Sex Differences in Diagnosis, Treatment, and Cardiovascular Outcomes in Homozygous Familial Hypercholesterolemia

Article · February 2024

DOI: 10.1001/jamacardio.2023.5597

19 authors, including:

Tycho R Tromp
Amsterdam University Medical Center
43 PUBLICATIONS **498** CITATIONS

SEE PROFILE

Mutaz Alkhnifsawi
University of Al-Qadisiyah
14 PUBLICATIONS **327** CITATIONS

SEE PROFILE

Dirk Blom
University of Cape Town
250 PUBLICATIONS **11,947** CITATIONS

SEE PROFILE

Krzysztof Chlebus
University of Gdańsk
71 PUBLICATIONS **1,242** CITATIONS

SEE PROFILE

JAMA Cardiology | Original Investigation

Sex Differences in Diagnosis, Treatment, and Cardiovascular Outcomes in Homozygous Familial Hypercholesterolemia

Janneke W. C. M. Mulder, MD; Tycho R. Tromp, MD, PhD; Mutaz Al-Khnifsawi, MD; Dirk J. Blom, MD, PhD; Krysztof Chlebus, MD, PhD; Marina Cuchel, MD, PhD; Laura D'Erasmo, MD, PhD; Antonio Gallo, MD, PhD; G. Kees Hovingh, MD, PhD; Ngoc Thanh Kim, MD; Jiang Long, MD, PhD; Frederick J. Raal, MD, PhD; Willemijn A. M. Schonck, MD; Handrean Soran, MD; Thanh-Huong Truong, MD, PhD; Eric Boersma, PhD; Jeanine E. Roeters van Lennep, MD, PhD; for the Homozygous Familial Hypercholesterolemia International Clinical Collaborators

IMPORTANCE Homozygous familial hypercholesterolemia (HoFH) is a rare genetic condition characterized by extremely increased low-density lipoprotein (LDL) cholesterol levels and premature atherosclerotic cardiovascular disease (ASCVD). Heterozygous familial hypercholesterolemia (HeFH) is more common than HoFH, and women with HeFH are diagnosed later and undertreated compared to men; it is unknown whether these sex differences also apply to HoFH.

OBJECTIVE To investigate sex differences in age at diagnosis, risk factors, lipid-lowering treatment, and ASCVD morbidity and mortality in patients with HoFH.

DESIGN, SETTING, AND PARTICIPANTS Sex-specific analyses for this retrospective cohort study were performed using data from the HoFH International Clinical Collaborators (HICC) registry, the largest global dataset of patients with HoFH, spanning 88 institutions across 38 countries. Patients with HoFH who were alive during or after 2010 were eligible for inclusion. Data entry occurred between February 2016 and December 2020. Data were analyzed from June 2022 to June 2023.

MAIN OUTCOMES AND MEASURES Comparison between women and men with HoFH regarding age at diagnosis, presence of risk factors, lipid-lowering treatment, prevalence, and onset and incidence of ASCVD morbidity (myocardial infarction [MI], aortic stenosis, and combined ASCVD outcomes) and mortality.

RESULTS Data from 389 women and 362 men with HoFH from 38 countries were included. Women and men had similar age at diagnosis (median [IQR], 13 [6-26] years vs 11 [5-27] years, respectively), untreated LDL cholesterol levels (mean [SD], 579 [203] vs 596 [186] mg/dL, respectively), and cardiovascular risk factor prevalence, except smoking (38 of 266 women [14.3%] vs 59 of 217 men [27.2%], respectively). Prevalence of MI was lower in women (31 of 389 [8.0%]) than men (59 of 362 [16.3%]), but age at first MI was similar (mean [SD], 39 [13] years in women vs 38 [13] years in men). Treated LDL cholesterol levels and lipid-lowering therapy were similar in both sexes, in particular statins (248 of 276 women [89.9%] vs 235 of 258 men [91.1%]) and lipoprotein apheresis (115 of 317 women [36.3%] vs 118 of 304 men [38.8%]). Sixteen years after HoFH diagnosis, women had statistically significant lower cumulative incidence of MI (5.0% in women vs 13.7% in men; subdistribution hazard ratio [SHR], 0.37; 95% CI, 0.21-0.66) and nonsignificantly lower all-cause mortality (3.0% in women vs 4.1% in men; HR, 0.76; 95% CI, 0.40-1.45) and cardiovascular mortality (2.6% in women vs 4.1% in men; SHR, 0.87; 95% CI, 0.44-1.75).

CONCLUSIONS AND RELEVANCE In this cohort study of individuals with known HoFH, MI was higher in men compared with women yet age at diagnosis and at first ASCVD event were similar. These findings suggest that early diagnosis and treatment are important in attenuating the excessive cardiovascular risk in both sexes.

JAMA Cardiol. doi:10.1001/jamacardio.2023.5597
Published online February 14, 2024.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Homozygous Familial Hypercholesterolemia International Clinical Collaborators appear in Supplement 2.

Corresponding Author: Jeanine E. Roeters van Lennep, MD, PhD, Department of Internal Medicine, Erasmus Medical Center Cardiovascular Institute, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, the Netherlands (j.roetersvanlennep@erasmusmc.nl).

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic biallelic disorder with a prevalence of 1 in 250 000 to 360 000.[1,2] Pathogenic variants in genes associated with low-density lipoprotein receptor (LDLR) function result in severely increased LDL cholesterol (LDL-C) levels. Variants in 3 of the causal genes—*LDLR*, *APOB*, and *PCSK9*—display autosomal semidominant inheritance, while variants in the *LDLRAP1* gene underlie a rare recessive form of HoFH.[3,4] The cumulative LDL-C burden is substantial from birth onwards, giving rise to a very high risk of premature atherosclerotic cardiovascular disease (ASCVD).[5] Patients with HoFH may already experience an ASCVD event before reaching adulthood or before the condition is diagnosed and treatment can be initiated.[3,6,7] Treatment generally consists of a combination of lipid-lowering therapies (LLTs), such as statins and ezetimibe, but also lipoprotein apheresis, and novel treatment strategies, such as proprotein convertase subtilisin/kexin type 9 inhibition, microsomal triglyceride transfer protein inhibition (lomitapide), or angiopoietinlike 3 (ANGPTL3) blockade (evinacumab).[8] Reaching guideline-recommended LDL-C goals in patients with HoFH is challenging, even with intensive combination treatment.[9]

The lifelong cholesterol burden and cardiovascular risk in patients with HoFH is much higher compared to patients with heterozygous familial hypercholesterolemia (HeFH) in whom only 1 allele in the genes associated with semidominantly inherited FH is mutated. Sex differences have been observed in the diagnosis and management of HeFH. Women with HeFH are often diagnosed later[10-13] and LLT is started later in life.[12] Studies have also reported that women with HeFH receive less potent LLT,[10,11,13,14] and that combination LLT is used less frequently.[10] This results in women having higher untreated and treated LDL-C levels than men both at young and old ages[10,12,15] and lower rates of achieving LDL-C goals.[10,11,13,16,17] Furthermore, women with HeFH often have prolonged pregnancy-related off-statin periods, since LLT is contraindicated during conception, pregnancy, and lactation.[18] These factors may explain why the excess ASCVD morbidity and mortality associated with HeFH is greater in women than in men.[19,20]

Against this background, similar sex differences might be expected in patients with HoFH, but these have not been studied. Using the largest global HoFH registry, we explored whether differences in age at diagnosis, risk factors, treatment, and ASCVD outcomes exist between women and men with HoFH.

