Children with Heterozygous Familial Hypercholesterolemia in the United States: Data from the Cascade Screening for Awareness and Detection-FH Registry

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Objective To describe enrollment characteristics of youth in the Cascade Screening for Awareness and Detection of FH Registry.

Study design This is a cross-sectional analysis of 493 participants aged <18 years with heterozygous familial hypercholesterolemia recruited from US lipid clinics (n = 20) between April 1, 2014, and January 12, 2018. At enrollment, some were new patients and some were already in care. Clinical characteristics are described, including lipid levels and lipid-lowering treatments.

Results Mean age at diagnosis was 9.4 (4.0) years; 47% female, 68% white and 12% Hispanic. Average (SD) highest Low-density lipoprotein cholesterol (LDL-C) was 238 (61) mg/dL before treatment. Lipid-lowering therapy was used by 64% of participants; 56% were treated with statin. LDL-C declined 84 mg/dL (33%) among those treated with lipid-lowering therapy; statins produced the greatest decline, 100 mg/dL (39% reduction). At enrollment, 39% had reached an LDL-C goal, either <130 mg/dL or ≥50% decrease from pre-treatment; 20% of those on lipid-lowering therapy reached both goals.

Conclusions Among youth enrolled in the Cascade Screening for Awareness and Detection of FH Registry, diagnosis occurred relatively late, only 77% of children eligible for lipid-lowering therapy were receiving treatment, and only 39% of those treated met their LDL-C goal. Opportunities exist for earlier diagnosis, broader use of lipid-lowering therapy, and greater reduction of LDL-C levels. *(J Pediatr 2021;229:70-7)*.

Individuals with familial hypercholesterolemia (FH) have elevated low-density lipoprotein cholesterol (LDL-C) levels from birth, resulting in an increased risk for atherosclerotic cardiovascular disease (ASCVD).[1,2] FH is a common inherited disorder, affecting 1 in 220 individuals in the US,[3] that can be diagnosed in the first years of life.[4] Observational data and post hoc analyses of primary prevention trials support the beneficial effects of lipid-lowering therapy in reducing ASCVD events in adults with FH,[2,5,6] and vascular imaging studies demonstrate stabilization or regression of subclinical atherosclerosis with statin therapy in children and adolescents with FH.[7-9] Statins are recommended for individuals with FH beginning at age 10 years ameliorate this risk.[1,5,10,11]

In 2013, the FH Foundation, a patient-centric research and advocacy organization, created the Cascade Screening for Awareness and Detection of FH (CASCADE-FH) Registry. CASCADE-FH is a national initiative designed to describe the characteristics of US individuals with FH, the trends in treatment, and clinical and patient-reported outcomes over time.[12-15] Through these efforts,

ASCVD	Atherosclerotic cardiovascular disease
CASCADE	Cascade Screening for Awareness and Detection
FH	Familial hypercholesterolemia
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol

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the goal of the FH Foundation is to increase FH awareness and improve long-term outcomes. The registry collects participant demographic and clinical characteristics, medications, laboratory values, imaging data and ASCVD events. Participants aged <18 years are enrolled by their clinician at any stage of care (ie, new patients or already in care) for both cross-sectional and prospective data collection at 6-month intervals. To date, more than 4500 children and adults have been enrolled in the registry.

We conducted a cross-sectional analysis of baseline characteristics, treatment patterns, and cardiovascular risk factors in 493 children and adolescents with heterozygous FH enrolled in the CASCADE-FH Registry between April 2014 and January 12, 2018, from 20 lipid clinics in the US. The goal of this analysis was to describe the characteristics of children and adolescents less than age 18 years with heterozygous FH at the time of enrollment in the CASCADE-FH Registry, including the use of lipid-lowering therapy at enrollment. We examined whether there were differences between children aged <10 years and those aged ≥10 years in terms of lipid-lowering therapy, lipid levels, and treatment response.

