Familial Hypercholesterolemia and Risk of Cardiovascular Disease: A Systematic Literature Review and Meta-analysis of Observational Studies

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BACKGROUND

- Familial hypercholesterolemia (FH) is a genetic disorder characterized by elevated serum levels of low-density lipoprotein cholesterol (LDL-C) from birth and early onset of cardiovascular disease (CVD [1].
- Determination of CVD risk associated with FH, therefore, becomes important for early adoption of CVD screening and prevention programs for better management of patients with FH and associated CVD risk [2].
- A quantitative assessment of the association between FH and CVD risk has not been reported.
- We performed a systematic literature review (SLR) and meta-analysis of observational studies to quantify the association between FH and the risk of CVD.

METHODOLOGY

- The SLR was conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [3], the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance for undertaking reviews in health care [4], and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5], based on a predefined search strategy in line with the inclusion criteria presented in **Table 1**.
- MEDLINE and EMBASE databases were searched through June 2022, along with reference scrutiny of relevant articles, to identify studies that included any measure of CVD risk (risk ratio (RR), odds ratio (OR), hazard ratio (HR), or ratios of incidence, mortality, and morbidity) in FH patients.
- Two reviewers independently screened the articles and extracted data, with differences resolved through consensus.
- Relative association measures (HR, OR, or RR) and 95% confidence intervals (CI) were pooled using a random effect model.
- Quality assessment of studies was conducted using the modified Newcastle-Ottawa tool [6].

Table 1. Study eligibility criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients with FH	• Not specific to FH (using a prospective definition of FH) • Non-human
Intervention	NA	NA
Comparators	NA	NA
Outcomes	Any measure of CVD risk (RR, OR, HR, rates, or ratios of incidence, mortality and morbidity) in patients with FH	No CVD risk estimate in FH or no CVD risk estimate in FH versus non-FH
Study designs	Any observational study designed to measure the relevant outcomes including cohort studies and cross-sectional studies.	• Randomised controlled trials • Case studies or reports • Letters and editorials
Limits	Language: English language	Non-English language

RESULTS

- The complete literature search identified 222 potential publications **(Figure 1)**. After title and abstract screening, 57 articles were identified as likely to contain CVD risk estimates and were retrieved for full-text screening. Of these, 25 studies [7-31], comparing FH patients versus non-FH patients, met the inclusion criteria.
- Eleven studies were based on registries in the United Kingdom (UK), Netherlands, Norway, Japan and Spain; nine studies were from single hospitals or families in Denmark, Netherlands, Australia, Brazil, France, and UK; and four studies were based on population surveys in Denmark, Netherlands, Spain, and United States (USA) **(Figure 2).**
- Across the studies, estimates of the rate of increased risk of CVD in FH were reported as follows: standardized mortality ratio (SMR) in seven studies; proportional mortality ratio (PMR) in one study; RR in four studies, HR and OR in five studies each. Two studies reported on risk frequency and one study reported CVD risk in terms of thoracic aorta calcium scoring and coronary calcium scoring, respectively.