Key Points

Question Are there sex differences in presentation at diagnosis, management, and atherosclerotic cardiovascular diseases (ASCVD) outcomes in patients with homozygous familial hypercholesterolemia (HoFH)?

Findings This cohort study of 751 patients with HoFH revealed no sex differences in age at diagnosis, treatment, and cardiovascular risk factors, except for a higher smoking prevalence in men. Men had higher incidence of myocardial infarction (MI), while other incident expressions of ASCVD morbidity were similar between sexes.

Meaning The findings indicate that HoFH represents a very high risk of premature ASCVD without clear sex differences, except a higher incidence of MI in men.

Methods

Patients and Data

The HoFH International Clinical Collaborators (HICC) registry collected data of patients with a clinical or genetic diagnosis of HoFH from a total of 88 institutions across 38 countries.[9] Using a retrospective cohort design, patients with HoFH who were alive during or after 2010 were eligible for inclusion. Data entry occurred between February 2016 and December 2020. The collected retrospective data included age at diagnosis, most recently present cardiovascular risk factors, untreated and most recent lipid levels, genetic data, ASCVD morbidity and mortality, and year when the ASCVD event or intervention occurred. Income status was defined based on country-specific data according to the 2019 World Bank definition (eTable 1 in Supplement 1).[21] Detailed description of data collection methods was published previously.[9] Data were analyzed from June 2022 to June 2023. Individual contributors were responsible for meeting local standards set by their institutional review board or ethics committee and obtaining approval. This study was conducted according to International Standards of Good Clinical Practice.

Clinical End Points

We evaluated sex differences in diagnosis, treatment, and ASCVD outcomes. For presentation at diagnosis, the main outcomes were age at diagnosis in years, presence of xanthomas at diagnosis, availability of genetic testing, and untreated lipid levels (total cholesterol, LDL-C, HDL cholesterol [HDL-C], and triglycerides) in mg/dL. We assessed the following risk factors at the last follow-up recorded: body mass index (calculated as weight in kilograms divided by height in meters squared), smoking (ever or never), diabetes, hypertension, and chronic kidney disease.

We evaluated treatment based on the latest recorded data and analyzed the type, number, and intensity of LLT received. For intensity of LLT, starting age and frequency of apheresis and statin intensity were investigated. Statin intensity was defined according to the American College of Cardiology/American Heart Association clinical practice guideline on cholesterol.[22] The proportion of women and men achieving recommended LDL-C goals at the last recorded visit was investigated, namely, less than 70 mg/dL for patients without ASCVD events and less than 55 mg/dL for patients with ASCVD (to convert to mmol/L, multiply by 0.0259).[2]

For cardiovascular outcomes, we compared the prevalence and incidence of nonfatal myocardial infarction (MI), angina pectoris, aortic stenosis, ischemic stroke, transient ischemic attack, peripheral artery disease, and cardiovascular and all-cause mortality between the sexes. We analyzed the prevalence and incidence of cardiovascular interventions, such as percutaneous coronary intervention (PCI), coronary artery

Table 1. Homozygous Familial Hypercholesterolemia Diagnosis: Demographic and Clinical Characteristics

Characteristic	No. (%)			P value
	Overall (N = 751)	Women (n = 389)	Men (n = 362)	
Diagnosis				
Age at diagnosis, median (IQR), y[a]	12 (5-27)	13 (6-26)	11 (5-27)	.53
Genetic information available	565 (75.2)	294 (75.6)	271 (74.9)	.89
Xanthomas at diagnosis	516 (68.7)	265 (68.1)	251 (69.3)	.78
Race[b]				
Asian	121 (16.1)	65 (16.7)	56 (15.5)	.39
Black	9 (1.2)	2 (0.5)	7 (1.9)	
White	338 (45.0)	181 (46.5)	157 (43.4)	
Multiple races	59 (7.9)	29 (7.5)	30 (8.3)	
Unknown	224 (29.8)	112 (28.8)	112 (30.9)	
Country income status				
High income	398 (53.0)	205 (52.7)	193 (53.3)	.92
Middle income	353 (47.0)	184 (47.3)	169 (46.7)	

[a] Total participants with age data = 711.

[b] Race data were collected through self-report by clinicians and reported to gain insights into the representativeness of this global patient cohort.

bypass grafting, carotid endarterectomy, and peripheral artery disease stenting. Age at first ASCVD event and ASCVD intervention were compared between the sexes. In addition, we compared composite outcomes: major adverse cardiovascular events (MACE), including cardiovascular mortality, MI, coronary artery bypass grafting, and PCI; major adverse cardiovascular and cerebrovascular events (MACCE), including MACE variables and ischemic stroke events; and a more comprehensive composite outcomes (MACCE + AVR) consisting of the MACCE variables plus aortic valve replacement (AVR), cerebrovascular disease stenting, carotid endarterectomy, peripheral artery disease stenting, and peripheral artery disease bypass.

Statistical Analysis

Continuous data are recorded as means (SDs) or medians with IQRs depending on the distribution, and categorical data as number with percentage. Differences between women and men in age at diagnosis, cardiovascular risk factors, LLT, ASCVD, and ASCVD intervention prevalence, age at first ASCVD event and intervention, were analyzed with a 2-sample *t* test or Mann-Whitney *U* test (continuous data) and χ^2 test or Fischer exact test (categorical data). Cardiovascular risk factors, LLT, ASCVD, ASCVD intervention prevalence, and age at onset were compared at the latest clinical evaluation recorded.