Methods

The CASCADE-FH Registry includes both retrospective data collection from a single record review and prospective data collection with updated clinical status and treatment information based on record review every 6 months and has been described in detail elsewhere.[12-15] The present analysis focuses on the data collected in youth at enrollment; also included is the highest pre-treatment LDL-C level as reported by the enrolling center. At each site, clinical personnel or research staff extracts data from the medical record. In addition to laboratory values and family history, other clinical characteristics including additional ASCVD risk factors are collected, such as the presence of obesity (defined as body mass index ≥95th percentile based on Centers for Disease Control and Prevention data), diagnosed hypertension or diabetes, and family history of premature ASCVD.[16] Clinical ASCVD was defined as coronary artery disease, myocardial infarction, stroke, transient ischemic attack, or coronary interventions. Premature ASCVD was defined as family history of premature cardiovascular disease (men <55 years/women <65 years) in a first- or second-degree relative.[11] Specific diagnostic criteria for heterozygous FH were gathered (eg, Simon Broome, MEDPED, Dutch Lipid Clinic criteria, genetic testing, clinician diagnosis) based on personal and family history of ASCVD, physical examination findings of xanthoma and arcus cornea, LDL-C and total cholesterol levels, and genetic testing results when available.[2,5] The protocol was approved by the Institutional Review Boards of all participating sites. Parents of prospectively enrolled subjects provided written consent; child assent was given as age-appropriate. This study has been registered at ClinicalTrials.gov (identifier NCT01960244).

Baseline characteristics of children and adolescent participants from the CASCADE-FH Registry were summarized as frequencies and percentages for categorical variables, and mean (SD) or median (IQR) for continuous variables. These characteristics are presented both overall and stratified by age (<10 years, ≥10 years). The 2011 Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommend statin initiation for children whose LDL-C level has not responded to lifestyle modification.[11] For the purpose of this analysis, lipid-lowering therapy was defined as the use of any of the following: statins (atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin, lovastatin, fluvastatin), ezetimibe, Vytorin, niacin, fibrate, bile acid sequestrants, phytosterols, omega-3 fatty acid supplements, psyllium, PCKS9 inhibitors, lomitapide, mipomersen, and LDL-C apheresis. To better distinguish the effect of neutraceuticals from other therapies, subgroup analyses were conducted with the following categories: neutraceutical lipid-lowering therapy (phytosterols, omega-3 fatty acid supplements, psyllium), non-neutraceutical lipid-lowering therapy (atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin, lovastatin, fluvastatin, ezetimibe, Vytorin, niacin, fibrate, bile acid sequestrants, PCKS9 inhibitors, lomitapide, mipomersen), and statins (atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin, lovastatin, fluvastatin). Although lipid-lowering therapy may be initiated at age 8 years, initiation is generally recommended by age 10,[11] and thus we used this age as the expected age of eligibility for lipid-lowering therapy initiation in our analysis. Comparisons of continuous characteristics were made using the *t* test or Wilcoxon rank-sum test. Categorical characteristics were compared using the χ^2 test.

The extent to which youth in the registry met treatment goals at enrollment was reported. Treatment goals were defined as LDL-C <130 mg/dL, or a ≥50% reduction from the highest pretreatment LDL-C levels, in accordance with US and international guidelines.[5,11] Two combined outcomes were reported, meeting either 1 or both of the LDL-C goals.

A subgroup analysis included subjects eligible for lipid-lowering therapy and compared participants who were and were not receiving lipid-lowering therapy. Eligibility for lipid-lowering therapy was defined as either age ≥10 years plus highest pretreatment LDL- C ≥160 mg/dL plus family history of premature cardiovascular disease, or age ≥10 years plus pretreatment LDL-C ≥190 mg/dL.[11] Multivariable logistic regression was performed to identify factors significantly associated with lipid-lowering therapy use among eligible patients. Covariates included in the final model were determined using a backward selection process with a *P* value for exclusion of .05. Generalized estimating equations were used in the final model to account for variation by site. The OR of lipid-lowering therapy use is presented, along with the corresponding 95% CI and *P* value. Candidate covariates included baseline LDL-C level (for comparisons of lipid-lowering therapy or statin use), highest pretreatment LDL-C level (for comparisons of LDL-C goal attainment), obesity, race/ethnicity, sex, age, family

history of FH, and family history of myocardial infarction. A similar subgroup analysis was conducted examining the same group, comparing those receiving statins and those not receiving statins.

