Maternally inherited hypercholesterolemia does not modify the cardiovascular phenotype in familial hypercholesterolemia

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Abstract:	Background: Familial Hypercholesterolemia (FH) is a codominant autosomal disease characterized by a high risk of cardiovascular disease when not in lipid- lowering treatment. However, there is a large variability in the clinical presentation in heterozygous subjects (HeFH). Maternal hypercholesterolemia has been proposed as a cardiometabolic risk factor later in life. Whether this phenotype variability depends on the mother or father origin of hypercholesterolemia is unknown. Aim s: The objective of this study was to analyze potential differences in anthropometry, superficial lipid deposits, comorbidities, and lipid concentrations depending on the parental origin of hypercholesterolemia within a large group of HeFH. Methods: Cross-sectional observational, multicenter, nation-wide study in Spain. We recruited adults with HeFH to study clinical differences according to the parental origin. Data on HeFH patients were obtained from the Dyslipidemia Registry of the Spanish Atherosclerosis Society. Results: HeFH patients were grouped in 1231 HeFH-mother-offspring aged 45.7 (16.3) years and 1174 HeFH-father-offspring aged 44.8 (16.7) years. We did not find any difference in lipid parameters (total cholesterol, triglycerides, LDLc, HDLc, and Lp(a)), nor in the comorbidities studied (cardiovascular disease prevalence, age of onset of cardiovascular disease, obesity, diabetes, and hypertension) between groups. Lipid-lowering treatment did not differ between groups. The prevalence of comorbidities did not show differences when they were studied by age groups. Conclusions: Our research with a large group of subjects with HeFH shows that a potential maternal effect is not relevant in FH. This implies that severe maternal hypercholesterolemia during pregnancy is not associated with additional risk in the FH affected offspring.

Highlights

- The clinical phenotype is highly variable among heterozygous FH subjects.
- Maternal hypercholesterolemia may be associated with higher cardiometabolic risk later in life.
- FH is a good model to study the effect of maternal hypercholesterolemia in the offspring.
- We did not find any difference in heterozygous FH with maternal or paternal origin.
- Our results do not support any relevant effect of maternal hypercholesterolemia in the offspring.

Graphical Abstract

Does parental inheritance influence the phenotype in familial hypercholesterolemia?

Dyslipidemia Registry Spanish Atherosclerosis Society

sea Sociedad Española de Arteriosclerosis

HeFH (≥6 points DLCN; 66% with + genetic diagnosis)

N=3281

Undermined

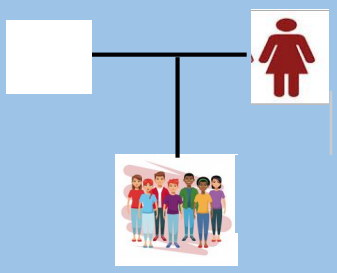
N= 884

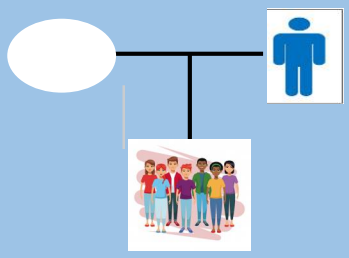
Maternally inherited

N= 1231

Paternally inherited

N=1174





	Maternal	P	Paternal
Age (years)	45.7	Non significant	44.8
Gender (women %)	52.5	Non significant	48.5
BMI (kg/m^2)	25.5	Non significant	25.7
LDL colesterol (mg/dL)	303.4	Non significant	301.9
Triglycerides (mg/dL)	126.2	Non significant	124.6
HDL colesterol (mg/dL)	55.8	Non significant	55.0
Diabetes (%)	1.8	Non significant	2.2
Hypertension (%)	6.2	Non significant	5.2
Obesity (%)	11.1	Non significant	12.6
Cardiovascular disease (%)	9.2	Non significant	9.3

No difference in the cardiometabolic phenotype

Full Title: Maternally inherited hypercholesterolemia does not modify the cardiovascular phenotype in familial hypercholesterolemia

Brief title: Maternal hypercholesterolemia effect in FH

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ABSTRACT

Background: Familial Hypercholesterolemia (FH) is a codominant autosomal disease characterized by a high risk of cardiovascular disease when not in lipid- lowering treatment. However, there is a large variability in the clinical presentation in heterozygous subjects (HeFH). Maternal hypercholesterolemia has been proposed as a cardiometabolic risk factor later in life. Whether this phenotype variability depends on the mother or father origin of hypercholesterolemia is unknown.

Aims: The objective of this study was to analyze potential differences in anthropometry, superficial lipid deposits, comorbidities, and lipid concentrations depending on the parental origin of hypercholesterolemia within a large group of HeFH.

Methods: Cross-sectional observational, multicenter, nation-wide study in Spain. We recruited adults with HeFH to study clinical differences according to the parental origin. Data on HeFH patients were obtained from the Dyslipidemia Registry of the Spanish Atherosclerosis Society.