Figure 2. PRISMA flow diagram

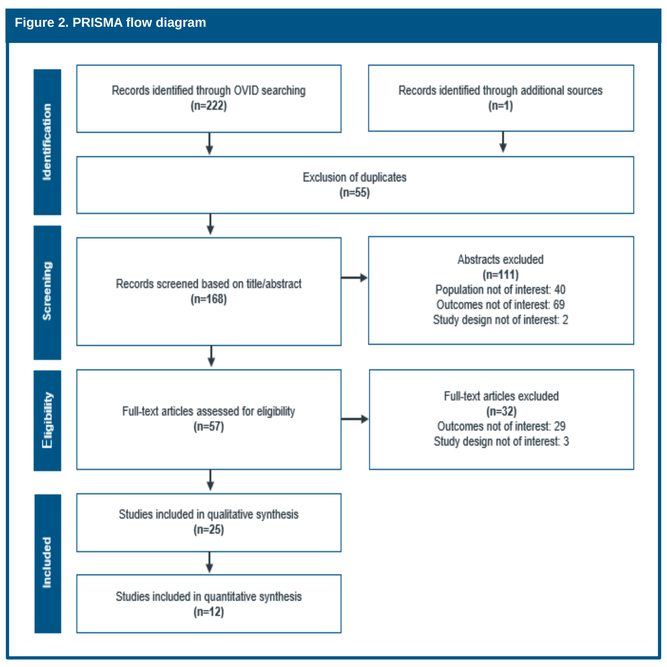


Figure 2. Characteristics on included studies

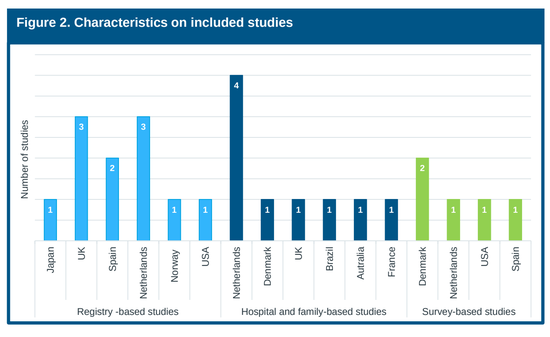


Figure 3. Study quality assessment

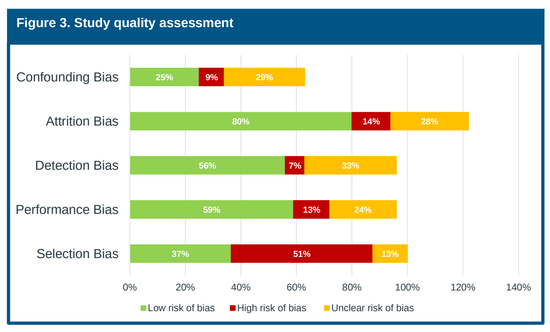
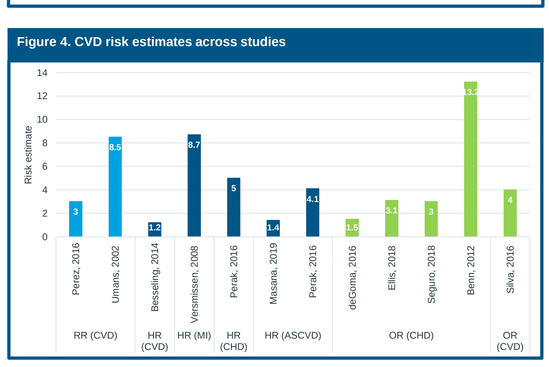


Figure 4. CVD risk estimates across studies



- Trends in risk assessment were observed by bias type **(Figure 3)**. Selection bias was the largest potential threat, with 51% of the selection bias criteria categorized as high risk.
- Across the included studies, the RR (95% CI) for CVD ranged from 3.0 (2.2-4.1) to 8.5 (5.3-13.8), HR (95% CI) ranged from 1.3 (1.0-1.5) to 8.7 (4.8-15.8), and OR (95% CI) ranged from 1.5 (0.8-2.8) to 13.2 (10.6-17.4) **(Figure 4)**.
- The risk of CVD was markedly high in men and in patients younger than 40 years **(Figure 5 and 6).**

Figure 5. Gender-specific CVD risk in FH

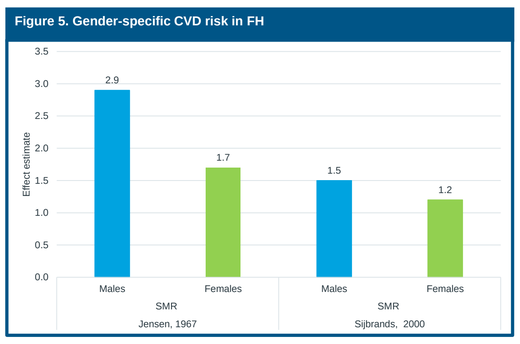
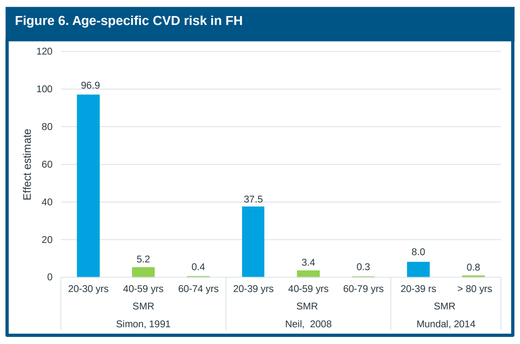