Results

Among the 4549 individuals enrolled in the database as of January 12, 2018, there were 493 participants aged <18 years at enrollment with heterozygous FH available for this analysis (Figure 1). Baseline characteristics are presented in Table. The average age at enrollment was 12.3 (SD, 3.5) years, with the majority (79.5%) aged ≥10 years. The average age at diagnosis was 9.4 (4.0) years. Nearly one-half (47.3%) were identified as female; 68.2% were white, 7.7% were black, 4.7% were Asian, and 12.2% were Hispanic. Race and ethnicity differed between age groups, with those aged <10 years more likely to be nonwhite. At enrollment, mean total cholesterol and LDL-C levels were elevated, 246 (70) mg/dL and 175 (59) mg/dL, respectively, even though the majority (66%) received lipid-lowering therapy. Levels of LDL-C were lower in registry participants aged ≥10 years ($P < .0001$); a higher proportion of older patients received lipid-lowering therapy (74.3% vs 33.7%; $P < .0001$). The average highest reported pretreatment LDL-C level was 238 (60.7) mg/dL. A family history of FH was present in 316 (64.1%) of CASCADE-FH Registry youth participants, and 172 (40.4%) had a family history of premature ASCVD (men <55 years/women <65 years) in a first-degree relative. A family history of premature ASCVD was more commonly reported in children aged ≥10 years. No youths had documented clinical ASCVD.

The majority of youths (36.5%; n = 180) were identified as having FH based on the clinical impression of the treating provider. FH was diagnosed using formal criteria in 18.7%, with MEDPED the most common criteria cited by the enrolling investigator (n = 63; 12.8%), followed by Simon Broome (n = 29; 5.9%). Only 8 patients (1.6%) of the entire group reported a confirmed FH genetic mutation.

We assessed for the presence of additional factors that would raise the risk of ASCVD in the youth enrolled in the CASCADE-FH Registry (Figure 2). More than one-third (35.1%; n = 173) had 1 additional cardiovascular risk factor, such as low high-density lipoprotein-cholesterol (HDL-C) concentration, obesity, diabetes, or hypertension, and 43 (8.7%) had 2 additional risk factors for ASCVD besides FH. Low HDL-C level was the most common additional risk factor, with obesity also common. Only 1 patient (0.2%) in the registry reported smoking.

Of the enrolled pediatric population, nearly two-thirds (314, 66.0%) were receiving lipid-lowering therapy at the time of enrollment (Table). Complete information on lipid-lowering therapy use was missing for 17 youths; they were reported to not be receiving statins, but their use of other lipid-lowering therapy was unknown. The mean age at the initiation of lipid-lowering therapy was 11.1 (3.2)

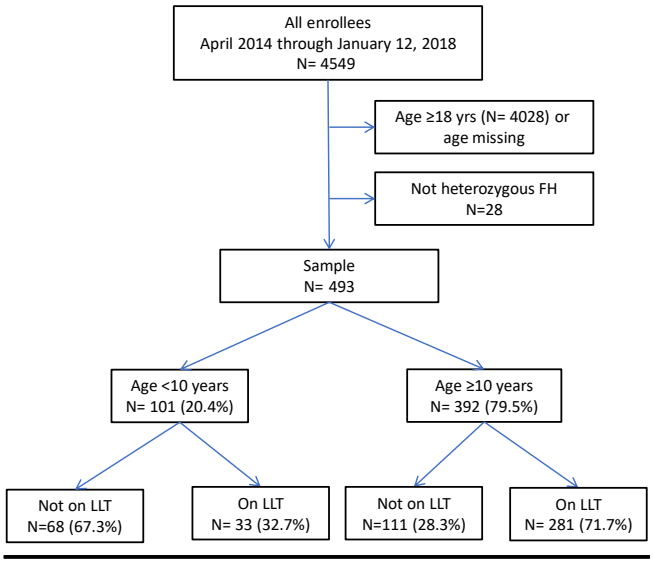

Figure 1. Participant flow sheet.

years. Statins were the most frequently reported lipid-lowering drugs, used by 277 (56.2%) participants, with atorvastatin and simvastatin the most common. Of participants aged ≥10 years, 261 (66.6%) were taking statins. Other therapies were much less commonly used, namely ezetimibe, which was used by only 5.7% of youths in the registry. Fibrates (none), niacin (1 patient), and bile acid resins (7 patients) were rarely reported, nor were any children taking medications reserved for homozygous FH (eg, lomitapide, mipomersen). No patients were taking PCSK9 inhibitors. Nutraceutical use was also reported, including phytosterols (5.1%) and fish oil (5.3%).[17,18] The type of lipid-lowering therapy used differed between children aged <10 years compared with those ≥10 years (Table), with nonstatin therapies more commonly reported in children aged <10 years, except ezetimibe, which was more commonly used in those aged ≥10 years. Children aged ≥10 years were more than twice as likely as those aged <10 years to be on pharmacotherapy ($P < .0001$). Higher baseline LDL-C level ($P = .0002$) and positive family history ($P = .04$) also predicted the use of lipid-lowering therapy, but not the presence of additional risk factors.

