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Risk factors for atherosclerotic cardiovascular disease in individuals with heterozygous familial hypercholesterolemia: a systematic review and meta-analysis

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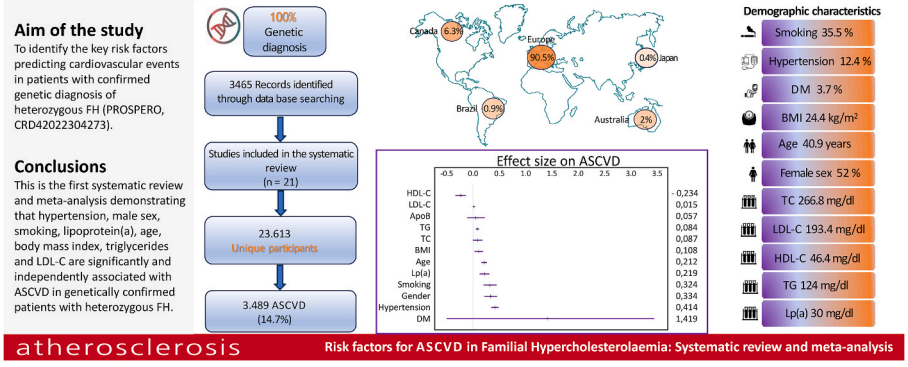
HIGHLIGHTS

- Key Question: What risk factors predict cardiovascular events in patients with genetically confirmed FH?
- Key Finding: Cardiovascular events were associated with hypertension, male sex, smoking, lipoprotein(a), older age, BMI, triglycerides and LDL cholesterol.
- Take-home Message: This first meta-analysis in genetically confirmed FH identifies ASCVD risk factors and supports early use of risk equations such as SAFEHEART-RE.

GRAPHICAL ABSTRACT



ABSTRACT

Background and aims: Familial hypercholesterolemia (FH) is a highly prevalent monogenic disorder characterized by elevated low-density lipoprotein-cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD). The risk factors associated with cardiovascular events in this population vary considerably among studies. This systematic review aims to identify the key risk factors predicting cardiovascular events in patients with a confirmed genetic diagnosis of heterozygous FH (PROSPERO, CRD42022304273).

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Methods and analysis: Cochrane Library, Embase, MEDLINE, Scopus, UpToDate and other literature databases were searched from inception to June 2023. Records were eligible if they included studies reporting risk factors for ASCVD endpoints in adult patients with a genetic diagnosis of FH. A meta-analysis was performed using MetaEasy.
Results: A total of 21 studies were identified, involving 23,613 individual participants and 3489 prevalent cardiovascular events. The sex distribution was 47.2% male and 52.8% female. Most of the studies were conducted in European populations, representing 90.5% of the total. The meta-analysis found associations between ASCVD and hypertension (effect size 0.414; 95% CI: 0.346-0.482), male sex (0.334; 0.213-0.456), smoking (0.324; 0.203-0.445), lipoprotein(a) (0.219; 0.127-0.312), age (0.212; 0.161-0.264), body mass index (0.108; 0.028-0.188), triglycerides (0.084; 0.057-0.111) and LDL-C (0.015; 0.002-0.028).
Conclusions: This is the first systematic review and meta-analysis demonstrating that hypertension, male sex, smoking, lipoprotein(a), age, body mass index, triglycerides and LDL-C are significantly and independently associated with ASCVD in genetically confirmed patients with heterozygous FH. These data can inform risk stratification models and optimise therapy in such patients.

1. Introduction

Familial hypercholesterolemia (FH) is an inherited and prevalent disorder of low-density lipoprotein (LDL) metabolism, characterised by lifelong elevated plasma concentrations of LDL-cholesterol (LDL-C) and premature atherosclerotic cardiovascular disease (ASCVD), particularly coronary artery disease (CAD). Its worldwide prevalence is approximately 1 in 300 individuals in the heterozygous form [1–3]. The most frequent causes of monogenic FH are pathogenic variants in the genes encoding the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) proteins [4,5].

A definitive diagnosis of heterozygous FH (heFH) can only be established through genetic testing that identifies the causal gene variant [6]. Several international expert panels have endorsed the use of genetic testing to improve risk stratification in patients with FH [7–9]. However, FH is often diagnosed using phenotypic criteria based on clinical and biochemical parameters, such as the Simon Broome, Dutch Lipid Clinic Network (DLCN) and Make Early Diagnosis to Prevent Early Death (MEDPED) criteria [10]. In addition, these criteria may not accurately discriminate between monogenic and polygenic or combined hypercholesterolemias, leading to false-positive classifications for FH [11–13].

