Long-term sex differences in atherosclerotic cardiovascular disease in individuals with heterozygous familial hypercholesterolaemia in Spain: a study using data from SAFEHEART, a nationwide, multicentre, prospective cohort study

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Summary

Background Sex differences in atherosclerotic cardiovascular disease (ASCVD) in familial hypercholesterolaemia have been reported but are not fully established. We aimed to assess sex differences in the risk of ASCVD and life-time burden of ASCVD in patients with heterozygous familial hypercholesterolaemia.

Methods SAFEHEART is a nationwide, multicentre, long-term prospective cohort study conducted in 25 tertiary care hospitals and one regional hospital in Spain. Participants in the SAFEHEART study aged 18 years or older with genetically confirmed familial hypercholesterolaemia were included in our analysis. Data were obtained between Jan 26, 2004, and Nov 30, 2022. ASCVD and age at onset were documented at enrolment and at follow-up. Our aim was to investigate the differences by sex in the risk and burden of ASCVD in patients with heterozygous familial hypercholesterolaemia, over the study follow-up and over the life course. The SAFEHEART study is registered with ClinicalTrials.gov, NCT02693548.

Findings Of the 5262 participants in SAFEHEART at the time of analysis, 3506 (1898 [54·1%] female and 1608 [45·9%] male participants) met the inclusion criteria and were included in the current study. Mean age was 46·1 years (SD 15·5) and median follow-up was 10·3 years (IQR 6·4–13·0). Mean on-treatment LDL-cholesterol at follow-up was 3·1 mmol/L (SD 1·4) in females and 3·0 mmol/L (1·5) in males. LDL-cholesterol reductions over time were similar in both sexes (1·39 mmol/L [95% CI 1·30–1·47] absolute reduction in females *vs* 1·39 mmol/L [1·29–1·48] in males; p=0·98). At enrolment, 130 (6·8%) females and 304 (18·9%) males (p<0·0001) had cardiovascular disease. During follow-up, 134 (7·1%) females and 222 (13·8%) males (p<0·0001) had incident cardiovascular events. Median age at first ASCVD event (mostly due to coronary artery disease) was 61·6 years (IQR 50·0–71·4) in females and 50·6 years (42·0–58·6) in males (p<0·0001). The adjusted hazard ratio for ASCVD in males compared with females during follow-up was 1·90 (95% CI 1·49–2·42) and for cardiovascular death was 1·74 (1·11–2·73). Major adverse cardiovascular disease event (MACE)-free survival from birth was lower in males than females (hazard ratio 3·52 [95% CI 2·98–4·16]; p<0·0001). Median MACE-free survival time was 90·1 years (95% CI 86·5–not estimable) in females and 71·0 years (69·2–74·6) in males. The age at which 25% of female participants have had a MACE event was 74·9 years, this figure was 55·5 years in male participants.

Interpretation Our findings suggest that the burden and risk of ASCVD are markedly lower in females than males with familial hypercholesterolaemia. The impact of sex needs to be considered to improve risk stratification and personalised management in patients with heterozygous familial hypercholesterolaemia.

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Introduction

Heterozygous familial hypercholesterolaemia, a prevalent genetic condition in the general population (estimated at approximately 1 in 300 individuals),[1] is a co-dominant and highly penetrant monogenic disease caused by pathogenic variants in genes involved in the

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Research in context

Evidence before this study

We reviewed the literature in PubMed from Jan 1, 1990, to Oct 20, 2023, using the terms "familial hypercholesterolaemia" AND "atherosclerotic cardiovascular disease" AND "women", with no language restrictions. 241 articles were found and they showed that sex is a key factor that might account partly for variations in atherosclerotic cardiovascular disease (ASCVD). However, sex differences in ASCVD risk in individuals with familial hypercholesterolaemia remain unclear, with a scarcity of robust, long-term, prospective data. Familial hypercholesterolaemia is a frequent co-dominant monogenic condition characterised by marked elevation of plasma LDL-cholesterol concentrations from birth and, consequently, a substantially increased risk of premature ASCVD. However, there is a considerable heterogeneity in the time of onset, severity, and progression of ASCVD among individuals with familial hypercholesterolaemia, even in individuals carrying the same causative gene variant. A key factor that might account partly for these variations is sex. Sex differences in ASCVD risk and burden among patients might be attributed to biology and to the management of familial hypercholesterolaemia, such as less intensive use of lipid lowering medication in women.

Added value of this study

This study provides an integrated approach to assessing sex differences in the risk and lifetime burden of ASCVD in patients with heterozygous familial hypercholesterolaemia using data from the SAFEHEART registry, a contemporary, multicentre, long-term, prospective cohort study. Our results show important sex differences in the burden and risk of ASCVD in individuals with familial hypercholesterolaemia. Female participants were less intensively treated than male participants, but both had similar LDL-cholesterol concentrations and reductions in LDL-cholesterol at follow-up. Female participants had a longer ASCVD-free survival time and lower risk of ASCVD and cardiovascular death than male participants, with the occurrence of events delayed by approximately 10 years. To our knowledge, this is the largest follow-up study of a genetically diagnosed familial hypercholesterolaemia population with the highest proportion of female participants that addresses the impact of sex in the long-term burden of ASCVD. These findings might help establish the need to consider the impact of sex in risk prediction and models of care in individuals with familial hypercholesterolaemia.

