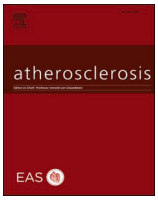
Atherosclerosis 408 (2025) 120400

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis



Clinical profile of familial hypercholesterolemia phenotype in adults attended in primary care in a large healthcare area

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ARTICLE INFO

Keywords:
Familial hypercholesterolemia
Cardiovascular risk
Cardiovascular atherosclerotic disease

ABSTRACT

Background and aims: To examine the clinical profile and associated clinical characteristics of heterozygous Familial Hypercholesterolemia clinical phenotype (FH) in adults attended in primary care in a large health area of the Community of Madrid, Spain.
Methods: Cross-sectional, multicenter study including 156,082 adults (≥18 years) from 69 health centers with at least one lipid profile between 2018 and 2021, using electronic health records (EHR). Severe hypercholesterolemia (SH) was defined as total cholesterol ≥300 mg/dL or LDL-cholesterol≥220 mg/dL and FH phenotype was defined as LDL-C ≥240 mg/dL (≥90th percentile within our study sample) or ≥160 mg/dL under lipid-lowering therapy (LLT), with triglycerides <200 mg/dL and normal TSH levels. Multivariate logistic regression was used to assess clinical associations.
Results: SH was present in 6187 individuals (3.96 %), and FH phenotype in 1600 (1.03 %; mean age 60.7 years; 72.7 % women). Compared with non-FH individuals, those with FH were more often female, on LLT (97.6 % vs. 79.0 %), and had lower prevalence of diabetes, hypertension, and obesity (all $p < 0.005$). Women with FH were more frequently treated but less often with high/very-high intensity LLT than men (25.3 % vs. 36.6 %; $p < 0.001$). All treated FH patients had LDL-C >130 mg/dL (vs. 60.4 % in non-FH), with higher levels in men (178.7 vs. 170.9 mg/dL; $p = 0.0015$). Female sex and LLT were independently associated with FH phenotype, while age, diabetes, hypertension, and obesity were inversely associated (all $p < 0.05$).
Conclusions: FH phenotype was identified in 1.03 %, of primary care patients. Women were more often treated but less likely to receive high-intensity or combined therapy compared to men. LDL-C levels were higher in men and intensive therapy reduced sex differences. LDL-C targets were largely unmet. EHR may aid early identification and improve preventive strategies.

1. Introduction

Familial hypercholesterolemia (FH) is a prevalent genetic condition characterized by very high plasma levels of LDL-C and a high cardiovascular risk early in life. It is most commonly caused by pathogenic mutations in the LDLR gene, but mutations in APOB and PCSK9 can also contribute to the disorder. These genetic alterations lead to impaired LDL clearance and persistent elevation of LDL-C levels. [1–6]. FH affects approximately 1 in 250–300 individuals in the general population. Despite this is a frequent disorder, FH is under-diagnosed and under-treated [5,7].

Early detection and treatment of FH is critical in reducing the risk of cardiovascular events and improving the long-term outcomes and quality of life of affected individuals and their families [5,7]. It has been

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https://doi.org/10.1016/j.atherosclerosis.2025.120400
Received 16 January 2025; Received in revised form 24 May 2025; Accepted 3 June 2025
Available online 4 June 2025

shown that to do screening for FH compared with no screening is cost-effective, regardless of the screening strategy [8,9].

Some strategies in primary care have been the use of electronic health records (EHR), [10–14], and the use of data from centralized laboratories identifying cases that are referral to lipid units, which may facilitate the implementation of universal and family-based cascade screening strategies for FH [10–16]. Therefore, internationally, case finding for FH is recommended using different criteria, such as the Dutch Lipid Clinic Network (DLCN), Simon Broome, or Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria [2,3,17]. There are also strategies for case detection based on cholesterol concentrations higher than the 99th percentile (general population in the UK) and clinical case-finding algorithm, the familial hypercholesterolemia case ascertainment tool (FAMCAT), that achieve greater accuracy than currently recommended approaches [10,11]. However, there are no randomized clinical trials or controlled non-randomized intervention studies evidence to determine the most appropriate healthcare strategy to systematically identify possible or definite clinical familial hypercholesterolemia in primary care or community settings [18].

This study assessed (i) "the prevalence of the FH clinical phenotype, based on LDL-C thresholds and clinical criteria", in primary-care setting, (ii) the treatment and degree of LDL-C levels, and (iii) the "clinical characteristics" of FH clinical phenotype in a large health area of the Community of Madrid (CAM) in Spain, using a centralized database. Although FH is a genetic condition present from birth, its clinical recognition and management are often influenced by age and sex. Sex-related differences may contribute to disparities in diagnosis and treatment. This approach could simplify and potentially achieve greater effectiveness in identification of cases with the highest risk of having FH. This would eventually allow us to implement strategies to prevent cardiovascular events in this high-risk population, as recommended by clinical practice guidelines [2,3,17].

2. Methods

2.1. Design and study population

this is an observational and multicenter study including 40 health centers and 29 local clinics from the Northwest Care Directorate (DANO) [19] of the Autonomous Community of Madrid (CAM), Spain. In the Spanish healthcare system, primary care is provided through health centers, which are larger facilities staffed by multidisciplinary teams including general practitioners, nurses and pediatricians. Additionally, local clinics are, often located in rural or less populated areas. DANO covers 1,093,819 subjects, with a health card (TSI) in the Primary Care computer system of Madrid (AP-Madrid) The primary-care teams in the health area are attended by 541 physicians [20]. According to the previous data, the proportion of men and women on a health card using the SIP-CIBELES application is 48 % and 52 %, respectively, a proportion that has been remained constant in the last five years.

A total of 930,002 adults aged 18 years or older (85 % of the population) were selected (from 2018 to 2021), of which 156,082 attended their health center and had blood analysis with a lipid profile available in the period studied (16.8 %).