The risk of ASCVD events among individuals with FH is highly variable [14,15], with an estimated average risk of 3 to 13 times higher than in the general population. Their life expectancy may be reduced by 20-30 years compared with unaffected subjects [16,17]. Owing to lifelong exposure to markedly elevated LDL-C levels, sudden cardiac death and acute myocardial infarction are the main causes of death in the FH population [18,19]. Consequently, there is a need to more accurately assess cardiovascular risk in FH patients to optimise lipid-lowering therapies (LLT) and maximise the use of healthcare resources.

Currently clinical guidelines classify all patients with FH as being at high risk, but do not adequately account for the substantial heterogeneity in ASCVD risk among these individuals. In recent years, several FH-specific risk stratification tools have been developed, including the SAFEHEART risk equation (SAFEHEART-RE), the Montreal–FH–SCORE and the FH-Risk-Score, which aim to guide the intensity of treatment [20–23].

Although previous systematic reviews have explored risk factors associated with ASCVD in FH [2,24], their findings have been inconsistent, possibly reflecting heterogeneity in the study population, as many included both genetically and clinically diagnosed patients. Therefore, we conducted a systematic review and meta-analysis to identify the risk factors associated with ASCVD events in a homogeneous population of genetically diagnosed patients with FH.

Fig. 1 summarises the study design and the main risk factors associated with ASCVD events in genetically confirmed heterozygous FH.

2. Patients and methods

2.1. Protocol and registration

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines and registered in PROSPERO (CRD42022304273) [24–26].

2.2. Information sources and search strategy

A comprehensive search was performed using the Virtual Library of the Andalusia Public Health System (SSPA), via GERION, the federated search engine of the Virtual Library. GERION provides integrated access to the following databases: CINAHL (trial), ClinicalKey, Cochrane Library, DynaMed, Embase, Espacenet, Experiments (trial), Fisterra,

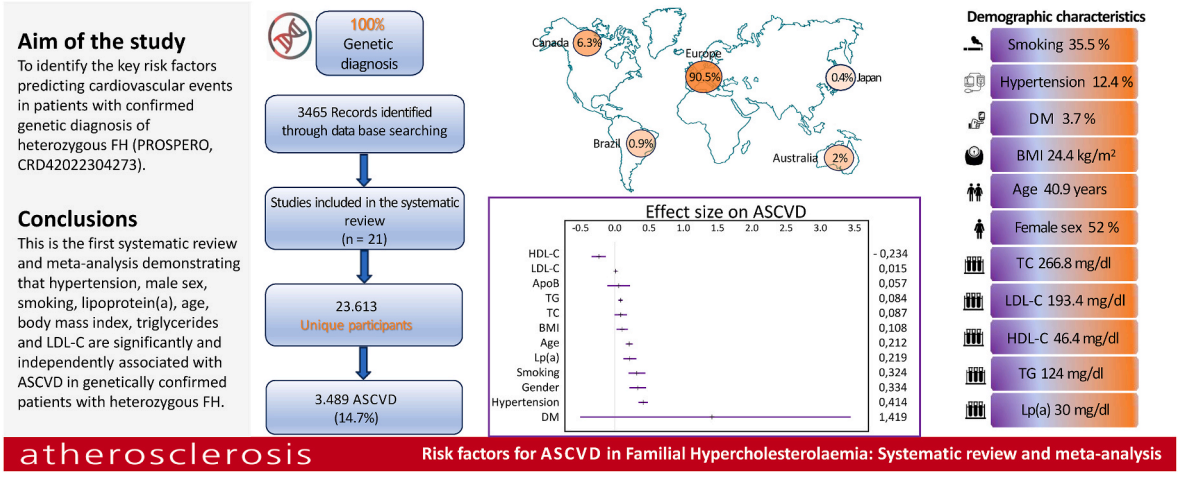

Fig. 1. Graphical abstract. Overview of the study design and the main demographic, clinical and lipid-related factors associated with atherosclerotic cardiovascular disease (ASCVD) events in adults with genetically confirmed heterozygous FH.

ÍnDICEs CSIC, LILACS, LISTA, MEDLINE, Micromedex, NEJM Resident 360, OpenDissertations, PEDro, PubPsych, Scopus, TESEO, Trip Database, UpToDate and Web of Science (WoS).

The bibliographic search employed the following keywords: "Family hypercholesterolemia", "risk factors", "cardiovascular events", and "systematic review" (Supplementary Table 1). The search strategy was performed using MeSH terms. The International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov were also searched for ongoing or recently completed trials, and PROSPERO was consulted for ongoing or recently completed systematic reviews.

The combined keywords included hyperlipoproteinemia, familial hypercholesterolemia or familial hypercholesterolaemia, heterozygous familial hypercholesterolemia, genetics, cardiovascular events, risk factors, and systematic review (Supplementary Table 2).

2.3. Study selection and eligibility criteria

2.3.1. Study designs

Eligible studies included full-text peer-reviewed publications, reports of a cohort/registry, case control, cross-sectional, case reports/series and surveys related to genetically confirmed heFH patients have been included. Only studies published in English or Spanish were considered.