Of the enrolled pediatric population, 315 (63.9%) were eligible for lipid-lowering therapy based on age, LDL-C level, and family history. Of those eligible, 241 (76.5%) reported using some type of lipid-lowering therapy; 229 (71.6%) were taking a statin, and 23 (7.3%) were taking a neutraceutical. Of note, not all youths receiving lipid-lowering therapy met the criteria for pharmacotherapy used in this analysis (age ≥10 years plus pretreatment LDL-C ≥160 mg/dL plus family history of premature cardiovascular disease, or age ≥10 years plus pretreatment LDL-C ≥190 mg/dL). Of the 314 pediatric patients receiving lipid-lowering therapy, 73 (23.2%) did not meet our prespecified eligibility criteria for lipid-lowering therapy

Table. Registry participant characteristics at enrollment

Characteristics	All youths (n = 493)	Age <10 y (n = 101)	Age ≥10 y (n = 392)	*P* Value
Demographics				
Age at enrollment, y, mean (SD)	12.3 (3.5)	7.0 (1.9)	13.7 (2.3)	<.0001
Age at diagnosis, y, mean (SD) (n = 488)	9.4 (4.0)	5.7 (2.4)	10.3 (3.8)	<.0001
Sex, n (%)				.3404
Female	233 (47.3)	52 (51.5)	181 (46.2)	
Male	260 (52.7)	49 (48.5)	211 (53.8)	
Race/ethnicity, n (%)				.0062
Hispanic	60 (12.2)	22 (21.8)	38 (9.7)	
White	336 (68.2)	56 (55.4)	280 (71.4)	
Black/African American	38 (7.7)	11 (10.9)	27 (6.9)	
Asian	23 (4.7)	5 (5.0)	18 (4.6)	
Other	36 (7.3)	7 (6.9)	29 (7.4)	
Lipid profile at enrollment (n = 491)				
Total cholesterol, mg/dL, mean (SD)	246 (70.2)	291 (87.3)	234 (59.7)	<.0001
LDL-C, mg/dL, mean (SD)	175 (58.7)	213 (52.6)	165 (56.2)	<.0001
HDL-C, mg/dL, mean (SD)	50.7 (13.3)	53.6 (13.2)	49.9 (13.2)	.0143
Triglycerides, mg/dL, median (IQR)	77 (57-109)	77 (60-102)	78 (57-112)	.8128
Highest pretreatment LDL-C	238 (60.7)	240 (85.2)	237 (52.5)	.7710
Additional cardiovascular risk factors, n (%)				
Low HDL	174 (35.3)	33 (32.7)	141 (36.0)	.5365
Obesity	75 (15.2)	17 (16.8)	58 (14.8)	.0003
Diabetes	7 (1.4)	1 (1.0)	6 (1.5)	.6426
Smoking	1 (0.2)	0 (0.0)	1 (0.3)	.6049
Hypertension	10 (2.0)	1 (1.0)	9 (2.3)	.3795
Family history of premature MI (n = 426)	172 (40.4)	22 (23.4)	150 (45.2)	.0001
Lipid-lowering therapy at enrollment, n (%)				
Any lipid-lowering therapy (n = 476)	314 (66.0)	33 (33.7)	281 (74.3)	<.0001
Statin	277 (56.2)	16 (15.8)	261 (66.6)	<.0001
Ezetimibe	28 (5.7)	1 (1.0)	27 (6.9)	.0045
Niacin	1 (0.2)	0 (0.0)	1 (0.3)	.5393
Bile acid sequestrants	7 (1.4)	4 (4.0)	3 (0.8)	.0781
Phytosterols	25 (5.1)	9 (8.9)	16 (4.1)	.3137
Fish oils/omega 3 fatty acids	26 (5.3)	4 (4.0)	22 (5.6)	.1813
Psyllium	19 (3.9)	8 (7.9)	11 (2.8)	.1375
FH diagnostic criteria, n (%)				
Dutch Lipid Clinic	0 (0.0)	0 (0.0)	0 (0.0)	.0012
Simon Broome	29 (5.9)	9 (8.9)	20 (5.1)	
MEDPED	63 (12.8)	14 (13.9)	49 (12.5)	
Clinical diagnosis	180 (36.5)	43 (42.6)	137 (34.9)	
Other/missing	125 (25.3)	30 (29.7)	95 (24.2)	
Multiple methods	96 (19.5)	5 (5.0)	91 (23.2)	
Confirmed FH genetic mutation	8 (1.6)	0 (0.0)	8 (2.0)	.1478