Figure 6. Age-specific CVD risk in FH



- Of the 25 included studies reporting data on an increased risk of CVD in FH patients, only 12 studies were meta-analyzed.
- When considering OR and RR equivalent to HR, pooling of individual risk estimates (using HR as the common measure of association across the 12 meta-analyzed studies) showed a significant association between FH and risk of CVD (HR 1.72; 95% CI 1.35-2.19; p<0.00001). There was a noticeable heterogeneity amongst these studies, with I^2 = 97% **(Figure 7).**
- Five studies using OR as the relative association measure were identified and included in the analysis. The summary OR for all studies with 95% CI is shown in **Figure 8**.
- Three studies using RR as the relative association measure were identified and included in the analysis. The summary RR for all studies with 95% CI is shown in **Figure 9**.
- Five studies using HR as the relative association measure were identified and included in the analysis. The summary HR for all studies with 95% CI is shown in **Figure 10**.

Figure 7. Forest plot of the association between FH and risk of CVD considering OR and RR equivalent to HR

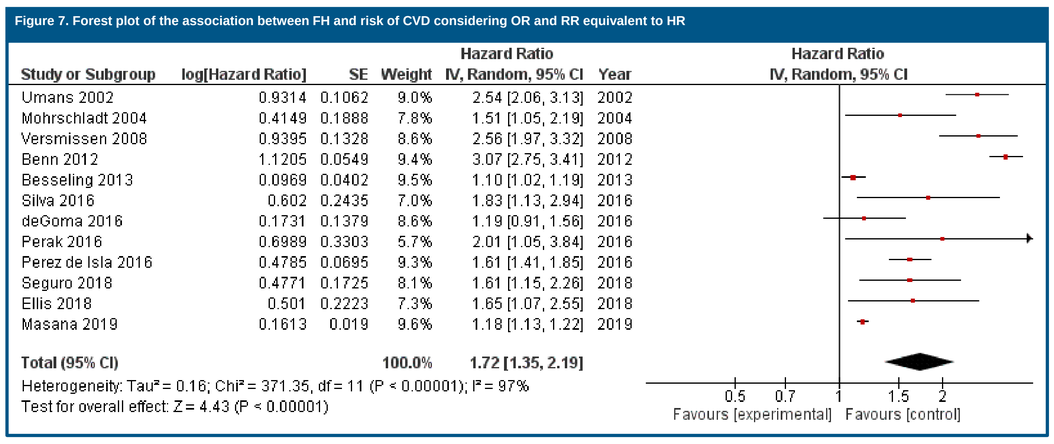


Figure 8. Forest plot of the association between FH and risk of CVD using OR as the association measure

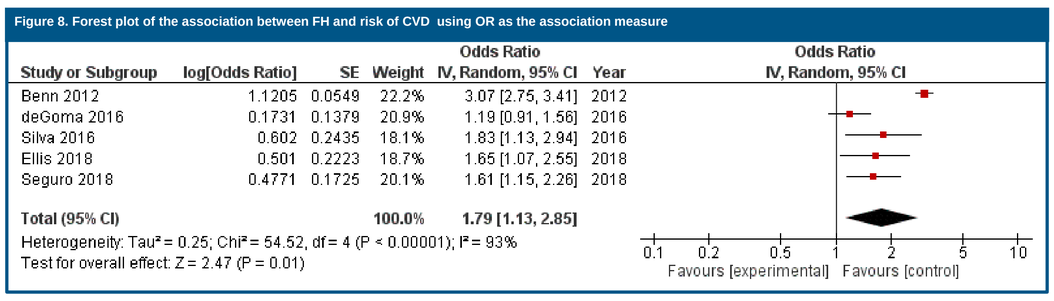


Figure 9. Forest plot of the association between FH and risk of CVD using RR as the association measure