Implications of all the available evidence

Early identification and treatment of familial hypercholesterolaemia needs to be improved to prevent ASCVD resulting from life-long high LDL-cholesterol. Greater use of high-intensity combination therapy is required to avoid ASCVD. Sex differences in the detection and management of familial hypercholesterolaemia have implications for models of care. Sex differences in the occurrence of first cardiovascular events in individuals with familial hypercholesterolaemia were also reported in the pre-statin era, with descriptions that the onset of myocardial infarction occurred in the third decade of life in men and in the fourth decade in women. The SAFEHEART data show that the appearance of the first ASCVD event is delayed by three decades of life in both male and female participants compared with the pre-statin era. This delay possibly relates to better management of patients with familial hypercholesterolaemia, including the use of ezetimibe and PCSK9 inhibitors. Our findings also show that early and effective management of familial hypercholesterolaemia might reduce lifetime cardiovascular risk to a level similar to that of the general population, in both men and women.

hepatic clearance of LDL-cholesterol from blood, namely in *LDLR*, *APOB*, and *PCSK9*.[2] Consequently, familial hypercholesterolaemia results in a marked elevation of plasma LDL-cholesterol concentrations from birth and a substantially increased risk of premature atherosclerotic cardiovascular disease (ASCVD), especially coronary artery disease.[3] However, there is a considerable heterogeneity in the time of onset, severity, and progression of ASCVD among individuals with familial hypercholesterolaemia, even in individuals carrying the same causative gene variant.[4] A key factor that might account partly for these variations is sex; however, there is no consensus on sex differences in ASCVD risk associated with familial hypercholesterolaemia.[5–8]

Using data from the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART),[9] we aimed to investigate the differences by sex in the burden of ASCVD in patients with heterozygous familial hypercholesterolaemia, over the study follow-up and over the life course.

Methods

Study design and participants

SAFEHEART is a contemporary, real-world practice, nationwide, multicentre, long-term prospective cohort study conducted in 25 tertiary care hospitals and one regional hospital in Spain. The enrolment of patients began on Jan 26, 2004, and is currently active.

Participants aged 18 years or older with a genetically confirmed diagnosis of heterozygous familial hypercholesterolaemia were included in our analysis.[9] Details of the methods used to create the registry are published elsewhere.[10] Data included in the present study were obtained between Jan 26, 2004, and Nov 30, 2022. DNA was isolated from whole blood and the genetic diagnosis and molecular classification of familial hypercholesterolaemia were performed as previously described.[11] Genetically confirmed familial hypercholesterolaemia was defined as the presence of a pathogenic or likely pathogenic variant in any of *LDLR*, *APOB*, or *PCSK9*. Patients with bi-allelic familial

hypercholesterolaemia (either simple homozygous or compound and double heterozygotes) were excluded. The selection flow diagram is in appendix 2 (p 2). Sex data were self reported (male, female, or other).

The SAFEHEART study was approved by the Clinical Research Ethics Committee of the University Hospital Fundación Jiménez Díaz, Madrid, Spain, and by the local ethics committees of the participating centres. All participants gave written informed consent. The SAFEHEART study is registered with ClinicalTrials.gov, NCT02693548.

Procedures

Participants were contacted annually by telephone by trained staff using a standardised protocol (including review of medical records or death certificates required to be provided by the participants [or relatives where appropriate]). Patients were managed as per routine clinical practice and based on international guidelines recommendations at the time.[3,5] Cardiovascular events during follow-up were reviewed and adjudicated by an independent committee at the coordinating centre.

Demographic and clinical characteristics and fasting plasma lipid and lipoprotein profiles were defined and measured as previously described.[12] Cardiovascular risk at enrolment in the SAFEHEART study was estimated according to the SAFEHEART-Risk Equation.[9] A participant was considered to be on maximum lipid-lowering medication if the treatment was theoretically able to decrease LDL-cholesterol 50% or more from baseline (lipid-lowering medications included simvastatin 20, 40, or 80 mg/day in combination with ezetimibe 10 mg/day, pravastatin 40 mg/day in combination with ezetimibe 10 mg/day, fluvastatin 80 mg/day in combination with ezetimibe 10 mg/day, atorvastatin 40 or 80 mg/day with or without combination with ezetimibe 10 mg/day, atorvastatin 10 or 20 mg/day in combination with ezetimibe 10 mg/day, rosuvastatin 20 or 40 mg/day with or without combination with ezetimibe 10 mg/day, rosuvastatin 10 mg/day in combination with ezetimibe 10 mg/day, or pitavastatin 4 mg/day in combination with ezetimibe 10 mg/day). Premature family history of ASCVD was defined as the occurrence of a first ASCVD event before 60 years of age in a first-degree relative.

Outcomes

Prevalent ASCVD at enrolment (ie, ASCVD present at the time of inclusion in the SAFEHEART cohort) was defined as having a personal history of any of the following events at enrolment: non-fatal myocardial infarction, non-fatal ischaemic stroke, percutaneous or surgical coronary revascularisation, peripheral artery revascularisation, or aortic valve replacement due to severe aortic valve stenosis according to current guidelines.[13] The age of participants at the time of onset of each prevalent ASCVD event was recorded.

	Overall cohort (n=3506)	Female participants (n=1898)	Male participants (n=1608)	p value female *vs* male
Female sex	1898 (54·1%)	..	..	..
Age, years	46·1 (15·5)	47·1 (15·8)	44·9 (15·0)	<0·0001
Hypertension	531 (15·1%)	292 (15·4%)	239 (14·9%)	0·67
Type 2 diabetes	161 (4·6%)	78 (4·1%)	83 (5·2%)	0·14
Smoking status	..	..	..	<0·0001
Never smoker	1741 (49·7%)	1107 (58·3%)	634 (39·4%)	..
Former smoker	879 (25·1%)	362 (19·1%)	517 (32·2%)	..
Current smoker	886 (25·3%)	429 (22·6%)	457 (28·4%)	..
BMI, kg/m²	26·5 (4·9)	26·0 (5·3)	27·1 (4·3)	<0·0001
BMI category, kg/m²	..	..	..	<0·0001
<18·5	65 (1·9%)	54 (2·8%)	11 (0·7%)	..
18·5 to <25·0	1425 (40·6%)	893 (47·0%)	532 (33·1%)	..
25·0 to <30·0	1261 (36·0%)	559 (29·5%)	702 (43·7%)	..
≥30·0	755 (21·5%)	392 (20·7%)	363 (22·6%)	..
Xanthomas	447 (12·7%)	244 (12·9%)	203 (12·6%)	0·84

Data are n (%) or mean (SD).

Table 1: **Characteristics of participants at enrolment in the study, overall and stratified by sex**

Incident ASCVD events over the study follow-up were defined as the first occurrence of any ASCVD event (event definition as for prevalent ASCVD) from inclusion in the cohort to the end of follow-up (Nov 30, 2022), in patients with or without prevalent ASCVD at enrolment. Assessment of occurrence of ASCVD events during life (from birth to end of study follow-up), named as life-long major adverse cardiovascular disease events (MACE), included events occurring before enrolment and those incident events occurring after enrolment.