Low HDL-C was defined as <40 mg/dL in males and <50 mg/dL in females. Obesity was defined as a body mass index ≥95th percentile based on Centers for Disease Control and Prevention data.

but nevertheless were reported to be on treatment. One-third of those not meeting the eligibility criteria were aged 8-9 years (22; 30.1%); other patients were younger than 8 years or had a lower baseline LDL-C level. Of the 8- and 9- year-olds on lipid-lowering therapy, 14 of 22 (63.6%) were taking a statin, and the remainder were using nutraceuticals alone. If age 6 years was used as the age cutpoint eligible for lipid-lowering therapy, 265 (71.0%) of those eligible were on some type of lipid-lowering therapy, with 243 (64.1%) taking a statin and 108 (29.0%) taking a neutraceutical (not mutually exclusive categories).

We examined the success in achieving the LDL-C reduction goal by measuring the decrease from the highest reported pretreatment LDL-C level to the LDL-C level at enrollment, calculated both in absolute terms (LDL-C <130 mg/dL) and as percent decrease (≥50%) from highest reported pretreatment LDL-C level. Data are shown for several subsets, including participants eligible for lipid-lowering therapy and not receiving lipid-lowering therapy, participants receiving neutraceuticals, non-neutraceutical lipid-lowering therapy, and statins specifically (**Figure 3**). In the full study group, the mean reduction in LDL-C level from the highest pretreatment LDL-C level was 60 mg/dL (24%). In those participants eligible for lipid-lowering therapy, LDL-C level declined by 80 mg/dL (31%). The greatest decreases in LDL-C level among those eligible for lipid-lowering therapy were seen in the 229 patients (72.7%) receiving statins; there was an average 38.6% decline from baseline in these patients (100 mg/dL). Overall, 27.6% achieved an LDL-C goal, either <130 mg/dL or a ≥50% decrease from the highest pretreatment LDL-C; both goals were achieved by 13% of the total group and by 20% of those on lipid-lowering therapy.

Discussion

We report the characteristics of an ethnically diverse group of children and adolescents enrolled in the CASCADE-FH Registry, the sole contemporary US pediatric FH cohort.

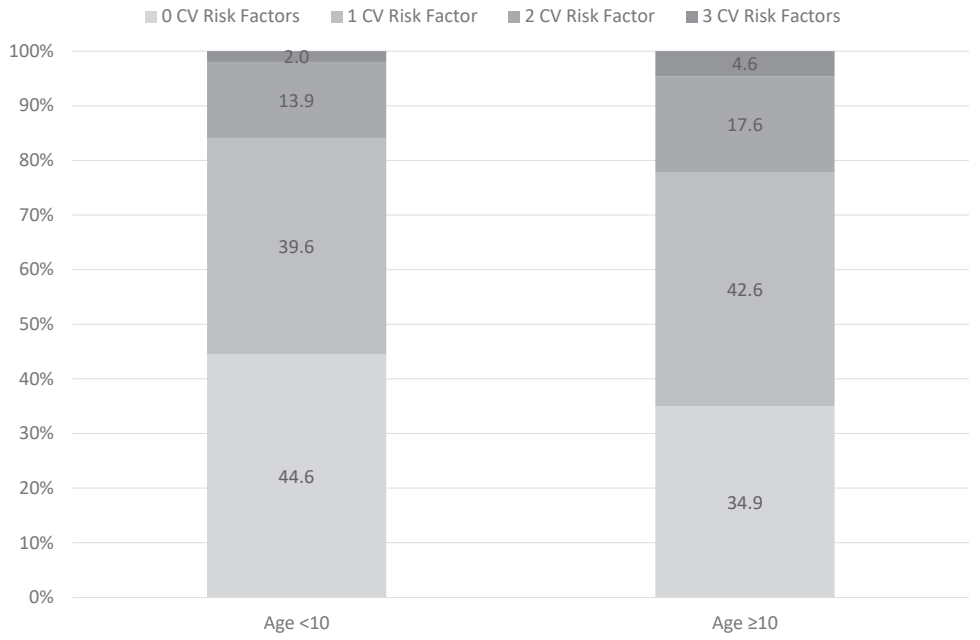

Figure 2. Presence of additional atherosclerotic cardiovascular disease risk factors, including low HDL-C, obesity, hypertension, smoking history, diabetes, and family history of early MI.