2.2. Inclusion and exclusion criteria

All subjects ≥18 years of age who consulted at their health centers from January 1, 2018 to December 31, 2021 and who had total cholesterol ≥300 mg/dL or LDL-C ≥220 mg/dL (severe hypercholesterolemia, SH) in any of the analyses carried out in this period were selected [3,17]. The FH phenotype was considered according to cut-off points in adults suggestive of FH if LDL-C concentrations were ≥240 mg/dL (≥160 mg/dL if on lipid-lowering treatment), with triglyceride levels <200 mg/dL and TSH <5 uIU/mL in the last analysis of the period studied, which corresponds approximately to the 90th percentile of the distribution of LDL values in the sample (233 mg/dl in women and 244 mg/dl in men). These criteria to define the FH clinical phenotype were derived based on established clinical guidelines, prior epidemiological studies, and practical considerations for use in primary care settings [2,3,17]. Moreover, LDL-C cutoffs to define the FH clinical phenotype were selected in alignment with percentile-based thresholds applied in FH detection, while treatment-adjusted values accounted for LLT effects. Exclusion criteria were applied to reduce misclassification due to secondary causes of hypercholesterolemia.

2.3. Data source

Anonymized data was obtained from the AP-Madrid database, which allows access to sociodemographic data, coding of diagnoses according to the second International Classification in Primary Care edition (ICPC-2) [21], and access to different general patient data (GPD) such as anthropometric measurements, laboratory data, and pharmacological prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification [22].

2.4. Variables

Sociodemographic variables, health center code, doctor identification, age and sex were selected. ***In this study, the term 'sex' refers to the biological classification (male/female) as recorded in medical records.***

Systolic and diastolic blood pressure (BP) (mmHg), weight (kg), height (cm), and body mass index (BMI, kg/m^2) were used when available. The time of evolution of the diagnosis of hyperlipidemia in the centralized database was also considered. The last blood test performed within the period of study was used, including fasting glucose (mg/dL), total cholesterol (mg/dL), LDL-C (mg/dL), HDL-C (mg/dL), triglycerides (mg/dL), creatinine (mg/dL), thyroid stimulating hormone (TSH) (uIU/mL), transaminases ALT (U/L) and AST (U/L), and GGT (U/L). Glomerular filtration rate (ml/min/1.73m2) was calculated with the CKD-EPI formula [23]. These analytical variables were obtained from samples obtained at health centers under baseline conditions of at least 8-h fasting and sent to the two reference laboratories in the health area. LDL-c was estimated by the Friedewald formula if triglycerides were <400 mg/dL. [24]. "LDL-C levels to consider control were selected to evaluate the effects of treatment. No formal correction for LLT intensity was applied; instead, different LDL-C threshold for treated individuals was used to account for treatment effects [2,3,17].

The cardiovascular risk factors and comorbidities considered were identified according to codes (ICPC-2) [21].

The pharmacological prescription was analyzed according to the classification by therapeutic groups used in AP-Madrid, which incorporates the ATC classification, i.e., the European coding system for pharmaceutical substances and medications [22]. The group of lipid-lowering drugs (C10, lipid-modifying agents) was analyzed with the following subgroups: C10AA01-C10AA08 (HMG CoA reductase inhibitors), C10AB (Fibrates), C10AC (Bile acid sequestrants), C10AX (Other agents lipid modifying agents: Omega-3, Ezetimibe), and group C10B (lipid modifying agents in combination). Other lipid-lowering drugs like PCSK9 inhibitors were not included because they are dispensed in the hospital pharmacies and are not available in primary-care records. The intensity of lipid-lowering treatment (LLT) was classified using the classification of Masana et al., into low, moderate, high, and very-high intensity treatment, according to the statin used, dose, and type of combination [25] and similar to the one use in SAFEHEART registry that considered the maximum dose of LLT when it is expected to produce at least a 50 % reduction in LDL-C baseline levels and would include high and very high intensity treatments [26].

While the specific guidelines followed by primary care physicians were not recorded in our database, FH diagnosis and management in Spain are generally guided by the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines, as well as

national recommendations from Hypercholesterolemia Familiar Foundation and primary care societies [3,27].

2.5. Data analysis

All variables were checked to detect anomalous values or other inconsistencies. Missing data were handled using complete case analysis for LDL-C-based FH clinical phenotype classification. The categorical variables were presented with their frequency distribution and percentage and 95 % confidence interval (95 % CI), and the quantitative variables with the mean, standard deviation (SD), and 95 % CI, if the variables followed a normal distribution. The association between categorical variables were performed with the Chi-square test or Fisher's exact test (if >25 % of the expected cases were <5). Comparisons of means were performed using the student *t*-test, after using Levene's test of homogeneity of variances, if the variables followed a normal distribution in the groups to be compared. For asymmetric variables, the non-parametric Mann-Whitney *U* test was used. Prevalence and control percentage of HF subjects were calculated according to the intensity of lipid-lowering treatment and different levels of LDL.

To evaluate the robustness of our findings and explore potential selection bias related to LDL-C thresholds, we performed a sensitivity analysis using alternative cutoff points to define the FH clinical phenotype. We applied two stricter thresholds corresponding to approximately the 95th percentile (≥260 mg/dL untreated or ≥170 mg/dL on treatment) and the 99th percentile (≥310 mg/dL untreated or ≥200 mg/dL on treatment).

To assess the individual prevalence effect of comorbidities and clinical conditions on the dependent variable (FH phenotype), multivariate logistic regression analysis was performed using the backward stepwise method, initially introducing into the model all the variables that showed association in the bivariate analysis up to a p-value <0.10. Backward stepwise regression was chosen as the variable selection method because it allows for a comprehensive assessment of all candidate variables before iteratively removing non-significant predictors, reducing the risk of premature exclusion of relevant factors. [28]. To explore whether the clinical predictors of the FH phenotype varied depending on the LDL-C threshold used, we conducted three separate multivariable logistic regression models corresponding to the 90th, 95th, and 99th percentiles of LDL-C. The same set of covariates was included in all models to assess the consistency of associations across definitions.