2.3.2. Participants

Studies enrolling adult participants (≥18 years of age) with a genetically confirmed diagnosis of FH were included. Patients diagnosed solely on clinical criteria (e.g. Simon Broome, DLCN or MEDPED) and those with homozygous FH were excluded (Supplementary Table 1).

2.3.3. Risk factors

Studies reporting risk factors for ASCVD endpoints were included. The risk factors assessed comprised age, sex, body mass index (BMI), type 2 diabetes mellitus (DM), smoking, hypertension, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and lipoprotein(a) [Lp(a)].

2.3.4. Comparator group

Comparisons were made between heFH patients with and without ASCVD.

2.4. Study records

Literature search results were uploaded to the Mendeley Bibliographic Manager and the Microsoft Excel spreadsheet to facilitate collaboration among reviewers during the study selection process.

The original Newcastle-Ottawa Scale (NOS) version for cohort and case-control studies, developed by Wells et al. [27] and available from the Ottawa Hospital Research Institute website, was used to assess study quality. This tool evaluates three domains (Supplementary Table 3): selection (up to four stars), comparability (up to two stars), and outcome (up to three stars). Quality assessment was conducted independently by two reviewers (MEMR and MJRJ), who independently screened the titles and abstracts yielded by the search against the inclusion criteria.

Full reports were obtained for all titles that appeared to meet the inclusion criteria or where eligibility was uncertain. The reviewers then screened the full-text reports to confirm inclusion. When necessary, study authors were contacted to resolve any questions regarding eligibility. Reviewers were not blinded to the journal titles, study authors, or institutions.

Data from the included full-text articles were independently extracted by the two reviewers into a standardised data extraction form, and any discrepancies were resolved through discussion. Based on the available data, it was subsequently determined whether the studies could be pooled for meta-analysis.

2.5. Outcomes

The primary objective was to evaluate the risk factors associated with the presence of ASCVD events in patients with a genetically confirmed diagnosis of heFH. ASCVD events were defined according to the standardised composite outcome, encompassing 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 computed tomography scan or magnetic resonance imaging or documented transient ischemic attack; 6) peripheral arterial disease: intermittent claudication, which was defined as classic symptoms or stenosis >50% on angiography or ultrasonography or abdominal aortic aneurism; 7) peripheral arterial revascularisation; 8) aortic valve replacement secondary to severe aortic stenosis and 9) cardiovascular deaths.

2.6. Data extraction

Each reviewer independently extracted the following information from the included articles: bibliographic details, study design, risk of bias assessment, exposures and outcomes, participant characteristics, numerical data (e.g., number of participants per group and number with ASCVD outcomes), effect estimates (both adjusted and unadjusted) and their standard errors. As the systematic review progressed, additional relevant information was also incorporated through an iterative process.

2.7. Statistical analyse

Meta-analyses were performed for the following variables: age, sex, BMI, hypertension, DM, smoking, TC, LDL-C, HDL-C, TG, and Lp(a). The units for lipid variables (TC, LDL-C, HDL-C and TG and for Lp(a)) were standardised to mg/dl. All meta-analyses report the number of studies per variable, the standardised mean differences (SMDs) with 95% confidence interval (CI), and the measurement units.

The number of studies included per analysis ranged from eight to seventeen. Heterogeneity was assessed using the I^2 statistic [28], and random-effects models were applied throughout.

Dichotomous risk variables were reported as risk ratios or odds ratios and continuous variables as mean differences or standardised mean differences, with a 95% CI. MetaEasy was used to generate forest plots, and Excel® was used to represent the data graphically [29]. MetaEasy allowed the combining of outcomes from various studies, which were disseminated in different formats. To that end dichotomous risk variables were always transformed to standardised mean differences (SMDs), so that they can be combined with continuous outcomes [29]. This resulted in a dimensionless effect size (ES), characterised by relating the mean difference to variability with the following interpretations for the magnitude of ES (Cohen's d value): >0.2 (small effect), d > 0.5 (medium effect), and >0.8 (large effect) [30].

3. Results

3.1. Study characteristics

Database searches initially identified 3465 studies, which were then reduced to 1407 after the detection and removal of duplicates (Fig. 2). Two additional studies were included after contacting the corresponding authors, resulting in a total of 1409 records. After applying the first filter by title and abstract, 1228 articles were excluded for not meeting the inclusion/exclusion criteria defined at the beginning of the search, leaving 181 articles for full-text review. Of these, 21 articles met the eligibility criteria [20,31–50], which represented 23,613 individual participants and 3489 cardiovascular events (14.7%) (Supplementary Table 4).

