controlled ITS studies)).

No studies were identified that fulfilled the inclusion criteria. However, we did identify three studies which would have been eligible for inclusion except for their study design. In these studies, before-and-after designs without a control group were used. Such designs are usually not eligible for informing the effectiveness of an intervention due to the inherent biases within them as a result of not having a control group ([EPOC 2017](#)). Apparent differences identified between the two periods could be due to reasons not related to the intervention.

Overall completeness and applicability of evidence

There were no studies included in this review.

Quality of the evidence

There were no studies included in this review.

Potential biases in the review process

We followed the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* with two review authors independently selecting studies and extracting data. We performed a thorough search of literature. It is possible that studies published in journals that were outside our search strategy may have been missed.

Agreements and disagreements with other studies or reviews

Three of the excluded studies were only excluded on study design, but participants and interventions were relevant to this review. All three studies were undertaken in General (Family) Practice; with two studies carried out in the UK ([Green 2016](#); [Weng 2018](#)) and the remaining study in Australia ([Bell 2013](#)). All three studies used different electronic health records reminders in individuals with raised cholesterol, one with postal invitation to participants ([Weng 2018](#)) and one with FH specialist nurse assessment ([Green 2016](#)). The Green study showed modest absolute improvement in detection of definite FH using initially Simon-Broome, then both Simon-Broome and the DLCN criteria ([Green 2016](#)). In the other two studies there was no evidence of an improvement in diagnosis, which could be due to small sample sizes ([Bell 2013](#); [Weng 2018](#)). Further, all three studies had short follow-up periods. Although these studies could not be included in the systematic review and were of poor quality, if the findings are confirmed in more robustly designed studies, this could suggest that interrogating the primary care electronic health records of individuals with raised cholesterol levels, may lead to an improvement in identifying people with FH.

There have been no previous published systematic reviews on this topic. However, there have been several narrative reviews on the detection of FH in primary care. For example, a paper by Lan outlines different screening methods for FH, which also included search of primary care electronic health records ([Lan 2019](#)). As part of their suggestions for future research in this area, the authors recommend clinical trials of screening protocols and testing interventions.

The NICE guidelines on identifying FH were updated following a structured review of the evidence and suggested that clinicians should systematically search primary care electronic healthcare records for individuals at risk of FH. Further, the condition should be suspected in individuals with total cholesterol greater than 7.5 mmol/L or personal or family history of premature coronary heart disease (or both) ([NICE 2017](#)). The guidelines recommend that, after excluding possible secondary causes for raised cholesterol, healthcare professionals should use either the Simon-Broome or DLCN criteria to make a clinical diagnosis of FH and refer individuals on to specialist care for genetic testing. Evidence from one of the (uncontrolled before-and-after) studies excluded from the current review informed recommendations in the NICE clinical guidelines ([Green 2016](#)). Other studies listed in the updated NICE guidelines as evidence for the use of primary care electronic health records, were also identified in our search results. However, we excluded

these as they did not provide a control group, which was one of our inclusion criteria (Bell 2014b; Gray 2008; Kirke 2015; Qureshi 2016; Troeung 2016). A more recent narrative review for the European Atherosclerosis Society Consensus Statement on identifying and managing FH (Nordestgaard 2013) cited one of the excluded papers (Benn 2012), but did not specifically consider the role of primary care or other community health professionals in identifying FH.

AUTHORS' CONCLUSIONS

Implications for practice

The review provided no evidence from randomised controlled trials or controlled non-randomised studies to inform the most effective healthcare strategy for identifying familial hypercholesterolaemia (FH) in primary care and other community settings. However, there is a potential role for searching primary care electronic health records.

Implications for research

A pragmatic trial design should be adopted to answer this research question using different diagnostic assessment criteria in primary care electronic health records. Genetic confirmation of FH should be included, as well as a detailed description of processes and outcome measures, particularly referral to specialists and both surrogate and disease outcome measures of cardiovascular disease. To identify later results for clinical outcome measures, at least one year study follow-up would be required. Considering the current evidence of the benefits of identifying FH, a study design using a true control group with no active identification maybe ethically unacceptable.