The cumulative incidence of all-cause mortality after HoFH diagnosis was studied with Kaplan-Meier and Cox proportional hazard regression. To estimate the cumulative incidence of cardiovascular end points, the Fine-Gray subdistribution hazard model was used to account for noncardiovascular death as competing risk (all-cause death was considered in relation to nonfatal end points).[23,24] Differences in cumulative incidence of all-cause mortality between the sexes were evaluated using the log-rank test and the hazard ratio (HR). Equality between the sexes for cardiovascular end points was assessed with the Gray test and Fine-Gray subdistribution hazard regression, resulting in subdistribution HRs (SHRs) with 95% CIs. The cumulative incidences of the ASCVD end points after HoFH diagnosis were compared between the sexes for the 75th percentile of MACCE + AVR follow-up duration. SHRs of possible influencing variables, such as untreated LDL-C, age at diagnosis, history of smoking, statin treatment, and country income status, were calculated per sex and for women and men combined for the maximum available follow-up duration. Analyses were performed using R version 4.2.1 (R Foundation). Statistical significance of all tests was set at 2-sided $P < .05$.

Results

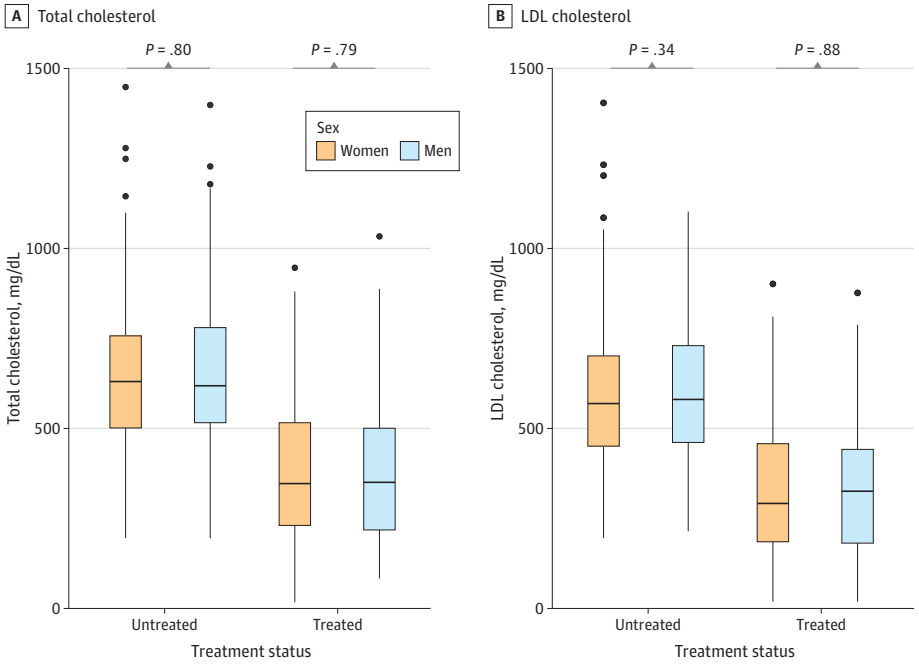
HoFH Diagnosis: Patient Characteristics and Presentation

The HICC registry included 389 women and 362 men, who had similar median (IQR) age at diagnosis (13 [6-26] years in women and 11 [5-27] years in men) (**Table 1**). Genetic information was available in 565 of 751 patients (75.2%), showing a similar proportion of women and men with 2 *LDLR* null variants (eTable 2 in Supplement 1). Mean (SD) untreated total cholesterol at a median (IQR) age of 13 (5-29) years was similar in women and men (645 [204] mg/dL in women vs 650 [201] mg/dL in men), as were untreated mean (SD) LDL-C levels (579 [203] mg/dL in women vs 596 [186] mg/dL in men) (**Figure 1**). Mean (SD) untreated HDL-C was significantly higher in women than men (42 [17] mg/dL in women vs 38 [16] mg/dL in men; $P = .007$), whereas median (IQR) triglycerides were significantly lower (100 [75-140] mg/dL in women vs 115 [79-161] mg/dL in men; $P = .01$) (eFigure 1 in Supplement 1).

Latest Clinical Evaluation: Patient Characteristics, LLT, ASCVD Prevalence, and Age at ASCVD Onset

The median (IQR) clinical follow-up duration (n = 709) of 9 (1-20) years from the time of HoFH diagnosis was the same in the sexes (**Table 2**). At the latest clinical evaluation, the median (IQR) age of registry participants was 28 (16-43) years (29 [17-42] years for women and 27 [14-44] years for men; $P = .68$). Smoking was significantly less common in women than in men (38 of 266 [14.3%] vs 59 of 217 [27.2%], respectively; $P < .001$), and the prevalence of other cardiovascular risk factors was similar in both sexes (Table 2).

Figure 1. Untreated and Treated Total Cholesterol and Low-Density Lipoprotein (LDL) Cholesterol Levels



Values are shown in median (IQR) in mg/dL (to convert to mmol/L, multiply by 0.0259).

Almost all women and men with HoFH were receiving LLT (262 of 276 women [94.9%] and 249 of 258 men [96.5%] $P = .49$). The most frequently used LLT for both women and men were statins (248 of 276 women [89.9%] and 235 of 258 men [91.1%]; $P = .74$), and most patients received high-intensity statin (161 of 276 women [58.3%] and 152 of 258 men [58.9%]; $P = .74$). Ezetimibe was used equally in women and men (170 of 276 [61.6%] and 164 of 258 [63.6%], respectively; $P = .70$). No sex differences were observed for any form or number of LLTs (Table 2). A total of 103 of 276 women (37.3%) and 96 of 258 men (37.2%) received 3 or more LLTs. Approximately one-third of the women and men received apheresis treatment (115 of 317 [36.3%] and 118 of 304 [38.8%], respectively; $P = .57$). In both sexes, the median frequency of apheresis was every other week, and the median (IQR) age of apheresis initiation was similar (16 [10-32] years in women vs 14 [9-22] years in men; $P = .33$).

Mean (SD) treated total cholesterol levels (377 [184] mg/dL in women and 373 [184] mg/dL in men) and LDL-C levels (321 [179] mg/dL in women and 323 [176] mg/dL in men) did not differ between the sexes at a median (IQR) follow-up of 11 (4-23) years after HoFH diagnosis (Figure 1). Mean (SD) treated HDL-C values were significantly higher in women than men (44 [18] mg/dL vs 41 [16] mg/dL, respectively; $P = .02$). No sex difference was observed in median (IQR) treated triglycerides (91 [62-131] mg/dL in women vs 96 [70-143] mg/dL in men) (eFigure 1 in Supplement 1). Overall, women and men receiving LLTs had a similar reduction of LDL-C after a median (IQR) 12 (6-23) years between the untreated and most recent laboratory levels (eFigure 3 in Supplement 1). Most women and men did not reach the currently recommended LDL-C goals (261 of 272 women [96.0%] and 246 of 254 men [96.9%]; $P = .82$).