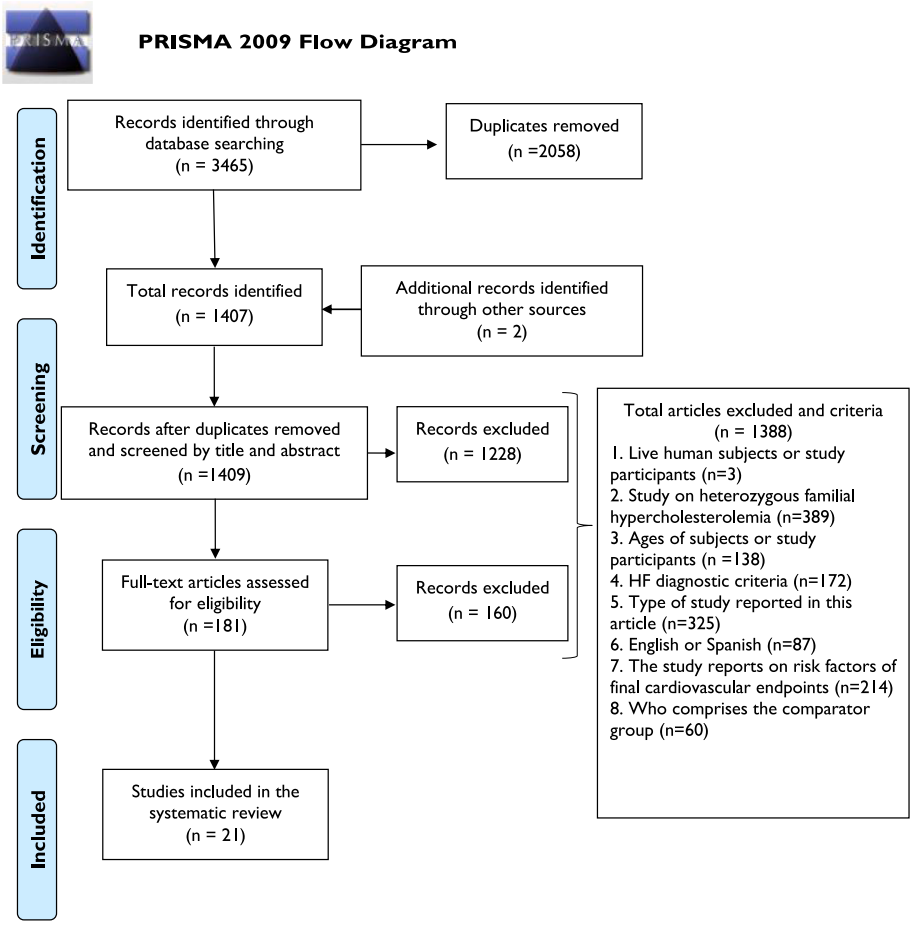

Fig. 2. Study selection and characteristics. Flow Diagram according to PRISMA recommendations. *21 studies were describing risk factors for ASCVD in genetically confirmed FH. ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia.

Among participants, 52.8% were women, with a weighted mean age of 40.9 years. The most prevalent cardiovascular risk factors were smoking (35.5%), hypertension (12.4%) and DM (3.7%), with a mean BMI of 24.4 kg/m^2. Regarding the lipid profile, the mean concentrations of TC, LDL-C, HDL-C, TG and Lp(a) were 266.8 mg/dl, 193.4 mg/dl, 46.4 mg/dl, 124 mg/dl and 30 mg/dl, respectively.

Most studies were conducted in European populations (90.5%), followed by those from Canada (6.3%), Australia (2%), Brazil (0.9%) and Japan (0.4%).

3.2. Meta-analysis

Ten studies identified the demographic variables age and male sex as risk factors associated with ASCVD events. In the aggregated result (Fig. 3), older patients experienced a higher number of events, with a mean ES of 0.212 (95% CI, 0.161-0.264), and male sex was significantly associated with the presence of events (mean ES 0.334; 95% CI, 0.213-0.456).

With regard to the risk factors analysed, hypertension (mean ES 0.414; 95% CI, 0.346-0.482), smoking (mean ES 0.324; 95% CI, 0.203-0.445), and a higher BMI (mean ES 0.108; 95% CI, 0.028-0.188) were significantly associated with the occurrence of ASCVD events. However, DM (mean ES 1.419; 95% CI, −0.603 to 3.442) showed no significant association with ASCVD. Hypertension and smoking remained significantly associated with ASCVD events across subgroup analyses stratified by geographical region (European vs non-European), study size (<500 vs ≥ 500 participants), and year of publication (<2015 vs ≥ 2015) (data not shown).