Internationally, considering the primary outcome measure proposed in this systematic review, the most commonly used diagnostic assessment criteria for FH is the Dutch Lipid Clinic

Network (DLCN) (Defesche 2004; Reiner 2011; Watts 2011). In the UK, Simon-Broome criteria is the most frequently used, as recommended by the original 2008 NICE guidelines on FH and the updated version in 2017 (NICE 2008; NICE 2017). Other assessment criteria have also been used worldwide, such as MedPed (Williams 1993), the Japanese criteria (Harada-Shiba 2012) and the Canadian criteria (Ruel 2018). It would be challenging to combine studies using different diagnostic assessment criteria. Although several of the criteria include genetic testing, such as DLCN and Simon-Broome criteria, currently genetic testing is not routinely performed in primary care (Green 2016; Qureshi 2016). Hence the primary outcome measure directly collated from primary care will be based on clinical phenotype. When genetically-confirmed FH is collated, this is currently based on the diagnosis of those people referred from primary to specialist care.

ACKNOWLEDGEMENTS

The authors would like to thank Jennifer Tranter for her contribution to the protocol and draft versions of this review.

The authors would like to thank the Nottingham City Clinical Commissioning Group for commissioning and funding this review as part of a programme grant development award. The authors would also like to thank Dr Christopher Respinger for his contribution to drafting the 'Why it is important to do this review' section, our patient representative Mr William Rowland for co-writing the lay summary.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amor-Salamanca 2017	Ineligible participants
Aref-Eshghi 2017	Ineligible participants
Bell 2012	No control group
Bell 2013	No control group
Bell 2014a	No control group
Bell 2014b	No control group
Bell 2015	No control group

Study	Reason for exclusion
Bender 2016	No control group
Benlian 2009	Ineligible participants
Benn 2012	No control group
Casula 2017	No control group
Elis 2020	No control group
Gray 2008	No control group
Green 2016	No control group
Jayne 2016	No control group
Kirke 2015	No control group
Nanchen 2015	Ineligible participants
NCT03253432	Ineligible participants
NCT03398954	Ineligible participants
NCT03520140	Ineligible participants
Qureshi 2016	No control group
Safarova 2016	No control group
Shipman 2014	No control group
Steyn 1998	Ineligible participants
Troeung 2016	No control group
Vickery 2017	No control group
Weng 2018	No control group
Zamora 2017	No control group

Characteristics of ongoing studies [ordered by study ID]

Arnold-Reed 2017

Study name	Detection and management of familial hypercholesterolaemia in primary care in Australia: protocol for a pragmatic cluster intervention study with pre-post intervention comparisons.
Methods	Pragmatic, cluster intervention study with pre-post intervention comparisons.
Participants	Patients aged above 18 years old in general practices in Australia.

Arnold-Reed 2017 (Continued)

Interventions	Primary care-based model of care (MoC) to improve detection and management of familial hypercholesterolaemia.
Outcomes	Primary outcomes: increase in number of familial hypercholesterolaemia index cases clinical identified and reduction in LDL-c of treated cases. Secondary outcomes: increase in number of family cases detected/contacted (including children) and cost implications of the method of care.
Starting date	July 2016.
Contact information	Dr Diane E Arnold-Reed: diane.arnold-reed@nd.edu.au
Notes	

APPENDICES
Appendix 1. Glossary of terms

Term	Definition
Definite FH (Simon Broome criteria)	Adult = total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-Cholesterol > 190 mg/dL (4.9 mmol/L) Child less than 16 years of age = total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-Cholesterol > 155 mg/dL (4.0 mmol/L) Plus at least one of the two: 1. plus physical finding = tendinous xanthomas, or tendinous xanthomas in first or second-degree relative OR 2. DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
Possible FH (Simon Broome criteria)	Adult = total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-Cholesterol > 190 mg/dL (4.9 mmol/L) Child = less than 16 years of age = total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-Cholesterol > 155 mg/dL (4.0 mmol/L) Plus at least one of the two: 1. family history of at least one of the following: - myocardial infarction at 60 years or younger in first-degree relative OR - myocardial infarction at 50 years or younger in second-degree relative OR 2. family history of elevated total cholesterol: - > 290 mg/dL (7.5 mmol/L) in adult first- or second-degree relative OR - > 260 mg/dL (6.7 mmol/L) in child, brother or sister aged younger than 16 years.