Statistical analysis

Descriptive results were reported as absolute and relative frequencies for categorical variables and as mean (SD) or median (IQR), as appropriate, for quantitative variables. Changes in plasma lipid and lipoprotein concentrations at follow-up were reported as mean (95% CI). Between-group differences were assessed using the χ^2 test for categorical variables, and Student's *t* test or Mann–Whitney *U* test for quantitative variables, as appropriate. Paired-samples Student's *t* test or Wilcoxon signed rank test were used to compare changes in lipid concentrations from inclusion to follow-up.

Kaplan–Meier curves were used to assess MACE-free survival curves from birth to end of follow-up. Log-rank test was estimated. Hazard ratios (HRs) with 95% CIs for incident ASCVD events were estimated using Cox-regression, unadjusted and subsequently adjusted by allele type (null *vs* defective), age, cardiovascular risk factors (hypertension, type 2 diabetes, smoking, and BMI), lipid fractions (LDL-cholesterol, HDL-cholesterol, triglycerides, and lipoprotein(a) [<50 mg/dL or ≥50 mg/dL]), lipid-lowering medication (no therapy *vs* monotherapy *vs* combination therapy [two or more];

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See **Online** for appendix 2

	Overall cohort (n=3506*)	Female participants (n=1898)	Male participants (n=1608)	Female *vs* male mean difference (95% CI)	p value female *vs* male
At inclusion in the SAFEHEART cohort					
Total cholesterol, mmol/L					
Overall	6·3 (1·7)	6·4 (1·7)	6·2 (1·8)	0·3 (0·2 to 0·4)	<0·0001
Among patients not on lipid-lowering medication	7·5 (2·0)	7·6 (2·0)	7·4 (2·0)	0·2 (−0·1 to 0·5)	0·24
Among patients taking lipid-lowering medication	6·0 (1·6)	6·2 (1·5)	5·9 (1·6)	0·3 (0·2 to 0·4)	<0·0001
LDL-cholesterol, mmol/L					
Overall	4·5 (1·6)	4·5 (1·6)	4·4 (1·7)	0·1 (0·0 to 0·3)	0·0067
Among patients not on lipid-lowering medication	5·6 (1·9)	5·6 (1·9)	5·6 (1·9)	0·0 (−0·3 to 0·3)	0·94
Among patients taking lipid-lowering medication	4·2 (1·5)	4·3 (1·4)	4·1 (1·5)	0·2 (0·1 to 0·3)	0·0029
Non-HDL-cholesterol, mmol/L					
Overall	5·0 (1·7)	5·0 (1·7)	5·0 (1·8)	0·1 (−0·1 to 0·2)	0·34
Among patients not on lipid-lowering medication	6·1 (2·0)	6·1 (2·0)	6·2 (2·1)	−0·1 (−0·4 to 0·2)	0·59
Among patients taking lipid-lowering medication	4·7 (1·5)	4·8 (1·5)	4·7 (1·6)	0·1 (−0·0 to 0·2)	0·23
HDL-cholesterol, mmol/L					
Overall	1·3 (0·3)	1·4 (0·3)	1·2 (0·3)	0·2 (0·2 to 0·3)	<0·0001
Among patients not on lipid-lowering medication	1·4 (0·4)	1·5 (0·4)	1·2 (0·3)	0·2 (0·2 to 0·3)	<0·0001
Among patients taking lipid-lowering medication	1·3 (0·3)	1·4 (0·3)	1·2 (0·3)	0·2 (0·2 to 0·2)	<0·0001
Triglycerides, mmol/L					
Overall	1·0 (0·7–1·3)	0·9 (0·7–1·2)	1·0 (0·8–1·5)	−0·2 (−0·2 to −0·2)	<0·0001
Among patients not on lipid-lowering medication	0·9 (0·7–1·3)	0·9 (0·7–1·2)	1·0 (0·8–1·5)	−0·2 (−0·3 to −0·1)	<0·0001
Among patients taking lipid-lowering medication	1·0 (0·7–1·3)	0·9 (0·7–1·2)	1·1 (0·8–1·5)	−0·2 (−0·2 to −0·2)	<0·0001
Lipoprotein(a), mg/dL					
Overall	23·5 (10·0–56·0)	24·0 (9·9–56·7)	23·1 (10·0–55·1)	2·5 (−0·3 to 5·3)	0·71
Among patients not on lipid-lowering medication	18·6 (7·9–45·9)	17·8 (7·6–47·5)	19·8 (8·6–45·5)	1·0 (−5·0 to 7·0)	0·74
Among patients taking lipid-lowering medication	24·3 (10·0–59·5)	24·8 (10·0–59·7)	23·6 (10·0–59·0)	2·9 (−0·2 to 6·0)	0·51
At the end of follow-up					
Total cholesterol, mmol/L	5·0 (1·5)	5·2 (1·5)	4·8 (1·5)	0·3 (0·2 to 0·4)	<0·0001
LDL-cholesterol, mmol/L	3·0 (1·4)	3·1 (1·4)	3·0 (1·5)	0·1 (0·1 to 0·2)	0·0028
Non-HDL-cholesterol, mmol/L	3·6 (1·5)	3·7 (1·4)	3·6 (1·5)	0·1 (0·0 to 0·2)	0·11
HDL-cholesterol, mmol/L	1·4 (0·4)	1·5 (0·4)	1·3 (0·3)	0·3 (0·2 to 0·3)	<0·0001
Triglycerides, mmol/L	1·0 (0·8–1·4)	1·0 (0·7–1·3)	1·1 (0·8–1·5)	−0·2 (−0·2 to −0·1)	<0·0001

Data are mean (SD) or median (IQR) unless otherwise specified. *Overall, n=3506 participants, except for lipoprotein(a): n=3398, and for non-HDL-cholesterol, HDL-cholesterol, and triglycerides all at the end of follow-up: n=3505.