Results: HeFH patients were grouped in 1231 HeFH-mother-offspring aged 45.7 (16.3) years and 1174 HeFH-father-offspring aged 44.8 (16.7) years. We did not find any difference in lipid parameters (total cholesterol, triglycerides, LDLc, HDLc, and Lp(a)), nor in the comorbidities studied (cardiovascular disease prevalence, age of onset of cardiovascular disease, obesity, diabetes, and hypertension) between groups. Lipid-lowering treatment did not differ between groups. The prevalence of comorbidities did not show differences when they were studied by age groups.

Conclusions: Our research with a large group of subjects with HeFH shows that a potential maternal effect is not relevant in FH. This implies that severe maternal hypercholesterolemia during pregnancy is not associated with additional risk in the FH affected offspring.

Keywords: heterozygous familial hypercholesterolemia, low-density lipoprotein receptor, HeFH phenotype, mother-offspring.

Abbreviations:

BMI: body mass index

FH: familial hypercholesterolemia

HeFH: heterozygous familial hypercholesterolemia

HDLc: high-density lipoprotein cholesterol

LDLc: low-density lipoprotein cholesterol

LDLR: low-density lipoprotein receptor

Lp(a): lipoprotein(a)

CVD: cardiovascular disease

SEA: Spanish Atherosclerosis Society

Introduction

Familial hypercholesterolemia (FH) is a codominant autosomal disease characterized by very high concentrations of low-density lipoprotein cholesterol (LDLc), superficial deposits of cholesterol in the form of corneal arcus and tendon xanthomas, and high risk of premature cardiovascular disease (CVD) in absence of adequate lipid-lowering treatment (1, 2). LDLc concentrations of heterozygous FH (HeFH) tend to be approximately twice that of the subjects of the general population and their CVD risk in the first decades of life, especially coronary disease, is up to 100 times higher (3). However, a characteristic of HeFH is the great variability in clinical presentation, including LDLc concentrations, and the presence of tendon xanthomas or coronary artery disease (4). This variability is multifactorial and has been associated with: the gene responsible for FH, with a more severe phenotype in carriers of *LDLR* mutations than in those with a mutation in *APOB, PCSK9,* or *APOE* (5, 6); the type of causal mutation, with worse phenotype in null-allele carriers than in defective allele carriers (7); the interaction with other genes, such as *ABCA1 or PSCK9* (8, 9); and the presence of CVD risk factors common to the general population, such as smoking, diabetes, low high-density lipoprotein cholesterol (HDLc), and high lipoprotein(a) (Lp(a)) levels (10). Despite all this, the origin of much of this clinical variation in HeFH remains unknown (1, 4).

One of the potential factors associated with the clinical variation of HeFH subjects is the parental origin of the genetic defect. Relatively frequent phenomena in nature that could explain differences in the phenotype in monogenic diseases are the so-called genomic imprinting that consists on the expression level of the alleles of a gene depend upon their parental origin (11); and a maternal effect, where the phenotype of

the offspring is determined not only by the postnatal environment and genotype but also by the environment during the gestation (12). These epigenetic phenomena are produced by modifications to chromatin mainly DNA methylation, histone acetylation, or the interaction of non-coding RNAs with DNA. The induction of DNA methylation is highly influenced by the maternal environment (13). Genomic imprinting genes have not been associated with FH (11). However, a maternal effect in HeFH has been attributed to a possible effect of maternal hypercholesterolemia during pregnancy that would condition a metabolic memory during adulthood (14). It has been reported that maternally derived HeFH subjects may have higher LDLc levels (15) and higher CVD mortality than paternally derived HeFH (16). It would be similar to what happens with the mother's smoking or diet rich in saturated fat during pregnancy (17), or low birth weight, with the risk of diabetes (18), arterial hypertension, or atheromatous cardiovascular disease in adulthood (19).

The effect of hypercholesterolemia during pregnancy favours the early development of arteriosclerosis lesions in newborns and an increased risk of diabetes and arterial hypertension in adulthood in different animal models (20, 21). Whether this effect exists in humans is not known. Lipid-lowering treatment is contraindicated during pregnancy and, given that cholesterol levels physiologically rise during the second and third trimesters of pregnancy, cholesterol rise is substantial in pregnant women with HeFH (22). Therefore, FH is a good model to identify whether severe hypercholesterolemia during pregnancy in HeFH women conditions the phenotype in the offspring and explains, at least in part, the differences that we find among adult subjects with HeFH.

The objective of this analysis was to identify potential differences in anthropometry, superficial lipid deposits, comorbidities, and lipid concentrations

between subjects with the maternal or paternal origin of hypercholesterolemia within a large group of HeFH.

Patients and Methods

Aim, design and participants

This cross-sectional observational multicenter nation-wide study in Spain was designed to identify differences in HeFH according to the parental origin of hypercholesterolemia. Data on HeFH patients were obtained from the Dyslipidemia Registry of the Spanish Atherosclerosis Society (SEA). The Dyslipidemia Registry of the SEA is an active online registry, where 65 certified lipid clinics across all regions of Spain report cases of various types of primary hyperlipidemias (23). Inclusion criteria and data collection were standardized among clinicians in 5 training sessions before case recruitment. Written informed consent was obtained from each patient included in the study; the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki; and the study protocol has been priorly approved by the Institution's ethics committee on research on humans (Comité Ético de Investigación Clínica de Aragón).