As shown in Fig. 4, higher LDL-C concentrations were observed in the ASCVD group, though with a small mean ES of 0.015 (95% CI, 0.002-0.028). Similarly, elevated TG (mean ES 0.084; 95% CI, 0.057-0.111) and Lp(a) levels (mean ES 0.219; 95% CI, 0.127-0.312) were also significantly associated with ASCVD occurrence. In contrast, no significant association was found for TC (mean ES 0.087; 95% CI, −0.003 to-0.177). Conversely, HDL-C showed a significant inverse association with ASCVD (mean ES -0.234; 95% CI, −0.336 to −0.133), indicating that lower HDL-C concentrations were more frequent among individuals with ASCVD. Fig. 5 summarises the overall effects of these risk factors in relation to ASCVD events in the FH population.

In summary, sensitivity and subgroup analyses were performed according to geographical region (European vs non-European), study size (<500 vs ≥ 500 participants), and publication period (<2015 vs. ≥ 2015). Hypertension and smoking remained robustly and consistently associated with ASCVD across all strata, with effect sizes for hypertension ranging from approximately 0.34 to 0.46 and for smoking from 0.26 to 0.47. By contrast, some variables showed context-dependent patterns: age and BMI were significant only in non-European cohorts, whereas HDL-C displayed a protective association only in European populations, and male sex and triglycerides became significant in larger studies (≥500 participants). More recent publications (≥2015) also showed greater precision and stability of the estimates for age, male sex and BMI. Overall, these findings support the robustness of the primary meta-analytic results and highlight that the strongest and most reproducible predictors of ASCVD in genetically confirmed heFH are hypertension and smoking.

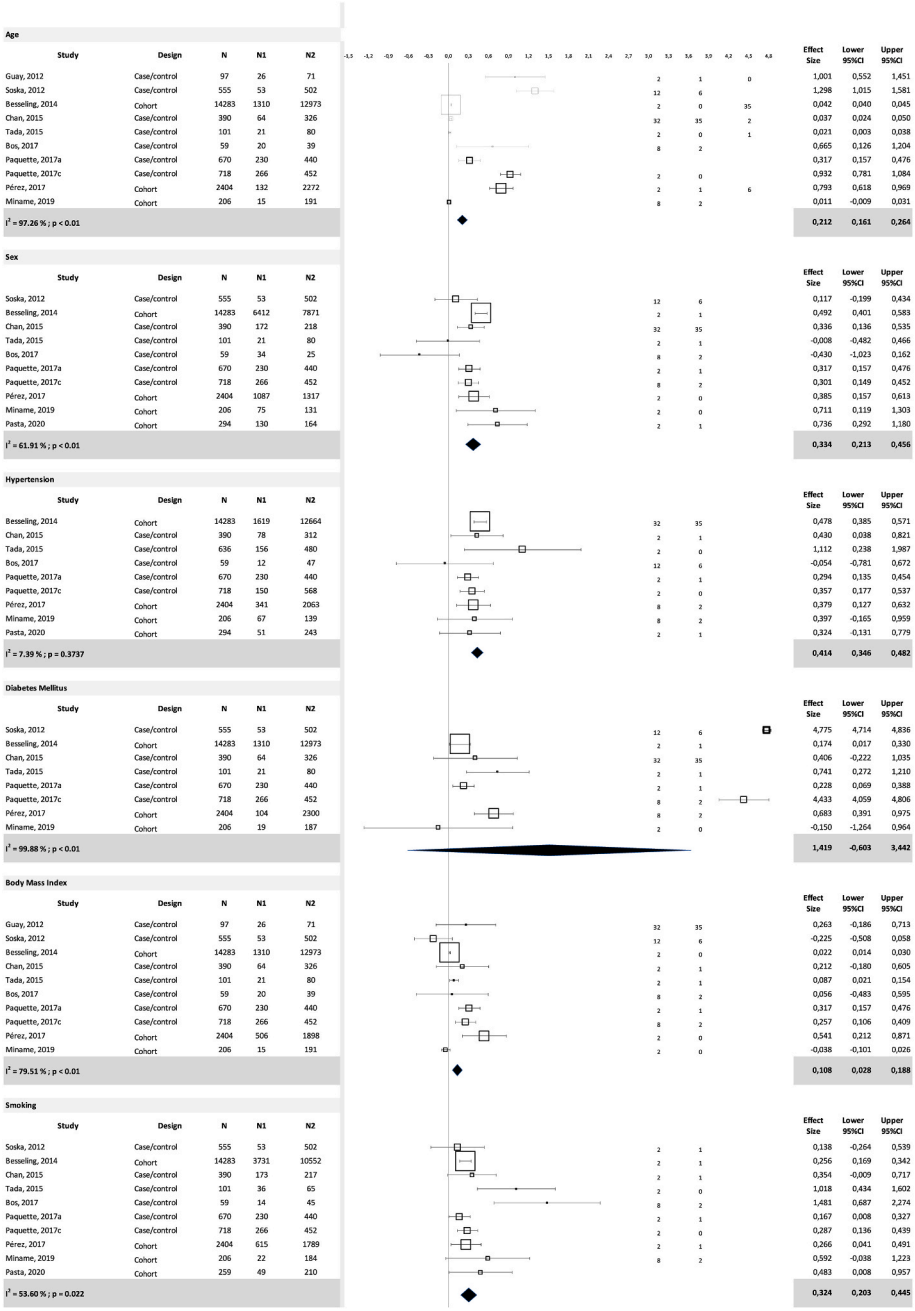

Fig. 3. Meta-analysis of risk factors. Forest plot represent individual study effects and the overall effects; horizontal lines represent 95% confidence intervals; The squares represent weights of each study The diamods represents the ES obtained according to the random/fixed effects model. CI, confidence interval.

