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Original Research

Sex-related differences in premature cardiovascular disease in familial hypercholesterolemia

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Diabetes mellitus;
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Abstract:

Background: Familial hypercholesterolemia (FH) is associated with an increased prevalence of premature atherosclerotic cardiovascular disease (ASCVD), however, little is known about sex-specific differences in premature ASCVD and its risk factors.

Objective: The present study seeks to assess the burden and risk factors for premature ASCVD among men and women with FH.

Methods: In this study we retrospectively examined sex-specific differences in ASCVD prevalence, risk factor burdens, and lipid treatment outcomes in 782 individuals with clinically or genetically confirmed FH treated in 5 U.S. lipid and genetics clinics. A generalized linear model using Binomial distribution with random study site effect and sex-stratified analysis was used to determine the strongest predictors of premature ASCVD, and lipid treatment outcomes. Covariates included age, sex, diabetes mellitus (DM), hypertension, and current smoking.

Results: Among the cohort, 98/280 men (35%) and 89/502 women (18%) had premature ASCVD (defined as <55 years in men and <65 years in women). Women with premature ASCVD had higher mean treated total cholesterol (216 vs. 179 mg/dl, p=<0.001) and LDL-C (135 vs. 109 mg/dl, p= 0.005).

Conclusion: These data confirm that high percentages of women and men with FH develop premature ASCVD, and suggest that FH may narrow the observed sex difference in premature ASCVD onset. These

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data support more aggressive prevention and treatment strategies in FH, including in women, to reduce non-lipid risk factors and residual hypercholesterolemia.

Introduction

Familial hypercholesterolemia (FH) is an inherited condition marked by elevated blood levels of low-density lipoprotein cholesterol (LDL-C) starting *in utero* due most often to a monogenic mutation in the LDL-receptor. Frequency is approximately 1 in 250 in the general population and higher in several founder groups. It is well established that individuals with FH have an elevated lifetime risk of atherosclerotic cardiovascular disease (ASCVD) and are also at an increased risk of premature ASCVD (defined as <55 years in men and <65 years in women).[1] However, less is known about sex differences in those with FH who develop early ASCVD, including age, relative impact of other risk factors, and treatment outcomes. This is clinically relevant because a large burden of traditional risk factors has been observed in general in individuals with premature ASCVD.[2] Additionally, it is well known that some ASCVD risk factors impart greater relative risks in women and are even 'risk equalizers' (i.e. diabetes, a very high total cholesterol to HDL cholesterol ratio $\geq$ 7.5, and LVH), and yet ASCVD risk in women is generally undertreated compared to men.[3–6] This sex-related gap has been attributed to a lower perceived risk of ASCVD by both female patients and their clinicians even when traditional ASCVD risk factors are present.[7] The aim of this study was to characterize sex-specific risk factor burdens and lipid treatment outcomes in individuals with FH and premature ASCVD.

Methods

Study Design: We retrospectively collected data on 782 adult patients receiving care for heterozygous FH at 5 US-based lipid and genetics clinics: Washington University in St Louis, Baylor College of Medicine, University of Texas Southwestern Medical Center at Dallas, Geisinger Health, and the Brown University Lifespan Hospital system. All data extraction was performed by trained research assistants who collected de-identified data for importation into a dedicated study database. Demographic data were self-reported. Patients were diagnosed with either heterozygous FH based on validated clinical criteria or genetic testing. Clinical criteria included, but were not limited to, Simon Broome, Dutch Lipid Clinic Network, Make Early Diagnosis to Prevent Early Death (MEDPED) and/or the American Heart Association schema for possible, probable, or definite FH. Genetically confirmed FH included mutations in the *LDLR, APOB*, or *PCSK9* genes. Given the heterogeneous means of diagnoses, patients with either a clinical or genetic diagnosis were characterized as having FH; and no distinction was made between patients who had a clinical or genetic diagnosis for the scope of this analysis. The institutional review boards at each site approved of the protocol, and waivers were obtained for retrospective data collection.

Laboratory Values and Medical History

Variables: Demographic data, medical history, and laboratory values were ascertained by electronic data extraction and/or retrospective chart review at each respective lipid clinic. Race and sex/gender was self-reported. Age was reported from the most recent clinic visit to the time of data collection. Lipid measurements were obtained through standardized commercial or institutional laboratories. Laboratory measurements were reported as the most recent on-treatment values. Treated lipid values were reported for patients receiving pharmacologic lipid lowering therapy.