We found that among nearly 500 children and adolescents with FH, the average age at diagnosis was age 9 years, despite national recommendations for selective lipid screening starting at age 2 years.[11] Furthermore, at enrollment, many children were not receiving lipid-lowering therapy (36.3%); nearly one-quarter (23.5%) of those meeting US guidelines for lipid-lowering therapy were not taking medications to lower lipid levels. Of the children receiving lipid-lowering therapy, only 39% achieved the degree of LDL-C reduction recommended in published guidelines, that is, <130 mg/dL or a decrease of ≥50% from baseline; only 20% met both goals.

Our findings were similar to the expanding literature on FH in childhood, corroborating concerns about late identification, less-than-optimal rates of statin therapy, and failure to reach guideline-recommended decreases in LDL-C level. The Spanish FH registry SAFEHEART[19] and the United Kingdom Paediatric Familial Hypercholesterolaemia Register[20] have reported their experience in participants aged <18 years (n = 392 and 300, respectively). At enrollment, 44% of the youths in SAFEHEART and 52.5% of those in the UK FH register were treated with statins, compared with 56.2% of US youths in the CASCADE-FH Registry. Similar to our experience, both the Spanish and UK groups reported low statin use in children aged <10 years. In these other pediatric FH cohorts, statin use increased over time, so that after 4 years of follow-up, two-thirds (68%) of SAFEHEART youths were being treated with statins. Also similar to our findings, less than one-half achieved a sufficient decrease in LDL-C level; 41.5% of Spanish youths in SAFEHEART and 41.5% of UK youths with FH had an LDL level <130 mg/dL. Similarly, in a cohort of 302 Norwegian children followed in an FH clinic, 59% were taking statins, and those on statins achieved a similar 33% reduction in LDL-C level, with 43% achieving their treatment goal.[21]

Most children in the CASCADE-FH Registry had a clinical diagnosis of FH or met the MEDPED criteria. In contrast to reports of youth with FH outside the US, only 8 children (1.6%) had confirmatory genetic testing. Thus, two-thirds of the children included in the UK registry had a genetic diagnosis, just over one-half (55%) of Spanish youths with FH had positive genetic test results, and a notable 99% of the pediatric Norwegian cohort were diagnosed by molecular testing. In Spain, Norway, and the UK, the most likely mechanism children are identified with FH is through genetic cascade screening from adult relatives. In contrast, in the US, cascade screening for FH is not performed systematically, and genetic testing has been rare to date. Providers and patients have been apt to forgo genetic testing due to the cost of testing, which was higher at the time the data were gathered and might not have been covered by insurance, and also because of concerns about privacy and insurability. An international FH expert consensus panel recommended considering genetic testing for FH in patients with definite or probable FH, as well as for their at-risk relatives.[22]

The age at diagnosis in our US cohort is arguably late for a genetic condition characterized by early ASCVD morbidity and mortality, suggesting that primary care providers might not be fully implementing early selective screening starting at age 2 years as is recommended for those with a family history of premature ASCVD. More education may be needed targeting primary care providers to reinforce the importance of selective screening starting at age 2 years for patients with high-risk family history. However, a family history of

