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CARDIOVASCULAR DISEASE AND STROKE (J.A. UNDERBERG AND J. NEWMAN, SECTION EDITORS)

Prevention of Atherosclerotic Cardiovascular Disease in Children with Familial Hypercholesterolemia

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Abstract

Purpose of Review Familial hypercholesterolemia (FH), a common inherited disorder of LDL-C metabolism that predisposes to premature cardiovascular disease, is underdiagnosed. Despite recommendations for screening all children and initiation of lipid-lowering medication beginning at 8–10 years of age, adherence to guidelines is low. Most individuals with FH are inadequately treated, especially women and children. The purpose of this review is to discuss current literature and recommendations for the diagnosis and treatment of heterozygous FH (HeFH) in the pediatric population.

Recent Findings Twenty-year outcome data demonstrate lower rates of atherosclerotic cardiovascular disease (ASCVD) related events and death in individuals with FH who were treated with statins from childhood, compared to those who initiated statins in adulthood. While diagnosis rates of FH are slowly improving, most clinicians do not adhere to recommendations for cholesterol screening in youth.

Summary Identifying youth with FH offers the opportunity for early intervention to prevent ASCVD and identify affected relatives through reverse cascade screening.

Keywords Familial hypercholesterolemia · Cascade screening · Cholesterol screening · Pediatric preventive cardiology · Cardiovascular disease · Children

Introduction

Familial hypercholesterolemia, a leading cause of premature ASCVD, is the best characterized disorder of lipid metabolism affecting the pediatric population. It is an autosomal co-dominant disorder of low-density lipoprotein cholesterol (LDL-C) metabolism which leads to high plasma levels of LDL-C. Present from birth, it predisposes to premature ASCVD-related events, such as myocardial infarction and stroke. In its heterozygous form, FH affects approximately 1 in 200–300 people [1], although some ethnic groups have a higher prevalence. Without treatment, approximately 50% of men and 30% of women experience an ASCVD-related event by age 50 and 60 years, respectively [2]. FH-related ASCVD is further accelerated by acquisition of additional risk factors (Fig. 1). HeFH is the most common monogenic disorder and potentially lethal genetic condition affecting humans, highlighting the importance of early detection and appropriate intervention.

HeFH guidelines recommend use of a hydroxymethylglutaryl-CoA reductase inhibitor (statin) starting at

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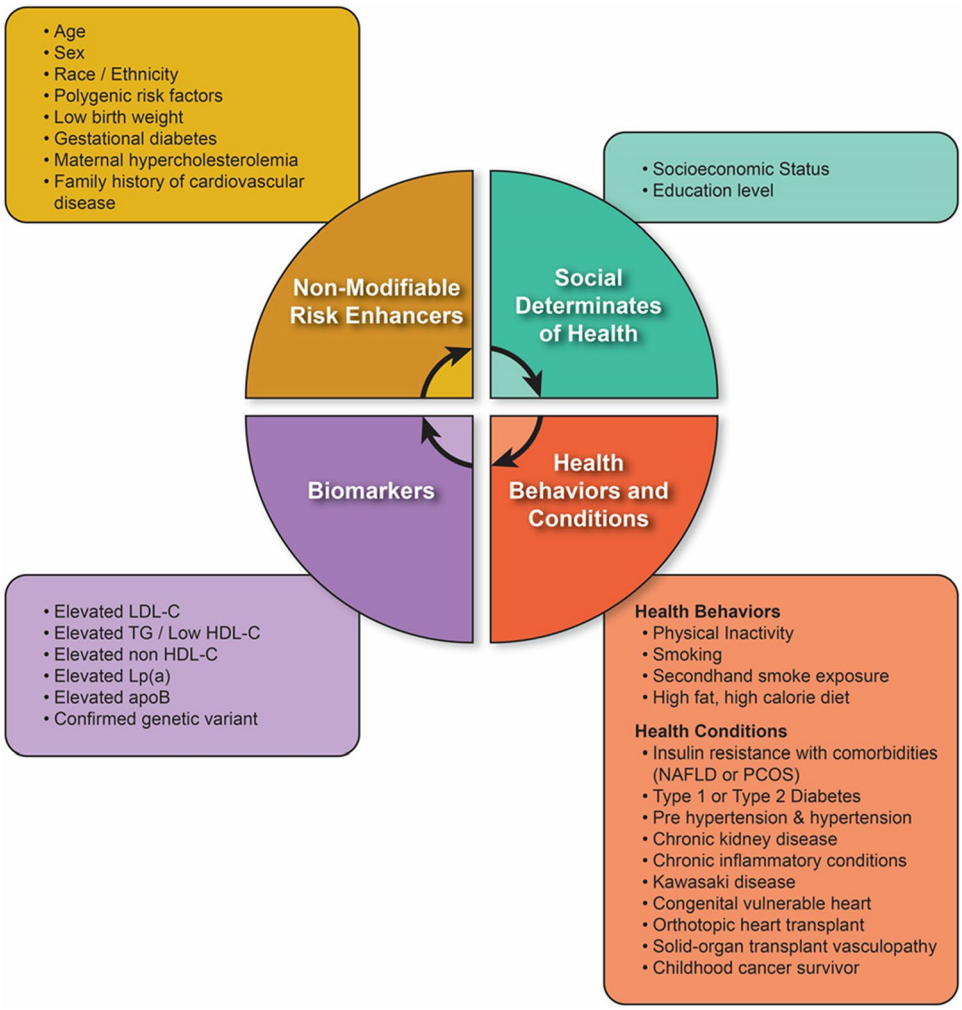