Appendix 2. Search methods - electronic searching

Database / Resources	Strategy
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(Continued)

CENTRAL, the Cochrane Library

via the Cochrane Library:
[\(www.cochranelibrary.com/\)](http://www.cochranelibrary.com/)

Searched: All years

- #1. MeSH descriptor: [Hyperlipoproteinemia Type II] explode all trees
- #2. familial hypercholesterolaemia:ti,ab
- #3. MeSH descriptor: [Hyperlipoproteinemias] explode all trees
- #4. "hyperlipoproteinemia type IIb"
- #5. (hyperlipoproteinemia type 2):ti,ab,kw
- #6. (hyperlipoproteinemia type 2b):ti,ab
- #7. "hyperlipoproteinemia type 2a"
- #8. "hyperlipoproteinemia type IIa"
- #9. MeSH descriptor: [Hyperlipidemia, Familial Combined] explode all trees
- #10. MeSH descriptor: [Hyperlipoproteinemia Type I] explode all trees
- #11. MeSH descriptor: [Hyperlipoproteinemia Type IV] explode all trees
- #12. "lipoprotein lipase deficiency"
- #13. "inherited hypercholesterolaemia"
- #14. "inherited hypercholesterolemia"
- #15. "familial hyperchylomicron"
- #16. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15

PubMed

(www.ncbi.nlm.nih.gov/pubmed)

(1946 to present)

- #1. "hypercholesterol*" [Title/Abstract]
- #2. "hyperlipoprotein*" [Title/Abstract]
- #3. "familial hypercholesterolemia" [Title/Abstract]
- #4. "familial hypercholesterolaemia" [Title/Abstract]
- #5. "familial hyperlipoproteinemia" [Title/Abstract]
- #6. "familial hyperlipoproteinaemia" [Title/Abstract]
- #7. "familial hypercholesterolemia with hyperlipidemias" [Title/Abstract]
- #8. "familial combined hyperlipidemia" [Title/Abstract]
- #9. "hypertriglyceridemia, familial" [Title/Abstract]
- #10. "hypertrigly*" [Title/Abstract]
- #11. "hyperlipoproteinemia TYPE 2" [Title/Abstract]
- #12. "hyperlipoproteinemia TYPE 2A" [Title/Abstract]
- #13. "hyperlipoproteinemia TYPE 2B" [Title/Abstract]
- #14. "hyperlipoproteinaemia TYPE 2" [Title/Abstract]
- #15. "hyperlipoproteinaemia TYPE 2A" [Title/Abstract]
- #16. "hyperlipoproteinaemia TYPE 2B" [Title/Abstract]
- #17. "combined hyperlipidemia, familial" [Title/Abstract]
- #18. "familial lipoprotein lipase deficiency" [Title/Abstract]

(Continued)

- #19. "autosomal dominant hypercholesterolemia"[Title/Abstract]
- #20. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)
- #21. "general practice"[Title/Abstract]
- #22. "primary health care"[Title/Abstract]
- #23. "general Practitioner"[Title/Abstract]
- #24. "GP"[Title/Abstract]
- #25. "community"[Title/Abstract]
- #26. (#21 or #22 or #23 or #24 or #25)
- #27. "detect*"[Title/Abstract]
- #28. "diagnosis"[Title/Abstract]
- #29. "diagnose*"[Title/Abstract]
- #30. "laborator*"[Title/Abstract]
- #31. "patholog*"[Title/Abstract]
- #32. "database"[Title/Abstract]
- #33. "record"[Title/Abstract]
- #34. "screen*"[Title/Abstract]
- #35. "mass screen"[Title/Abstract]
- #36. "family"[Title/Abstract]
- #37. "familial"[Title/Abstract]
- #38. "audit"[Title/Abstract]
- #39. (#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38) #40.(#20 and #26 and #39)

MEDLINE (OvidSP)

(1946 to present)

1. (familial or inherited) adj2 (hypercholesterol?emia\$.tw.
2. Hyperlipoproteinemia Type II/
3. (Hyperlipoprotein?emia\$) adj (type II or type IIa or type IIb or type 2 or type 2a or type 2b).tw.
4. 1 or 2 or 3
5. general practice\$.tw.
6. GP.tw.
7. (primary adj (health or care)).tw.
8. ((family or community) adj (medicine or practice)).tw.
9. Primary Health Care/
10. exp General Practice/
11. 5 or 6 or 7 or 8 or 9 or 10