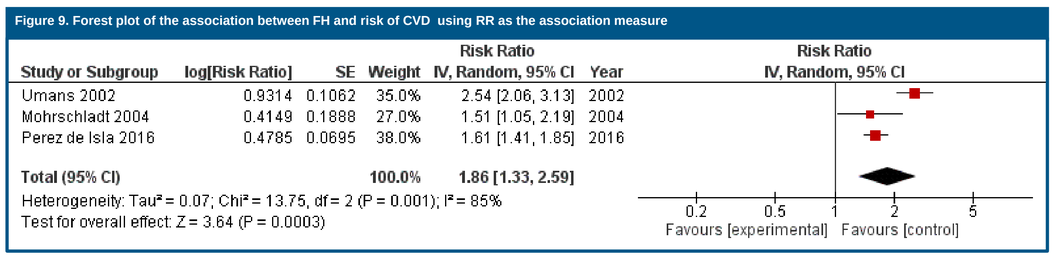
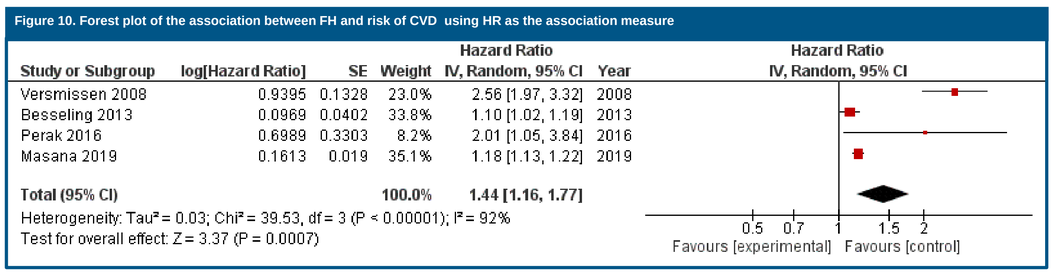


Figure 10. Forest plot of the association between FH and risk of CVD using HR as the association measure



CONCLUSION

- The current meta-analysis suggests that FH significantly increases CVD risk. Consequently, patients with FH should be routinely screened for CVD.
- Age and sex also appeared to have an impact on CVD risk in FH patients. More research is needed to determine how these factors interact with FH to influence the risk of CVD.