Fig. 1 Global risk factors. A number of risk factors, conditions, and enhancers have been identified that are known to cause or increase the likelihood of premature ASCVD in adults. Although noninvasive studies have demonstrated an associated risk in children, including those with HeFH, outcome studies are lacking. Until further evidence becomes available, the presence of risk factors, conditions, and enhancers in children with HeFH may be helpful in properly assessing risk and helping define therapeutic targets

8–10 years of age to decrease the lifetime exposure to atherogenic lipoproteins, the underlying cause of atherosclerosis. This process starts at an early age and accelerates by age 20 [3]. Currently, HeFH is largely underdiagnosed, with less than 10% of affected adults being aware of their condition [2].

Such findings are the basis for the 2011 recommendation from the National Heart, Lung and Blood Institute (NHLBI) and American Academy of Pediatrics (AAP) for universal cholesterol screening of all children, regardless of their health status or family history, and selective screening of those 2 years of age and older with risk factors and conditions. The goal of screening is to identify those with HeFH and initiate appropriate treatment, starting at a young age [4] (Table 1). This recommendation is in contrast to previous guidelines which advocated only selective screening [5]. In this review, we discuss current recommendations for diagnosis and treatment of youth with HeFH 18 years of age and younger, with the goal of preventing ASCVD-related premature morbidity and mortality in this high-risk population.

Overview of HeFH in Children

Diagnostic Criteria

The diagnosis of HeFH is based on clinical criteria, demonstration of a pathogenic gene variant, or both. There are three established algorithms (plus a fourth recommendation) for clinical diagnosis of HeFH, all of which may be applied to children (Table 2). The Simon-Broome Register [6] and Dutch Lipid Clinic Network [2] criteria rely on physical findings and family history in addition to the results of genetic testing. The MEDPED (Make Early Diagnosis, Prevent Early Death) criteria [7] utilize only total cholesterol and family history. Each has benefits and limitations when applied to children. To facilitate the diagnosis in children, the American Heart Association (AHA) recommended a fourth method that relies only on laboratory values and reported history [8].

While physical findings and family history are helpful, their ability to identify children with FH is limited.