Fewer women than men had experienced a MI at the latest clinical evaluation (31 of 389 [8.0%] vs 59 of 362 [16.3%], respectively; $P < .001$). However, mean (SD) age at first MI did not differ between sexes (39 [13] years for women and 38 [13] years for men; $P = .81$). There were no significant sex differences in the prevalence of aortic stenosis, angina pectoris, ischemic stroke or transient ischemic attack, or peripheral artery disease (Table 2). The age at onset of aortic stenosis (median [IQR], 20 [14-30] years for women and 20 [11-33] years for men), angina pectoris (mean [SD], 30 [15] years for women and 29 [14] years for men), ischemic stroke or transient ischemic attack (median [IQR], 33 [29-39] years for women and 43 [37-43] years for men), and peripheral artery disease (median [IQR], 33 [24-49] years for women and 36 [21-46] years for men) were also comparable (eFigure 2 in Supplement 1).

Although fewer women had undergone a PCI (34 of 389 [8.7%] vs 57 of 362 men [15.7%]; $P = .005$), we observed no sex difference in prevalence of other ASCVD interventions: 56 of 389 women (14.4%) and 64 of 362 men (17.7%) underwent a coronary artery bypass grafting and AVR occurred in 24 of 389 women (6.2%) vs 28 of 362 men (7.7%) (Table 2). For all ASCVD interventions (PCI, coronary artery bypass grafting, AVR, and carotid intervention), the age at first ASCVD intervention was comparable in women and men (eFigure 2 in Supplement 1). In total, 37 patients died, 18 women (5.3%) and 19 men (6.1%) ($P = .77$). Median (IQR) age at death was similar between the sexes (32 [23-48] years in women vs 43 [16-54] years in men; $P = .89$).

Cumulative Incidence of ASCVD After HoFH Diagnosis

At 16 years (75th percentile of MACCE + AVR follow-up) after HoFH diagnosis, the cumulative incidence of first MI was significantly lower in women than in men (5.0% in women; 95%

Table 2. Clinical Characteristics at Latest Evaluation

Characteristic	No.	No. (%)			*P* value
		Overall (N = 751)	Women (n = 389)	Men (n = 362)	
Birth year, median (IQR)	745	1983 (1972-1997)	1984 (1972-1997)	1986 (1971-1999)	.72
Latest age, median (IQR), y	727	28 (16-43)	29 (17-42)	27 (14-44)	.68
Time since diagnosis, median (IQR), y	709	9 (1-20)	9 (1-20)	9 (1-20)	>.99
Risk factors					
BMI, mean (SD)	386	23.9 (6.1)	23.8 (6.0)	24.1 (6.3)	.61
Smoking (ever)	483	97 (20.1)	38 (14.3)	59 (27.2)	<.001
Diabetes	603	23 (3.8)	9 (2.9)	14 (4.8)	.29
Hypertension	590	93 (15.8)	46 (14.9)	47 (16.7)	.62
Chronic kidney disease	421	6 (1.4)	3 (1.4)	3 (1.5)	>.99
Type of LLT					
Statin	534	483 (90.4)	248 (89.9)	235 (91.1)	.74
Ezetimibe	534	334 (62.5)	170 (61.6)	164 (63.6)	.70
Apheresis	621	233 (37.5)	115 (36.3)	118 (38.8)	.57
PCSK9 inhibitor	534	108 (20.2)	56 (20.3)	52 (20.2)	>.99
Lomitapide	534	41 (7.7)	21 (7.6)	20 (7.8)	>.99
Evinacumab	534	13 (2.4)	7 (2.5)	6 (2.3)	>.99
Mipomersen	534	1 (0.19)	0 (0)	1 (0.39)	.48
Resins	534	31 (5.8)	16 (5.8)	15 (5.8)	>.99
Fibrates	534	6 (1.12)	1 (0.36)	5 (1.94)	.11
LLTs					
0	534	23 (4.3)	14 (5.1)	9 (3.5)	.84
1		120 (22.5)	62 (22.5)	58 (22.5)	
2		192 (35.9)	97 (35.1)	95 (36.8)	
≥3		199 (37.3)	103 (37.3)	96 (37.2)	
Mean (SD)	534	2 (1)	2 (1)	2 (1)	.51
Statin intensity					
High	534	313 (58.6)	161 (58.3)	152 (58.9)	.74
Moderate		60 (11.2)	28 (10.1)	32 (12.4)	
Low		6 (1.1)	2 (0.7)	4 (1.6)	
Unknown dose		104 (19.5)	57 (20.7)	47 (18.2)	
No statin		51 (9.6)	28 (10.1)	23 (8.9)	
ASCVD prevalence					
Angina pectoris	751	95 (12.6)	46 (11.8)	49 (13.5)	.55
Percutaneous coronary intervention	751	91 (12.1)	34 (8.7)	57 (15.7)	.005
Coronary artery bypass grafting	751	120 (16.0)	56 (14.4)	64 (17.7)	.26
Myocardial infarction	751	90 (12.0)	31 (8.0)	59 (16.3)	<.001
Carotid intervention[a]	751	15 (2.0)	5 (1.3)	10 (2.8)	.19
Ischemic stroke or TIA	751	13 (1.7)	8 (2.1)	5 (1.4)	.58
Peripheral artery disease	634	42 (6.6)	17 (5.0)	25 (8.4)	.12
Aortic valve disease prevalence					
Aortic stenosis	751	169 (22.5)	90 (23.1)	79 (21.8)	.73
Aortic valve replacement	751	52 (6.9)	24 (6.2)	28 (7.7)	.48