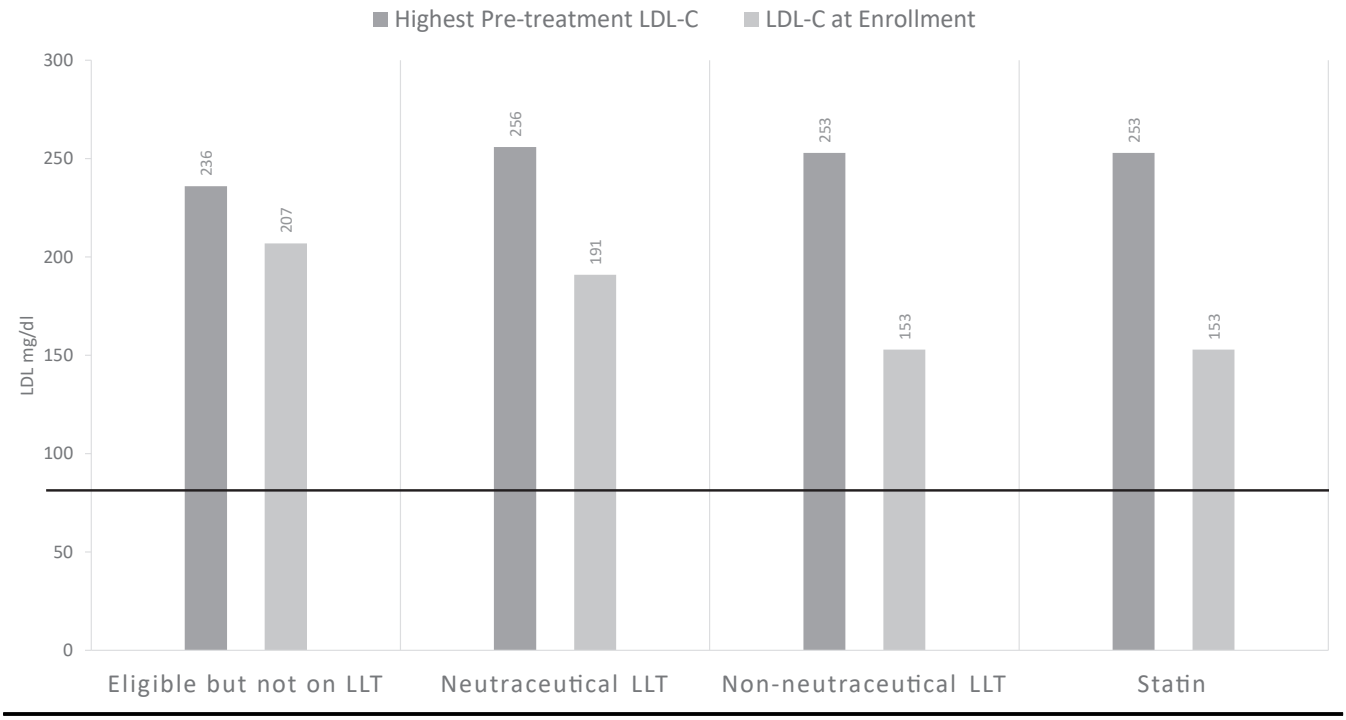

Figure 3. LDL-C levels in various subgroups, including participants eligible for lipid-lowering therapy but not receiving lipid-lowering therapy (eg, lifestyle modifications alone), those receiving nutraceutical lipid-lowering therapy (eg, psyllium, phytosterols, omega-3 fatty acids), those receiving non-nutraceutical lipid-lowering therapy (bile acid sequestrants, niacin, ezetimibe, statins), and those specifically taking statins. Data are shown as mean highest pretreatment and enrollment LDL-C levels, in mg/dL. The solid line indicates a goal LDL-C of 130 mg/dL.

premature ASCVD is not always present in children with FH, as reported elsewhere.[23,24] The average age of identification is younger than might be expected if cases were identified solely by universal screening at age 9-11 years, as recommended by the 2011 Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[11] Our finding that a family history of ASCVD was more frequently reported in children aged 10 years and older compared with the younger age group supports the assertion that FH is identified in US children by a blend of opportunistic screening based on family history and partial adherence to the recommendation for universal cholesterol testing at age 9-11 years. Another possible explanation for the late identification at age 9 may be that statins are not recommended by the 2011 National Heart, Lung, and Blood Institute guidelines until age 10 years (age 8 years in those with a particularly concerning family history or very high LDL-C level).[11] Pediatricians might not be testing—or perhaps not referring to specialist care—until the age at which a statin might be prescribed.

We were able to examine additional ASCVD risk factors in US youths with FH and found that nearly two-thirds had cardiovascular risk factors beyond FH including low HDL-C level, hypertension, diabetes, and obesity. Obesity was seen slightly less frequently in our cohort than in the US population overall (15.2% vs 18.5% in the US overall)[25] and at higher rates than in children with FH in the UK, of whom 11.1% were obese (vs 21.1% of children without FH in the UK).[20] Only 1 patient in our registry reported smoking, compared with 6% in the SAFEHEART cohort.