Table 2: **Lipid and lipoprotein concentrations at study inclusion and end of follow-up, overall and stratified by sex**

drugs considered were statins, ezetimibe, and PCSK9 inhibitors), and family history of premature cardiovascular disease. Statistical analyses were performed using SPSS (version 26) and R (version 4.2.3, through RStudio version 2023.03.0). Kaplan–Meier curves were obtained with Stata (version 12.0). Tests were two-sided and statistical significance was defined as p<0·05.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 5262 participants in SAFEHEART at the time of analysis, 3506 (1898 [54·1%] female and 1608 [45·9%] male participants) met the inclusion criteria and were included in the current study. Median follow-up was 10·3 years (IQR 6·4–13·0; 10·3 years [6·6–12·9] for females and 10·5 years [6·2–13·0] for males). Overall, 1910 (54·5%) participants had 10 or more years of follow-up. An *LDLR* variant was detected in 3283 (93·6%) participants (1757 [92·6%] females and 1526 [94·9%] males); *APOB* variants were present in 205 (5·8%) participants (127 [6·7%] females and 78 [4·9%] males); and *PCSK9* variants were identified in 18 (0·5%) participants (14 [0·7%] females and four [0·2%] males).

All participants included in the study were White. On average, females were significantly older than males (mean age 47·1 years [SD 15·8] for females *vs* 44·9 years [15·0] for males; p<0·0001; table 1). 676 (35·6%) females and 631 (39·2%) males were aged 18 to younger than 40 years at enrolment; 1456 (76·7%) females and 1338 (83·2%) males were younger than 60 years at

enrolment. Males were more frequently smokers or former smokers than females and had a significantly higher BMI (26·0 kg/m² [SD 5·3] for females *vs* 27·1 kg/m² [4·3] for males; p<0·0001). There were no sex differences in the prevalence of hypertension or type 2 diabetes (table 1). 736 (38·8%) females were menopausal at inclusion and 1237 (65·1%) were menopausal at the end of the follow-up.

At enrolment, 2885 (82·3%) participants were on lipid-lowering medication, with no differences by sex (1553 [81·8%] females *vs* 1332 [82·8%] males; p=0·43); however, more male than female participants were receiving high-intensity statins (728 [46·9%] females *vs* 714 [53·6%] males) or combination therapy (690 [44·4%] females *vs* 755 [56·7%] males; p=0·0009 for both). At the end of follow-up, 3112 (88·7%) participants were on statins (1673 [88·1%] females *vs* 1439 [89·4%] males; p=0·20), 2335 (66·6%) were on ezetimibe (1227 [64·6%] females *vs* 1108 [68·9%] males; p=0·0078), and 769 (21·9%) were on PCSK9 inhibitors (354 [18·7%] females *vs* 415 [25·8%] males; p<0·0001). 2608 (74·4%) participants were on maximum lipid-lowering medication (1373 [72·3%] females *vs* 1235 [76·8%] males; p=0·0027). At the end of follow-up, median time on treatment with statins was 19 years (IQR 14–26; 20 years [14–27] for females *vs* 19 years [13–25] for males; p=0·073), with ezetimibe was 11 years (6–16; 11 years [6–16] for females *vs* 12 years [7–17] for males; p<0·0001), and for PCSK9 inhibitors was 4 years (2–5; 3 years [2–5] for females *vs* 4 years [2–5] for males; p=0·60).

Plasma lipid and lipoprotein concentrations at enrolment and at the end of follow-up are shown in table 2. Absolute and relative changes in lipid concentrations from enrolment to end of follow-up are in appendix 2 (p 4). At enrolment, 27 (1·4%) females and 39 (2·4%) males had an LDL-cholesterol concentration less than 1·8 mmol/L (<70 mg/dL); 994 (52·4%) females and 787 (48·9%) males had an LDL-cholesterol concentration 4·1 mmol/L or more (≥160 mg/dL). LDL-cholesterol reduction during follow-up was similar in both sexes: 1·39 mmol/L (95% CI 1·30–1·47) absolute reduction in females and 1·39 mmol/L (1·29–1·48) in males (p=0·98), which corresponded to relative reductions of 24·9% (95% CI 23·2–26·5) in females and 25·4% (23·6–27·2) in males (p=0·66). At the last visit, 622 (17·7%) participants had an LDL-cholesterol concentration less than 1·8 mmol/L (276 [14·5%] females and 346 [21·5%] males). At the last visit, 378 (10·8%) participants had an LDL-cholesterol concentration less than 1·4 mmol/L (<55 mg/dL; 154 [8·1%] females and 224 [13·9%] males). At enrolment, a similar proportion of female and male participants had a lipoprotein(a) concentration of 50 mg/dL or more (516 [28·1%] of 1838 females and 434 [27·8%] of 1560 males with known values; p=0·87).

The prevalence of ASCVD at enrolment was lower in females (130 [6·8%]) than in males (304 [18·9%]; p<0·0001), mostly due to coronary artery disease (table 3). The prevalence of severe aortic valve disease or aortic valve replacement were similar between male and female participants.

The incidence of ASCVD during follow-up was lower in females (134 [7·1%]; 0·70 events per 100 person-years) than in males (222 [13·8%]; 1·39 events per 100 person-years; p<0·0001), mostly due to coronary artery disease events (table 4). After adjusting for age, the risk of incident ASCVD was greater in males than in females (HR 2·53 [95% CI 2·03–3·13]; figure 1A). The risk did not change after additionally adjusting for the type of allelic defect (null *vs* defective). After further adjustment for cardiovascular risk factors (hypertension, type 2 diabetes, smoking, and BMI), lipid fractions (LDL-cholesterol, HDL-cholesterol, triglycerides, and lipoprotein(a) <50 mg/dL or ≥50 mg/dL), previous ASCVD,

	Overall cohort (n=3506)	Female participants (n=1898)	Male participants (n=1608)	p value female *vs* male
Any cardiovascular disease	434 (12·4%)	130 (6·8%)	304 (18·9%)	<0·0001
Coronary artery disease	415 (11·8%)	119 (6·3%)	296 (18·4%)	<0·0001
Angina	231 (6·6%)	77 (4·1%)	154 (9·6%)	<0·0001
Myocardial infarction	227 (6·5%)	51 (2·7%)	176 (10·9%)	<0·0001
Coronary revascularisation	289 (8·2%)	65 (3·4%)	224 (13·9%)	<0·0001
Cerebrovascular disease	57 (1·6%)	29 (1·5%)	28 (1·7%)	0·62
Stroke	27 (0·8%)	16 (0·8%)	11 (0·7%)	0·59
Transient ischaemic attacks	32 (0·9%)	16 (0·8%)	16 (1·0%)	0·64
Carotid artery disease	20 (0·6%)	7 (0·4%)	13 (0·8%)	0·085
Peripheral artery disease (aorta or limb arteries)	51 (1·5%)	19 (1·0%)	32 (2·0%)	0·015
Aortic valve replacement	14 (0·4%)	6 (0·3%)	8 (0·5%)	0·40

Data are n (%): absolute and relative frequencies. Angina includes both chronic or stable angina and unstable angina.