HeFH subjects were eligible for inclusion in this analysis if they had a clinical or genetic diagnosis of HeFH. Clinical diagnosis was based on the diagnostic criteria proposed by the Dutch Lipid Clinics Network: 6–8 points (probable) and >8 points (definitive). Genetic diagnosis was based on tested carrier status of a known pathogenic mutation for FH. Pathogenicity definition of mutations followed the American College of Medical Genetics ACMG recommendations (1). Homozygous FH subjects were excluded for this study. Patients in whom the parental inheritance of FH was unknown were not included in the final analysis.

Study variables

Clinical interview

For HeFH, the registry includes, among other data, personal and family health history, anthropometry, physical examination, laboratory data, presence of CVD, age at which statin treatment began, history of lipid-lowering treatment, and genetic data regarding mutations in *LDLR*, *APOB,* or *PCSK9* (positive, negative or unknown).

Family health history

Information about parental transmission of hypercholesterolemia was self-reported and confirmed from the patient's medical records. CVD is defined as: coronary (myocardial infarction, coronary revascularization procedure, sudden death); cerebral (stroke with>24 h neurological deficit without evidence of bleeding in brain imaging tests); peripheral vascular disease (intermittent claudication with ankle arm index<0.9, or arterial revascularization of lower limbs) or symptomatic or asymptomatic abdominal aortic aneurysm.

Laboratory tests

Lipid and lipoprotein levels are included in fasting state not using lipid-lowering medication for at least 6 weeks.

Definitions

Arterial hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported use of antihypertensive medication. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Diabetes mellitus (DM) was defined as the use of antidiabetic medications. Current smoker was defined as being currently smoking or having smoked in the last

year. Former smoker was defined as a subject having smoked at least 50 cigarettes in his lifetime, but not having smoked in the last year.

We conducted this study in accordance with the Declaration of Helsinki for the protection of the rights and welfare of people participating in biomedical research.

Statistical Analyses

Variables were summarized as mean (standard deviation) or percentage. Unadjusted differences between parental groups were tested with the Student-t test or the Chi-squared Test as appropriate. Linear and logistic regression models adjusted for age and sex were used to model the observed clinical characteristics, and to test the differences between parental origins. Differences in prevalence of comorbidities were tested with logistic regression models adjusted for age, sex, and BMI. A sensitivity analysis was performed restricting the dataset to those subjects with confirmed genetic mutation. All data analyses were performed with SPSS version 22 and R version 3.6.0. A post -hoc power calculation was performed to analyzed for cardiovascular disease prevalence difference according to the parental origin of FH. $P < 0.05$ has been considered statistically significant.

Results

Clinical characteristics

HeFH patients were grouped in 1231 HeFH-mother-offspring and 1174 HeFH-father-offspring, aged 45.7 (16.3) years and 44.8 (16.7) years, respectively. In the registry, in 884 subjects the parental origin of the disease could not be determined. The main characteristics of the three groups are presented in Table 1 and Supplemental Table 1. Subjects without information in the parental origin were older than the other two groups. No other differences were found between parental origins in the rest of the studied variables including total cholesterol, triglycerides, LDLc, HDLc, and Lp(a)),

DLCN scores, or lipid-lowering treatment intensity or duration. There were not differences between HeFH with maternal or paternal origin in all these variables after age and gender adjustment (Table 2), and when only HeFH subjects with genetic confirmation were considered (Table 3). All variables were analyzed stratifying by sex without statistical differences between men and women. (Supplemental Tables 4-7).

Prevalence of cardiovascular disease, obesity, diabetes and hypertension.

The prevalence of these morbidities is presented in Tables 4 and 5. They do not differ between groups even after adjustment for age, gender, and BMI when appropriate (not adjusted for BMI in anthropometric results). As expected, the prevalence of DM was low in both groups and there were not even hints of differences between groups in the studied diseases. We estimate that of our sample has 80% power to detect a relative risk 1.367 between two groups of 1202 persons when the overall prevalence is 12 cases per 100 with an alpha threshold of 0.05.

Prevalence of cardiovascular disease, obesity, diabetes and hypertension by age group.

To further identify potential differences in morbidity prevalence and different evolution according to age, we studied all variables and morbidities by age decades. None of the studied variables show differences between groups of parental origin. The prevalence of DM, CVD, LDLc concentration and blood pressure increased in a similar magnitude as age increased (Figure).

Discussion

Several studies had suggested that maternal hypercholesterolemia might increase adult CVD in the offspring (20). We studied this issue in a large group of HeFH and we did

not find any significant differences in the phenotype including CVD, DM, hypertension or plasma levels of lipids according to the parental origin of the genetic defect. FH is a good model to study the effect of hypercholesterolemia in offspring due to the large increase in lipid levels that women with FH have during pregnancy, often with concentrations of total cholesterol twice that of mothers without FH and higher than 400 mg/dL. Our findings do not support that maternal hypercholesterolemia has a deleterious effect on the offspring.