All tests were two-tailed, and a p-value <0.05 was considered statistically significant. The statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) for Windows v.24 (IBM, Armonk, New York, USA).

2.6. Ethical aspects

The data were requested from the Technical Support Unit of the Madrid Health Service (SERMAS) from a single, centralized, and anonymized database. With this, international data protection standards and current Spanish legislation were respected. In the database, there was a dissociation between identifying data and clinical data, respecting the autonomy of the patient and the rights and obligations of clinical information and documentation, and only the researchers had access to the information.

The study received a favorable report from the Northwest Local Research Commission of Madrid (code 04/2022).

3. Results

Of the 156,082 participants ≥18 years with an available lipid profile, 6187 had SH (3.96 % of the laboratory tests, 95 % CI 3.87–4.06 %) with a mean age of 59.6 (SD, 14.2), and 1600 had FH phenotype (1.03 %, 95 % CI 0.98–1.08 %) with a mean age of 60.7 (SD, 13.8) years. Fig. 1 represents the step-by-step process for patient inclusion in the study, detailing the criteria applied at each stage of selection.". "None of the patients with a FH clinical phenotype had a formal diagnosis recorded in their medical history"

Table 1 shows the clinical characteristics of the populations with severe hypercholesterolemia, according to Familial hypercholesterolemia clinical phenotype status compared with individuals with non-FH clinical phenotype. Those cases with FH clinical phenotype were more frequently women (72.7 % vs. 66.6 %), had less frequency of hypertension (33.3 % vs 37.6 %), diabetes (4.5 % vs 11.3 %) and obesity (8.6 % vs 11.5 %), and more patients were on LLT (97.8 % vs. 79.1 %). Fig. 2 shows the distribution of FH clinical phenotype according to sex and age groups. The higher frequency of FH clinical phenotype in men was under the age 25 years ($p = 0.34$), while in women it was between 55 and 74 years of age($p < 0.05$), with no significant differences in other age groups.

Differences in clinical characteristics between men and women with FH clinical phenotype are shown in Table 2. Men were younger (54.8 vs. 62.9 years, respectively); and have higher LDL-C, triglycerides, Non-HDL-C, and glucose levels than women. No differences were found in the proportion of subjects with cardiovascular disease.

Table 3 shows the proportion of subjects with LLT and the intensity

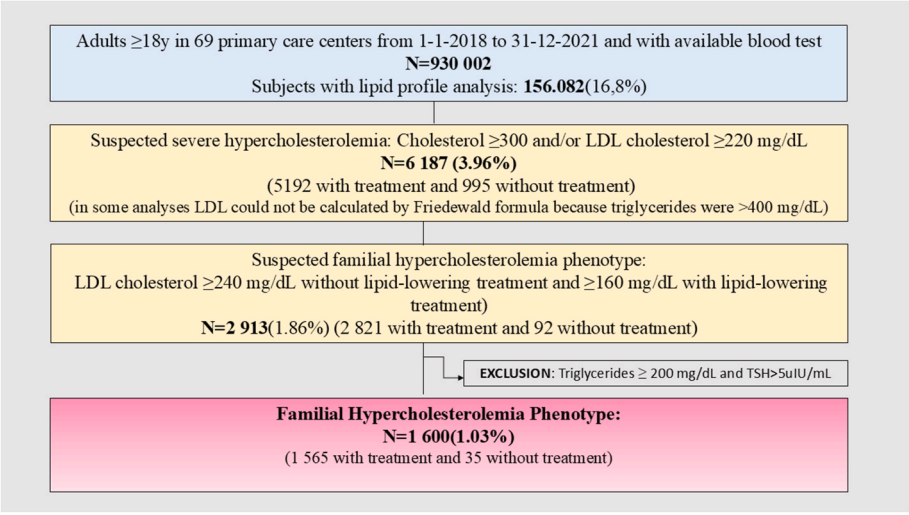

Fig. 1. Step-by-step process for patient inclusion in the study.

Table 1
Clinical characteristics of the populations with severe hypercholesterolemia, according to Familial hypercholesterolemia clinical phenotype status.

	Overall	Without FH phenotype	With FH phenotype	p-value
N, %	6187	4587 (74.1)	1600 (25.9)	<0.001
Men, N, %	1971 (31.9)	1534 (33.4)	437 (27.3)	<0.001
Age, years	59.9 (14.1)	59.6 (14.2)	60.7 (13.8)	0.065
Conventional SBP, mmHg	131.0 (12.8)	132.1 (17.1)	127.8 (18.1)	0.439
Conventional DBP, mmHg	77.0 (11.2)	77.5 (11.9)	77.1 (11.2)	0.212
Body mass index, kg/m^2	28.9 (6.8)	29.3 (7.1)	26.8 (5.7)	0.547
Diabetes mellitus, %	590 (9.5)	518 (11.3)	72 (4.5)	<0.001
Hypertension, %	2259 (36.5)	1726 (37.6)	533 (33,3)	0.002
Hypercholesterolemia[a], %	5095 (82.4)	3664 (79.9)	1431 (89.4)	<0.001
Obesity (BMI>30), %	666 (10.8)	529 (11.5)	137 (8.6)	<0.001
Glucose (mg/dL)	97.1 (24.2)	99.0 (26.2)	91.7 (21.9)	<0,001
Cholesterol (mg/dL)	333 (47.1)	345.1 (40,1)	300.9 (40,9)	0.141
LDL-C (mg/dL)	177.4 (41.7)	164.1 (40.1)	212.7 (42.8)	<0.001
HDL-C (mg/dL)	62.6 (22.4)	60.8 (23,0)	67.7 (18,7)	0.055
Triglycerides (mg/dL)	194.7 (29.1)	219.9 (31.2)	124.0 (27.2)	<0.001
non-HDL-C	239.4 (40.7)	241.7 (41.0)	233.2 (41.0)	0.269
e-GFR (mL/min/ 1,73m2)	90.1 (16.4)	90.5 (16.8)	88.8 (15.3)	0.113
TSH (nIU/mL)	3.9 (0.9)	4.5 (1.1)	2.3 (1.1)	<0.001
Previous ASCVD, %	611 (9.9)	474 (10.3)	137 (8.6)	0.041
Lipid lowering therapy, %	5176 (83.9)	3614 (79.0)	1562 (97.6)	<0.001

