



BMJ Open Risk factors for cardiovascular events in patients with heterozygous familial hypercholesterolaemia: protocol for a systematic review

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ABSTRACT

Introduction Heterozygous familial hypercholesterolaemia (heFH) is the most common monogenic cause of premature atherosclerotic cardiovascular disease. The precise diagnosis of heFH is established by genetic testing. This systematic review will investigate the risk factors that predict cardiovascular events in patients with a genetic diagnosis of heFH.

Methods and analysis Our literature search will cover publications from database inception until June 2023. We will undertake a search of CINAHL (trial), clinicalKey, Cochrane Library, DynaMed, Embase, Espacenet, Experiments (trial), Fisterra, InDICES CSIC, LILACS, LISTA, Medline, Micromedex, NEJM Resident 360, OpenDissertations, PEDro, Trip Database, PubPsych, Scopus, TESEO, UpToDate, Web of Science and the grey literature for eligible studies. We will screen the title, abstract and full-text papers for potential inclusion and assess the risk of bias. We will employ the Cochrane tool for randomised controlled trials and non-randomised clinical studies and the Newcastle–Ottawa Scale for assessing the risk of bias in observational studies. We will include full-text peer-reviewed publications, reports of a cohort/registry, case–control and cross-sectional studies, case report/series and surveys related to adults (≥18 years of age) with a genetic diagnostic heFH. The language of the searched studies will be restricted to English or Spanish. The Grading of Recommendations, Assessment, Development and Evaluation approach will be used to assess the quality of the evidence. Based on the data available, the authors will determine whether the data can be pooled in meta-analyses.

Ethics and dissemination All data will be extracted from published literature. Hence, ethical approval and patient informed consent are not required. The findings of the systematic review will be submitted for publication in a peer-reviewed journal and presentation at international conferences.

PROSPERO registration number CRD42022304273.

INTRODUCTION

Familial hypercholesterolaemia (FH) is a disorder of the metabolism of low-density lipoprotein (LDL) particles. FH is characterised

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a protocol for a systematic review that will use unified genetic criteria to generate a well-defined sample to investigate the predictive risk factors of incident cardiovascular events in people diagnosed with heterozygous familial hypercholesterolaemia.
- ⇒ We used Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines to report the present protocol and will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines for reporting the results of the systematic review.
- ⇒ This study will assess more than 10 different data sources.
- ⇒ Risk of bias and evidence quality will be assessed using the Cochrane tool, Newcastle–Ottawa Scale and Grading of Recommendations, Assessment, Development and Evaluation.
- ⇒ A potential limitation may be the diversity of different study designs, as well as wide-ranging results, which may limit comparative analysis.

by elevated plasma levels of LDL-cholesterol, owing to an inherited genetic defect causing their reduced clearance by the liver. FH affects approximately 1/300 individuals in the heterozygous (heFH) form and 1/300 000 in the homozygous form.^{1–4} The most frequent causes of monogenic FH are mutations encoding the LDL receptor (LDLR), apolipoprotein B (APOB) and proprotein convertase subtilisin/kexin type 9 proteins.^{5–7} Additional mutations in the apolipoprotein E and LDLR adaptor protein 1 genes can cause a rare autosomal dominant and a very rare autosomal recessive form of FH, respectively.^{8,9}

Technological advances have increased the accuracy of diagnosing heFH. The precise diagnosis of heFH can be established with genetic testing that identifies the responsible

gene variant. In 2018, an international expert panel¹⁰ endorsed the utility of genetic testing for the care of patients with heFH for: (a) making a definitive diagnosis, (b) improving risk stratification, (c) addressing the increasing need for more potent therapies, (d) improving adherence to treatments, and (e) increasing the precision and cost-effectiveness of cascade testing.^{4 11–14}

Traditionally, heFH diagnostic algorithms have been used based on clinical and analytical criteria such as the Simon Broome diagnostic criteria, the Dutch Lipid Clinic Network (DLCN) criteria and Make Early Diagnosis to Prevent Early Death (MEDPED) criteria.^{15 16} Concordance rates between the three sets of criteria for the diagnosis of heFH can be low.¹⁷ These classifications criteria are capable of diagnosing primary hypercholesterolaemia but do not discriminate between patients with monogenic and polygenic hypercholesterolaemia.^{3 18 19}

