# Familial hypercholesterolemia-Plus: is the metabolic syndrome changing the clinical picture of familial hypercholesterolemia?

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**Purpose of review**
The purpose of this review article was to describe recent advances in our knowledge about how diabetes and metabolic syndrome are changing the face of familial hypercholesterolemia.

**Recent findings**
Heterozygous familial hypercholesterolemia, most commonly caused by disruption to LDL receptor function, leads to lifelong elevation of LDL cholesterol and increased risk of atherosclerotic cardiovascular disease. Familial hypercholesterolemia was originally described as a form of 'pure' hypercholesterolemia, in the sense that levels of LDL were uniquely affected. Studies of familial hypercholesterolemia among individuals of predominantly Western European descent conformed to the perception that individuals with familial hypercholesterolemia tended to be lean and otherwise metabolically healthy. More recently, as we have studied familial hypercholesterolemia in more diverse global populations, we have learned that in some regions, rates of diabetes and obesity among familial hypercholesterolemia patients are very high, mirroring the global increases in the prevalence of metabolic disease.

**Summary**
When diabetes and metabolic disease coexist, they amplify the cardiovascular risk in familial hypercholesterolemia, and may require more aggressive treatment.

**Keywords**
diabetes, familial hypercholesterolemia, metabolic syndrome

## INTRODUCTION

Heterozygous familial hypercholesterolemia (FH) is among the most common inherited conditions in humans, affecting nearly 1 in 300 individuals. FH is characterized clinically by lifelong elevated LDL cholesterol (LDL-C) levels and increased risk of atherosclerotic cardiovascular disease (ASCVD) [1]. The underlying molecular cause of FH in most cases is a pathogenic variant in the LDL receptor (*LDLR*) gene. Less common causes of FH include pathogenic variants in apolipoprotein B-100 (APOB) that reduces its affinity for the LDLR, or gain-of-function variants in PCSK9 that increase the lysosomal degradation of the LDLR. In all of these instances, the underlying pathophysiology is impaired clearance through the LDLR [2]. Reflecting this mechanism, the biochemical profile of patients with FH is classically thought of as elevation of LDL-C, without alterations in other lipoproteins. However, given the increasing prevalence of diabetes, obesity, and the metabolic syndrome worldwide [3], some individuals with familial hypercholesterolemia will have concomitant metabolic disturbances. Here, we review how comorbid metabolic disease is changing the clinical face of FH.

Many of the early learnings regarding FH arose from large national cohorts in Western European countries, such as the Netherland and Spain, which gave the impression of FH affecting predominantly lean, metabolically healthy individuals. For example, among more than 25 000 individuals from a Dutch national registry of patients with FH, mean BMI was 23.5, and median triglyceride level was 97 mg/dl [4]. Similarly, in a cohort of 2404 Spanish patients with FH, the mean BMI was 26.5 and

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## KEY POINTS

- Familial hypercholesterolemia was originally thought of a condition that occurs primarily in lean and otherwise metabolically healthy individuals.
- Studying familial hypercholesterolemia in more diverse global populations has revealed that in some regions, many patients with FH have concomitant metabolic disease including diabetes and obesity (so-called 'FH-plus').
- When the metabolic syndrome or diabetes is present in an individual with familial hypercholesterolemia, the risk of atherosclerotic cardiovascular disease is significantly increased.
- Recognizing the presence of FH-plus may provide opportunities for further optimizing the care of these patients.



triglyceride level 97.6 mg/dl [5]. These studies suggested that FH occurs predominantly in lean, metabolically healthy individuals.

One particularly notable finding from cohorts of individuals of European ancestry with FH was the apparently low prevalence of diabetes. Indeed, in a large cohort of Dutch patients with FH, the prevalence of diabetes was 1.75% compared to 2.93% in unaffected relatives (hazard ratio 0.62, 95% confidence interval 055–0.69) [4]. Similar results were observed in a cohort of Canadian patients with FH, among whom the prevalence of diabetes was 2.1%, which was about half the prevalence among the general Canadian population of similar age [6], and in a Spanish cohort, in which the prevalence of diabetes was 5.9% among FH patients compared to 9.4% in the general population [7]. These observations suggested that the presence of FH may actually be protective against diabetes. Mechanistically, this could relate to protection from LDL receptor-mediated uptake of cholesterol into pancreatic beta cells, which has been established as a pathway leading to islet dysfunction and impaired insulin secretion in animal models [8–12].