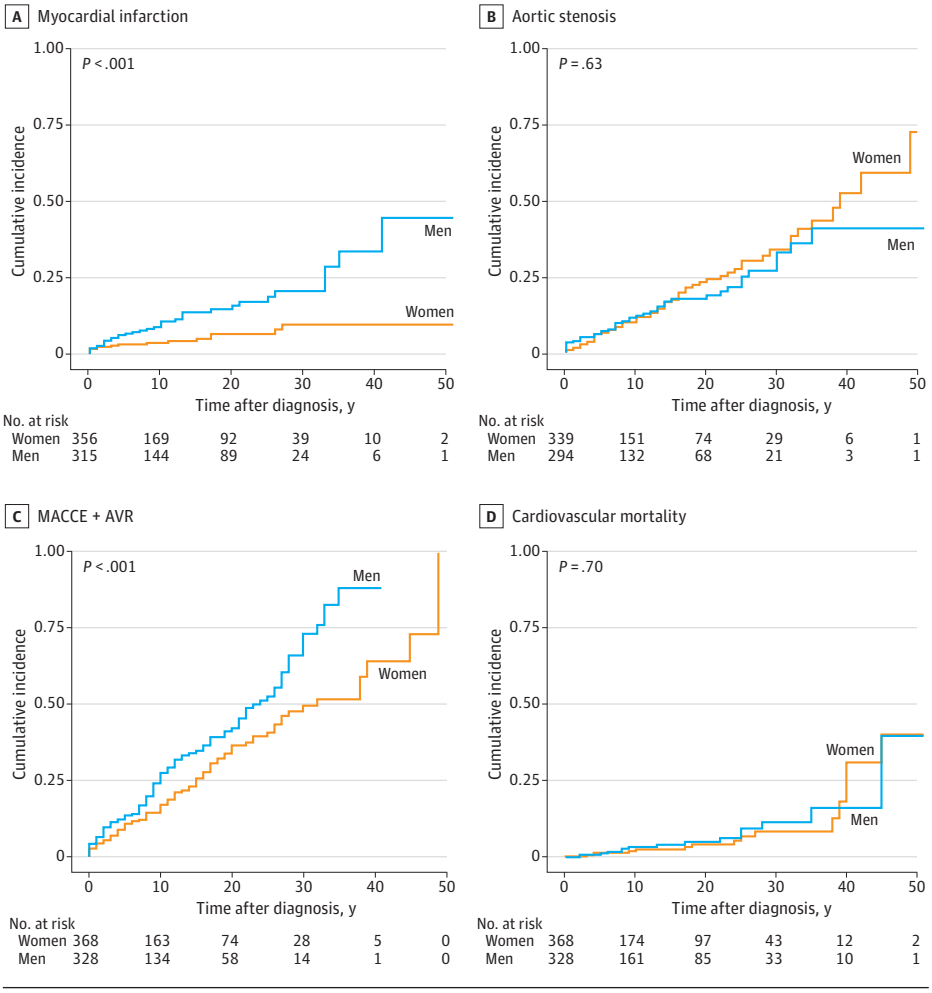
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin-kexin type 9; TIA, transient ischemic attack.

[a] Carotid intervention contains carotid endarterectomy and carotid stenting.

CI, 2.2-7.8 vs 13.7% in men; 95% CI, 8.7-18.7; SHR, 0.37; 95% CI, 0.21-0.66), as was the cumulative incidence of first PCI (6.5% in women; 95% CI, 3.1-9.8 vs 15.0% in men; 95% CI, 9.8-20.2; SHR, 0.42; 95% CI, 0.26-0.69) and first MACCE + AVR event (27.7% in women; 95% CI, 21.5-34.0 vs 36.5% in men; 95% CI, 29.5-43.5; SHR, 0.63; 95% CI, 0.48-0.83) (**Figures 2** and **3**). The cumulative incidence functions of other MACCE + AVR outcomes including aortic stenosis (SHR, 1.11; 95% CI, 0.75-1.63) were comparable between women and men (Figures 2 and 3). No statistically significant sex difference was observed for the cumulative incidence of all-cause mortality (3.0% in women vs 4.1% in men; HR, 0.76; 95% CI, 0.40-1.45) (eFigure 6 in Supplement 1) and cardiovascular mortality post-HoFH diagnosis (2.6% in women vs 4.1% in men; SHR 0.87; 95% CI, 0.44-1.75). As shown in Figure 3, the significantly lower hazard of women compared to men with regards to MACCE + AVR seems to be driven by MI and PCI, whereas the probability of occurrence of other ASCVD morbidity were comparable in the sexes (Figure 3).

In unadjusted and age-adjusted models investigating the influence of variables on the cumulative incidence function of women and men combined, age at diagnosis in years (model 2 SHR age-adjusted, 1.07; 95% CI, 1.04-1.10), high-income country (model 2 SHR age-adjusted, 0.56; 95% CI, 0.34-0.92), and

Figure 2. Cumulative Incidence of First Event After Diagnosis of Homozygous Familial Hypercholesterolemia



AVR indicates aortic valve replacement; MACCE, major adverse cardiovascular and cerebrovascular events.

untreated LDL-C in mg/dL (model 2 SHR age-adjusted per 20 mg/dL, 1.03; 95% CI, 1.01-1.06) were significantly associated with MACCE + AVR events (eTable 3 in Supplement 1). Patients with prior or current smoking had an increased risk of MACCE + AVR events in the age-adjusted model 1 (SHR age-adjusted, 1.59; 95% CI, 1.07-2.37) (eTable 3 in Supplement 1).

Discussion

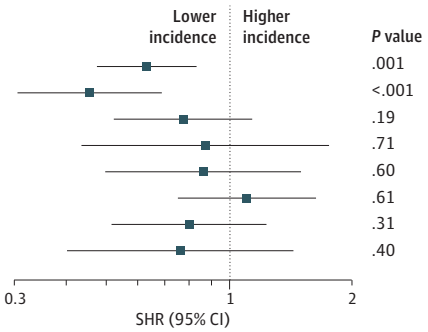
In this cohort study we showed that the age at diagnosis and untreated LDL-C levels did not differ between women and men in the largest international registry of HoFH patients. Apart from smoking, which was less common in women, the prevalence of other cardiovascular risk factors did not differ by sex. Treatment selection and intensity, and subsequently treated LDL-C levels at 9 years after diagnosis were similar for women and men. Both women and men with HoFH have an extremely high risk of premature ASCVD and showed a similar age at onset of the first ASCVD event. Men showed a statistically significant higher prevalence and incidence of MI and PCI and a nonsignificant higher incidence of all-cause and cardiovascular mortality. The prevalence and incidence of other cardiovascular outcomes was comparable between the sexes.

In the HICC registry, median age at diagnosis was in the early teenage years and comparable between women and men (13 vs 11 years respectively). This contrasts with several HeFH studies which observed that women with HeFH were diagnosed later in life than men.[10-13] The largest cohort of patients with HeFH, the Familial Hypercholesterolemia Studies Collaboration (FHSC), reporting on 42 167 patients (21 999 [53.6%] women) showed that women were diagnosed on average 3 years later compared to men: 46 vs 43 years $P < .001$.[10] HoFH is usually diagnosed in childhood or adolescence, as the extreme hypercholesterolemia frequently is accompanied by skin and tendon xanthomata. Both for women and men with HoFH in our study, delayed diagnosis was significantly associated with an increased incidence of MACCE + AVR outcomes. This further underlines the importance of early screening, diagnosis, and treatment in both sexes.