Patients with monogenic heFH have an average risk of atherosclerotic cardiovascular disease (ASCVD) that is 3–13 times higher than the general population^{20 21} and their life expectancy may be shortened by 20–30 years compared with unaffected subjects. Owing to increased exposure to high levels of LDL-cholesterol elevated from birth,^{5 6 22–25} sudden death and acute myocardial infarction are the main causes of death in heFH.⁹

ASCVD in patients with FH is highly variable. There is a need to more accurately estimate such risk in patients with heFH to enhance and optimise lipid-lowering treatment and maximise the use of healthcare resources.^{26–31} Current guidelines recommend against using existing algorithms such as the Framingham risk score in heFH as they are derived from general population data and significantly underestimate lifetime ASCVD risk in this group.^{15 16} Many risk factors for ASCVD in the population with heFH have been well described and continue to be investigated.^{32–38} Risk equations have also been published, such as the SAFEHEART-risk equation (RE) and FH risk score.^{19 39 40}

To our knowledge, there are no systematic reviews of the risk factors associated with incident ASCVD events based on patients with heFH diagnosed purely on genetic criteria. Previous studies have included patients without a pathogenic or likely pathogenic variant for heFH.^{2 41} To address this shortcoming, we aim to carry out a systematic review to investigate risk factors predictive of incident ASCVD events in patients with genetically confirmed heFH.

METHODS AND ANALYSIS

This protocol is reported in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines⁴² and has been registered with PROSPERO (CRD42022304273).

Eligibility criteria

Studies will be selected according to the criteria outlined below:

Study designs

Our literature search will cover publications from database inception until June 2023. We will include full-text peer-reviewed publications, reports of a cohort/registry, case-control, cross-sectional, case reports/series and surveys related to patients with genetically confirmed heFH. The language of the studies will be in English or Spanish.

Participants

We will include studies examining adult patients (≥ 18 years of age) with a genetic diagnosis of heFH. Patients with only a clinical diagnosis of heFH (eg, Simon Broome, DLCN or MEDPED) will be excluded, as well as studies on children and adolescents.

Risk factors

Studies that report risk factors of ASCVD endpoints will be included. Risk factors include age, sex, body mass index, type 2 diabetes mellitus, smoking, family history of cardiovascular disease, hypertension, LDL-cholesterol, high-density lipoprotein-cholesterol, triglycerides and lipoprotein(a). Other additional risk factors identified through the search will also be included.

Comparator group

Matched/unmatched controls with heFH.

Search strategy

A general search will be undertaken in the BV-SSPA (Biblioteca Virtual del Sistema Sanitario Público de Andalucía) library, which includes the following databases: CINAHL (trial), clinicalKey, Cochrane Library, DynaMed, Embase, Espacenet, Experiments (trial), Fisterra, ÍNDICES CSIC, LILACS, LISTA, Medline, Micromedex, NEJM Resident 360, OpenDissertations, PEDro, Trip Database, PubPsych, Scopus, TESEO, UpToDate and Web of Science.

The keywords for the bibliographical search are: “Family hypercholesterolemia”, “risk factors”, “cardiovascular events” and “review systematic” (table 1). The search strategy will be performed by Medical Subject Heading or Descriptores en Ciencias de la Salud (DECS) terms.

The International Clinical Trials Registry Platform search portal and ClinicalTrials.gov will also be searched for ongoing or recently completed trials, and PROSPERO will be searched for ongoing or recently completed systematic reviews.

An additional search will be extracted through the BV-SSPA and will be exported to Mendeley, where the data will be shared with the different reviewers. The combined keywords are hyperlipoproteinemia type II, familial hypercholesterolaemia or familial hypercholesterolaemia, heterozygous familial hypercholesterolemia, genetics, cardiovascular events, risk factors and systematic review.

Table 1 Search strategy

Search strategy	
1	Hyperlipoproteinemia Type II
2	(Familial hypercholesterolemia or familial hypercholesterolaemia)
3	Heterozygous familial hypercholesterolemia
4	Genetics
5	Adults
6	Coronary Disease or Atherosclerosis
7	Mortality or Mortality Premature
8	Myocardial Infarction
9	Stroke
10	Heart Failure
11	Peripheral Vascular Diseases
12	Myocardial Ischemia
13	Cardiovascular Disease
14	Chronic kidney disease
15	Risk or Risk Factors or Incidence or Prognosis
16	prevalence or "risk factors" or incidence or prevalence or prognosis
17	(familial hypercholesterolemia or Hyperlipoproteinemia Type II) and ('systematic review' or 'meta-analysis').
18	1 or 2
19	2 or 4
20	3 or 5
21	18 and 19 and 20
22	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
23	15 or 16
24	21 and 22 and 23
25	24 or 17

Study records

Literature search results will be uploaded to Mendeley and Microsoft Excel to facilitate collaboration among reviewers during the study selection process.

