BMJ Open

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

María Elena Mansilla-Rodríguez ,[1] Manuel J Romero-Jimenez,[1] Alina Rigabert Sánchez-Junco,[2] Eva Nadiedja Gutierrez-Cortizo,[1] José Luis Sánchez-Ramos,[3] Pedro Mata,[4] Jing Pang ,[5] Gerald F Watts[6]

To cite: Mansilla-Rodríguez ME, Romero-Jimenez MJ, Rigabert Sánchez-Junco A, *et al*. Risk factors for cardiovascular events in patients with heterozygous familial hypercholesterolaemia: protocol for a systematic review. *BMJ Open* 2023;**13**:e065551. doi:10.1136/bmjopen-2022-065551

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-065551).

Received 24 July 2022
Accepted 17 February 2023

For numbered affiliations see end of article.

Correspondence to
Dr Manuel J Romero-Jimenez; mjesus.romero.sspa@juntadeandalucia.es

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, ÍnDICEs 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.

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.

INTRODUCTION

Familial hypercholesterolaemia (FH) is a disorder of the metabolism of low-density lipoprotein (LDL) particles. FH is characterised 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 panel[10] 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 guidelines[42] 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 risks 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 $\chi 2$ 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.

Author affiliations
[1]Vascular Risk Unit, Hospital Infanta Elena, Huelva, Spain
[2]Hospital Juan Ramon Jimenez, Huelva, Spain
[3]Health Sciences. Nurse University, Universidad de Huelva, Huelva, Spain
[4]Fundación de Hipercolesterolemia Familiar, Madrid, Spain
[5]School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia
[6]Cardiometabolic Service, Department of Cardiology and Internal Medicine, Royal Perth Hospital, School of Medicine, University of Western Australia, Perth, Western Australia, Australia

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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests All authors have completed the BMJ Group uniform disclosure form declaration of interests statement. PM collaborates with research grants from Amgen and Sanofi and collaboration for familial hypercholesterolaemia studies. GW declares receiving consulting fees from Amgen, Novartis, Arrowhead and Pfizer; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from Amgen, Novartis and Arrowhead; receiving support for attendance at meetings and/or trips from Amgen and Novartis; and participation in a Data Safety Monitoring Board or Advisory Board for Arrowhead and AstraZeneca. JP is supported by grants from the National Health and Medical Research Council (Australia), the Western Australian Department of Health and the Royal Perth Hospital Research Foundation. The other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
María Elena Mansilla-Rodríguez http://orcid.org/0000-0001-9283-9572
Jing Pang http://orcid.org/0000-0002-9700-6948

REFERENCES

1 Watts GF, Gidding SS, Mata P, *et al*. Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. *Nat Rev Cardiol* 2020;17:360–77.
2 Hu P, Dharmayat KI, Stevens CAT, *et al*. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Circulation* 2020;141:1742–59.
3 Zamora A, Masana L, Comas-Cufí M, *et al*. Familial hypercholesterolemia in a european mediterranean population-prevalence and clinical data from 2.5 million primary care patients. *J Clin Lipidol* 2017;11:1013–22.
4 Vuorio AF, Turtola H, Piilahti K-M, *et al*. Familial hypercholesterolemia in the Finnish North Karelia. *ATVB* 1997;17:3127–38.
5 Plana N, Rodríguez-Borjabad C, Ibarretxe D, *et al*. Familial hypercholesterolemia in childhood and adolescents: a hidden reality. *Clínica e Investig En Arterioscler (English Edition)* 2017;29:129–40.
6 Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. *Nat Rev Cardiol* 2019;16:9–20.
7 Wald DS, Bestwick JP. Reaching detection targets in familial hypercholesterolaemia: comparison of identification strategies. *Atherosclerosis* 2020;293:57–61.
8 Pirillo A, Garlaschelli K, Arca M, *et al*. Spectrum of mutations in italian patients with familial hypercholesterolemia: new results from the LIPIGEN study. *Atheroscler Suppl* 2017;29:17–24.
9 Garcia CK, Wilund K, Arca M, *et al*. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. *Science* 2001;292:1394–8.
10 Sturm AC, Knowles JW, Gidding SS, *et al*. Clinical genetic testing for familial hypercholesterolemia. *J Am Coll Cardiol* 2018;72:662–80.
11 National Institute for Health and Care Excellence. Familial hypercholesterolaemia: identification and management. clinical guideline [CG71]. NICE Guid; 2019.
12 Watts GF, Sullivan DR, Hare DL, *et al*. Integrated guidance for enhancing the care of familial hypercholesterolaemia in australia. *Heart Lung Circ* 2021;30:324–49.
13 Brunham LR, Ruel I, Aljenedil S, *et al*. Canadian cardiovascular society position statement on familial hypercholesterolemia: update 2018. *Can J Cardiol* 2018;34:1553–63.
14 Lázaro P, Pérez de Isla L, Watts GF, *et al*. Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. *J Clin Lipidol* 2017;11:260–71.
15 Genest J, Hegele RA, Bergeron J, *et al*. Canadian cardiovascular society position statement on familial hypercholesterolemia. *Can J Cardiol* 2014;30:1471–81.
16 Varghese MJ. Familial hypercholesterolemia: a review. *Ann Pediatr Cardiol* 2014;7:107–17.
17 Chan DC, Pang J, Hooper AJ, *et al*. A comparative analysis of phenotypic predictors of mutations in familial hypercholesterolemia. *J Clin Endocrinol Metab* 2018;103:1704–14.
18 Haralambos K, Whatley SD, Edwards R, *et al*. Metabolic syndrome and risk of coronary, cerebral, and peripheral vascular disease in a large dutch population with familial hypercholesterolemia. *J Clin Lipidol* 2017;13:1–7.
19 Wong B, Kruse G, Kutikova L, *et al*. Cardiovascular disease risk associated with familial hypercholesterolemia: a systematic review of the literature. *Clin Ther* 2016;38:1696–709.
20 Santos RD, Gidding SS, Hegele RA, *et al*. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the international atherosclerosis society severe familial hypercholesterolemia panel. *Lancet Diabetes Endocrinol* 2016;4:850–61.
21 Pérez de Isla L, Alonso R, Mata N, *et al*. Coronary heart disease, peripheral arterial disease, and stroke in familial hypercholesterolaemia: insights from the SAFEHEART registry (Spanish familial hypercholesterolaemia cohort study). *Arterioscler Thromb Vasc Biol* 2016;36:2004–10.