These results are in line with other studies that did not found difference in lipids and lipoprotein levels between HeFH who had inherited FH maternally or paternally (24). In addition, Tonstad et al., neither observed any difference in the carotid intima-media thickness and prevalence of plaque between HeFH children in spite of the parental origin (25). However, Van der Graf et al. had previously observed that maternal hereditary hypercholesterolemia slightly increases TC, LDLc and apolipoprotein B levels in their offspring later in life (15); and maternally inherited FH was associated with significantly higher excess mortality than FH transmitted by fathers (relative risk 2.2; p= 0.048) in HeFH carrying the V408M mutation in the *LDLR* gene (16). Probably the different inclusion criteria between studies or the number of subjects studied can explain the differences found.

Our study also provides relevant information regarding the role of hypercholesterolemia during pregnancy, regardless of its cause, in the subsequent development of cardiovascular complications. Previous information in models suggests that maternal hypercholesterolemia accelerates the development of arteriosclerosis in offspring in both rabbits (26) and mice (27), regardless of whether hypercholesterolemia in the mother was induced by genetic manipulation, diet, or both, and independent of postnatal LDLc concentration (19). The effect of hypercholesterolemia during

pregnancy in humans has been much less studied. In a postmortem study of the aortic arch and abdominal aorta of 156 normocholesterolaemic children aged 1-13 years, who died of trauma and other causes. (Fate of Early Lesions in Children Study) showed an association between maternal cholesterol and the presence of initial lesions of arteriosclerosis in children (20). However, this has not been subsequently confirmed.

During pregnancy, a physiological increase in maternal cholesterol levels occurs. It is an adaptive mechanism responding to the higher demands of cholesterol during prenancy and it is known as "maternal physiological hypercholesterolemia" (28). In addition, some women have an alteration, called as "maternal supraphysiological hypercholesterolemia" which is associated with fetoplacental vascular modifications. Nevertheless, maternal hypercholesterolemia does not affect neonatal lipid levels (29, 30) because cholesterol plasma concentration in the fetus is a highly regulated process mostly independent of maternal plasma cholesterol. The cholesterol in the fetus is comes from *de novo* synthesis or placenta transport. Cholesterol is transported in the human placenta from mother to fetus through cholesterol uptake by the placenta from maternal lipoproteins, crossing trophoblast and endothelium and efflux from it to acceptors in the fetus. In the apical side of the syncytiotrophoblast (STB), the cholesterol uptake from the maternal circulation comes from LDL and HDL particles throughout the low-density lipoprotein and SR-BI receptors, respectively. It is secreted at the basal side facing the villous stroma (12, 31, 32). The mechanisms which the cholesterol is transported to the endothelial cells to finally reach the fetal circulation are mostly unknown (33, 34) but two highly regulated proteins, ABCA1 and ABCG1 are responsible of translocating placenta cholesterol to lipid-free apolipoproteins A1 and HDL particles (35) without the participation of the LDL receptor which is poorly expressed at the basal side of the syncytiotrophoblast (30) .

The main clinical implication of our results is that the clinical management of subjects with HeFH should not be different depending on whether the inheritance is maternal or paternal, since the lipid phenotype and long-term complications are similar in both groups. There is a tendency in the clinical practice of cardiovascular diseases to underuse effective cardiac medications among women than among men (36–38) and this could be accentuated in FH since family history of premature cardiovascular disease is a risk-enhancing factors in the general population (39), and premature cardiovascular disease is less common in HeFH women (10). Therefore, the risk of having a history of early disease is greater if the inheritance is paternal. This potential bias is not observed in our study since clinical management is very similar between subjects with paternal or maternal inheritance. Neither the years of statin, nor the percentage of subjects with high-intensity lipid-lowering treatment was different depending on paternal inheritance. This is most likely due to the fact that the patients in our study come from specialized units (23) where therapeutic recommendations are mostly based on individual risk factors according to current guidelines (40). We think our data are solid about the absence of a relevant clinical effect in hypercholesterolemia of monogenic origin. However, if other forms of hypercholesterolemia during pregnancy play a relevant role later in life should be explored.

Some aspects of our study could be discussed. The parental assignment has been self-reported, although, it was rechecked in the medical records. For this reason, 27% of the subjects were excluded from the analysis since the allocation could not be verified. Second, the diagnosis of HeFH was based on clinical criteria and genetic diagnosis was not available in 10.1% and 11.5% of HeFH with maternal and paternal origin, respectively, although we did not find any difference when considering only those subjects with a positive genetic diagnosis.

In conclusion, our results from a large group of subjects with HeFH do not support differences in the lipid phenotype, cardiovascular disease prevalence, age of onset of cardiovascular disease or cardiometabolic complications such as DM and hypertension in relation to the maternal or paternal origin of hypercholesterolemia. These findings imply that maternal hypercholesterolemia does not confer an additional risk to offspring later in life, and that a potential maternal effect is not relevant in FH.

Conflict of interest

The authors declare no conflict of interest

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Author contribution statement

Conceptualization, VM-B and FC; Data Curation VM-B, AMB, MS-T, NP, XP, AB, RS-H and FC. Formal Analysis VM-B, ML and FC; Funding Acquisition, FC; Investigation, VM-B, AMB, MS-T,NP,XP ,AB, RS-H and FC; Methodology, VM-B, ML and FC; Project Administration, FC; Resources, FC; Software ML; Writing - Original Draft Preparation: VM-B, FC; Review: all authors.