REFERENCES

1. Najam, O. and K.K. Ray, Familial hypercholesterolemia: a review of the natural history, diagnosis, and management. Cardiology and therapy, 2015. 4(1): p. 25-38.
2. Hill, J.S., et al., Genetic and environmental factors affecting the incidence of coronary artery disease in heterozygous familial hypercholesterolemia. Arteriosclerosis and Thrombosis: A Journal of Vascular Biology, 1991. 11(2): p. 290-297
3. Higgins, J.P., et al., Cochrane handbook for systematic reviews of interventions. 2019: John Wiley & Sons.
4. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in health care. Systematic Reviews CRD, University of York 2009.
5. Page, M.J., et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Systematic reviews, 2021. 10(1): p. 1-11.
6. Wells, G.A., et al., The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Applied Engineering in Agriculture, 2014. 18(6): p. 727-734.
7. Jensen, J., D.H. BLANKENHORN, and V. Kornerup, Coronary disease in familial hypercholesterolemia. Circulation, 1967. 36(1): p. 77-82.
8. Slack, J., Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. The Lancet, 1969. 294(7635): p. 1380-1382.
9. Mabuchi, H., et al., Development of coronary heart disease in familial hypercholesterolemia. Circulation, 1989. 79(2): p. 225-232.
10. Group, S.B.R., Risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ: British Medical Journal, 1991: p. 893-896.
11. Neil, H., et al., Mortality in treated heterozygous familial hypercholesterolaemia: implications for clinical management. Scientific Steering Committee on behalf of the Simon Broome Register Group. Atherosclerosis, 1999. 142(1).
12. Sijbrands, E.J., et al., Additional risk factors influence excess mortality in heterozygous familial hypercholesterolaemia. Atherosclerosis, 2000. 149(2): p. 421-425.
13. Sijbrands, E.J., et al., Mortality over two centuries in large pedigree with familial hypercholesterolaemia: family tree mortality study Commentary: Role of other genes and environment should not be overlooked in monogenic disease. bmj, 2001. 322(7293): p. 1019-1023.
14. Umans-Eckenhausen, M.A., et al., Low-density lipoprotein receptor gene mutations and cardiovascular risk in a large genetic cascade screening population. Circulation, 2002. 106(24): p. 3031-3036.
15. Mohrschladt, M., et al., Cardiovascular disease and mortality in statin-treated patients with familial hypercholesterolemia. Atherosclerosis, 2004. 172(2): p. 329-335.
16. Alonso, R., et al., Cardiovascular disease in familial hypercholesterolaemia: influence of low-density lipoprotein receptor mutation type and classic risk factors. Atherosclerosis, 2008. 200(2): p. 315-321.
17. Neil, A., et al., Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. European heart journal, 2008. 29(21): p. 2625-2633.
18. Versmissen, J., et al., Efficacy of statins in familial hypercholesterolaemia: a long-term cohort study. BMJ, 2008. 337.
19. Benn, M., et al., Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. The Journal of Clinical Endocrinology & Metabolism, 2012. 97(11): p. 3956-3964.
20. Besseling, J., et al., Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. Atherosclerosis, 2014. 233(1): p. 219-223.
21. Mundal, L., et al., Mortality Among Patients With Familial Hypercholesterolemia: A Registry-Based Study in Norway, 1992–2010. Journal of the American Heart Association, 2014. 3(6): p. e001236.
22. Pérez de Isla, L., et al., Coronary heart disease, peripheral arterial disease, and stroke in familial hypercholesterolaemia: insights from the SAFEHEART Registry (Spanish Familial Hypercholesterolaemia Cohort Study). Arteriosclerosis, Thrombosis, and Vascular Biology, 2016. 36(9): p. 2004-2010.
23. Robinson, J.G., et al., Determining when to add non-statin therapy: a quantitative approach. Journal of the American College of Cardiology, 2016. 68(22): p. 2412-2421.
24. Silva, P.R., et al., Predictors of cardiovascular events after one year of molecular screening for Familial hypercholesterolemia. Atherosclerosis, 2016. 250: p. 144-150.
25. Degoma, E.M., et al., Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States: data from the CASCADE-FH registry. Circulation: Cardiovascular Genetics, 2016. 9(3): p. 240-249.
26. Galaska, R., et al., Assessment of subclinical atherosclerosis using computed tomography calcium scores in patients with familial and nonfamilial hypercholesterolemia. Journal of Atherosclerosis and Thrombosis, 2016: p. 31161.
27. Perak, A.M., et al., Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. Circulation, 2016. 134(1): p. 9-19.
28. Beheshti, S., et al., Relationship of Familial Hypercholesterolemia and High Low-Density Lipoprotein Cholesterol to Ischemic Stroke. Circulation, 2018. 138(6): p. 578-589.
29. Ellis, K.L., et al., Elevated lipoprotein (a) and familial hypercholesterolemia in the coronary care unit: Between Scylla and Charybdis. Clinical cardiology, 2018. 41(3): p. 378-384.
30. Séguro, F., et al., Genetic diagnosis of familial hypercholesterolemia is associated with a premature and high coronary heart disease risk. Clinical cardiology, 2018. 41(3): p. 385-391.
31. Masana, L., et al., Incidence of cardiovascular disease in patients with familial hypercholesterolemia phenotype: analysis of 5 years follow-up of real-world data from more than 1.5 million patients. Journal of clinical medicine, 2019. 8(7): p. 1080.