Table 1 Recommendations for cholesterol screening of youth ≤ 21 years [4]

Age (years)	Selective screening*	Universal screening**
< 2	No	No
2–8	Yes	No
9–11	Yes	Yes
12–16	Yes	No
17–21	Yes	Yes

Both selective and universal cholesterol screening can be performed fasting or non-fasting, by venipucture or fingerstick and measured using point of care or laboratory methodology

*If any of the following criteria are met:

• Parent, grandparent, aunt/uncle, or sibling with myocardial infarction, angina, stroke, coronary artery bypass graft, stent, or angioplasty (age < 55 years in males, < 65 in females)

• Parent with total cholesterol ≥ 240 mg/dL or known hypercholesterolemia

• Child has diabetes (type 1 or 2), hypertension, BMI ≥ 95%ile or uses tobacco

• Child has a special risk condition (post orthotopic heart transplant, chronic kidney disease, end-stage kidney disease, post renal transplant, Kawasaki disease with current or regressed aneurysms, chronic inflammatory disease such as systemic lupus erythematosus or juvenile idiopathic arthritis, human immunodeficiency virus infection, or nephrotic syndrome)

**Universal screening includes all children regardless of their health status or family history

Physical manifestations of hypercholesterolemia are rare during childhood, while family histories are often incomplete, inaccurate, or unavailable. Many families are unaware of the health histories of relatives and access to their medical records unlikely.

Clinicians should be aware that over the past 50 years, the typical presentation of adults with HeFH has changed, resulting in what the authors term "the unnatural family history." The high prevalence of statin use in adults has significantly altered the traditional history of elevated levels of cholesterol and premature ASCVD. A growing number of adults have received treatment for hypercholesterolemia without a confirmed diagnosis, and as a result, are less likely to have characteristic physical findings of HeFH or have experienced a premature ASCVD-related event.

Prevalence of HeFH

Recent studies estimate the prevalence of HeFH between 1 in 200–300, with slight variations depending on the study population and diagnostic criteria used. A meta-analysis estimated the prevalence at 1 in 311 in the general population, based upon data from over 10 million individuals [9]. Among those with a diagnosis of ASCVD, the prevalence was 1 in 17 [10], and among those with ASCVD under 50 years of age, the prevalence rose to 1 in 5 [11]. In the USA, 1 in 250 adults has diagnostic criteria consistent with HeFH [12]. Pediatric prevalence studies found HeFH in 1 in 267 Australian [13] and 1 in 267 US adolescents [12].

Risk Enhancers

Other conditions enhance the risk for premature ASCVD in individuals with and without HeFH (Fig. 1). Studies of risk stratification in youth with HeFH are limited due to the extended length of time from diagnosis to the onset of ASCVD. Therefore, our current understanding is primarily extrapolated from studies in adults. Only conditions linked to ASCVD in individuals with HeFH are reviewed here. The reader is referred to the NHLBI Guidelines [4] or the AHA High-Risk Pediatric Populations statement [14••] for comprehensive reviews of the impact of risk enhancers in the general pediatric population.

In adults with HeFH, the presence of additional plasma lipids and lipoproteins abnormalities, namely, low high-density lipoprotein cholesterol (HDL-C) and/or elevated triglycerides (TG) [15], is independently associated with ASCVD-related events. The degree of LDL-C elevation and duration of exposure is critical in determining risk. Adults with HeFH and high LDL-C have earlier onset of ASCVD [2, 16–18], lending support for early treatment of HeFH. Following 20 years of statin therapy started in childhood, young adults with HeFH had, compared to their affected parent who started statin therapy later in life, lower rates of both ASCVD-related events (1%) and death (0%) at age 39 than their affected parent at a comparable age (26% and 7%, respectively) [19••].

Lipoprotein (a) [Lp(a)] is a plasma lipoprotein consisting of an LDL-like particle linked to apolipoprotein (a). It is well characterized in adults; observational and genetic evidence support an independent, causal relationship between high Lp(a) and increased risk of ASCVD [20, 21]. Individuals with both HeFH and high Lp(a) are at very high risk for premature ASCVD [22]. In a study of children with HeFH, those from families with early-onset ASCVD were 3X more likely to have Lp(a) ≥ 50 mg/dL compared to children from families with late-onset ASCVD. Family history of early ASCVD was more predictive of a child's Lp(a) level than the child's peak LDL-C [23].