Table 3: **Prevalent cardiovascular disease at enrolment in the SAFEHEART cohort, overall and stratified by sex**

	Overall cohort (n=3506)	Female participants (n=1898)	Male participants (n=1608)	p value female *vs* male
First cardiovascular events (fatal or non-fatal)	356 (10·2%)	134 (7·1%)	222 (13·8%)	<0·0001
Non-fatal cardiovascular events	285 (8·1%)	110 (5·8%)	175 (10·9%)	<0·0001
Non-fatal acute coronary syndrome	113 (3·2%)	33 (1·7%)	80 (5·0%)	<0·0001
Coronary revascularisation	84 (2·4%)	34 (1·8%)	50 (3·1%)	0·011
Non-fatal stroke	35 (1·0%)	17 (0·9%)	18 (1·1%)	0·51
Peripheral artery revascularisation	26 (0·7%)	10 (0·5%)	16 (1·0%)	0·11
Aortic valve replacement	27 (0·8%)	16 (0·8%)	11 (0·7%)	0·59
Fatal cardiovascular events	100 (2·9%)	41 (2·2%)	59 (3·7%)	0·0075
Fatal acute coronary syndrome	23 (0·7%)	2 (0·1%)	21 (1·3%)	<0·0001
Fatal stroke	12 (0·3%)	8 (0·4%)	4 (0·2%)	0·38
Cardiovascular death	65 (1·9%)	31 (1·6%)	34 (2·1%)	0·29

Data are n (%): absolute and relative frequencies. Acute coronary syndrome includes unstable angina and myocardial infarction.

Table 4: **Incident cardiovascular events during study follow-up, overall and stratified by sex**

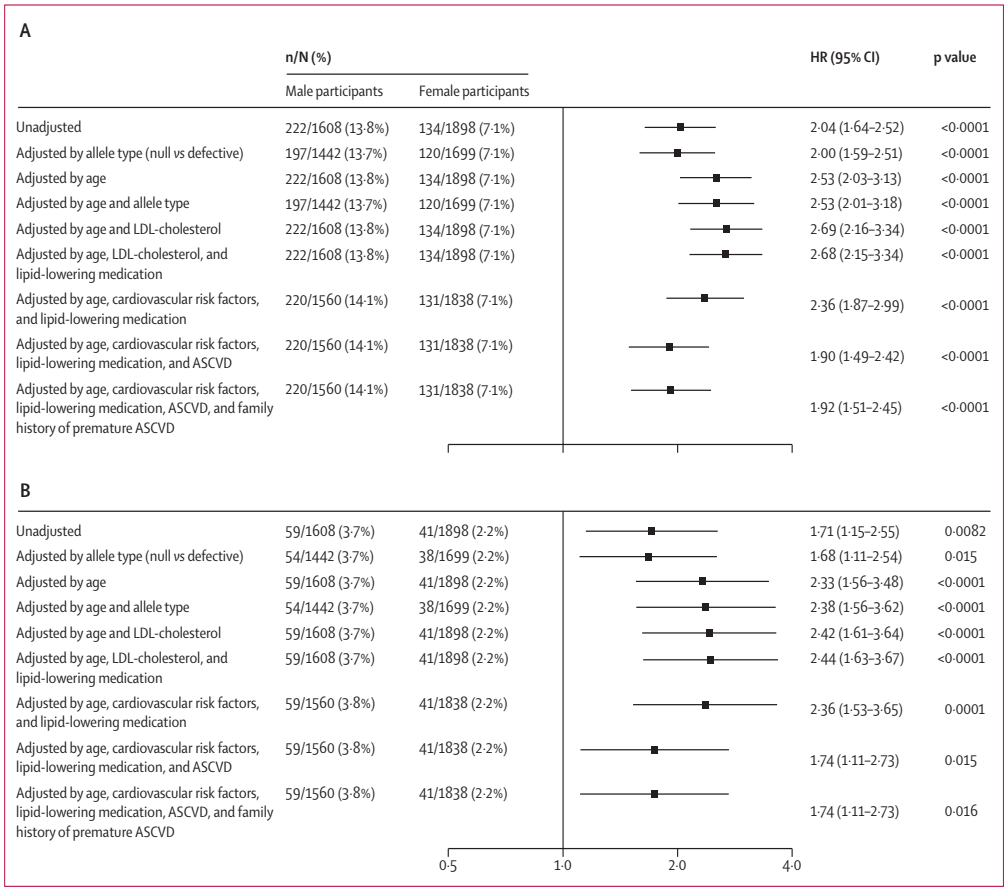

Figure 1: **Risk of cardiovascular events in male participants compared with female participants with heterozygous familial hypercholesterolaemia from inclusion in the SAFEHEART cohort to the end of follow-up**

(A) Risk of incident ASCVD events. (B) Risk of cardiovascular death. Cardiovascular risk factors include hypertension, type 2 diabetes, smoking, high BMI, LDL-cholesterol, HDL-cholesterol, triglycerides, and lipoprotein(a) <50 mg/dL or ≥50 mg/dL. Lipid-lowering medication refers to no therapy versus monotherapy versus combination therapy (two or more); drugs considered are statins, ezetimibe, and PCSK9 inhibitors. Including an interaction term between LDL-cholesterol and lipid-lowering medication was not significant in all models. Overall, there were 3506 participants and 356 cardiovascular events; the model in which lipoprotein(a) is included had 3398 participants and 351 cardiovascular events. ASCVD=atherosclerotic cardiovascular disease. HR=hazard ratio.

and lipid-lowering medication, the risk was still significantly higher in males versus females (HR 1·90 [95% CI 1·49–2·42]; figure 1A). The median age at which a first ASCVD event occurred was 53·1 years (IQR 43·7–64·7), with significantly earlier presentation in males (50·6 years [42·0–58·6]) than in females (61·6 years [50·0–71·4]; p<0·0001).