4. Discussion

This systematic review and meta-analysis is the first to comprehensively evaluate the risk factors associated with ASCVD events in a population with a genetically confirmed diagnosis of heterozygous FH. These risk factors were age, male sex, hypertension, smoking, BMI, LDL-C, TG and Lp(a).

4.1. Previous studies

Previous meta-analyses studies have shown inconsistent results regarding the association between traditional risk factors and ASCVD events in FH, probably owing to patient selection bias through the duplication of patients across multiple publications, and the inclusion of heterogeneous FH populations using both clinical and molecular criteria [24]. We have extended these reports by focusing solely on individual patients to avoid the duplication of data. We also restricted our study selection to those with genetically diagnosed FH to improve the homogeneity of the study population, thereby strengthening the validity of the findings and providing a better understanding of the specific risk factors associated with genetically confirmed FH.

4.2. Risk factors

In relation to demographic variables, the average age of this population is younger than that reported by others [15,51,52]. This is probably owing to patients being diagnosed genetically earlier and being derived from cascade screening programmes. Consistent with previous studies, we found that male sex was associated with the presence of ASCVD [20, 53]. In a recent study, we found that the burden and risk of ASCVD were

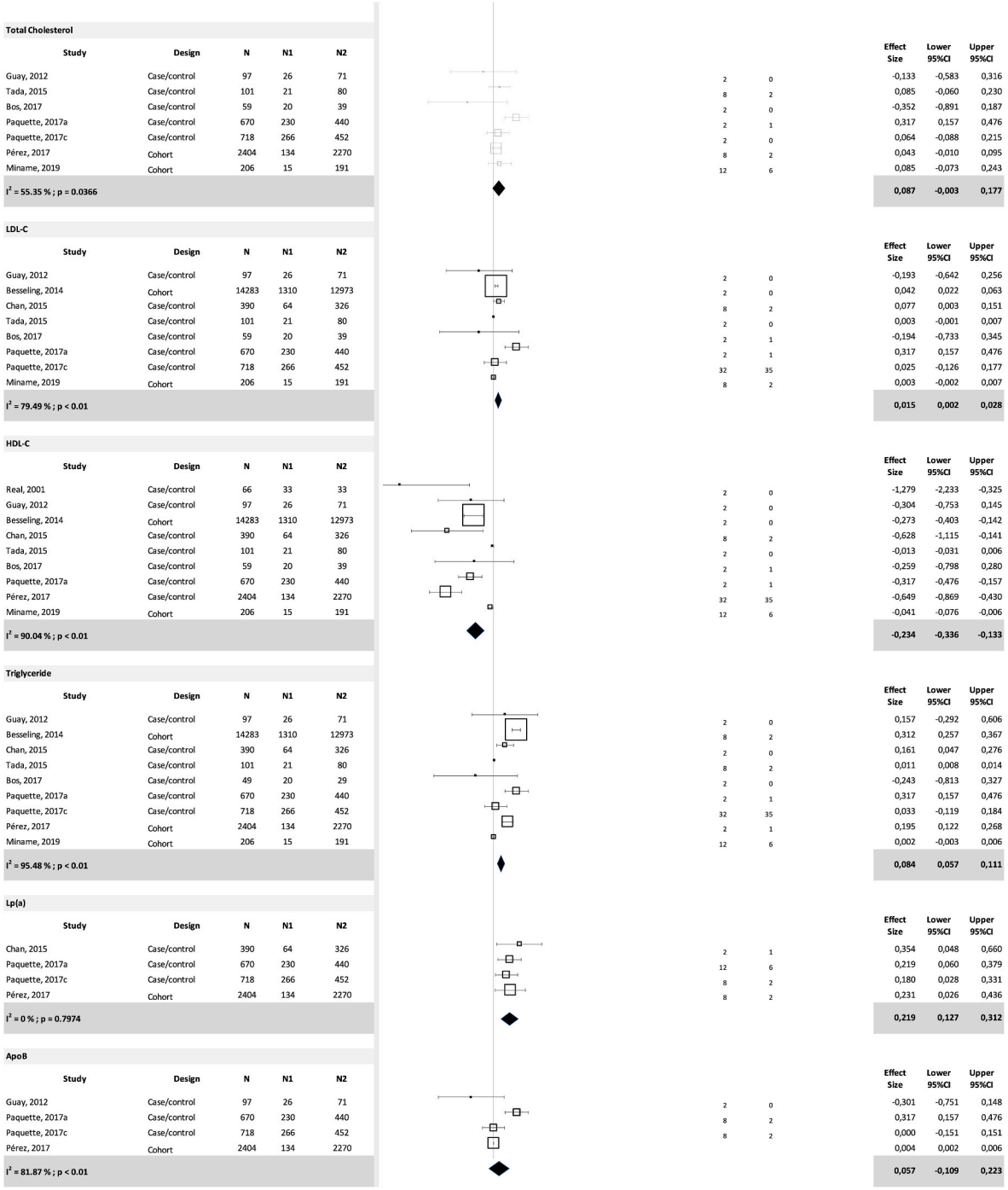

Fig. 4. Meta-analysis of lipid parameters. Forest plot represent individual study effects and the overall effects; horizontal lines represent 95% confidence intervals; The squares represent weights of each study. The diamods represents the ES obtained according to the random/fixed effects model. CI: confidence interval. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. Lp(a): lipoprotein(a).