The limitations notwithstanding, when reliable family history is available, it is the strongest risk predictor of a child having HeFH. In children with [24, 25] and without [26] HeFH, a family history of ASCVD is a strong independent risk factor for future ASCVD-related events.

In adults, the presence of a pathogenic genetic variant for HeFH increases the risk for ASCVD at all LDL-C levels compared to individuals without a pathogenic variant [27].

Table 2 Diagnostic criteria for heterozygous familial hypercholesterolemia in children

Simon Broome criteria [6]

Definite or Probable diagnosis of HeFH requires elevated cholesterol:

- Total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL if ≤ 15 years
- Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL if ≥ 16 years

PLUS

One or more additional findings:

Definite HeFH: additional findings

1. Tendon xanthoma in the child, first-degree relative, or second-degree relative
2. Genetic testing of a confirmed pathogenic variant *(LDLR, ApoB, or PCSK9)*

POSSIBLE HeFH: additional findings

1. Family history of myocardial infarction ≤ 60 years in a first-degree relative or ≤ 50 years in a second-degree relative
2. Family history of a total cholesterol ≥ 290 mg/dL in a first or second-degree relative who is ≥ 16 years, or ≥ 260 mg/dL a sibling who is ≤ 15 years

MEDPED criteria [7]

A child is considered to have HeFH if total cholesterol meets or exceeds the threshold listed below. Thresholds vary based upon whether or not there is a first-, second-, or third-degree relative known to have HeFH

Child's age ≤ 19 years	Does the child have one or more relatives with HeFH?			
	Yes			No
	First degree	Second degree	Third degree	N/A
Total cholesterol	≥ 220 mg/dL	≥ 230 mg/dL	≥ 240 mg/dL	≥ 270 mg/dL

Dutch lipid clinic network criteria [2]

Diagnosis of HeFH is based on the total number of points obtained. *Definite* HeFH, > 8 points. *Probable* HeFH, 6–8 points. *Possible* HeFH, 3–5 points. *Unlikely* HeFH, < 3 points

Criterion:	Points
Family history:	
First-degree relative with known premature ASCVD (< 55 years in men, < 60 years in women), OR first-degree relative with LDL-C ≥ 95%ile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR pediatric first-degree relative with LDL-C ≥ 95%ile	2
Clinical history:	
Patient with premature ASCVD (< 55 years in men, < 60 years in women)	2
Patient with premature cerebral or peripheral vascular disease	1
Physical examination:	
Tendinous xantomata	6
Arcus cornealis with onset prior to 45 years	4
Patient's cholesterol levels	
LDL-C ≥ 330 mg/dL	8
LDL-C 250–329 mg/dL	5
LDL-C 190–249 mg/dL	3
LDL-C 155–189 mg/dL	1
Genetic testing	
Pathogenic variant in *LDLR*, *APOB*, or *PCSK9*	8

American Heart Association criteria [8]

Children (≤ 18 years) with LDL-C ≥ 160 mg/dL **AND**

Family history of elevated cholesterol or premature ASCVD **AND**

No evidence of secondary causes of hypercholesterolemia

In contrast, the presence or absence of a pathogenic variant in children with HeFH may not be as predictive for ASCVD. This, in part, may be due to an age-related decline in the ability to distinguish FH from other causes of hypercholesterolemia based solely upon the level of LDL-C. Less overlap of LDL-C values is seen in children [28–31], making the diagnosis of HeFH based upon the level of LDL-C more likely in children vs. adults. The increased risk imposed by a pathogenic variant

may simply distinguish adults with high LDL-C from birth from those who acquired LDL-C elevation later in life due to unhealthy lifestyle choices.

Screening Guidelines for HeFH

There are three different strategies to identify adults and children with HeFH: traditional and reverse cascade screening, selective screening of individuals at-risk of HeFH with or without a known affected family member, and universal screening regardless of health status and risk factors.

Historically, traditional cascade screening has been the primary strategy to identify individuals with HeFH, i.e., testing of first and second-degree relatives of an adult index case who has high hypercholesterolemia and premature ASCVD. The effectiveness of cascade screening varies from 0.4–2 additional cases per index case [32–34]. Modeling has demonstrated that while cascade screening is helpful, it is not sufficient to achieve high detection rates [35]. Limited data is available about the impact of reverse cascade screening, i.e., using a child with FH as the index case.