Acknowledgments

All authors have read and approved the final manuscript.

Data availability:

Data available upon reasoned request.

Ethics approval:

The study protocol has been priorly approved by the Institution's ethics committee on research on humans (Comité Ético de Investigación Clínica de Aragón).

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Figure legends

Prevalence of cardiovascular disease (panel A), and diabetes (panel B), LDL cholesterol concentration (panel C) and systolic blood pressure (panel D) according to age decades.

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Figure(s)

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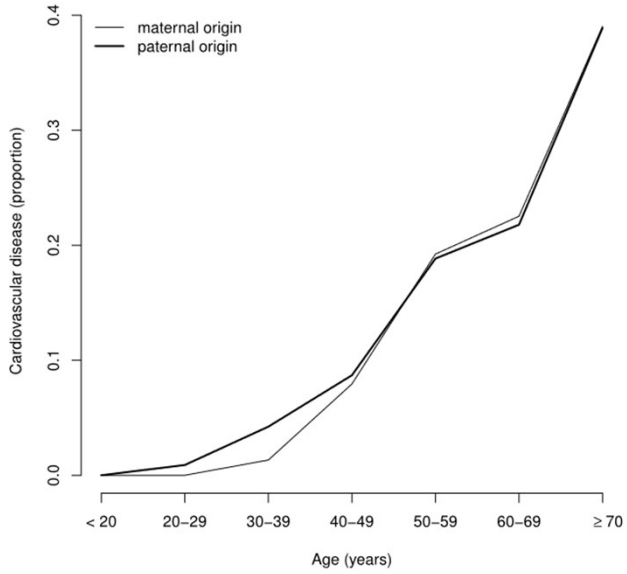
A



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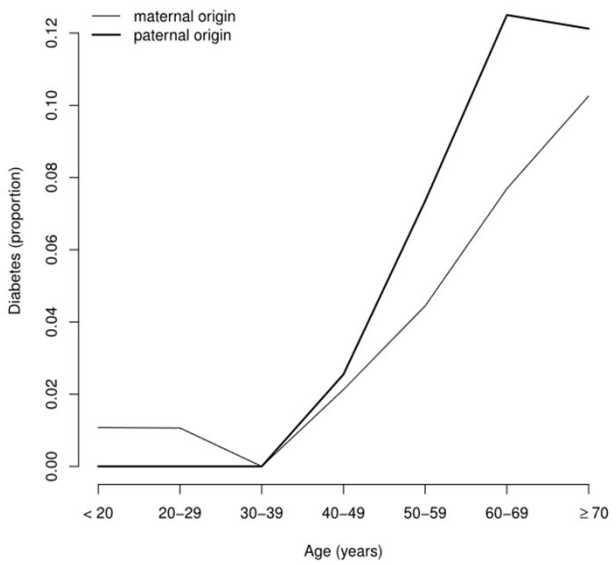

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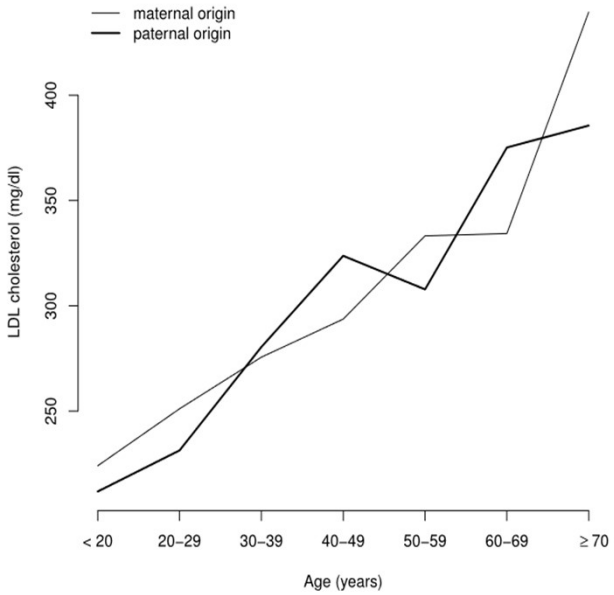

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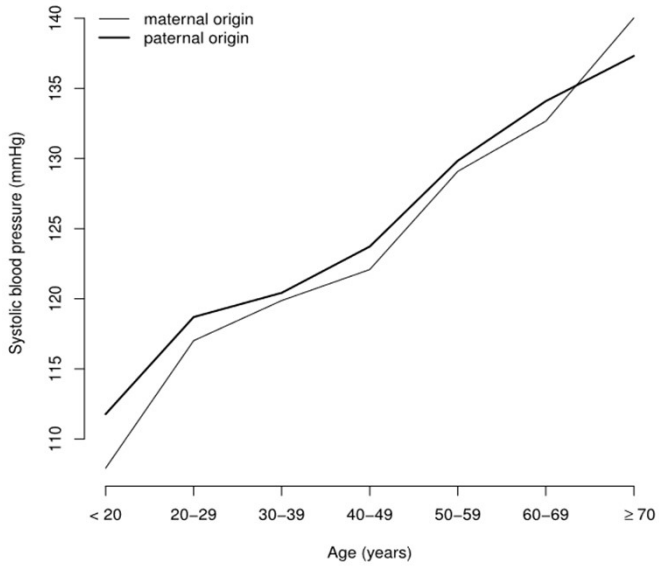

Table 1 Clinical and biochemical characteristics of the HeFH subjects according to the FH parental origin.