markedly higher in men than in women with FH, likely due to both biological differences, hormonal effects on metabolism and endothelial function, and probably higher HDL-C levels in females [15]. In the present meta-analysis, 52% of the population were women, a higher percentage than in previous studies where they were underrepresented. This provides greater statistical power to investigate the effect of male sex on ASCVD risk, as well as to identify the need to improve risk stratification and personalised treatment in women with FH [53].

Our results also demonstrate that smoking, hypertension, and BMI were associated with ASCVD events. Elevated levels of LDL-C are a hallmark of FH and, in combination with the endothelial dysfunction produced by hypertension and smoking, exponentially increase the progression of atherosclerosis and coronary disease [54]. Furthermore, overweight and obesity, associated with a more adverse lipid profile and insulin resistance, favour a proinflammatory and proatherogenic state that significantly increases the risk of cardiovascular events [55]. Taken together, our findings reinforce the notion that these modifiable risk factors play a crucial role in the development of ASCVD beyond elevated LDL-C in patients with FH.

Unlike previous studies [56,57], we did not find that DM significantly increased the risk of developing ASCVD. The precise reason for this is unclear. FH has been described as a protective factor for DM [3],

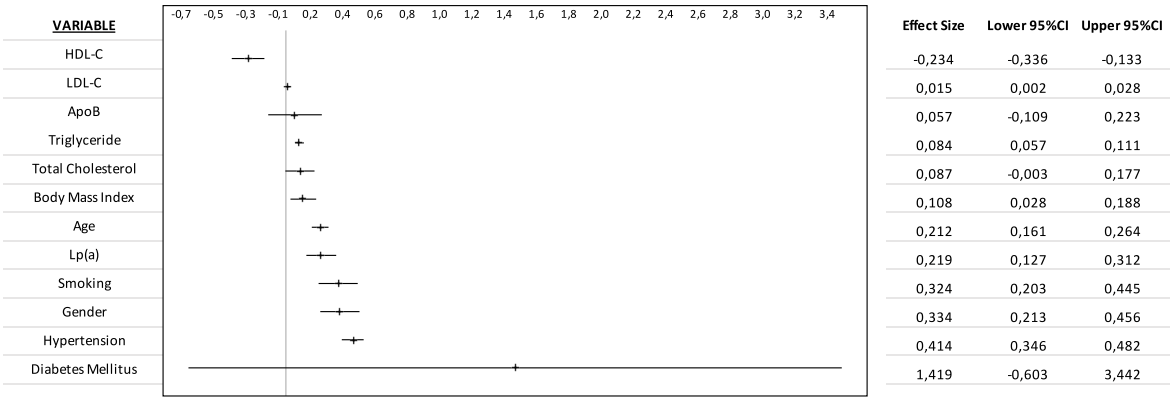

Fig. 5. Summary of the ES of the risk factors on ASCVD, ordered by magnitude. Horizontal lines represent 95% confidence intervals. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. Lp(a): lipoprotein(a).

with evidence suggesting that the presence of FH gene mutation improves insulin function by protecting pancreatic beta cells against LDL particles [58]. In contrast to other studies that included patients diagnosed phenotypically [59,60], the lower prevalence of DM (3.7%) in the present analysis might not have yielded sufficient statistical power to detect a significant association with ASCVD events among patients with a genetically confirmed diagnosis of FH.