Two reviewers will simultaneously and independently screen the titles and abstracts yielded by the search against the inclusion criteria. Full reports will be obtained for all titles that appear to meet the inclusion criteria or where there is any uncertainty. The reviewers will then screen the full-text reports and decide whether these meet the inclusion criteria. We will seek additional information from study authors where necessary to resolve questions about eligibility. The reviewers will not be blind to the journal titles or to the study authors or institutions.

Data from included full-text articles will be extracted independently by the two reviewers into the standardised data extraction form and any conflicts will be resolved through discussions, and if necessary, a third reviewer will resolve any persisting discrepancies. Based on the data available, we will determine

whether the studies can be pooled for meta-analyses. If required, we will contact the corresponding author cited in the publications to obtain any missing data.

Outcome measures

The primary outcome is to assess the risk factors associated with the presence of ASCVD events in patients with a molecular diagnosis of heFH. This will allow us to avoid selection bias and be more accurately estimate the vascular risk in this population.

ASCVD events are defined as the presence of any of the following: (1) myocardial infarction; (2) angina pectoris: diagnosed as classic symptoms in combination with at least one unequivocal result of one of the following: exercise test, nuclear scintigram or >70% stenosis on a coronary angiogram; (3) percutaneous coronary intervention; (4) coronary artery bypass grafting; (5) ischaemic stroke demonstrated by CT scan or MRI or documented transient ischaemic attack; (6) peripheral arterial disease: intermittent claudication, which was defined as classic symptoms or stenosis >50% on angiography or ultrasonography or abdominal aortic aneurysm; (7) peripheral arterial revascularisation; (8) aortic valve replacements secondary to severe aortic stenosis and (9) cardiovascular deaths.

Data extraction

Each reviewer will extract the following information from the articles: bibliographical information, study design, risk of bias assessment, exposure(s) and outcomes, characteristics of study participants, numerical results (number of participants per group, number with outcome), effect estimates (adjusted and unadjusted) and their SEs.

Through the iterative process of undertaking the systematic review, any additional information that is relevant will also be included.

Data synthesis

If studies are sufficiently homogeneous in terms of design and comparator, we will conduct a meta-analysis using a random-effects model, or fixed if there is no heterogeneity. We will analyse the data of randomised trials separately from those of non-randomised comparative studies. We will report dichotomous outcomes as risk ratios or ORs and continuous variables as mean differences or standardised mean differences, with a 95% CI. A detailed qualitative synthesis of the findings will be provided in a narrative table if a meta-analysis is not possible. We will use Comprehensive Meta-Analysis software to generate forest plots to represent the data graphically if appropriate.

The heterogeneity will be determined by χ^2 and I^2 tests. The interpretation of the heterogeneity will be as follows: I^2 : 0%–40% unimportant heterogeneity; 30%–60% moderate heterogeneity; 50%–90% substantial heterogeneity and 75%–100% considerable heterogeneity. Funnel plot will be applied to assess the publication bias in the included studies.

Risk of bias assessment and quality of evidence

An assessment of literature quality will be performed independently by two reviewers. Any disagreement will be resolved through discussion and consensus among researchers. For randomised controlled trials and non-randomised trials, we will employ the Cochrane Collaboration risk of bias tool to assess the quality of the studies included.⁴³ For observational studies, we will use the Newcastle–Ottawa Scale.⁴⁴ The quality of evidence for all outcomes will be judged using the Grading of Recommendations, Assessment, Development and Evaluation working group methodology.⁴⁵

Patient and public involvement

None.

ETHICS AND DISSEMINATION

The results of this systematic review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. All data will be extracted from published literature. Hence, ethical approval and patient informed consent are not required. The findings of the systematic review will be submitted for publication in a peer-reviewed journal and presentation at international conferences.

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Contributors MEM is the guarantor. MJR-J, ARS-J and MEM drafted the manuscript and developed the search strategy. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. ARS-J and JLS-R provided statistical expertise. GW, JP, PM and ENG-C read and provided feedback. All authors reviewed and approved the final manuscript.

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