Both untreated levels at diagnosis and treated total cholesterol and LDL-C levels at the latest clinical evaluation were similar for women and men in this HoFH registry. Apart from a Canadian study published in 1993, there are no published data

Figure 3. Subdistribution Hazard Ratios (SHRs) by Sex for Cardiovascular End Points After Diagnosis of Homozygous Familial Hypercholesterolemia (HoFH)

Outcome	Cumulative incidence (%)		SHR (95% CI), women vs men
	Women	Men	
MACCE + AVR	27.7	36.5	0.63 (0.48-0.83)
Myocardial infarction and PCI	10.0	22.0	0.46 (0.30-0.69)
CABG	16.3	20.9	0.77 (0.52-1.14)
Cardiovascular mortality	2.6	4.1	0.87 (0.44-1.75)
Other MACCE + AVR components[a]	6.5	5.6	0.86 (0.50-1.50)
Aortic stenosis	19.8	17.8	1.11 (0.75-1.63)
Angina pectoris	10.8	13.3	0.80 (0.52-1.23)
All-cause mortality[b]	3.0	4.1	0.76 (0.40-1.45)



The cumulative incidence is shown for 16 years' follow-up post-HoFH diagnosis (75th percentile). The SHRs are calculated for the full follow-up duration. Aortic stenosis includes all patients with a clinical diagnosis of aortic stenosis with and without aortic valve replacement. AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MACCE, major adverse cardiovascular and cerebrovascular events.

[a] Contains AVR, cerebrovascular disease stenting, carotid endarterectomy, and peripheral artery disease stenting or bypass.

[b] Shown as normal hazard ratio based on a Cox regression model.

on sex-related differences in HoFH. The Canadian study included 21 patients with HoFH (13 women) and found no sex differences in plasma cholesterol.[25] However, they did not sex-stratify data or conduct a formal analysis. The currently available literature in patients with HeFH report contradicting data regarding sex differences in cholesterol levels with some reporting higher[10,12,15] and some similar[11,20] LDL-C levels in women compared to men, but none reporting higher LDL-C levels in men. HDL-C levels were higher and triglycerides lower in women with HoFH, which has also been observed in patients with HeFH.[11,13,20,26]

We observed no sex differences in LLT type and potency at the latest clinical evaluation. In addition, LDL-C goal achievement was comparable in both sexes albeit low (4.0% in women and 3.1% in men), similar to previous findings in patients with HoFH.[27-29] Therefore, it is important that patients with HoFH are treated as early as possible with combination LLT. Moreover, this underscores the necessity of new LLTs and access in all countries to these newer LLTs, such as lomitapide and evinacumab, to further reduce the LDL-C levels to get more patients to goal.

In contrast to our finding that women and men with HoFH receive equal LLT, numerous studies reported that women with HeFH were treated with LLT less often,[10,11,13] at a later age,[12] with less potent or combination LLT,[10,11,13,14] and less often achieve LDL-C goals than men with HeFH.[10,11,13,16,17] A possible explanation for the lack of sex differences in patients with HoFH with regard to treatment is the severity of the condition and the intensiveness of required treatment, which is offered in specialized lipid clinics.

In this study, MI and PCI prevalence and incidence were higher in men. We observed no sex differences in other ASCVD morbidities. The age at onset of the different ASCVD end points, including MI and aortic stenosis, was similar for women and men. The previously mentioned study in patients with HoFH stated that there were no sex differences observed in coronary heart disease, although a formal analysis was not performed.[25] In the general population, women have a lower risk of ASCVD before menopause.[30,31] Consequently, on average, women experience a first ASCVD event approximately 7 to 10 years than men.[31-34] A reduced gap in age at onset of cardiovascular disease has been observed between women and men with HeFH in some studies[19,20] but not others.[11,12,26,35] Except for prevalence and incidence of PCI, we did not observe a difference in AVR or other cardiovascular intervention treatments between women and men with HoFH. While age at onset of MI did not differ between the sexes, prevalence and incidence of MI was higher in men than women, comparable to the sex difference in MI event rate in the general population. We do not have a conclusive explanation for this finding. Considering the premenopausal age of the women in this study, they may still have experienced some hormonal cardiovascular protection in relation to the development of MI. For instance, estrogens have been linked to increased LDLR activity and plaque stability.[36,37] At the other hand, we do not exclude the possibility that the diagnosis of MI is more often missed in women, similar to previous reports of general population studies that observed that women more often had silent or missed MIs.[38-40]

Strengths and Limitations

Previous cohort studies consisted of small numbers of patients with HoFH and therefore were not powered to analyze women and men separately. The HICC registry is the largest and most detailed registry with contemporary clinical worldwide data on HoFH. Therefore, the HICC registry is the first and only dataset in which detailed sex-specific analyses could be performed. In addition, survival analyses could be performed in which competing risk was accounted for to prevent overestimation of the outcome.

A limitation is that the HICC registry only captures patients with HoFH who were diagnosed and received treat-

ment from 2010 onwards. Therefore, we do not know if sex differences exist in undiagnosed, untreated, or prematurely deceased patients with HoFH. Also, not all world regions are currently covered in the HICC registry. In particular our findings might not be representative for low-income countries. In addition, not all racial and ethnic groups were adequately represented. Furthermore, sex-specific risk factors were not part of the dataset and therefore female-specific risk factors, such as age at menarche, could not be investigated. For the Turkish subgroup, only living patients at data entry were included, and therefore mortality might be higher and underestimated. Information on relevant nonlipid risk factors (in particular smoking) were lacking in substantial numbers of patients, as data were not systematically collected at standard follow-up intervals after HoFH diagnosis. This especially hampered the ASCVD analyses. There were some missing data in follow-up time of the ASCVD outcome. Therefore, age at onset and cumulative incidence of ASCVD outcomes might be overestimated and underestimated, respectively.

Conclusions

To our knowledge, this is the first study to assess sex differences in patients with HoFH. We observed no sex differences in diagnosis, most risk factors, or treatment. Women and men with HoFH experience an excessive risk of ASCVD caused by extreme hypercholesterolemia. Although prevalence and incidence of MI and PCI was higher in men (comparable to findings from the general population), the age at MI and PCI onset was similar between the sexes. Other ASCVD morbidity, interventions, and age at occurrence were comparable in women and men. Additional research is needed to better understand this phenomenon, with particular focus on female-specific ASCVD risk factors. The findings indicate that both women and men with HoFH have a very high risk of premature ASCVD, suggesting that early diagnosis and treatment are important steps in attenuating excessive cardiovascular risk in both sexes.