(Continued)

12. (((medical or health or patient\$ or electronic) and record\$ or database\$ or data or audit or reminder\$ or tool\$)) or (diagnos\$ or identif\$ or detect\$).tw.
13. 11 and 12
14. laborator\$.tw.
15. Laboratories/
16. patholog\$.tw.
17. Pathology/or Pathology, Clinical/
18. 14 or 15 or 16 or 17
19. (record\$ or database\$ or data or audit or tool\$ or diagnos\$ or identif\$ or detect\$).tw.
20. 18 and 19
21. screen.tw.
22. mass screening/
23. 21 or 22
24. 23 and (11 or 18)
25. ((family or relative\$) and test\$).tw.
26. 13 or 20 or 24 or 25
27. 4 and 26

Embase (Ovid SP)

(1974 to present)

1. HYPERLIPOPROTEINEMIA/
2. Hypercholesterolaemia.mp.
3. Hypercholesterolaemia.tw.
4. Hyperlipoproteinemia.mp
5. hyperlipoproteinemia.tw.
6. familial hypercholesterolaemia/
7. hypertriglycer\$.tw.
8. hyperlipid\$.tw.
9. lipoprotein lipase deficienc\$.tw.
10. hyperlipoproteinemia Type 2.tw.
11. autosomal dominant hypercholesterol\$.tw.
12. familial hypertriglyceridemia\$.tw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. general practice.tw.
15. GP.tw.
16. primary health care.tw.
17. community.tw.

(Continued)

18. 14 or 15 or 16 or 17
19. laboratory.tw.
20. laboratories.tw.
21. screen.tw.
22. mass screening.tw.
23. detection.tw.
24. audit.tw.
25. record.tw.
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 13 and 18 and 26

CINAHL (EBSCOHost) (1937 to present)	S1 (MH "familial hypercholesterolemia" OR MH "hypertriglyceridemia" OR MH "hyperlipidemia" OR MH "hyperlipoproteinemia") S2 (TI "clinic" OR TI "clinical practice" OR TI "general practice" OR TI "gp" OR TI "general practitioner" OR TI "community" OR TI "primary care" OR TI "primary health care" OR TI "primary healthcare") S3 (TI "detection" OR TI "database" OR TI "laboratory" OR TI "audit" OR TI "screening" OR TI "mass screening" OR TI "records" OR TI "identification" OR TI "identity") S4 S1 AND S2 AND S3
ProQuest Dissertations & Theses (www.proquest.com/) (1861 to present)	ti(familial hypertriglyceridemia) OR ti(hypercholesteremia) OR ti(hyperlipidemia) OR ti(familial combined hyperlipidemia) AND ti(mass screening) OR ti(audit) OR ti(diagnosis) OR ti(identify) OR ti(identify risk) OR ti(database) OR ti(detection) AND ti(general practice) OR ti(general practitioners) OR ti(clinical practice) OR ti(primary care) OR ti(primary health care) OR ti(communitiy)
WEB OF SCIENCE (CPCI-S) (1898 to present)	#1 TS=(familial hypercholesterolaemia) OR TS=(familial hypercholesterolemia) OR TS=(hyperlipidaemia) OR TS=(hyperlipidemia) OR TS=(familial combined hyperlipidaemia) OR TS=(familial combined hyperlipidemia) OR TS=(hyperlipoproteinaemia) OR TS=(hyperlipoproteinemia) OR TS=(familial hypertriglyceridemia) OR TS=(familial hypertriglyceridaemia) #2 TI=(screen) OR TI=(mass screen) OR TI=(audit) OR TI=(detect*) OR TI=(identify) OR TI=(identification) OR TI=(record) OR TI=(diagnose) OR TI=(diagnosis) #3 TI=(GP) OR TI=(general practice) OR TI=(general practitioner) OR TI=(primary health) OR TI=(primary health care) OR TI=(primary healthcare) OR TI=(laboratory) OR TI=(community) #4 #1 AND #2 AND #3
SCOPUS (Elsevier) (1823 to present)	familial PRE/1 hypercholesterolaemia OR hyperlipidemia OR hyperlipidaemia OR hyperlipoproteinemia OR hyperlipoproteinaemia OR hypertriglycerolaemia OR hypercholesterolaemia OR hypercholesterolemia AND mass PRE/1 screening OR diagnosis OR audit OR detect OR record OR database OR identify OR identification AND general practice OR general practitioner OR GP OR primary health care OR primary healthcare OR community OR laboratory OR clinic OR clinical practice
ISRCTN registry (www.isrctn.com/) (All years)	(hypercholesterolaemia) OR (hypercholesterolemia) OR (hyperlipidemia) OR (hyperlipidaemia) OR (hyperlipoproteinaemia) OR (hyperlipoproteinemia) OR (hypertryglycerolaemia) within Condition: (familial hypercholesterolaemia) OR (familial hypercholesterolemia)