Values are mean +standard deviation (SD) or n (%). *p < 0,05. SBP: systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.; e-GFR, estimated glomerular filtration rate; TSH, Thyroid stimulating hormone; ASCVD, atherosclerotic cardiovascular disease. P values refer to FH vs non-FH comparisons.
[a] Previous diagnosis of hypercholesterolemia in clinical records.

of treatment according to FH clinical phenotype. 5176 individuals were receiving any LLT, and 1562 of them had the FH phenotype (30.2 %). Only 28.6 % of the whole population, and 28.4 % of the FH phenotype group, were receiving high- or very-high-intensity LLT. A lower proportion of women were treated with high/very-high LLT (26.0 % vs 34.1 % in men; 25.3 % vs 36.6 % in those with FH clinical phenotype, p < 0.001).

Supplemental Table S1 shows LDL-Cholesterol levels according to LLT intensity and sex. Mean LDL-C levels varied across treatment intensity categories, with higher values observed among those receiving more intensive therapy. Notably, LDL-C levels remained above target in all groups. Statistically significant sex differences in LDL-C levels were observed in patients receiving low- and moderate-intensity lipid-lowering therapy. Among individuals treated with low and moderate-intensity therapy, men had significantly higher mean LDL-C level than women (p = 0.005). No significant differences were found in the high- or very high-intensity treatment groups (p > 0.05). Overall, LDL-C levels were significantly higher in men than in women across the full sample (178.7 vs. 170.9 mg/dL; p = 0.0015).

Supplemental Table S2 shows the sensitivity analysis using LDL-C thresholds corresponding to the 95th and 99th percentiles confirmed the consistency of the FH clinical phenotype across definitions. A cutoff of 95th percentile identified 1432 individuals (0.92 % of the population), while using 99th percentile 964 individuals (0.62 %) were identified. Across all definitions, the clinical profile of those classified as FH phenotype remained similar, with mean age around 60 years, a predominance of women, and comparable rates of diabetes, hypertension, and obesity. Mean LDL-C levels increased with stricter thresholds, as expected. However, the proportion of patients receiving high- or very high-intensity LLT remained low (ranging from 28.4 % to 30.5 %).

Fig. 3 shows the distribution of LDL-C levels in adults treated with LLT according to FH clinical phenotype. As expected, all the FH clinical phenotype subjects had LDL-C levels above 130 mg/dL vs 60.4 % in the group without FH clinical phenotype. Pre-specified LDL-C goals of <70 mg/dL, 70–99 mg/dL, and 100–129 mg/dL were achieved by none of the patients with FH, and by 3.7 %,/13.8 %, and/22.1 % of non-FH subjects.

Multivariable logistic regression analysis identified several factors independently associated with the FH clinical phenotype. In the overall population, women had a significantly higher likelihood of presenting the FH phenotype compared to men (OR: 1.414; 95 % CI: 1.233–1.622; p < 0.001). Increasing age was inversely associated with the FH phenotype (OR: 0.995; 95 % CI: 0.990–1.000; p = 0.050). However, this association lost statistical significance after adjusting for LDL-C levels. Diabetes (OR: 0.357; 95 % CI: 0.275–0.962; p < 0.001), hypertension (OR: 0.824; 95 % CI: 0.730–0.930; p = 0.002), and obesity (OR: 0.771; 95 % CI: 0.627–0.947; p = 0.013) were all inversely associated with the FH phenotype. LLT showed the strongest positive association with the FH phenotype (OR: 14.470; 95 % CI: 10.215–20.498; p < 0.001).

When stratified by sex, the inverse association with age remained significant in women (OR: 0.992; 95 % CI: 0.986–0.998; p = 0.008), but not in men (p = 0.852). The inverse associations with diabetes and hypertension were consistent across both sexes.

Obesity was only significantly associated with the FH phenotype in women (OR: 0.749; 95 % CI: 0.588–0.987; p = 0.019), but not in men (p = 0.319). Notably, the association between LLT and FH phenotype was stronger in women (OR: 23.064; 95 % CI: 14.264–37.293; p < 0.001) than in men (OR: 6.178; 95 % CI: 5.721–10.270; p < 0.001), suggesting potential differences in treatment patterns or intensity by sex." (Table 4 overall, 4A men,4B women).

The multivariable logistic regression models across the 90th, 95th, and 99th LDL-C percentiles showed consistent patterns of association with the FH clinical phenotype.

(Supplemental Table S3**).** In all models, younger age, female sex (in the 90th and 95th percentile models), absence of diabetes, hypertension, and obesity, and the use of LLT were significantly associated with a higher likelihood of FH clinical phenotype.

The strength of association for LLT increased with stricter LDL-C thresholds, Sex was no longer a significant predictor in the 99th percentile model, suggesting a more balanced distribution at the highest LDL-C levels.