ARTICLE INFORMATION

Accepted for Publication: December 15, 2023.

Published Online: February 14, 2024. doi:10.1001/jamacardio.2023.5597

Author Affiliations: Department of Internal Medicine, Erasmus Medical Center Cardiovascular Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands (Mulder, Roeters van Lennep); Department of Vascular Medicine, Amsterdam University Medical Centers, Academic Medical Center, Amsterdam, the Netherlands (Tromp, Hovingh, Schonck); University of Al-Qadisiyah, College of Pharmacy, Diwaniya City, Iraq (Al-Khnifsawi); Department of Medicine, Division of Lipidology and Cape Heart Institute, University of Cape Town, Cape Town, South Africa (Blom); 1st Department of Cardiology, Medical University of Gdańsk, Gdańsk, Poland (Chlebus); National Centre of Familial Hypercholesterolaemia, Gdańsk, Poland (Chlebus); Department of Medicine, Division of Translational Medicine and Human Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Cuchel); Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy (D'Erasmo); Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, Sorbonne Université, Institut national de la santé et de la recherche médicale UMR 1166, Assistance Publique–Hôpitaux de Paris, Hôpital Pitié-Salpètrière, Paris, France (Gallo); Vietnam National Heart Institute, Bach Mai Hospital, Hanoi, Vietnam (Kim); Department of Cardiology, Hanoi Medical University, Hanoi, Vietnam (Kim); Department of Atherosclerosis, Beijing Anzhen Hospital, Capital Medical University, The Key Laboratory of Remodeling-Related Cardiovascular Diseases, Ministry of Education, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China (Long); Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa (Raal); Department of Diabetes, Endocrinology and Metabolism and Manchester National Institute of Health Research/Wellcome Trust Clinical Research Facility, Manchester University NHS Foundation Trust, Manchester, United Kingdom (Soran); Faculty of Medicine, Phenikaa University, Hanoi City, Vietnam (Truong); Vietnam Atherosclerosis Society, Hanoi, Vietnam (Truong); Department of Cardiology, Erasmus Medical Center Cardiovascular Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands (Boersma).

Author Contributions: Dr Mulder had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Obtained funding: All authors.
Administrative, technical, or material support: All authors.
Supervision: All authors.

Conflict of Interest Disclosures: Dr Blom reported personal fees from Amryt, Amgen, Sanofi, and Novartis and grants from LIB Therapeutics outside the submitted work. Dr Chlebus reported grants from Ministry of Health Poland during the conduct of the study and personal fees from Sanofi, Amgen, and Novartis outside the submitted work. Dr Cuchel reported grants from the National Heart, Lung, and Blood Institute during the conduct of the study and grants from Regenxbio and Regeneron and personal fees from Ultragenyx outside the submitted work. Dr D'Erasmo reported grants from Amryt and personal fees from Amryt, Swedish Orphan Biovitrum, Bayer, Novartis, Amarin, Aurora Biopharma, and Daiichi Sankyo outside the submitted work. Dr Gallo reported personal fees from Amgen, Sanofi, Novartis, Viatris, Amarin, Ultragenyx, Amryt, and MSD and grants from Amgen and Sanofi outside the submitted work. Dr Raal reported consulting fees for professional input and/or delivered lectures from Novartis, Sanofi, Regeneron, Amgen, and LIB Therapeutics outside the submitted work. Dr Soran reported personal fees from Amryt, Amgen, Akcea, Swedish Orphan Biovitrum, Ultragynex, Kowa, and Amarin and grants from Amryt, Amarin, and Akcea outside the submitted work. Dr Roeters van Lennep reported grants from Novartis (paid to institution) outside the submitted work. No other disclosures were reported.

Funding/Support: In-house funding at each institution was used to cover the efforts of contributors for data collection and entry. The creation and the maintenance of the REDCap database and support of a study coordinator for bulk data entry was provided in house by Dr Cuchel at the University of Pennsylvania. Dr Cuchel received support through National Heart, Lung, and Blood Institute grant P01HL059407. Support of the registry coordinators (Drs Tromp and Schonck) was provided in house by Dr Hovingh at Amsterdam University Medical Center. The Homozygous Familial Hypercholesterolemia International Clinical Collaborators Registry is an investigator-initiated project supported by funding from the academic institutions of the collaborators. The European Atherosclerosis Society provided funding to support a registry coordinator.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The Homozygous Familial Hypercholesterolemia International Clinical Collaborators appear in Supplement 2.

Data Sharing Statement: See Supplement 3.

REFERENCES

1. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype-phenotype relationship, and clinical outcome. *Eur Heart J*. 2015;36(9):560-565. doi:10.1093/eurheartj/ehu058

2. Cuchel M, Raal FJ, Hegele RA, et al. 2023 update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *Eur Heart J*. 2023;44(25):2277-2291. doi:10.1093/eurheartj/ehad197

3. Cuchel M, Bruckert E, Ginsberg HN, et al; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. a position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. 2014;35(32):2146-2157. doi:10.1093/eurheartj/ehu274

4. Sturm AC, Knowles JW, Gidding SS, et al; the Familial Hypercholesterolemia Foundation. Clinical genetic testing for familial hypercholesterolemia: JACC scientific expert panel. *J Am Coll Cardiol*. 2018;72(6):662-680. doi:10.1016/j.jacc.2018.05.044

5. Kramer AI, Akioyamen LE, Lee S, et al. Major adverse cardiovascular events in homozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2022;29(5):817-828. doi:10.1093/eurjpc/zwab224

6. Bertolini S, Calandra S, Arca M, Averna M, Catapano AL, Tarugi P; Italian Study Group of Homozygous Familial Hypercholesterolemia. Homozygous familial hypercholesterolemia in Italy: clinical and molecular features. *Atherosclerosis*. 2020;312:72-78. doi:10.1016/j.atherosclerosis.2020.08.027

7. Raal FJ, Sjouke B, Hovingh GK, Isaac BF. Phenotype diversity among patients with homozygous familial hypercholesterolemia: a cohort study. *Atherosclerosis*. 2016;248:238-244. doi:10.1016/j.atherosclerosis.2016.03.009

8. Tromp TR, Cuchel M. New algorithms for treating homozygous familial hypercholesterolemia. *Curr Opin Lipidol*. 2022;33(6):326-335. doi:10.1097/MOL.0000000000000853