After adjusting by age, the risk of cardiovascular death during the study was greater in males than in females (HR 2·33 [95% CI 1·56–3·48]; figure 1B). The risk was still significantly greater in males than in females after full adjustment for cardiovascular risk factors, lipid fractions, previous ASCVD, and lipid-lowering medication (HR 1·74 [1·11–2·73]).

MACE-free survival time was shorter for males than for females (HR 3·52 [95% CI 2·98–4·16]; log-rank test p<0·0001; figure 2), with the curves starting to separate at approximately 35 years of age. Median survival time free of MACE was approximately 20 years longer in females (90·1 years [95% CI 86·5–not estimable]) than males (71·0 years [69·2–74·6]). The age at which 25% of female participants had had a MACE event was 74·9 years; this figure was 55·5 years in male participants. Results from analysis accounting for non-cardiovascular deaths as competing risks were consistent with these findings (appendix 2 p 3).

Discussion

To our knowledge, this is the largest follow-up study (with the highest proportion of female participants) of a population with genetically diagnosed familial hypercholesterolaemia that addresses the impact of sex on the long-term burden of ASCVD. The results suggest that there are important sex differences in cardiovascular risk over the long term, with a markedly lower burden of ASCVD in females than males, independent of age,

standard cardiovascular risk factors, previous ASCVD, lipid-lowering medication, and family history of premature ASCVD. Even after adjustment for all these factors, the risk of ASCVD remained around 90% higher in male than female participants. Additionally, ASCVD events occurred approximately 10 years later in female than male participants, with sex differences starting to be apparent as early as age 35–40 years. At age 55·5 years, 25% of male participants had had an ASCVD event. However, this figure was not reached until age 74·9 years in female participants.

ASCVD is the leading cause of morbidity and mortality in females, but risk in females is frequently under-recognised.[14] Women have been traditionally under-represented in cardiovascular clinical trials, limiting the ability to develop sex-specific strategies and their implementation in clinical guidelines.[15] Although there are differences in the risk for ASCVD between males and females in the general population, the divergence in this risk and its determinants in individuals with familial hypercholesterolaemia are yet to be fully elucidated.[16] Sex differences in the ASCVD burden over life in individuals with familial hypercholesterolaemia might be attributed to both biological differences and sex disparities in the management of the condition. Sex-specific biological differences might include, among others, hormonal effects on metabolism and endothelial function, and higher HDL-cholesterol in females. Sex disparities in management of the condition include women being diagnosed later and receiving lipid-lowering medication at a lower intensity than men,[7,8,17] which was also shown in our study. Sex disparities related to underdiagnosis in females (ie, missed diagnosis of cardiovascular disease), as females often present with different symptoms than males, might also explain the greater difference found for non-fatal cardiovascular events between female and male participants (5·8% *vs* 10·9%) than for fatal events (2·2% *vs* 3·7%). We also showed that some other risk factors, such as smoking and higher BMI, were less prevalent in female participants than male participants, and that HDL-cholesterol was higher in females. All these factors might contribute to sex differences in cardiovascular risk in individuals with familial hypercholesterolaemia, although they probably do not explain in full the variation in risk over time found in our study in which additional sex-related biological factors might play a role.

LDL-cholesterol is a cumulative and causal risk factor for ASCVD[18] and its lifetime burden determines the risk of ASCVD. Patients with familial hypercholesterolaemia have life-long high LDL-cholesterol from birth if untreated, and some reports also suggest that LDL-cholesterol concentrations are already slightly higher in girls than boys.[16,19,20] On the other hand, resilient familial hypercholesterolaemia is a recent concept defined as patients with familial hypercholesterolaemia who do not develop premature ASCVD or do so late in life, resembling a similar risk and life expectancy to the general population.[21] We previously reported that resilient familial hypercholesterolaemia is more frequent in women than in men,[21] which is supported by the findings of the present study. Additionally, the operational definition of severe familial hypercholesterolaemia by the International Atherosclerosis Society includes male sex as one of the high-risk features to consider.[22] The results of our study support this consideration of male sex, along with other factors, to define severe familial hypercholesterolaemia. Moreover, the characteristics of the female participants who ultimately developed a MACE event were similar to those already associated with resilient familial hypercholesterolaemia, including older age, higher prevalence of cardiovascular risk factors, and a worse lipid profile.[21]

Some previous studies have suggested that women are less likely to receive high-intensity statins or combination therapy than men.[8,17] Moreover, the proportion of patients with familial hypercholesterolaemia who are on lipid-lowering medication and have below guideline-recommended LDL-cholesterol concentrations is lower in women than men.[17,23] These disparities are already present in childhood and adolescence.[20] In our study, a similar proportion of female and male participants were on statins and had received such medications for a similar duration of time; however, a lower proportion of females were treated with high-intensity statins, with combination therapy, or were on maximum lipid-lowering medication. Despite this observation, there were no clinically meaningful sex differences in LDL-cholesterol concentrations at enrolment or at follow-up, and both groups had similar reductions in LDL-cholesterol over time. A previous study from SAFEHEART showed that management of patients early in childhood and adolescence can improve their LDL-cholesterol concentrations,[24] which might translate to lower rates of ASCVD events over 20 years.[25] In our

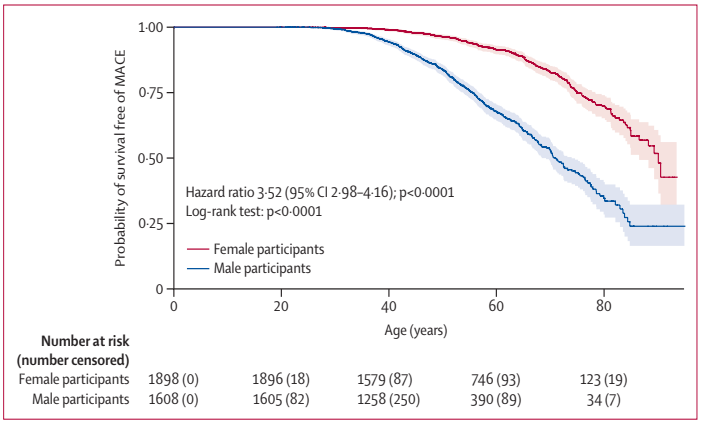

Figure 2: **Kaplan–Meier curves for survival free of MACE from birth to end of follow-up in female and male participants with familial hypercholesterolaemia**
MACE=major adverse cardiovascular events.

study, female and male participants had similar LDL-cholesterol values at enrolment and follow-up, despite females being less intensively treated with lipid-lowering medication. We think that factors such as LDL-cholesterol concentration and response to lipid-lowering medication might play a key role in the interpretation of this finding.