As anticipated, elevated LDL-C was predictive of the presence of ASCVD events. Given that LDL-C levels vary based on lifestyle factors, polygenic traits and lipid-lowering treatments, it is not altogether unexpected that the ES was relatively low in the meta-analysis. Our results also found that HDL-C was inversely associated with the presence of ASCVD events, although the magnitude of the effect was modest. This aligns with current evidence suggesting that HDL-C functionality, rather than HDL-C concentration alone, may be more relevant to ASCVD risk. Therefore, future studies should assess HDL functionality in patients with FH [61–64].

It is well-established that elevated plasma triglyceride concentrations, particularly due to the accumulation of triglyceride-rich lipoproteins (TRLs) and their remnants, are atherogenic, and this may also be important in patients with FH. Elevated TRLs, in combination with high LDL-C, significantly increase ASCVD by promoting the formation of atherogenic plaques. TRL remnants also impair endothelial function and activate inflammation, which can further exacerbate the development of ASCVD in this population. In contrast to other lipoproteins (LDL, HDL and TRLs), Lp(a) is a highly heritable risk factor associated with ASCVD in patients with FH [51,65–67], consistent with our analysis showing no significant heterogeneity in analyses of the association between Lp(a) and ASCVD events [68–70].

4.3. Strengths and limitations

The strengths of the present analysis are the inclusion of a homogenous population with a genetic diagnosis of FH, providing a novel and specialized approach to enhance the validity and reliability of risk stratification among the FH population. However, our study does have limitations. The sample size was relatively small, which might have led to reduced statistical power to detect true effects between risk variables and ASCVD outcomes. Our analyses found that considerable heterogeneity was present in several pooled analyses. However, random-effects models were used throughout to account for variability between individual studies. **While the ASCVD outcomes were well-defined and standardised in our protocol, we cannot exclude the possibility that minor discrepancies among the various studies in reporting ASCVD outcomes might have influenced the results and the precision of predictor variable assessments. Data on antihypertensive and LDL-lowering medications are not available in all studies, which therefore could not be accounted for in the meta-analysis.** Moreover, some risk factors, such as LDL-C and Lp(a), were reported in different formats (e.g. continuous vs dichotomous variables) across studies, which challenged our analysis. Nevertheless, we used MetaEasy to combine results from the studies presented in various formats and to transform them into SMDs and ES within a single meta-analysis.

4.4. Clinical implications and conclusions

The risk of ASCVD among FH individuals is highly heterogeneous, with other traditional risk factors also modulating the ASCVD risk in FH patients. Our meta-analysis suggests that simple clinical predictors, such as age, male sex, hypertension, smoking, BMI, Lp(a), TG, and LDL-C levels, are associated with ASCVD events in genetically diagnosed FH populations. Further studies should investigate the clinical utility of coronary artery calcium (CAC) and polygenic risk scores for predicting ASCVD in FH patients [69,71–74].

Notably, the assessment of individual risk factors does not provide an overall risk assessment in patients with FH. Existing ASCVD risk equations for the general population are, however, not validated and potentially underestimate the ASCVD risk in FH patients [75]. Hence, the use of FH-specific global risk assessment that comprehensively incorporates the risk factors identified in the population of FH is clinically important. In recent years, risk stratification algorithms have been developed and externally validated, such as the SAFEHEART-RE, the Montreal–FH–SCORE, and the FH-Risk-Score [20–23,76–78]. Whether these risk scores can improve risk stratification and guide personalised care plans in FH patients at higher risk remains to be demonstrated.

Disclosure of interest

All authors have completed the uniform disclosure form declaration of interests statement. Pedro Mata collaborates with research grants from Amgen and Sanofi and collaboration for Familial Hypercholesterolemia Studies. Gerald F Watts 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. Manuel Jesús Romero-Jiménez has received payments for presentations from Amgen, Sanofi and has received support for attendance at meetings from Amgen, Novartis, and

Sanofi. The other authors declare no competing interests.

Ethical approval

All data were extracted from published literature. Hence, ethical approval and patient informed consent are not required.

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Fundación Hipercolesterolemia Familiar has contributed as an institution to developing the protocol.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Pedro Mata** received research grants from Amgen and Sanofi. **Gerald F Watts** declares receiving consulting fees from Amgen, Novartis, Arrowhead, CSL Sequirus, Esperion, Novo Nordisk and Sanofi; 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, Novo Nordisk and Novartis; and Research Grants from Amgen, Arrowhead, Marea, and Novartis. **Manuel Jesús Romero-Jiménez** payments for presentations from Amgen, Sanofi. Receiving support for attendance at meetings from Amgen, Novartis and Sanofi. The other authors declare no competing interests.

Acknowledgements

MEMR is the guarantor. MEMR, ARSJ, and MJRJ 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. ARSJ, JLSR, and DCF provided statistical expertise. GFW, PM, ENGC, JP, and DCF read and provided feedback. All authors reviewed and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2026.120650.

Data availability

The results of this systematic review were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Data supporting the study conclusions can be obtained from the corresponding author upon reasonable request.

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