FH parental origin	Mother	Father	Unknown
N	1231	1174	884
Age (years)	45.7 (16.3)	44.8 (16.7)	54.7 (13.9)
Sex (women), N (%)	646 (52.5)	569 (48.5)	504 (57.0)
Tobacco (current smoker), N (%)	278 (23.0)	267 (23.2)	187 (21.8)
BMI (Kg/m^2)[a]	25.5 (4.6)	25.7 (4.8)	26.9 (4.5)
Waist circumference (cm)	78.9 (61.7)	78.3 (56.8)	81.1 (45.4)
Systolic blood pressure (mmHg)	124.9 (17.2)	125.7 (16.5)	129.8 (17.2)
Diastolic blood pressure (mmHg)	76.0 (11.4)	76.0 (10.8)	79.0 (10.4)
Corneal arcus, N (%)	331 (28.8)	336 (30.5)	290 (34.6)
Tendon xanthoma, N (%)	109 (9.2)	110 (9.8)	88 (10.4)
Total cholesterol (mg/dL)	384.5 (183.5)	381.8 (176.9)	397.6 (184.8)
Triglycerides (mg/dL)	126.2 (97.6)	124.6 (79.5)	144.2 (118.9)
LDL cholesterol (mg/dL)[b]	303.4 (180.5)	301.9 (175.2)	313.4 (182.7)
HDL cholesterol (mg/dL)[c]	55.8 (15.8)	55.0 (14.6)	55.4 (15.9)
Lipoprotein(a) (mg/dL)	46.6 (51.8)	47.2 (53.1)	55.6 (63.2)
DLCN score (points)[d]	14.0 (5.3)	13.7 (5.4)	12.8 (5.3)
Positive genetic diagnosis, N (%)	868 (70.5)	792 (67.5)	513 (58.0)
Statin treatment duration (years)	8.8 (7.9)	8.7 (7.9)	8.8 (7.5)

[a]BMI denotes body mass index; [b]LDL, low-density lipoprotein; [c]HDL, high-density lipoprotein; [d]DLCN, Dutch lipid clinics network. Data are summarized as mean (SD) or N (percentage)

Table 2. Sex and age adjusted comparions in clinical and biochemical characteristics of the HeFH subjects according to the FH parental origin.

FH parental origin	Mother	Father	p
N	1231	1174	
Tobacco (smoker) N (%)	278 (23.0)	267 (23.2)	0.93
BMI (Kg/m^2)[a]	25.4	25.6	0.34
Waist circumference (cm)	81.2	80.6	0.81
Systolic blood pressure (mmHg)	125.1	126.1	0.14
Diastolic blood pressure (mmHg)	75.5	75.6	0.85
Corneal arcus, N (%)	292 (25.4)	283 (27.5)	0.26
Tendon xanthoma, N (%)	106 (9)	109 (9.7)	0.59
Total cholesterol (mg/dL)	372.2	371.9	0.97
Triglycerides (mg/dL)	132.1	130.6	0.68
LDL cholesterol (mg/dL)[b]	295.0	295.4	0.95
HDL cholesterol (mg/dL)[c]	50.8	50.4	0.48
Lipoprotein(a) (mg/dL)	44.6	45.9	0.61
DLCN score (points)[d]	14.2	13.9	0.10
Positive genetic diagnosis, N (%)	868 (70.5)	792 (67.5)	0.256
LDLR mutation, N (%)	814 (93.8)	749 (94.6)	0.492
APOB mutation, N (%)	44 (5.1)	36 (4.5)	0.619
Statin treatment duration (years)	7.5	7.6	0.69
Age at first CVD event (years)	34.5	35.5	0.29
High-intensity statin N (%)	811 (65.9)	750 (63.9)	0.59

Ezetimibe use, N (%)	661 (53.7)	621 (52.9)	0.71

[a]BMI denotes body mass index; [b]LDL, low-density lipoprotein; [c]HDL, high-density lipoprotein; [d]DLCN, Dutch lipid clinics network. Linear and logistic regression models were used to calculate conditionally age and sex adjusted estimates for a 40 years old man (values in cells) and to test for differences. Data are summarized as mean (SD) or N (percentage)

Table 3. Sex and age adjusted comparions in clinical and biochemical characteristics of the genetical confirmed HeFH subjects according to the FH parental origin