Selective screening of children with risk factors for premature ASCVD was initially recommended in 1992 [5] and was the sole method utilized until 2011 [36]. The CARDIAC project, which included 20,000 children, found the prevalence of elevated LDL-C to be higher in children who did not meet selective screening criteria compared to those that did. In this study population, application of selective screening would have failed to identify 37% of children who met criteria for pharmacotherapy [37]. Based on these findings, in 2011, universal cholesterol screening was recommended [4]. This recommendation, however, has been controversial, receiving an "I" recommendation from the United States Preventive Services Task Force (USPSTF) [38]. Notably, the USPSTF concluded they were unable to recommend for or against universal screening based upon their methodology. Adherence to universal cholesterol screening of children by the US clinicians remains low, with most reported screening rates falling below 5% [39–43].

Data suggest that universal screening in childhood combined with reverse cascade screening may represent an optimal approach to improve detection of HeFH. In a US health care system with over 50% of children screened for hypercholesterolemia [40], children served as the proband for cascade screening of family members [44]. A similar experience was reported in Beijing [45].

Clinical Evaluation

History, Physical Examination, and Family History

Youth with HeFH are asymptomatic. HeFH does not predispose children to becoming overweight or obese, although unhealthy lifestyle choices may exacerbate LDL-C elevation and contribute to excessive weight gain. Physical manifestations, such as xanthoma, xanthelasma, and thickening of the Achilles' tendons, are extremely rare in children and, when present, should prompt investigation for other causes, such as homozygous familial hypercholesterolemia [46], sitosterolemia [47, 48], and primary sclerosing cholangitis [49]. Family history can be helpful but is often incomplete, unreliable, or unavailable and fails to identify as many as 30–60% of youth with hypercholesterolemia [50].

Laboratory Testing

Recommendations for cholesterol screening in youth are shown in Table 1. While the primary aim of cholesterol screening is to identify HeFH [51], use of a lipid panel may detect other abnormalities which, if present, do not exclude the possibility of HeFH.

Initial screening results suggestive of HeFH should be confirmed with repeat testing. Tests to exclude secondary causes, including thyroid, liver, and kidney abnormalities, are required. Follow-up testing is recommended 3–6 months after implementation of lifestyle changes. Lp(a) testing is recommended in all youth with clinically suspected or genetically confirmed HeFH [21]. Routine measurement of apo B, apo A1, and advanced lipoprotein analysis is not recommended [4] at this time, although may be helpful in selected cases. The evaluation of a child with suspected HeFH should include all non-modifiable and modifiable risk enhancers [52].

Genetic Testing

Genetic testing of individuals with HeFH is recommended to facilitate diagnosis, initiate, and inform recommendations for intensity of lipid-lowering therapy and to identify affected relatives through reverse cascade screening [53, 54, 55•]. Genetic testing may provide closure for some parents and caregivers, validating the need for long-term pharmacotherapy.

Pathogenic variants exhibit significant variability in phenotype, both within the same family and among carriers with the same mutation in different populations. Therefore, while genetic testing can provide diagnostic confirmation and enhance risk stratification, genetic counseling, and clinical decision-making, it must be combined with biochemical testing, imaging when indicated, family history and outcomes studies in order to develop treatment recommendations [55•]. The absence of genetic testing should not delay treatment of individuals with a clinical diagnosis of HeFH nor in those in whom no genetic variant is found.

The optimal age for genetic testing is unclear. Clinicians should consider the potential for unintended consequences of genetic testing, especially in children. Counseling prior to genetic testing is necessary, including a discussion of cost, testing limitations, potential for psychological harm, stigmatization, and discrimination [56]. Clinicians should familiarize themselves with current recommendations for genetic testing in children, as there are ethical considerations unique to their population [56].