Our study was necessarily limited, as are all observational analyses of registry data. Treatments were not randomized, and adherence to treatments was unknown, limiting the assessment of LDL-C–lowering efficacy. The diagnosis of FH could have been made informally earlier, with referral tied to the age of statin initiation; however, this is likely to have been infrequent given the low awareness of FH among primary care providers.[26] Patients were from referral populations seen by specialists, often with a special interest in pediatric FH. Although many major medical centers are represented, the CASCADE-FH Registry does not comprise a nationally representative sample, making it impossible to estimate the degree to which youths with FH are being identified and referred. Furthermore, the enrolled participants might not represent all of a given sites' pediatric patients with FH; indeed, enrollment continues to accrue. Information on genetic diagnoses were quite limited and lipoprotein(a) levels were not collected during this initial phase of the registry, because they were rarely assessed in children at the time the registry was formed. Of note, the participant sample comprises a mixture of those followed previously by the enrollment site and newly diagnosed cases; newly diagnosed cases might have been started on treatment at the enrollment visit or would not necessarily have had time to achieve treatment goals. The data reported here are not longitudinal, and future analyses will address this question.

In adult patients in the CASCADE-FH Registry, substantial improvements in goal achievement were seen after enrollment.[27]

We found that children with FH in the US are diagnosed later and report lower rates of statin use,[5,23,28] and that a substantial proportion failed to achieve an LDL-C level <130 mg/dL or a ≥50% reduction, as recommended by US and other international guidelines, at least at the time of enrollment in the registry. These findings stand in contrast to randomized controlled clinical trial data demonstrating good short- and medium-term statin efficacy and tolerability,[29] a single long-term follow-up study demonstrating high rates of statin use over a decade after childhood initiation, and lower ASCVD event rates in those treated in childhood compared with their parents over 2 decades of follow-up.[30-32]

Youths enrolled in the CASCADE-FH Registry had clinical characteristics typical of FH, with 35% having a family history of premature ASCVD and 64% having a family history of FH, yet the diagnosis of FH occurred relatively late (age 9 years). One-third of children with FH in the CASCADE-FH Registry had additional modifiable ASCVD risk factors beyond FH, suggesting opportunities to optimize reduce the risk of ASCVD in youths with FH. Only 77% of the children eligible for lipid-lowering therapy were receiving treatment, providing an opening for improved care through lipid-lowering therapy initiation. Opportunities exist for earlier diagnosis, broader use of lipid-lowering therapy (with an emphasis on statins), and greater LDL-C reduction. Future analyses of the CASCADE-FH Registry will describe the longitudinal follow-up of these high-risk youths, including the duration and intensity of therapy; explore racial/ethnic differences; assess for uncommon adverse effects of lipid-lowering therapy and rare comorbidities of FH; and investigate how data collection and feedback to the sites may influence future practice patterns.

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50 Years Ago in *The Journal of Pediatrics*

From Aspirin to Magnets: 50 Years of Pediatric Ingestions

Deeths T, Breeden J. Poisoning in Children—A Statistical Study of 1057 Cases. J Pediatr 1971;78:299-305.

Deeths and Breeden collected data on pediatric ingestion admissions at Milwaukee Children's Hospital from 1962 to 1968 and took special note of the number of patients treated for aspirin and hydrocarbon ingestions. Their findings were part of a broader problem throughout the US, with an estimated 2 million poisonings and 400 deaths per year in patients under 5 years of age. Although there were variations from year to year in the particular ingestions, there were no discernable improvements in ingestions of aspirin or hydrocarbons.

It is within this epidemic of ingestions that national legislation began to take effect and protect children. Just before the study period, in 1957, poison control centers were first mandated to collect and report data to the US Food and Drug Administration, and in 1961, *The Child Protection Act* first banned dangerous and hazardous toys. In 1966, aspirin packaging requirements were changed to decrease toxic pediatric ingestions. Finally, the Consumer Product Safety Commission was created with the *Poison Prevention Packaging Act* in 1970. Together, these legislative actions changed the market for medications and toys which could be ingested by young children. Since then, the number of fatalities due to poisoning for children less than 5 years of age has decreased from 216 deaths in 1972 to 30 deaths in 2016.[1]

Despite the success of this legislation, there are still challenges today. In 2018, there were nearly 1 million calls to Poison Control Centers for exposures to children 5 years old and younger, representing more than 40% of reported exposures.[2] New products often represent the greatest threats, and recent trends in exposures include laundry detergent pods and rare earth magnets. These products fall within broad categories, household chemicals and toys, that continue to represent common ingestions for children since the 1950s. As clinicians and advocates, pediatricians must remain diligent and coordinate with Poison Control Centers to quickly note trends in exposures and notify the public, the Consumer Product Safety Commission, and legislators when products pose dangers to young children.

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