FH parental origin	Mother	Father	p
N	868	792	
Tobacco (smoker), N (%)	207 (24.4)	171 (22.0)	0.28
BMI (Kg/m^2)[a]	25.3	25.4	0.55
Waist circumference (cm)	83.0	82.4	0.85
Systolic blood pressure (mmHg)	125.1	126.1	0.19
Diastolic blood pressure (mmHg)	74.9	74.7	0.68
Corneal arcus, N (%)	202 (24.9)	192 (25.9)	0.68
Tendon xanthoma, N (%)	83 (10.0)	84 (11.0)	0.54
Total cholesterol (mg/dL)	373.6	372.7	0.92
Triglycerides (mg/dL)	123.1	124.2	0.77
LDL cholesterol (mg/dL)[b]	297.8	297.7	0.99
HDL cholesterol (mg/dL)[c]	51.2	50.1	0.15
Lipoprotein(a) (mg/dL)	42.6	43.8	0.64
DLCN score[d]	16.4	16.4	0.74
Statin treatment duration (years)	8.0	8.6	0.10
Age at first CVD event (years)	33.9	34.6	0.61
High-intensity statin, N (%)	582 (67.1)	508 (64.2)	0.51
Ezetimibe use, N (%)	495 (57.0)	430 (54.3)	0.29

[a]BMI denotes body mass index; [b]LDL, low-density lipoprotein; [c]HDL, high-density lipoprotein; [d]DLCN, Dutch lipid clinics network. Linear and logistic regression models were used to calculate

conditionally age and sex adjusted estimates for a 40 years old man (values in cells) and to test for differences. Data are summarized as mean (SD), median (interquartile range) or N (percentage)

Table 4. Sex and age adjusted comparison of comorbidities of subjects according to the FH parental origin

FH parental origin	Mother	Father	P(adj.)
N	1231	1174	
Diabetes, N (%)	22 (1.8)	25 (2.2)	0.43
High blood pressure, N (%)	73 (6.2)	59 (5.2)	0.19
Cardiovascular disease, N (%)	113 (9.2)	109 (9.3)	0.92
Overweight or obesity, N (%)	700 (57.1)	676 (57.9)	0.68
Obesity, N (%)	136 (11.1)	147 (12.7)	0.21

Conditionally age and sex adjusted estimates for a 40 years old man. Test for raw differences using Chi^2 test and regression tests (P (adj.)) from adjusted logistic models.

Table 5. Sex and age adjusted comparison of comorbidities of the genetically confirmed HeFH subjects according to the FH paternal origin

FH parental origin	Mother	Father	p
N	868	792	
Diabetes	13 (1.6)	17 (2.2)	0.29
High blood pressure	43 (5.3)	37(4.9)	0.68
Cardiovascular disease	77 (8.9)	67 (8.4)	0.75
Overweight or obesity	464 (53.8)	434 (55.3)	0.58
Obesity	80 (9.3)	85 (10.8)	0.28

Conditionally age and sex adjusted estimates for a 40 years old man. Test for raw differences using Chi^2 test and regression tests (P (adj.)) from adjusted logistic models.

CRediT author statement

- The corresponding author is responsible for ensuring that the descriptions are accurate and agreed by all authors.
- The role(s) of all authors should be listed, using the relevant above categories.
- Authors may have contributed in multiple roles.
- CRediT in no way changes the journal's criteria to qualify for authorship.

Author contribution statement

Conceptualization, VM-B and FC; Data Curation VM-B, AMB, MS-T, NP, XP, AB, RS-H and FC. Formal Analysis VM-B, ML and FC; Funding Acquisition, FC; Investigation, VM-B, AMB, MS-T,NP,XP ,AB, RS-H and FC; Methodology, VM-B, ML and FC; Project Administration, FC; Resources, FC; Software ML; Writing - Original Draft Preparation: VM-B, FC; Review: all authors.

Zaragoza, Dec 10, 2020

Fernando Civeira, MD, PhD

Supplemental Table 1. Missing/Available data in table 1

FH parental origin	Mother	Father	Unknown	Mother	Father	Unknown
N	1231	1174	884	1231	1174	884
		MISSING			AVAILABLE	
Age (years)	0	0	0	1231	1174	884
Sex (women)	0	0	0	1231	1174	884
Tobacco (current smoker)	23	21	25	1208	1153	859
BMI (Kg/m^2)[a]	7	10	6	1224	1164	878
Waist circumference (cm)	0	0	0	1231	1174	884
Systolic blood pressure (mmHg)	51	55	39	1180	1119	845
Diastolic blood pressure (mmHg)	51	55	39	1180	1119	845
Corneal arcus	83	73	46	1148	1101	838
Tendon xanthoma	50	47	40	1181	1127	844
Total cholesterol (mg/dL)	0	0	0	1231	1174	884
Triglycerides (mg/dL)	0	0	0	1231	1174	884
LDL cholesterol (mg/dL)[b]	0	0	0	1231	1174	884
HDL cholesterol (mg/dL)[c]	0	0	0	1231	1174	884
Lipoprotein(a) (mg/dL)	349	343	273	882	831	611
DLCN score[d]	0	0	0	1231	1174	884
Statin treatment duration (years)	152	149	132	1079	1025	752

[a]BMI denotes body mass index; [b]LDL, low-density lipoprotein; [c]HDL, high-density lipoprotein; [d]DLCN, Dutch lipid clinics network.