Sex differences in the occurrence of first cardiovascular event in individuals with familial hypercholesterolaemia were also previously reported in the pre-statin era.[26] Mabuchi and colleagues[26] reported an overall incidence of myocardial infarction over life of about 22% in men and 10% in women with heterozygous familial hypercholesterolaemia, with the occurrence of myocardial infarction first noted in the third and fourth decades of life for men and women, respectively.[26] These event rates are higher than those found in our present analysis. We also showed in a previous study that the onset of ASCVD was earlier in men than women, and age at onset was earlier for both men and women (45·5 years for men and 52·0 years for women) than in the present study.[27] The differences between older analyses and the present study might be related to the more optimal management of patients with familial hypercholesterolaemia. Previous and current results from SAFEHEART suggest that the occurrence of the first ASCVD event is delayed in life when compared with the pre-statin era in both males and females. Our findings suggest that early and effective management of familial hypercholesterolaemia might reduce lifetime cardiovascular risk to become similar to the general population in both male and female individuals, although this point should be further investigated.

The results of our study suggest that cardiovascular events in individuals with familial hypercholesterolaemia are mostly due to coronary artery disease and that sex differences also apply to coronary artery disease, in agreement with previous studies.[16,25,26] A retrospective cohort study from the Simon-Broome registry showed that men with familial hypercholesterolaemia had higher prevalence of previous coronary artery disease and were diagnosed and commenced taking lipid-lowering medication earlier than women.[7] However, excess cardiovascular morbidity compared with the general population without familial hypercholesterolaemia was higher in women than men, especially at a young age.[7]

The present study shows the risk of incident events over a prospective long follow-up, confirming sex differences in the incidence of both non-fatal events and, more strikingly, of fatal events. Male participants had almost 3-times higher incidence of non-fatal acute coronary syndrome events, and although the absolute numbers of fatal events were much lower in both sexes, incidence of fatal acute coronary syndrome events was 13 times higher in males than in females. One contributor to this difference might be that females with familial hypercholesterolaemia might have been exposed to less coronary total plaque burden over life.[26] In a previous report from SAFEHEART, the presence of coronary atherosclerotic disease assessed through coronary CT angiography was almost absent in patients with familial hypercholesterolaemia younger than 30 years, especially in women.[28] Moreover, female sex was associated with a lower coronary atherosclerotic burden overall.[28,29] A study published in 2023, conducted not specifically in patients with familial hypercholesterolaemia but in general patients who underwent clinically indicated coronary CT angiography, found that the development of coronary atherosclerosis was approximately 12 years later in women than men.[30]

Our data reflect contemporary real-world practice and follow-up of patients with familial hypercholesterolaemia. The inclusion of only patients with genetically defined familial hypercholesterolaemia avoids including false positive cases with a clinical phenotype resembling that of familial hypercholesterolaemia but that are caused by other lipid disorders such as polygenic hypercholesterolaemia or combined familial hypercholesterolaemia. Some limitations should also be acknowledged. Participants were from a European, White, population. More than half the participants in SAFEHEART were followed up in specialised lipid clinics, where management of familial hypercholesterolaemia might be more optimal (and with access to more novel drugs) than in other settings. Potential survival bias before enrolment in the study should be considered (patients who have died before they could have been captured by the registry, potentially having the most severe phenotypes). Finally, although it is expected that most participants from this cohort might die from cardiovascular causes, we cannot rule out competing risks with other non-cardiovascular causes of death.

In summary, there are important sex differences in the burden and risk of ASCVD in individuals with familial hypercholesterolaemia, especially of coronary artery disease. Although female participants were, on average, treated less intensively and had similar LDL-cholesterol concentrations and similar reductions in LDL-cholesterol during follow-up than male participants, females had longer ASCVD-free survival time and lower ASCVD-adjusted risk than males, with the occurrence of events delayed by more than a decade. These findings might help inform and implement clinical and public health strategies and underscore the need to account for sex when developing risk stratification and personalised care for patients with heterozygous familial hypercholesterolaemia.

Contributors

LPdI, AJV-V, RAl, JLD-D: conceptualisation, data curation, investigation, formal analysis, methodology, supervision, validation, visualisation of data, writing of the original draft, and reviewing and editing the manuscript. GFW: conceptualisation, data curation, investigation, methodology, supervision, validation, visualisation of data, writing of the

original draft, and reviewing and editing the manuscript. OM-G, Rag, RAr, MM, and MJR: conceptualisation, investigation, supervision, validation, visualisation of data, and reviewing and editing the manuscript. RA-O: data curation, formal analysis, methodology, validation, visualisation of data, writing of the original draft, and reviewing and editing the manuscript. PÁ-B, DM, JMC, PG-B, MC, AM, JFSM-T, CF, MAB, MD, RdA, AMH, AG-E, TP, FF, LB: conceptualisation, investigation, supervision, validation, visualisation of data, and reviewing and editing the manuscript. PM: conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, visualisation of data, writing of the original draft, and reviewing and editing the manuscript. LPdI, AJV-V, RA-O, and PM accessed and verified the data. All authors had access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

AJV-V reports current or past participation as an investigator in research grants to Imperial College London from Pfizer, Amgen, MSD, Sanofi-Aventis, Daiichi Sankyo, and Regeneron; consultancy fees from Bayer and Regeneron; and honoraria for lecturers from Ferrer, European Atherosclerosis Society, and USA National Lipid Association; all outside the submitted work. GFW reports current or past participation in research grants to his institution; contracts or grants from Amgen, Novartis, Arrowhead, Silence Therapeutics, and the National Health and Medical Research Council (Australia); consulting fees from Esperion, CSL Sequiris, and Novartis; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen and Novartis; and support for attending meetings or travel from Arrowhead and Silence Therapeutics. All other authors declare no competing interests.