Clinical Management

Dietary Management

A diet low in saturated and trans fats is fundamental to lower LDL-C. Dietary management of HeFH is best implemented in a stepwise, family-centered approach, using the Cardiovascular Health Integrated Lifestyle Diet 2-LDL diet (CHILD 2-LDL) to lower cholesterol [4]. In those who have an elevated TG, incorporating a CHILD 2-TG diet may also be beneficial. Data supporting these recommendations are limited; one of the only studies to evaluate the impact of the CHILD-1 diet on LDL-C reported a 5.1 mg/dL reduction [57]. For more information, the reader is referred to a recent review of dietary studies in children [58].

It is import for the family to understand that a high-fat diet can further exacerbate the LDL-C elevation caused by FH, while a low-fat diet, in the absence of lipid-lowering therapy, cannot completely mitigate the LDL-C elevation. Consistent modeling of healthy behaviors by the parents or caregivers is critical for the child to be successful. Counseling by an experienced Dietitian Nutritionist is strongly recommended for families with HeFH; when access is limited, clinicians are encouraged to utilize online resources. The assessment and stepwise approach to dietary counseling has previously been reviewed [59].

Nutritional Supplements and Nutraceuticals

Data regarding use of dietary supplements in children are sparse. Generally, supplements are not effective and/or not recommended. Fish oils rich in omega-3 fatty acids (O-3-FAs) are frequently recommended for children with hypercholesterolemia. However, O-3-FAs primarily lower triglycerides and may elevate LDL-C. Soluble fiber and garlic have little or no efficacy in LDL-C reduction. The active ingredient contained in red yeast rice is identical to lovastatin; due to lack of regulation and oversight of supplements, data are limited and red yeast rice is not recommended for children. Plant stanols and sterols can lower LDL-C modestly but may adversely impact fat-soluble vitamin absorption and are not generally recommended for children [60]. "Flush-free niacin," inositol hexaniacinate, which does not contain niacin (and therefore does not lower LDL-C), may be hepatotoxic. Both immediate-release and slow-release niacin primarily lower LDL-C, but are often associated with intolerable flushing. Due to widespread availability and marketing as "natural," families often believe dietary supplements are safer than prescription medications; however, none has been proven to be either safe or effective in youth.

Pharmaceutical Treatment

In the USA, statins are the first-line pharmacotherapy recommended for HeFH. All commercially available statins are FDA approved, pravastatin, rosuvastatin, and pitavastatin starting at 8 years of age, all others at age 10, with an LDL-C level persistently ≥ 160 mg/dL after 3 to 6 months of lifestyle modification, and a clinical presentation consistent with FH [2, 3, 14••, 61]. A target LDL-C level of < 130 mg/dL or a 50% reduction from baseline is frequently used in clinical practice, although data to support this recommendation in youth is lacking.

Compared to clinical trials and population-based outcome data in older adults, much less data is available to guide clinical decision-making in youth. A recent review of 10 studies involing 1191 children demonstrated efficacy of statins with respect to LDL-C lowering and identified no safety concerns [62]. When combined with Mendelian randomization studies of LDL-C lowering, both "the lower, the better" and "the younger, the better" emerge as important concepts in pediatric HeFH management. Such concepts are harmonious with data suggesting the burden of advanced, irreversible atherosclerotic disease in adults is attributable to delayed initiation of pharmacotherapy [63].

Importantly, pediatric guidelines do not differ with respect to recommendations for statin therapy based on gender. While some clinicians may be hesitant to prescribe statins in girls due to potential teratogenic effects related to pregnancy, with appropriate counseling and monitoring, there are no contraindications in doing so.

Ezetimibe is FDA approved for children starting at 10 years of age. Some bile acid sequestrants are approved, but their use is limited by relatively lower efficacy compared to statins (less LDL-C reduction) and GI side effects. Other pharmacotherapy options commonly used in adults (including proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, bempedoic acid, and inclisirin) are not currently approved for use in children. Lipoprotein apheresis is limited to children with homozygous FH.

Imaging

Routine imaging for children with HeFH is not recommended; however, imaging is frequently necessary for

clinical care of children with homozygous FH. The reader is referred to existing guidelines for diagnosis and treatment [46].