A history of ASCVD was defined through objective testing for coronary, peripheral, and/or cerebrovascular disease or a cardiovascular event, including angina, myocardial infarction (MI), coronary angioplasty, peripheral arterial surgery, claudication, peripheral angioplasty, transient ischemic attack, stroke and/or carotid endarterectomy. Premature ASCVD was defined as age <55 years in men and <65 years in women. The presence of ASCVD was comprehensively assessed at the initial visit and re-addressed at subsequent visits.

Statistical Methods: The prevalence of ASCVD was evaluated in the entire cohort and stratified by sex. The association of sex with demographic and clinical variables was assessed univariately using a Chi-squared test for categorical variables and a t-test for continuous variables. Triglycerides were compared using Mann-Whitney U test due to non-normal distribution. Missing data were imputed using multiple imputation methodology. Multiple imputation was performed using the MICE algorithm in R (https://www.jstatsoft.org/article/view/v045i03), which allows for the imputation of both continuous and categorical variables. Missing values were imputed for BMI, smoking, diabetes, and hypertension. The imputation was done with five imputed datasets. (Pre-treatment cholesterol values could not be imputed because they were not missing at random. Imputation of these values may have resulted in a biased estimate as subjects who were not on treatment were more likely to have missing both treated and untreated LDL-C values). Prediction of ASCVD was assessed in a generalized linear mixed effects model with binomial distribution, where study

center was modeled as a random effect to account for within site correlation. Sex-stratified analysis was used to determine the strongest predictors of premature ASCVD. Covariates included age, sex, diabetes mellitus (DM), hypertension, and current smoking. In addition, we assessed for the predictors of ASCVD stratified by sex including all covariates. Standard regression diagnostics were performed. The standard criteria of a 2-sided p-value <0.05 for statistical significance was used in this study. The analyses were performed using R statistical software version 4.0.

Results

Clinical characteristics of the 280 men and 502 women included in this analysis are shown in Table 1. Women were well represented in our cohort. Women in the cohort tended to be older than the men (mean age 55±15 years vs. 52±14 years, p<0.001). A total of 187 patients had a diagnosis of premature ASCVD. The incidence of premature ASCVD in men n = 98 was 35% and in women n= 89 was 18%. Treated LDL-C levels across all individuals with FH were significantly higher in women than in men (125 ± 48 mg/dL vs. 116 ± 51 mg/dL respectively, p =0.02).

Traditional risk factors in those with premature ASCVD are shown in Table 2. The prevalence of hypertension, current smoking, and diabetes mellitus were two-fold greater amongst those with premature ASCVD as compared to those without premature ASCVD, N=148 (80%) vs. N=213 (40%), p <0.001 for hypertension, N=29 (16%) vs. N= 40 (8%), p= 0.002 for current smoking, and N= 60(32%) vs. N=91 (15%), p<0.001 for diabetes. No difference was noted in treated LDL-C levels in patients with and without premature ASCVD respectively mean value 122 mg/dL mg/dL in both group, p=0.28.

Analysis by sex (Tables 3 and 4) further highlights the nearly two-fold higher prevalence of traditional ASCVD risk factors in both men and women with premature ASCVD. The prevalence of hypertension was N=80 (83%) vs. N= 69 (45%), p <0.001 in men with and without premature ASCVD respectively and N= 68 (77%) vs. N= 144 (39%), p<0.001 in women with and without premature ASCVD re-

Table 1 Baseline characteristics of Men and Women with Familial Hypercholesterolemia.

	Men	Women	*P*- value
N	280	502	-
Age	52 ±14	55 ± 15	**<0.001**
White (N)	200 (71%)	356 (71%)	
Blacks (N)	55 (20%)	97 (19%)	
Premature Cardiovascular Disease	98 (35%)	89 (18%)	
BMI (mean, SD)	30 (5)	30 (8)	0.55
Treated Total Cholesterol (mg/dL)	189 (60)	208 (55)	< 0.001
Treated LDL-C (mg/dL)	116 (50)	125 (48)	**0.020**
Treated HDL-C (mg/dL)	47 (14)	58 (17)	**<0.001**
Treated Triglycerides* (mg/dL)	47 (34-72)	48 (34-72)	**0.802**
Hypertension	149 (60%)	212 (46%)	**<0.001**
Current Smoking	27 (11%)	42 (9%)	**0.58**
Diabetes Mellitus	61 (22%)	89 (18%)	**0.16**

*Nonnormal distribution, median value and interquartile range reported

Table 2 Baseline characteristics of Individuals with Familial Hypercholesterolemia with and without Premature Atherosclerotic Cardiovascular Disease.