9. Tromp TR, Hartgers ML, Hovingh GK, et al; Homozygous Familial Hypercholesterolaemia International Clinical Collaborators. Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *Lancet*. 2022;399(10326):719-728. doi:10.1016/S0140-6736(21)02001-8

10. EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet*. 2021;398(10312):1713-1725. doi:10.1016/S0140-6736(21)01122-3

11. 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. doi:10.1016/j.atherosclerosis.2017.10.006

12. 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;315:131-137. doi:10.1016/j.atherosclerosis.2020.10.895

13. 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(11):e019286. doi:10.1161/JAHA.120.019286

14. Zamora A, Masana L, Comas-Cufí M, et al; XULA and ISV-Girona groups. Familial hypercholesterolemia in a European Mediterranean population-Prevalence and clinical data from 2.5 million primary care patients. *J Clin Lipidol*. 2017;11(4):1013-1022. doi:10.1016/j.jacl.2017.05.012

15. 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(3):748-755.e2. doi:10.1016/j.jacl.2018.02.021

16. Saadatagah S, Alhalabi L, Farwati M, et al. The burden of severe hypercholesterolemia and familial hypercholesterolemia in a population-based setting in the US. *Am J Prev Cardiol*. 2022;12:100393. doi:10.1016/j.ajpc.2022.100393

17. Schmidt N, Dressel A, Grammer TB, et al. Lipid-modifying therapy and low-density lipoprotein cholesterol goal attainment in patients with familial hypercholesterolemia in Germany: the CaReHigh Registry. *Atherosclerosis*. 2018;277:314-322. doi:10.1016/j.atherosclerosis.2018.08.050

18. Klevmoen M, Bogsrud MP, Retterstøl K, et al. Loss of statin treatment years during pregnancy and breastfeeding periods in women with familial hypercholesterolemia. *Atherosclerosis*. 2021;335:8-15. doi:10.1016/j.atherosclerosis.2021.09.003

19. Ahmad Z, Li X, Wosik J, et al. Premature coronary heart disease and autosomal dominant hypercholesterolemia: increased risk in women with LDLR mutations. *J Clin Lipidol*. 2016;10(1):101-108.e1-3. doi:10.1016/j.jacl.2015.09.003

20. Krogh HW, Mundal L, Holven KB, Retterstøl K. Patients with familial hypercholesterolaemia are characterized by presence of cardiovascular disease at the time of death. *Eur Heart J*. 2016;37(17):1398-1405. doi:10.1093/eurheartj/ehv602

21. The World Bank. Data World Bank national accounts. GNI per capita, Atlas method (current US$)—high income, middle income, low income. Accessed March 3, 2021. https://data.worldbank.org/indicator/NY.GNP.PCAP.CD?locations=XD-XP-XM

22. 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(24):e285-e350. doi:10.1016/j.jacc.2018.11.003

23. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation*. 2016;133(6):601-609. doi:10.1161/CIRCULATIONAHA.115.017719

24. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144

25. Moorjani S, Roy M, Torres A, et al. Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia. *Lancet*. 1993;341(8856):1303-1306. doi:10.1016/0140-6736(93)90815-X

26. Alonso R, Mata N, Castillo S, et al; Spanish Familial Hypercholesterolaemia Group. Cardiovascular disease in familial hypercholesterolaemia: influence of low-density lipoprotein receptor mutation type and classic risk factors. *Atherosclerosis*. 2008;200(2):315-321. doi:10.1016/j.atherosclerosis.2007.12.024

27. Di Taranto MD, Giacobbe C, Buonaiuto A, et al. A real-world experience of clinical, biochemical and genetic assessment of patients with homozygous familial hypercholesterolemia. *J Clin Med*. 2020;9(1):219. doi:10.3390/jcm9010219

28. Alonso R, Díaz-Díaz JL, Arrieta F, et al. Clinical and molecular characteristics of homozygous familial hypercholesterolemia patients: insights from SAFEHEART registry. *J Clin Lipidol*. 2016;10(4):953-961. doi:10.1016/j.jacl.2016.04.006

29. Kayikcioglu M, Tokgozoglu L, Yilmaz M, et al. A nation-wide survey of patients with homozygous familial hypercholesterolemia phenotype undergoing LDL-apheresis in Turkey (A-HIT 1 registry). *Atherosclerosis*. 2018;270:42-48. doi:10.1016/j.atherosclerosis.2018.01.034

30. Saeed S, Dweck MR, Chambers J. Sex differences in aortic stenosis: from pathophysiology to treatment. *Expert Rev Cardiovasc Ther*. 2020;18(2):65-76. doi:10.1080/14779072.2020.1732209

31. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145(8):e153-e639. doi:10.1161/CIR.0000000000001052

32. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. *Circ Res*. 2016;118(8):1273-1293. doi:10.1161/CIRCRESAHA.116.307547

33. Mehta LS, Beckie TM, DeVon HA, et al; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133(9):916-947. doi:10.1161/CIR.0000000000000351

34. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, et al; EUGenMed Cardiovascular Clinical Study Group. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J*. 2016;37(1):24-34. doi:10.1093/eurheartj/ehv598

35. Allard MD, Saeedi R, Yousefi M, Frohlich J. Risk stratification of patients with familial hypercholesterolemia in a multi-ethnic cohort. *Lipids Health Dis*. 2014;13:65. doi:10.1186/1476-511X-13-65

36. Hussain Y, Ding Q, Connelly PW, et al. G-protein estrogen receptor as a regulator of low-density lipoprotein cholesterol metabolism: cellular and population genetic studies. *Arterioscler Thromb Vasc Biol*. 2015;35(1):213-221. doi:10.1161/ATVBAHA.114.304326

37. Yerly A, van der Vorst EPC, Baumgartner I, Bernhard SM, Schindewolf M, Döring Y. Sex-specific and hormone-related differences in vascular remodelling in atherosclerosis. *Eur J Clin Invest*. 2023;53(1):e13885. doi:10.1111/eci.13885

38. van der Ende MY, Juarez-Orozco LE, Waardenburg I, et al. Sex-based differences in unrecognized myocardial infarction. *J Am Heart Assoc*. 2020;9(13):e015519. doi:10.1161/JAHA.119.015519

39. de Torbal A, Boersma E, Kors JA, et al. Incidence of recognized and unrecognized myocardial infarction in men and women aged 55 and older: the Rotterdam Study. *Eur Heart J*. 2006;27(6):729-736. doi:10.1093/eurheartj/ehi707

40. Lichtman JH, Leifheit EC, Safdar B, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction: evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). *Circulation*. 2018;137(8):781-790. doi:10.1161/CIRCULATIONAHA.117.031650