4. Discussion

This large study in primary care identifies identified an FH clinical phenotype prevalence of 1.03 %, with one in four of these cases classified as severe hypercholesterolemia. These findings highlight the burden of FH clinical phenotype in primary care and reinforce the need for improved detection and management strategies. Although 98 % are receiving LLT, most of them (two thirds) are with low/moderate intensity medications despite this population is at high or very high cardiovascular risk. Moreover, LDL-C goals were not achieved in any of them.

Our study also showed that none of the patients with an FH clinical phenotype had a formal FH diagnosis documented in their medical records. This finding underscores the challenge of FH recognition in primary care and suggests that many cases may remain undiagnosed or misclassified.

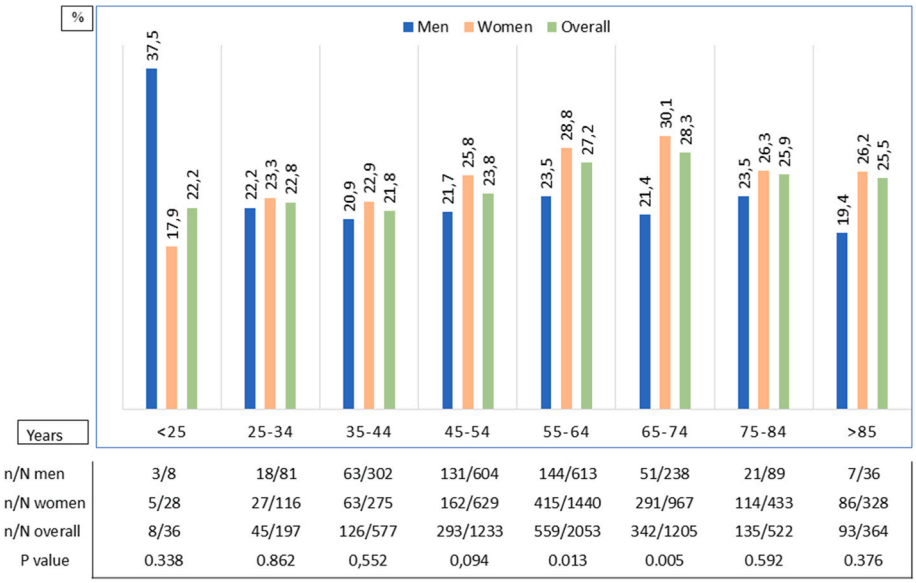

Fig. 2. Percentage of familial hypercholesterolemia phenotype according to sex and age groups
n: number of cases; N: sample size; p: p-value of the difference in percentages (Men–Women).

Table 2
Clinical characteristics of the populations with Familial hypercholesterolemia clinical phenotype according to sex.

	Overall	Men	Woman	p-value
N, %	1600	437 (27.3)	1163 (72.7)	<0.001
Age, years	60.7 (13.8)	54.8 (12.3)	62.9 (13.7)	<0.001
Conventional SBP, mmHg	127.8 (18.1)	129.1 (17.8)	127.4 (18.2)	0.177
Conventional DBP, mmHg	77.1 (11.2)	79.3 (12.3)	76.4 (10.7)	<0.001
Body mass index, kg/m^2	26.9 (5.7)	27.3 (5.2)	26.8 (5.7)	0.746
Diabetes mellitus, %	72 (4.5)	25 (5.7)	47 (4.0)	0.149
Hypertension, %	533 (33,3)	135 (30.9)	398 (34,2)	0.208
*Hypercholesterolemia, %	1431 (89.4)	386 (88.3)	1045 (89.9)	0.377
Obesity (BMI>30), %	137 (8.6)	36 (8.2)	101 (8.7)	0.776
Glucose (mg/dL)	91.7 (21.9)	95.2 (27.0)	90.5 (27,1)	<0,001
Cholesterol (mg/dL)	300.9 (40.9)	301.0 (47,6)	300.9 (38,2)	0.955
LDL-C (mg/dL)	212.7 (42.1)	222.2 (53.9)	209.2 (37.4)	<0.001
HDL-C (mg/dL)	67.7 (18.7)	58.4 (15,6)	71.2 (18,6)	<0.001
Triglycerides (mg/dL)	124.0 (27.2)	132.1 (28.1)	120.9 (27.1)	<0.001
non-HDL-C	233.2 (41.0)	242.6 (46.4)	229.7 (38.2)	<0.001
e-GFR (mL/min/1,73m2)	88.8 (15.3)	93.3 (14.4)	87.1 (15.3)	<0.001
TSH (nIU/mL)	2.3 (1.1)	2.1 (0.9)	2.3 (1.1)	<0.001
Previous ASCVD, %	137 (8.6)	38 (8.7)	99 (8.5)	0.907
Lipid lowering therapy, %	1562 (97.6)	420 (96.1)	1142 (98.5)	0.004

Values are mean +standard deviation (SD) or n (%). *p < 0,05. SBP: systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol. LDL-C, low-density lipoprotein cholesterol; e-GFR, estimated glomerular filtration rate; TSH, Thyroid stimulating hormone; ASCVD, atherosclerotic cardiovascular disease. *Previous diagnosis of hypercholesterolemia in clinical records.

Table 3
Lipid-lowering drug treatment according to its intensity, sex, and presence of familial hypercholesterolemia clinical phenotype.