	Premature ASCVD	No Premature ASCVD	P- value
N	187	595	-
Age	56 ±11	53 ± 15	
White (N)	130 (70%)	426 (72%)	0.074
Blacks (N)	45 (24%)	107 (18%)	
BMI (mean, SD)	31(6)	29 (7)	<0.001
Treated Total Cholesterol (mg/dL)	197 (72)	203 (51)	0.348
Treated LDL-C (mg/dL)	122 (60)	122 (45)	0.97
Treated HDL-C (mg/dL)	50 (16)	56 (17)	**<0.001**
Treated Triglycerides*	54 (36,86)	46 (32,68)	**0.003**
Hypertension	148 (80%)	213 (40%)	**<0.001**
Current Smoking	29 (16%)	40 (8%)	**0.002**
Diabetes Mellitus	60 (32%)	91 (15%)	**<0.001**

*Nonnormal distribution, median value and interquartile range reported

Table 3 Baseline characteristics of Men with Familial Hypercholesterolemia with and without Premature Atherosclerotic Cardiovascular Disease.

	Premature ASCVD	No Premature ASCVD	*P*- value
N of Men	98	182	-
Age	55 ± 10	50 ± 15	
White (N)	70 (71%)	130 (71%)	0.380
Blacks (N)	22 (22%)	33 (18%)	
BMI (mean, SD)	31 (5)	29 (5)	0.0001
Treated Total Cholesterol (mg/dL)	179 (65)	196 (55)	0.041
Treated LDL-C (mg/dL)	109 (53)	120 (50.0)	**0.123**
Treated HDL-C (mg/dL)	43 (11)	50 (14)	**<0.001**
Treated Triglycerides* (mg/dL)	56 (38–89)	44(32–64)	**0.004**
Hypertension	80 (83%)	69 (45%)	**<0.001**
Current Smoking	14 (15%)	13 (9%)	**0.192**
Diabetes Mellitus	35 (36%)	27 (15%)	**<0.001**
Statin Use	82 (84%)	114 (63%)	**<0.001**
High Intensity Statin Use	70 (85%)	64 (56%)	**<0.001**
Ezetimibe Use	57 (58%)	55 (30%)	**<0.001**
PCKS9 Inhibitor Use	26 (27%)	13 (7%)	**<0.001**

*Nonnormal distribution, median value and interquartile range reported

Table 4 Baseline characteristics of Women with Familial Hypercholesterolemia with and without Premature Atherosclerotic Cardiovascular Disease.

	Premature ASCVD	No Premature ASCVD	P- value
N of Women	89	413	-
Age	58 ± 11	55 ± 15	
White (N)	60 (67%)	296 (72%)	0.167
Blacks (N)	6 (7%)	43 (10%)	
BMI (mean, SD)	31 (8)	29 (7)	0.047
Treated Total Cholesterol (mg/dL)	216 (74)	206 (49)	0.120
Treated LDL-C (mg/dL)	135 (65)	123 (42)	**0.118**
Treated HDL-C (mg/dL)	57 (17)	59 (17)	**0.422**
Treated Triglycerides (mg/dL)	54 (33-84)	46 (34-70)	**0.114**
Hypertension	68 (77%)	144 (39%)	**<0.001**
Current Smoking	15 (17%)	27 (7%)	**0.009**
Diabetes Mellitus	25 (28%)	64 (16%)	**0.008**
Statin Use	69 (78%)	275 (67%)	**0.059**
High Intensity Statin Use	57 (83%)	128 (47%)	**<0.001**
Ezetimibe Use	46 (52%)	117 (28%)	**<0.001**
PCKS9 Inhibitor Use	18 (20%)	21 (5%)	**<0.001**

spectively. Women, but not men, with premature ASCVD vs. those without were more likely to be current smokers, N=15 (17%) vs. N=27 (7%), p=0.009 in women and N= 14 (15%) vs. N= 13(9%), p= 0.192 in men. Men and women with premature ASCVD had significantly higher BMI compared to their counterparts without ASCVD.