Recently we have gained a more global perspective on the clinical features of FH as a result of the Familial Hypercholesterolemia Studies Collaboration, which included more than 60 000 individuals from 56 countries [13▪▪]. This analysis revealed that in certain regions, such as the Eastern Mediterranean, the prevalence of diabetes among patients with familial hypercholesterolemia is much greater (26.5%) as is mean BMI (29.1). In an analysis of the Gulf FH Registry including 3713 patients with FH from five countries in the Arabian Gulf, the prevalence of diabetes was 28%. These findings highlight that in certain populations FH can frequently coexist with other metabolic disturbances.

Metabolic disease can also exacerbate dyslipidemia, particularly in patients with an underlying genetic susceptibility, and in some cases may contribute to the manifestation of severe hypercholesterolemia, which may overlap with an FH phenotype. This was illustrated in a study of patients from the UK Biobank, in which the presence of obesity, diabetes, and hypertension, and an increased LDL-C polygenic risk score all increased the likelihood of a patient manifesting a phenotype of hyperlipidemia [14]. These findings suggest that when aspects of the metabolic syndrome are present, they can increase the likelihood of a patient developing a clinical phenotype similar to FH.

## EFFECT OF DIABETES AND METABOLIC SYNDROME ON CARDIOVASCULAR RISK IN FAMILIAL HYPERCHOLESTEROLEMIA

When diabetes or the metabolic syndrome is present, they can have a major impact on the risk of ASCVD in patients with FH. In a prospective cohort study of five European and North American cohorts of patients with FH including 2401 individuals, the prevalence of the metabolic syndrome, defined as three or more of the following: BMI at least 30, SBP at least 130 mmHg, fasting blood glucose at least 5.6 mmol/l, HDL cholesterol less than 1.3 mmol/l in women and less than 1mmol/L in men, and triglycerides at least 1.7 mmol/l, was 14% [15▪]. Patients with FH who also had the metabolic syndrome had a significantly increased 10-year risk of major adverse cardiovascular events (hazard ratio 4.59, 95% CI 2.27–9.30).

A subsequent study examined the effect of diabetes on incident cardiovascular events in patients with FH, using data from three prospective cohort studies encompassing 3383 patients with FH, 6917 non-FH controls, and more than 100 000 person-years of follow-up [16▪▪]. The prevalence of diabetes in the FH patients was 7%. The 10-year risk of an ASCVD event was 5.1% in non-FH nondiabetes population, 14.8% in nondiabetes FH, 15.9% in diabetes non-FH, 30.8% in patients with FH and diabetes, and 50.7% in FH patients with a previous history of ASCVD. Interestingly, the 10-year risk of incident ASCVD was equivalent in FH patients with diabetes (30.8%) as in non-FH patients with a previous history of ASCVD (30.0%). These findings suggest that the presence of diabetes in patients with FH is a marker of very high cardiovascular risk that mandates aggressive treatment. Similar findings were reported in a nationwide Swedish registry, which found increased cardiovascular risk in patients with diabetes and phenotypic FH (defined by the baseline LDL-C value and history of premature

ASCVD) compared to patients with diabetes alone, or control individuals [17].

How should these recent findings be incorporated into treatment decisions for patients with FH? Guidelines for the treatment of FH generally provide recommendations for treatment of FH in the setting of primary prevention or secondary prevention [18–20]. The observation that diabetes increases the cardiovascular risk in FH to a similar degree as the presence of ASCVD in non-FH patients suggests that FH patients with diabetes should be treated to secondary prevention targets.

## SUMMARY

Although patients with FH were historically considered to be otherwise metabolically healthy with a low incidence of diabetes, more recent global data from more diverse regions has revealed a high prevalence of diabetes and metabolic syndrome in patients with FH from certain populations, mirroring the global increases in rates of diabetes and metabolic syndrome. When metabolic disease is present in FH patients, it amplifies the cardiovascular risk and therefore mandates more aggressive treatment. Recognizing the shift towards increased rates of diabetes and metabolic disease among patients with FH may provide opportunities to refine the diagnosis of this condition and further optimize its treatment.

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### Conflicts of interest

*There are no conflicts of interest.*

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- ■ of special interest
- ■■ of outstanding interest

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