	Overall, on treatment	Without FH phenotype	With FH phenotype	P value
	N = 5174	N = 3613 (69.8 %)	N = 1561 (30.2 %)	
Intensity				
Low N, (%)	604 (11.7)	384 (10.6)	220 (14.1)	
Men	137 (8.2)	95 (7.6)	42 (10.0)	
Women	467 (13.3)	289 (12.2)	178 (15.6)	<0.001
Moderate N, (%)	2797 (54.0)	1936 (53.6)	861 (55.1)	
Men	814 (48.9)	601 (48.2)	213 (50.8)	
Women	1983 (56.5)	1333 (56.4)	648 (56.7)	<0.001
High N, (%)	1204 (23.3)	837 (23.2)	367 (23.5)	
Men	456 (27.4)	333 (26.7)	123 (29.4)	
Women	748 (21.3)	504 (21.3)	244 (21.3)	<0.001
Very high N, (%)	276 (5.3)	200 (5.5)	76 (4.9)	
Men	112 (6.7)	82 (6.6)	30 (7.2)	
Women	164 (4.7)	118 (5.0)	46 (4.0)	<0.001
***Others (%)**	293 (5.7)	256 (7.1)	37 (2.4)	
Men	144 (8.6)	134 (10.8)	10 (2.4)	
Women	149 (4.2)	122 (5.2)	27 (2.4)	<0.001

P values refer to male vs female comparisons.
Intensity and class of lipid-lowering treatment. Reference 25.
Low: Simvastatin 10 mg, Pravastatin 10–20 mg, Lovastatin 10–20 mg, Fluvastatin 40 mg, Pitavastatin 1 mg, Ezetimibe 10 mg as monotherapy.
Moderate: Atorvastatin 10–20 mg, Rosuvastatin 5–10 mg, Simvastatin 20–40 mg, Pravastatin 40 mg, Lovastatin 40 mg, Fluvastatin 80 mg as monotherapy and combinations of ezetimibe 10 mg with Pitavastatin 2–4 mg, Simvastatin 10 mg, Pravastatin 20 mg, Lovastatin 20 mg, Fluvastatin 40 mg, Pitavastatin 1 mg.
High: Atorvastatin 40–80 mg, Rosuvastatin 20–40 mg monotherapy and combinations of ezetimibe 10 mg with Atorvastatin 10–20 mg, Rosuvastatin 5–10 mg, Simvastatin 20–40 mg, Pravastatin 40 mg, Lovastatin 40 mg, Fluvastatin 80 mg, Pitavastatin 2–4 mg.
Very high: Atorvastatin 40–80 + Ezetimibe 10 Rosuvastatin 20–40 + Ezetimibe 10. No IPCSK9 data available-.
*Others: Fibrates, resins, omega 3-.

The high proportion of participants on LLT suggests that our study primarily captures prevalent cases rather than incident cases of hypercholesterolemia. This selection may influence treatment patterns and LDL-C control rates, as untreated individuals or those with undiagnosed FH may be underrepresented in our cohort.

The FH clinical phenotype was significantly more frequent in women than in men, and women were also more likely to receive LLT. Despite the higher frequency of the FH clinical phenotype and greater overall use of LLT among women, a smaller proportion received high- or very high-intensity therapy (25.3 % vs 36.6 %). In addition, "despite escalating treatment intensity, mean LDL-C levels remained elevated across

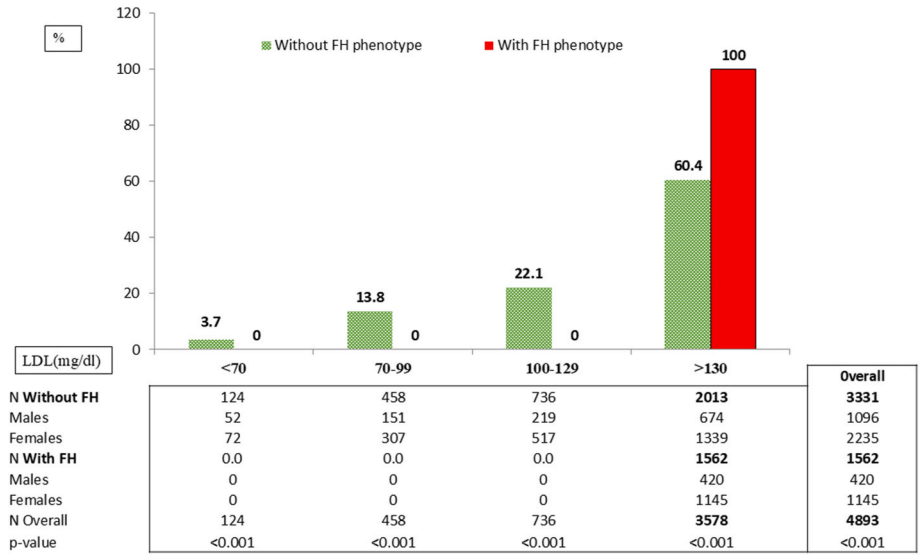

Fig. 3. Distribution of levels of LDL-c* in subjects treated with lipid-lowering drugs according to familial hypercholesterolemia (FH) phenotype. LDL-C, low-density lipoprotein cholesterol. P values refer to FH vs non-FH *If available and the total sample if it was a HF phenotype since the LDL criterion is present in the definition with 97.6 % on LLT).

Table 4
Multivariable logistic regression analysis general (4 overall) and stratified by sex (4A men) (4B women) of factors associated with Familial hypercholesterolemia clinical phenotype.

4.OVERALL	Wald	β[a]	OR (Exp (β))[b]	p[c]
Age	3.85	−0.005	0.995 (0.990–1.000)	0.050
Sex (women vs men)	24.46	0.346	1.414 (1.233–1.622)	0.000
Diabetes (yes/no)	60.64	−1.031	0.357 (0.275–0.962)	0.000
Hypertension (yes/no)	9.81	−0.193	0.824 (0.730–0.930)	0.002
Obesity (yes/no)	6.15	−0.261	0.771 (0.627–0.947)	0.013
Lipid lowering therapy (yes/no)	226.18	2.672	14.470 (10.215–20.498)	0.000
4A. MEN				
Age	0.03	−0.001	1.001 (0.991–1.011)	0.852
Diabetes (yes/no)	22.10	−1.056	0.348 (0.224–0.540)	0.000
Hypertension (yes/no)	5.16	−0.256	0.744 (0.621–0.965)	0.023
Obesity (yes/no)	0.99	−0.199	0.820 (0.555–1.212)	0.319
Lipid lowering therapy (yes/no)	49.53	1.821	6.178(5.721–10.270)	0.000
4B. WOMEN				
Age	6.97	−0.008	0.992 (0.986–0.998)	0.008
Diabetes (yes/no)	38.91	−1.025	0.359 (0.260–0.495)	0.000
Hypertension (yes/no)	4.61	−0.158	0.854 (0.738–0.987)	0.033
Obesity (yes/no)	5.53	−0.289	0.749 (0.588–0.987)	0.019
Lipid lowering therapy (yes/no)	163.82	3.138	23.064 (14.264–37.293)	0.000