A comparison of clinical characteristics and ASCVD risk factors is shown in Table 5. Women with premature ASCVD had higher on-treatment total cholesterol (216 vs. 179 mg/dl, p<0.001) and LDL-C (135 vs. 109 mg/dl, p= 0.005). The strongest predictors of premature ASCVD in all individuals with FH were smoking [OR 2.40 (95% CI 1.41, 4.05) p=0.001] and hypertension [OR 4.36 (95% CI 2.91, 6.67) p<0.001] (Table 6). Sex-stratified analyses further highlighted differences in predictors of premature ASCVD in men and women. In men, the strongest predictors of premature ASCVD were hypertension (OR 3.83, 95% CI 2.09, 7.90, p<0.001) and diabetes mellitus (OR 1.89 95% CI 1.04, 3.43, p=0.036). In women, the strongest predictors of premature ASCVD were hypertension (OR 4.25, 95% CI 2.47, 7.57, p<0.001) and smoking (OR 2.54, 95% CI 1.25, 5.00, p < 0.001). Treated LDL-C was not a significant predictor of ASCVD in either men or women (Table 6).

Discussion

In this cohort of 782 men and women with FH cared for by lipid or genetic specialists across several regions of the U.S. we found the prevalence of premature ASCVD to be

Table 5 Comparison of Men vs. Women with Familial Hypercholesterolemia and Premature Atherosclerotic Cardiovascular Disease.

	Men	Women	P- value
N	98	89	-
Age	55 ± 10	58 ± 11	
White (N)	70 (71%)	60 (67%)	0.836
Blacks (N)	22 (22%)	6 (7%)	
BMI (mean, SD)	31 (5)	31 (8)	0.603
Treated Total Cholesterol (mg/dL)	179 (65)	216 (74)	**<0.001**
Treated LDL-C (mg/dL)	109 (53)	135 (65)	**0.005**
Treated HDL-C (mg/dL)	43 (11)	57 (17)	**<0.001**
Treated Triglycerides* (mg/dL)	56 (38–89)	54 (33–84)	0.513
Hypertension	80 (83%)	68 (77%)	0.40
Current Smoking	14 (15%)	15 (17%)	0.80
Diabetes Mellitus	35 (36%)	25 (28%)	0.34
Statin Use	82 (84%)	69 (78%)	0.38
High Intensity Statin Use	70 (85%)	57 (83%)	0.81
Ezetimibe Use	57 (58%)	46 (52%)	0.46
PCKS9 Inhibitor Use	26 (27%)	18 (20%)	0.40

*Nonnormal distribution, median value and interquartile range reported

Table 6 The Strongest Predictors of Premature Atherosclerotic Cardiovascular in Individuals with Familial Hypercholesterolemia.

	All Individual with FH		Men		Women	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	*P* value
Current Smoking	2.40 (1.41–4.05)	**0.001**	**2.01 (0.87–4.67)**	0.100	2.54 (1.25–5.00)	**0.008**
Hypertension	4.36 (2.91–6.67)	**<0.001**	3.83 (2.09–7.90)	**<0.001**	4.25 (2.47–7.57)	**<0.001**
Diabetes Mellitus	1.43 (0.96–2.12)	0.076	1.89 (1.04–3.43)	**0.036**	1.18 (0.67–2.04)	0.565

around 24% overall and 35% in men vs. 18% in women. These findings are comparable to those previously published through the CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE-FH®) registry that demonstrated the prevalence of premature ASCVD to be 36% and 12% in men and women respectively.[8] The prevalence of premature ASCVD is estimated at around 11% according to a study of over 1.2 million patients seen in the US Department of Veterans Affairs healthcare system.[9] The prevalence of premature ASCVD in our cohort of patients with FH is approximately 2-3-fold higher than that in the general U.S. population. These data confirm that a diagnosis of FH confers substantially elevated risk for premature ASCVD compared to the general population.

In our cohort, women had significantly higher treated LDL-C levels compared to men regardless of ASCVD status. In previously published data through the CASCADE-FH registry women were less likely than men to receive statin therapy, high-intensity statin therapy, and achieve their LDL-C goals.[10] When compared to men with premature ASCVD, women with premature ASCVD had significantly higher on treatment total and LDL-C values despite the lack of difference in high-intensity statin, ezetimibe, and PCSK9 inhibitor use. The reason behind the discrepancy in LDL-C merits further investigation. It is important to note that some of the patients in our cohort may have been co-enrolled in the CASCADE-FH registry, contributing to an overlap in the patients used for these studies. This overlap may limit how these data sets are compared to each other. However, there are limited data on women with FH and CASCADE is one of the very few large registries available that allows for these data to be compared. Electronic health record data from other cohorts including patients without a diagnosis of FH, show that women with coronary artery disease are not prescribed adequate doses of lipid lowering therapy and are less likely to reach their LDL-C therapeutic threshold.[11,12] The UK Simon Broom FH registry reported that women between the ages of 30-50 years had a significantly higher CVD related morbidity when compared to men.[13] These findings, in addition to the ones in our study highlight the importance of optimization of lipid lowering therapy and risk factor reduction, particularly in young women. Notably, men and women with premature ASCVD were more likely to be obese than those without premature ASCVD. Taken together, these findings shed light on multifactorial drivers for premature ASCVD beyond LDL-C in men and women with FH. Importantly, the risk of premature ASCVD appears to be exacerbated by modifiable risk factors (i.e. hypertension, diabetes mellitus, and smoking), suggesting that early and aggressive treatment of hypertension and diabetes, and interventions to target smoking cessation may reduce the burden of ASCVD in these individuals who are already at heightened risk of ASCVD due to their lifelong exposure to elevated LDL-C. While optimizing lifestyle measures of diet and exercise will not adequately control LDL-C levels in individuals with FH, these measures can have a robust impact on controlling