(Continued)

Clinical Trials.gov (www.clinicaltrials.gov) (All years)	ADVANCED SEARCH Condition: familial hypercholesterolemia Study type: All studies
WHO International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/clinical-trials-registry-platform) (All years)	ADVANCED SEARCH Search 1: Title: hypercholesterolaemia AND Condition: familial hypercholesterolaemia Search 2: Title: hypercholesterolemia AND Condition: familial hypercholesterolemia

Appendix 3. Handsearching

Resources	Strategy
HEART UK (heartuk.org.uk) (All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia
The FH Foundation (https://the.fhfoundation.org/) (All years)	
National Institute for Health and Care Excellence (www.nice.org.uk/) (All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia
Scottish Intercollegiate Guidelines Network (www.sign.ac.uk) (All years)	
National Institute for Health and Care Excellence Clinical Knowledge Summaries (cks.nice.org.uk/)(All years)	
HEART UK Annual Scientific Conference(s) (heartuk.org.uk) (All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia OR familial hypercholesterolaemia OR autosomal dominant familial hypercholesterolemia
British Cardiovascular Society Conference(s) (www.bcs.com) (All years)	
European Atherosclerosis Society Conference(s) (www.eas-society.org) (All years)	
Journals (reference lists): <i>Heart</i> (heart.bmj.com/) (All years)	familial hypercholesterolaemia OR familial hypercholesterolemia OR hyperlipidemia OR hyperlipidaemia OR inherited hypercholesterolaemia OR inherited hypercholesterolemia OR hyperlipoproteinaemia OR hyperlipoproteinemia

(Continued)

Atherosclerosis (www.atherosclerosis-journal.com) (All years)

Journal of Clinical Lipidology (www.lipidjournal.com/) (All years)

Current Opinion in Lipidology (www.ovid.com/site/catlog/journals/439.jsp) (All years)

Journal of Inherited Metabolic Disease (link.springer.com/journal/10545) (All years)

HISTORY

Protocol first published: Issue 3, 2018

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities

Protocol stage: (draft the protocol): NQ, JK, SW, JLB, JT*, MLDS

Review stage: (select studies for inclusion): NQ, JT*, MLDS, JLB

Review stage: (data extraction): SW, JT*, MLDS, JLB

Review stage: (enter data into RevMan) MLDS, HA-H

Review stage: (writing the final review) NQ, JK, SW, JLB, MLDS, HA-H

Update stage: (update the review) NQ, JK, SW, HA-H

JT: Jennifer Tranter (please refer to 'Acknowledgements').

DECLARATIONS OF INTEREST

Nadeem Qureshi: chief investigator on UK National Institute of Health research projects on identifying familial hypercholesterolaemia and plans to pursue further research in this area. Also chief investigator on UK National Institute of Health research projects on familial breast hypercholesterolaemia.

Maria Luisa R Da Silva: none known.

Hasidah Abdul-Hamid: none known.

Stephen Weng: member of the Clinical Practice Research Datalink Independent Scientific Advisory Committee at the UK Medicines and Health Regulatory Agency. Holds independent research grant funding from AMGEN and is academic advisor to Qealth.

Joe Kai: none known.

Jo Leonardi-Bee: receives funding from the MRC and Health Technology Assessment in relation to other grants within the topic of familial hypercholesterolaemia.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

- Nottingham City Clinical Commissioning Group, UK

Commissioned and funded this review as part of a programme grant development award.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol, eligibility criteria included before-and-after studies. However, further review by the Cochrane Editorial team, and in line with EPOC guideline ([EPOC 2017](#)), uncontrolled before-and-after studies were removed. The title have been updated to reflect the objective of this review.