INPLASY PROTOCOL

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None declared.

Association between Familial Hypercholesterolemia and Risk of Cardiovascular Events in different subgroups: A Meta-Analysis of 1.1 Million Subjects

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Review question / Objective: **To assess the risk of CVE and death in patients with FH in different subgroups.**
Information sources: **We searched the PubMed, MEDLINE, and Web of Science databases to identify cohort studies reporting the outcome of cardiovascular events in patients with FH, from database inception to June 2021. We also reviewed the reference lists of relevant articles to identify additional studies. A broad search strategy, as follows: "familial hypercholesterolemia" AND ("prognosis" OR "follow-up"), was used. Two researchers independently screened the literature, evaluated quality, and extracted data.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 November 2021 and was last updated on 03 November 2021 (registration number INPLASY2021110010).

INTRODUCTION

Review question / Objective: **To assess the risk of CVE and death in patients with FH in different subgroups.**

Condition being studied: **Familial hypercholesterolemia (FH) is an autosomal dominant hereditary disease characterized by a considerable increase in lifetime total cholesterol (TC) and low-density lipoprotein (LDL), including mutations in LDLR, APOB, PCSK9 and other genes. Exposed to high cholesterol from birth, patients with FH experience the occurrence and development of atherosclerotic lesions in the heart, brain, and peripheral arteries, leading to an increased risk of premature coronary heart disease (CHD), among which acute myocardial infarction (MI) and sudden cardiac death are the leading causes of death. Previous systematic**

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reviews estimated that patients with FH had a significantly higher risk of cardiovascular disease (CVD), with or without lipid-lowering therapy. A recent meta-analysis of 1.1 million individuals showed that the prevalence rate of FH in the general population is approximately 0.32%. Therefore, optimizing lipid management to reduce the incidence of CVD and improve long-term prognosis remains an important clinical and public health issue. However, it remains controversial whether there are differences in the different subgroups of cardiovascular events among patients with FH, especially those with CHD or ACS. In addition, the clinical diagnostic criteria for FH have been controversial. So the purpose of this study was to explore the effects of FH on cardiovascular outcomes in different subgroups through meta-analysis in short-term and long-term follow-up.

METHODS

Search strategy: We searched the PubMed, MEDLINE, and Web of Science databases to identify cohort studies reporting the outcome of cardiovascular events in patients with FH, from database inception to June 2021. We also reviewed the reference lists of relevant articles to identify additional studies. A broad search strategy, as follows: "familial hypercholesterolemia" AND ("prognosis" OR "follow-up"), was used. Two researchers independently screened the literature, evaluated quality, and extracted data.

Participant or population: Familial hypercholesterolemia.

Intervention: No.

Comparator: Patients with non familial hypercholesterolemia.

Study designs to be included: Cohort study.

Eligibility criteria: Inclusion criteria were: 1) cohort study; 2) included participant groups with and without FH; 3) outcome was at least one cardiovascular event (including non-fatal MI, angina, percutaneous coronary intervention or coronary artery bypass grafting, heart failure, stroke, TIA and peripheral vascular disease); 4) provided risk ratio, survival curve, or event rate to calculate the relative risk ratio (RR); and 5) If the same study publishes results from different periods, include the most recent study data.

Information sources: We searched the PubMed, MEDLINE, and Web of Science databases to identify cohort studies reporting the outcome of cardiovascular events in patients with FH, from database inception to June 2021. We also reviewed the reference lists of relevant articles to identify additional studies. A broad search strategy, as follows: "familial hypercholesterolemia" AND ("prognosis" OR "follow-up"), was used. Two researchers independently screened the literature, evaluated quality, and extracted data.

Main outcome(s): Outcome was at least one cardiovascular event (including non-fatal MI, angina, percutaneous coronary intervention or coronary artery bypass grafting, heart failure, stroke, TIA and peripheral vascular disease) or death (all-case death or cardiac death).

Quality assessment / Risk of bias analysis: Two investigators independently extracted data, including the first author's name, date of publication, country, cohort years, sample size, number of events, follow-up time, and hazard ratio (HR) or RR. In the case of disagreement, a third researcher was consulted. Exposure data included the definitions and criteria for FH, number of participants, and duration of follow-up. Outcome data included the definitions of cardiovascular outcomes, number of participants with and without FH, multivariate-adjusted risk estimates (RR, HR, or odds ratio [OR]), and variables included in the multivariate analysis. We used the Newcastle–Ottawa Scale (NOS) to evaluate the quality of the included studies.

Strategy of data synthesis: The RR and 95% confidence interval (CI) were used

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together with the effect size. The results of each cohort study were reported as RR, HR, OR, or binary frequency data. We used algebraic methods to convert the OR and frequency data to RR. If feasible, we used adjusted risk estimates from a multivariate model.We performed a separate meta-analysis using the DerSimonian–Laird random-effects model to obtain a pooled RR for each outcome measure and the primary endpoint of cardiovascular events and death. When multiple outcomes were reported, we analyzed the results of cardiovascular events, cardiac death, and all cause death.We used Cochran's Q test to assess differences between studies, and the I2 statistic was used to quantify the proportion of inconsistencies observed in the results. Values of I2≥50% and P≤0.10 indicated no heterogeneity among studies and a fixed-effect model was used for analysis. We also used Cochran's Q test to calculate the heterogeneity between subgroups. Sensitivity analysis was performed for the results of the meta-analysis, and a funnel plot was drawn for publication bias analysis. If there was publication bias, we used the trim-and-fill method and Egger's test to verify whether publication bias affected the stability of the combined effect size. The test level was α=0.05. Subgroup analysis was performed based on outcome events, study population, diagnostic criteria, and follow-up time.

Subgroup analysis: Subgroup analysis included different clinical outcomes, different study populations, different diagnostic criteria, different follow-up time and different races.

Sensitivity analysis: We used the method of omitting one study at a time to conduct a sensitivity analysis for risk of total cardiovascular events and death.

Language: English.

Country(ies) involved: China.

Keywords: familial hypercholesterolemia; cardiovascular events; cardiac death; all-cause of death; prognosis; meta-analysis.

Contributions of each author:

Author 1 - Yani Yu - Performed the experiments and analyzed the data and wrote original draft.
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Author 2 - Lei Chen.
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Author 4 - Zihao Fu.
Author 5 - Qi Liu.
Author 6 - Haijing Zhao.
Author 7 - Yuqi Liu - designed the research.
Author 8 - Yundai Chen - designed the research.

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