blood pressure and preventing or controlling diabetes mellitus, which should also be important goals, in addition to smoking prevention and/or cessation, in the treatment of FH.

Strengths and limitations

Our study has several limitations. Our analysis was retrospective, and residual confounding may have contributed to our findings. Additionally, patient data in our study compiled from separate lipid specialty clinics from around the U.S. which may have introduced selection bias as well as limited the availability of certain information. Furthermore, our relatively small sample size may have limited our ability to demonstrate between-group differences in LDL-C control and/or ASCVD as well its risk factors. The data presented in the current study are cross-sectional in nature. Patients who may not have been on lipid lowering therapy at the time of this data collection may have been new to the clinic and requested trials of lifestyle modifications initially, followed by lipid treatment at a later date. Furthermore, data on medication adherence was not available in our cohort. Another notable limitation is the limited use of combination therapies in this cohort. The data for our cohort reflects treatments over the span of the last decade during which time certain lipid lowering therapies were not as readily available or adopted. Given the ever-changing landscape of lipid lowering therapeutics with regard to availability and cost, some of the most up to date practices may not be captured in this cohort. A strength of our study is that our cohort was enriched with women, a demographic group that historically has been understudied in FH care.

Conclusion

FH is a common genetic disorder with an estimated prevalence of 1 in 250 U.S. adults, in whom the relative risks of cardiovascular morbidity and mortality including premature ASCVD, surpass that of the general population. The present study has demonstrated sex-related disparities in risk factors for ASCVD and in lipid control in individuals with FH, which have important implications for primary and secondary prevention in this high-risk group. Premature ASCVD in individuals with FH appears to be driven by risk factors beyond just LDL-C. Comprehensive evaluation and management of all ASCVD risk factors in in men and women alike, is key to reducing ASCVD burden.

Disclosures/Conflicts of Interest

Dr Aspry has contracted research paid to institution from Amgen, Akcea, Esperion, and Novartis. She received speaker honoraria in 2020–2021 from MedScape/WebMD, and the National Lipid Association. Dr Ahmad serves on the advisory board for Esperion. Dr Ballantyne receives significant grant/research support that is paid to the institution from Abbott Diagnostic, Akcea, Amgen, Esperion, Novartis, Regeneron, Roche Diagnostic, National Institutes of Health, American Heart Association, and American Diabetes Association. He is a consultant for Abbott Diagnostics, Althera, Amarin, Amgen, Arrowhead, Astra Zeneca, Corvidia, Denka Seiken, Esperion, Genentech, Gilead, Matinas BioPharma Inc, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. Dr Goldberg receives modest honoraria from Esperion and Merck, and significant honoraria from the National Lipid Association. She receives modest research grants from Amarin, Amgen, and Pfizer and significant research grants from Novartis, Regeneron, Sanofi, and Ionis/Akcea. The remaining authors have no disclosures to report.

CRediT authorship contribution statement

Anandita Agarwala: Conceptualization, Project administration, Writing – review & editing. **Elena Deych:** Conceptualization, Project administration, Writing – review & editing. **Laney K. Jones:** Conceptualization, Project administration, Writing – review & editing. **Amy C. Sturm:** Conceptualization, Project administration, Writing – review & editing. **Karen Aspry:** Conceptualization, Project administration, Writing – review & editing. **Zahid Ahmad:** Conceptualization, Project administration, Writing – review & editing. **Christie M. Ballantyne:** Conceptualization, Project administration, Writing – review & editing. **Anne C. Goldberg:** Conceptualization, Project administration, Writing – review & editing.

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