[a] β coefficient.
[b] Odds ratio (95 % confidence interval).
[c] *p*: *p*-value of Wald test with one degree of freedom.

all groups, suggesting potential issues with treatment adequacy, adherence, or the need for combination therapies. These results reinforce the importance of individualized treatment strategies.

Despite being undertreated, men had higher LDL-C levels. This may reflect differences in treatment response, adherence, or baseline LDL-C burden. On the other hand, in the high- and very high-intensity treatment groups, LDL-C levels between men and women were similar, suggesting a potential equalizing effect of more intensive therapy. These results underscore the importance of considering sex in the evaluation of treatment adequacy and in strategies to optimize lipid control.

Other factors contributing to FH clinical phenotype were a younger age and the use of LLT. On the other hand, the presence of diabetes, hypertension, or obesity were associated with a lower likelihood of having FH clinical phenotype. Just as an illustration, extrapolating these prevalence figures in absolute numbers, the FH clinical phenotype could represent around 9703 adults with this condition, referred to the total population in Madrid community (province) with tests available in the period examined; that is, based on the population of Madrid with healthcare card in 2021 (6,794,867 subjects), with 85 % being older than 18 years (5,775,636 subjects), and 16.8 % with tests available. The identification of these almost 10,000 adults could help to design strategies to establish a correct diagnosis of FH [29,30].

Undertreatment and failure to achieve recommended treatment LDL-C goals may be explained in part to underdiagnosis since primary-care professionals are not familiar with the characteristics and importance of diagnosis of FH and it can be confused with other types of hyperlipidemias Another reason may be the lack of knowledge of the importance of treatment and achievement of therapeutic goals in FH, which could cause therapeutic inertia with lack of initiation or intensification of treatment. The identification of an FH clinical phenotype in primary care does not imply that these patients have received a formal FH diagnosis by their healthcare provider. This situation is consistent with previous studies in which the degree of control is clearly suboptimal [31,32]. Some previous studies have suggested that women are less likely to receive high-intensity medication than men [31]. Moreover, women in the study were older and had a higher proportion of the FH clinical phenotype. They also received more LLT, yet the proportion of cardiovascular disease was similar between sexes. This may be explained by the larger representation of women in the sample, possibly due to their greater tendency to seek healthcare. These findings support the data provided in the Spanish SAFEHEART registry that reports that female participants were, on average, treated less intensively [6]. On the other hand, the lower presence of diabetes, obesity and hypertension in FH phenotype, highlights a fact that differentiates it from other hypercholesterolemia such as polygenic and combined familial hypercholesterolemia, which have a greater relationship with the risk factors described [33]. Associated variables could play a role in refining future FH detection algorithms, improving identification strategies in primary care settings by incorporating clinical characteristics such as family history of hypercholesterolemia beyond LDL-C levels alone [11,15]. Our multivariable analysis showed that women were more likely to present the FH clinical phenotype compared to men. Additionally, age was inversely associated with FH only in women, suggesting earlier detection in

younger females. Use of LLT was strongly associated with the FH phenotype, particularly in women, who showed higher odds of receiving treatment than men. However, this did not translate into better LDL-C control, highlighting possible treatment disparities and the need for sex-specific management strategies in FH.

In the initial multivariable model, age showed an inverse association with the FH clinical phenotype. However, this association lost statistical significance after adjusting for LDL-C levels. This finding suggests that the effect of age on the likelihood of presenting the FH phenotype may be mediated, at least in part, by LDL-C levels—given that LDL-C is a more direct marker of the condition. Younger patients may have higher untreated LDL-C levels, which could explain the initial association with age. Also, the consistency of associations across LDL-C thresholds in the multivariable models reinforces the robustness of the FH clinical phenotype. Younger age, absence of metabolic comorbidities, and use of LLT were consistently associated with the phenotype. Notably, female sex was a predictor only at lower thresholds, suggesting that sex differences may diminish at more extreme LDL-C levels.

Our results indicate that LDL-C control of patients with FH phenotype in primary care remains suboptimal compared to the nationwide SAFEHEART registry, where FH (in which) patients are managed in specialized lipid clinics or in selected primary care units, Population in our study had higher LDL-C levels and lower use of high-intensity LLT [6,26]. This suggests a gap in FH management at the primary care level, likely due to differences in diagnosis, treatment optimization.

The relatively low prevalence of prior ASCVD (8.6 %) despite a high LLT treatment rate (97 %) suggests that LLT strategies in primary care may be effectively contributing to cardiovascular risk reduction although it is insufficient. Also, this lower prevalence may have several potential explanations to be considered, including survivor bias, differences in risk factor control, and unmeasured confounders such as genetic susceptibility or protective lifestyle factors.

There are studies on systematic detection of FH cases through automated registries and case-screening methods in clinical practice that can favor the identification and detection of FH. These studies conclude that massive data screening and patient profiling are effective tools and easily applicable in clinical practice for the detection of patients with FH [10–14,14,15,29,34,35]. However, there is no evidence to help determine which method is the most appropriate for the systematic identification of FH in non-specialist settings [36].