22 Abul-Husn NS, Manickam K, Jones LK, *et al*. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science* 2016;354:aaf7000.
23 Khera AV, Won H-H, Peloso GM, *et al*. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol* 2016;67:2578–89.
24 Trinder M, Li X, DeCastro ML, *et al*. Risk of premature atherosclerotic disease in patients with monogenic versus polygenic familial hypercholesterolemia. *J Am Coll Cardiol* 2019;74:512–22.
25 Elis A, Leventer-Roberts M, Bachrach A, *et al*. The characteristics of patients with possible familial hypercholesterolemia-screening a large payer/provider healthcare delivery system. *QJM* 2020;113:411–7.
26 Mundal LJ, Hovland A, Igland J, *et al*. Association of low-density lipoprotein cholesterol with risk of aortic valve stenosis in familial hypercholesterolemia. *JAMA Cardiol* 2019;4:1156–9.
27 Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/apha/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of cardiology/american heart association task force on clinical practice guidelines. *Circulation* 2019;139:e1046–81.
28 Gidding SS, Champagne MA, de Ferranti SD, *et al*. The agenda for familial hypercholesterolemia: a scientific statement from the American heart association. *Circulation* 2015;132:2167–92.
29 Watts GF, Gidding S, Wierzbicki AS, *et al*. Integrated guidance on the care of familial hypercholesterolaemia from the international FH foundation. *Int J Cardiol* 2014;171:309–25.
30 Mata P, Alonso R, Pérez de Isla L, *et al*. Dyslipidemia and aortic valve disease. *Curr Opin Lipidol* 2021;32:349–54.
31 Pérez de Isla L, Watts GF, Alonso R, *et al*. Lipoprotein (a), LDL-cholesterol, and hypertension: predictors of the need for aortic valve replacement in familial hypercholesterolaemia. *Eur Heart J* 2021;42:2201–11.
32 Vuorio A, Watts GF, Schneider WJ, *et al*. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. *J Intern Med* 2020;287:2–18.
33 Mangili LC, Mangili OC, Bittencourt MS, *et al*. Epicardial fat is associated with severity of subclinical coronary atherosclerosis in familial hypercholesterolemia. *Atherosclerosis* 2016;254:73–7.
34 Emanuelsson F, Nordestgaard BG, Benn M. Familial hypercholesterolemia and risk of peripheral arterial disease and chronic kidney disease. *J Clin Endocrinol Metab* 2018;103:4491–500.
35 Tada H, Kawashiri MA, Nohara A, *et al*. Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on the prevalence of coronary artery disease in patients with severe hypercholesterolaemia. *Eur Heart J* 2017;38:1573–9.
36 Paquette M, Dufour R, Baass A. ABO blood group is a cardiovascular risk factor in patients with familial hypercholesterolemia. *J Clin Lipidol* 2018;12:383–9.
37 Cegla J, Neely RDG, France M, *et al*. Heart UK consensus statement on lipoprotein (a): a call to action. *Atherosclerosis* 2019;291:62–70.
38 Ohta N, Hori M, Takahashi A, *et al*. Proprotein convertase subtilisin/kexin 9 V4I variant with LDLR mutations modifies the phenotype of familial hypercholesterolemia. *J Clin Lipidol* 2016;10:547–55.
39 Paquette M, Bernard S, Cariou B, *et al*. Familial hypercholesterolemia-risk-score: a new score predicting cardiovascular events and cardiovascular mortality in familial hypercholesterolemia. *ATVB* 2021;41:2632–40.
40 Pérez de Isla L, Alonso R, Mata N, *et al*. Predicting cardiovascular events in familial hypercholesterolemia. *Circulation* 2017;135:2133–44.
41 Akioyamen LE, Genest J, Chu A, *et al*. Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: a systematic review and meta-analysis. *J Clin Lipidol* 2019;13:15–30.
42 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
43 Higgins JPT, Thomas J, Chandler J, *et al*. *Cochrane handbook for systematic reviews of interventions*. 2nd edn. Chichester (UK): Hohn Wiley & Sons, 2019.
44 Wells GA, Shea B, O'Connell D, *et al*. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa The Ottawa Hospital; Available: www.ohri.ca/programs/clinical_epidemiology/oxford.asp
45 Balshem H, Helfand M, Schünemann HJ, *et al*. Grade guidelines: 3. rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.