Supplemental Table 2. Missing/Available data in table 3

FH parental origin	Mother	Father	Mother	Father
N	868	792	868	792
	MISSING		AVAILABLE	
Age (years)	0	0	868	792
Sex (women)	0	0	868	792
Tobacco (smoker)	18	16	850	776
BMI (Kg/m^2)[a]	6	7	862	785
Waist circumference (cm)	0	0	868	792
Systolic blood pressure (mmHg)	35	42	833	750
Diastolic blood pressure (mmHg)	35	42	833	750
Corneal arcus	55	50	813	742
Tendon xanthoma	33	28	835	764
Total cholesterol (mg/dL)	0	0	868	792
Triglycerides (mg/dL)	0	0	868	792
LDL cholesterol (mg/dL)[b]	0	0	868	792
HDL cholesterol (mg/dL)[c]	0	0	868	792
Lipoprotein(a) (mg/dL)	180	169	688	623
DLCN score[d]	0	0	868	792
Statin treatment duration (years)	85	94	783	698

[a]BMI denotes body mass index; [b]LDL, low-density lipoprotein; [c]HDL, high-density lipoprotein; [d]DLCN, Dutch lipid clinics network.

Supplemental Table 3. Missing/Available data in table 4

FH parental origin	Mother	Father	Mother	Father
N	868	792	868	792
	MISSING		AVAILABLE	
Diabetes	21	22	847	770
High blood pressure	47	41	821	751
CVD[a]	0	0	868	792
Overweight or obesity	6	7	862	785
Obesity	6	7	862	785

[a]CVD: Cardiovascular disease

Supplemental Table 4. Age adjusted differences in clinical and biochemical characteristics of the HeFH MEN according to the FH parental origin.

FH parental origin	Mother	Father	p
N	585	605	
Tobacco (smoker)	22.7%	23.6%	0.73
BMI (Kg/m2)	25.5	25.5	0.85
Waist circumference (cm)	82.1	80.0	0.56
Systolic blood pressure (mmHg)	125.5	126.2	0.42
Diastolic blood pressure (mmHg)	75.4	75.6	0.73
Corneal arcus	24.6%	28.1%	0.18
Tendon xanthoma	8.8%	10.2%	0.40
Total cholesterol (mg/dL)	367.4	372.7	0.60
Triglycerides (mg/dL)	134.3	125.8	0.14
LDL cholesterol (mg/dL)	290.1	296.6	0.52
HDL cholesterol (mg/dL)	50.5	51.0	0.52
Lipoprotein(a) (mg/dL)	44.6	46.2	0.65
DLCN score (points)	14.1	13.9	0.46
Statin treatment duration (years)	7.4	7.5	0.73
Age at first CVD event (years)	34.7	35.6	0.40

BMI denotes body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; DLCN, Dutch lipid clinics network. Conditionally age adjusted estimates for a 40 years old participant

Suppemental Table 5. Age adjusted differences in clinical and biochemical characteristics of the HeFH WOMEN according to the FH parental origin.

FH parental origin	Mother	Father	p
N	646	569	
Tobacco (smoker)	22.9%	22.3%	0.82
BMI (Kg/m2)	24.2	24.6	0.18
Waist circumference (cm)	72.2	73.1	0.77
Systolic blood pressure (mmHg)	118.9	120.1	0.19
Diastolic blood pressure (mmHg)	73.6	73.5	0.94
Corneal arcus	19.8%	20.3%	0.83
Tendon xanthoma	7.8%	7.7%	0.93
Total cholesterol (mg/dL)	367.7	361.5	0.53
Triglycerides (mg/dL)	105.0	110.3	0.18
LDL cholesterol (mg/dL)	286.1	280.2	0.55
HDL cholesterol (mg/dL)	60.6	59.3	0.14
Lipoprotein(a) (mg/dL)	44.7	45.7	0.77
DLCN score (points)	13.9	13.4	0.11
Statin treatment duration (years)	7.4	7.5	0.83
Age at first CVD event (years)	36.3	37.5	0.53

BMI denotes body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; DLCN, Dutch lipid clinics network. Conditionally age adjusted estimates for a 40 years old participant

Supplemental Table 6. Age adjusted comparison of comorbidities of HeFH MEN according to the FH parental origin.

FH parental origin	Mother	Father	p
N	585	605	
Diabetes	1.7%	1.7%	0.88
High blood pressure	6.2%	5.8%	0.73
Cardiovascular disease	8.6%	8.1%	0.69
Overweight or obesity	58.1%	55.8%	0.47
Obesity	11.2%	12.0%	0.66

Conditionally age adjusted estimates for a 40 years old participant.

Supplemental Table 7. Age adjusted comparison of comorbidities of the genetically confirmed HeFH WOMEN according to the FH parental origin

FH parental origin	Mother	Father	p
N	463	389	
Diabetes	0.8%	1.7%	0.07
High blood pressure	2.3%	2.1%	0.76
Cardiovascular disease	2.2%	2.0%	0.77
Overweight or obesity	30.8%	35.8%	0.14
Obesity	9.7%	12.4%	0.18

Conditionally age adjusted estimates for a 40 years old participant.