A 2021 Cochrane review reports that there is no evidence from randomized controlled trials or controlled non-randomized studies of interventions to determine the most appropriate healthcare strategy to systematically identify possible or definite clinical FH in primary care or other community settings. [3,17]. However, it seems reasonable to think that the combination of early detection through screening of computerized medical history records or laboratory records, or other data sources, combined with the application of the usual algorithms used in clinical practice, can improve the detection of FH index-cases that must be confirmed by genetic diagnosis or at least by clinical phenotyping. Some studies concluded that the incorporation of automated case-finding from electronic medical records with clinical follow-up in primary care can enhance FH identification and the subsequent incorporation of genotyping showed the best detection rate [10,11,37]. In addition, recent studies have confirmed the limited utility of the Dutch Lipid Clinic Network Score (DLCNS) in routine clinical practice, mainly due to the frequent unavailability of key information required for its calculation. As a result, a single off-treatment LDL-C threshold of 190 mg/dL has been proposed to improve the identification of index cases, given its greater practicality and reliability under real world conditions [38].

Our study indicates that FH clinical phenotype patients were undertreated. To improve physician awareness and treatment adherence, strategies such as electronic health records (EHR)-based decision-support tools, structured CME programs, national screening initiatives, and enhanced collaboration between primary care, lipid specialists, the Spanish Familial Hypercholesterolemia Foundation and patient organization should be considered.

While our study identifies FH based on clinical criteria, genetic confirmation through genotyping is essential to definitively diagnose FH and facilitate familial cascade screening in affected families. The integration of genetic screening into primary care strategies could improve early detection and optimize family-based interventions.

4.1. Strength of the study

This study has several strengths. First, it is based on a large, real-world primary care dataset, allowing for a comprehensive assessment of FH phenotype prevalence and lipid management in routine clinical practice. Second, the use of electronic health records (EHRs) enables an objective evaluation of LDL-C levels and treatment patterns, minimizing recall bias. Third, the study provides valuable insights into sex-based differences in LLT utilization, highlighting potential disparities in FH management. The sensitivity analysis using LDL-C thresholds corresponding to the 95th and 99th percentiles confirmed the robustness of the FH clinical phenotype. Lastly, by identifying clinical characteristics associated with FH phenotype, our findings contribute to the development of future FH screening strategies in primary care.

4.2. Limitations

Several limitations of the present study need to be mentioned. Given that the analysis was cross-sectional, no causal conclusions can be drawn from the multivariate analysis; and the direction of the associations cannot be warranted. In our study the availability of lipid panels in only 16.8 % of the study population introduces a potential selection bias, as individuals undergoing lipid testing are more likely to have pre-existing cardiovascular risk factors or a history of dyslipidemia. This could lead to an overestimation of the prevalence of FH phenotype.

A potential selection bias may have been introduced due to our inclusion criteria, which required LDL-C levels of ≥240 mg/dL (or ≥160 mg/dL under LLT). As a result, well-treated FH clinical phenotype patients with LDL-C levels below 160 mg/dL were not included, potentially leading to an overestimation of under treatment rates. Also, our inclusion criteria ***(90th percentile within our study sample) lacks genetic validation, and other studies have suggested using a more stringent 99th percentile cutoff to improve specificity*** [10] but given that we were looking for clinical characteristics in the primary care setting, it seemed more reasonable to have a larger sample size. ***While a higher threshold could reduce the inclusion of individuals with polygenic hypercholesterolemia, it may also lead to underdiagnoses of FH cases affected by LLR or phenotypic variability.***

An additional limitation of our study is the lack of data on secondary causes of hypercholesterolemia and measurements of adherence to diet and LLT could not be evaluated, as these variables were not available in the electronic health records. The overrepresentation of women in both the overall population and among subjects with FH clinical phenotype in primary care may have influenced the observed prevalence estimates. Women's increased healthcare engagement may lead to higher detection rates.

In addition, as the mean age of our cohort is around 60 years, it is likely that a significant proportion of female participants were post-menopausal, contributing in part to the observed sex differences. However, menopausal status was not recorded in our database, preventing a direct analysis of its impact.

An additional limitation of our study is that population was derived from individuals with available lipid panels, which may have selectively included patients receiving active lipid management in primary care. This could contribute to the observed high LLT treatment rate and low ASCVD prevalence. Additionally, patients with prior ASCVD may be more likely to be managed in specialized settings, potentially leading to their underrepresentation in our study cohort.

Another additional limitation of our study is the lack of genetic testing and detailed family history assessment, which limits our ability to confirm true FH cases. This approach may have led to the inclusion of individuals with polygenic hypercholesterolemia rather than monogenic FH.

4.3. Conclusions

The frequency of FH phenotype in a large primary-care setting was one in 100 patients, with moderate undertreatment but, importantly, of insufficient intensity, and therapeutic goals were not achieved at all. Women with an FH phenotype were more likely to receive treatment, but less likely than men, to be prescribed high- or very high-intensity LLT. The main independent factors directly associated with FH phenotype were female sex and lipid-lowering treatment, and age, diabetes, hypertension, and obesity were inversely associated with FH.

Identification by computerized records may allow the establishment of cardiovascular preventive strategies and earlier detection. These findings can serve to detect FH patients in primary care and might help inform and implement clinical and public health strategies for increase FH detection.

CRediT authorship contribution statement

Teresa Gijón Conde: Conceptualization, Methodology, wrote the manuscript and performed the analysis. Jose R Banegas: Methodology, wrote the manuscript, Reviewing and Editing. Carolina Farre: Methodology and Reviewing Rodrigo Alonso: Reviewing and Editing. Pedro Mata: Reviewing and Editing. All authors discussed the results and provided critical feedback and helped shape the final manuscript.

Financing

No.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to express our sincere gratitude to the Technical Support Unit of the Madrid Health Service (SERMAS)

To the Technical Support Unit of the Madrid Health Service (SERMAS)

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2025.120400.

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