Data sharing

Data collected in the SAFEHEART registry is kept by the Spanish Familial Hypercholesterolaemia Foundation and cannot be shared with third parties owing to registry governance and participants' current informed consents preventing this. Qualified researchers may approach the Foundation for collaboration in research studies that align with the mission and aims of the Foundation, and the request may be considered on the basis of scientific merits, resources available, and fulfillment of ethical and governance requirements. For more information contact fhfsecretaria@colesterolfamiliar.org.

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References

1 Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Circulation* 2020; **141:** 1742–59.

2 Watts GF, Gidding SS, Hegele RA, et al. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. *Nat Rev Cardiol* 2023; **20:** 845–69.

3 Watts GF, Gidding SS, Mata P, et al. Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. *Nat Rev Cardiol* 2020; **17:** 360–77.

4 Mata P, Alonso R, Pérez de Isla L. Atherosclerotic cardiovascular disease risk assessment in familial hypercholesterolemia: does one size fit all? *Curr Opin Lipidol* 2018; **29:** 445–52.

5 Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; **41:** 111–88.

6 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. *J Am Coll Cardiol* 2019; **73:** e285–350.

7 Iyen B, Qureshi N, Weng S, et al. Sex differences in cardiovascular morbidity associated with familial hypercholesterolaemia: a retrospective cohort study of the UK Simon Broome register linked to national hospital records. *Atherosclerosis* 2020; **315:** 131–37.

8 Amrock SM, Duell PB, Knickelbine T, et al. Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry. *Atherosclerosis* 2017; **267:** 19–26.

9 Pérez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation* 2017; **135:** 2133–44.

10 Mata N, Alonso R, Badimón L, et al. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). *Lipids Health Dis* 2011; **10:** 94.

11 Bourbon M, Alves AC, Alonso R, et al. Mutational analysis and genotype–phenotype relation in familial hypercholesterolemia: the SAFEHEART registry. *Atherosclerosis* 2017; **262:** 8–13.

12 Ellis KL, Pérez de Isla L, Alonso R, Fuentes F, Watts GF, Mata P. Value of measuring lipoprotein(a) during cascade testing for familial hypercholesterolemia. *J Am Coll Cardiol* 2019; **73:** 1029–39.

13 Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022; **43:** 561–632.

14 Vogel B, Acevedo M, Appelman Y, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet* 2021; **397:** 2385–438.

15 Mas-Llado C, Gonzalez-Del-Hoyo M, Siquier-Padilla J, et al. Representativeness in randomised clinical trials supporting acute coronary syndrome guidelines. *Eur Heart J Qual Care Clin Outcomes* 2023; **9:** 796–805.

16 Roeters van Lennep JE, Tokgözoğlu LS, Badimon L, et al. Women, lipids, and atherosclerotic cardiovascular disease: a call to action from the European Atherosclerosis Society. *Eur Heart J* 2023; **44:** 4157–73. .

17 Vallejo-Vaz AJ, Stevens CAT, Lyons ARM, et al. Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet* 2021; **398:** 1713–25.

18 Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017; **38:** 2459–72.

19 Holven KB, Narverud I, van Lennep JR, et al. Sex differences in cholesterol levels from birth to 19 years of age may lead to increased cholesterol burden in females with FH. *J Clin Lipidol* 2018; **12:** 748–55.e2.

20 Dharmayat KI, Vallejo-Vaz AJ, Stevens CAT, et al. Familial hypercholesterolaemia in children and adolescents from 48 countries: a cross-sectional study. *Lancet* 2024; **403:** 55–66.

21 Pérez de Isla L, Watts GF, Muñiz-Grijalvo O, et al. A resilient type of familial hypercholesterolaemia: case-control follow-up of genetically characterized older patients in the SAFEHEART cohort. *Eur J Prev Cardiol* 2022; **29:** 795–801.

22 Santos RD, Gidding SS, Hegele RA, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. *Lancet Diabetes Endocrinol* 2016; **4:** 850–61.

23 Ryzhaya N, Cermakova L, Trinder M, et al. Sex differences in the presentation, treatment, and outcome of patients with familial hypercholesterolemia. *J Am Heart Assoc* 2021; **10:** e019286.

24 Saltijeral A, Pérez de Isla L, Alonso R, et al. Attainment of LDL cholesterol treatment goals in children and adolescents with familial hypercholesterolemia. The SAFEHEART follow-up registry. *Rev Española Cardiol (English Ed)* 2017; **70**: 444–50.

25 Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med* 2019; **381:** 1547–56.

26 Mabuchi H, Koizumi J, Shimizu M, Takeda R. Development of coronary heart disease in familial hypercholesterolemia. *Circulation* 1989; **79:** 225–32.

27 Pérez de Isla L, Alonso R, Mata N, et al. Coronary heart disease, peripheral arterial disease, and stroke in familial hypercholesterolaemia: insights from the SAFEHEART registry (Spanish Familial Hypercholesterolaemia Cohort Study). *Arterioscler Thromb Vasc Biol* 2016; **36:** 2004–10.

28 Pérez de Isla L, Alonso R, Gómez de Diego JJ, et al. Coronary plaque burden, plaque characterization and their prognostic implications in familial hypercholesterolemia: a computed tomographic angiography study. *Atherosclerosis* 2021; **317:** 52–58.

29 Pérez de Isla L, Alonso R, Muñiz-Grijalvo O, et al. Coronary computed tomographic angiography findings and their therapeutic implications in asymptomatic patients with familial hypercholesterolemia. Lessons from the SAFEHEART study. *J Clin Lipidol* 2018; **12:** 948–57.

30 van Rosendael SE, Bax AM, Lin FY, et al. Sex and age-specific interactions of coronary atherosclerotic plaque onset and prognosis from coronary computed tomography. *Eur Heart J Cardiovasc Imaging* 2023; **24:** 1180–89.