Future Directions

Given the ethical and logistical challenges of randomized controlled trials (RCTs), which attempt to associate long-term treatments started at young ages with ASCVD-related outcomes, such studies are highly unlikely. While long-term RCTs would be ideal, it is more likely that clinicians who treat children with HeFH will continue to rely on epidemiologic, observational and Medellin randomization studies, expert opinion, and short-term RCTs to help inform clinical decision making and public policy.

Conclusion

HeFH is the best characterized and the most common potentially lethal genetic disease affecting children. Universal, selective and reverse cascade cholesterol screening represents unique opportunities to identify and initiate safe and effective treatment to prevent premature ASCVD in children with HeFH and their families. It is this ability to reliably detect HeFH during childhood, identify affected family members through reverse cascade screening, and offer treatment to prevent premature ASCVD that underscores the urgent need for clinicians to implement universal cholesterol screening in childhood. Although long-term outcome studies in youth with HeFH are limited, other types of evidence (observational studies, meta-analyses, and Medellin randomization studies), as well as expert opinion continue to help inform guidelines, intended to help define best practices for the diagnosis and treatment of this high-risk population.

Declarations

Conflict of Interest Amy L. Peterson is serving on the steering committee for the ORION-13 and ORION-16 trials (sponsored by Novartis Pharmaceuticals) (payments are made to her institution); she is on the Scientific Advisory Committee for Familial Hypercholesterolemia Foundation (unpaid); and she is an AHOY Committee member for the American Heart Association (unpaid) and the Health Quality and Research Committee for the National Lipid Association (unpaid), and on the Board of Directors for the American Board of Clinical Lipidology (unpaid). Catherine J. McNeal is on the Speaker's Bureau for Novo Nordisk. Don P. Wilson reports no disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Benn M, Watts GF, Tybjærg-Hansen A, Nordestgaard BG. Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J. 2016;37(17):1384–94.
2. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478–90.
3. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S1-8.
4. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5:S213–56.
5. National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89(3):495–501.
6. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ. 1991;303(6807):893–6.
7. Williams RR, Hunt SC, Schumacher MC, Hegele RA, Leppert MF, Ludwig EH, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol. 1993;72(2):171–6.
8. Gidding SS, Champagne MA, Ferranti SDd, Defesche J, Ito MK, Knowles JW, et al. The Agenda for Familial Hypercholesterolemia. Circulation. 2015;132(22):2167–92.
9. Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia. Meta-Analyses of 11 Million Subjects. 2020;75(20):2553–66.
10. Hu P, Dharmayat KI, Stevens CAT, Sharabiani MTA, Jones RS, Watts GF, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease. Circulation. 2020;141(22):1742–59.
11. De Backer G, Besseling J, Chapman J, Hovingh GK, Kastelein JJ, Kotseva K, et al. Prevalence and management of familial hypercholesterolaemia in coronary patients: an analysis of EUROASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis. 2015;241(1):169–75.
12. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES)CLINICAL PERSPECTIVE. Circulation. 2016;133(11):1067–72.
13. Pang J, Martin AC, Mori TA, Beilin LJ, Watts GF. Prevalence of Familial Hypercholesterolemia in Adolescents: Potential Value of Universal Screening? J Pediatr. 2016;170:315–6.
14. •• de Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart

Association. Circulation. 2019;139(13):e603–34. **This comprehensive scientific statement reviews diagnostic evaluation and treatment recommendations for children with medical conditions, including HeFH, known to significantly increase their lifetime ASCVD risk.**

15. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J. 2011;32(11):1345–61.
16. Raal FJ, Pilcher GJ, Waisberg R, Buthelezi EP, Veller MG, Joffe BI. Low-density lipoprotein cholesterol bulk is the pivotal determinant of atherosclerosis in familial hypercholesterolemia. Am J Cardiol. 1999;83(9):1330–3.
17. Pérez de Isla L, Alonso R, Mata N, Fernández-Pérez C, Muñiz O, Díaz-Díaz JL, et al. Predicting Cardiovascular Events in Familial Hypercholesterolemia: The SAFEHEART Registry. Circulation. 2017.
18. Hopkins PN, Stephenson S, Wu LL, Riley WA, Xin Y, Hunt SC. Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia. Am J Cardiol. 2001;87(5):547–53.
19. •• Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med. 2019;381(16):1547–56. **This landmark cohort study reports lower rates of ASCVD events in adults with HeFH treated with statins since childhood compared to their parents with HeFH who started treatment in adulthood. None of the adults treated since childhood reported significant side effects from long-term statin therapy.**
20. Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. J Am Coll Cardiol. 2017;69(6):692–711.
21 Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, McNeal CJ, Nordestgaard BG, et al. Use of Lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol. 2019;13(3):374–92.
22. Ellis KL, Pang J, Chieng D, Bell DA, Burnett JR, Schultz CJ, et al. Elevated lipoprotein(a) and familial hypercholesterolemia in the coronary care unit: between Scylla and Charybdis. Clin Cardiol. 2018;41(3):378–84.
23. Zawacki AW, Dodge A, Woo KM, Ralphe JC, Peterson AL. In pediatric familial hypercholesterolemia, lipoprotein(a) is more predictive than LDL-C for early onset of cardiovascular disease in family members. J Clin Lipidol. 2018;12(6):1445–51.
24 Wiegman A, Rodenburg J, de Jongh S, Defesche JC, Bakker HD, Kastelein JJP, et al. Family history and cardiovascular risk in familial hypercholesterolemia. Data in More Than 1000 Children. Circulation. 2003;107(11):1473–8.
25. de Jongh S, Lilien MR, Bakker HD, Hutten BA, Kastelein JJP, Stroes ESG. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. Atherosclerosis. 2002;163(1):193–7.
26. Leander K, Hallqvist J, Reuterwall C, Ahlbom A, de Faire Ulf. Family history of coronary heart disease, a strong risk factor for myocardial infarction interacting with other cardiovascular risk factors: results from the Stockholm Heart Epidemiology Program (SHEEP). Epidemiology. 2001;12(2):215–21.
27. Khera AV, Won H-H, Peloso GM, Lawson KS, Bartz TM, Deng X, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. 2016;67(22):2578–89.
28. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. Lancet. 2001;357(9251):165–8.
29. Huijgen R, Hutten BA, Kindt I, Vissers MN, Kastelein JJ. Discriminative ability of LDL-cholesterol to identify patients with familial hypercholesterolemia: a cross-sectional study in 26,406 individuals tested for genetic FH. Circ Cardiovasc Genet. 2012;5(3):354–9.
30. Starr B, Hadfield SG, Hutten BA, Lansberg PJ, Leren TP, Damgaard D, et al. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. Clin Chem Lab Med. 2008;46(6):791–803.
31. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ. 2007;335(7620):599.
32. Bell DA, Pang J, Burrows S, Bates TR, van Bockxmeer FM, Hooper AJ, et al. Effectiveness of genetic cascade screening for familial hypercholesterolaemia using a centrally co-ordinated clinical service: an Australian experience. Atherosclerosis. 2015;239(1):93–100.
33. Jannes CE, Santos RD, de Souza Silva PR, Turolla L, Gagliardi AC, Marsiglia JD, et al. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. Atherosclerosis. 2015;238(1):101–7.
34. Bhatnagar D, Morgan J, Siddiq S, Mackness MI, Miller JP, Durrington PN. Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia. BMJ. 2000;321(7275):1497–500.
35 Morris JK, Wald DS, Wald NJ. The evaluation of cascade testing for familial hypercholesterolemia. Am J Med Genet A. 2012;158a(1):78–84.
36. Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122(1):198–208.
37. Ritchie SK, Murphy EC, Ice C, Cottrell LA, Minor V, Elliott E, et al. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. Pediatrics. 2010;126(2):260–5.
38. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, Garcia FA, et al. Screening for lipid disorders in children and adolescents: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;316(6):625–33.
39. Dixon DB, Kornblum AP, Steffen LM, Zhou X, Steinberger J. Implementation of lipid screening guidelines in children by primary pediatric providers. J Pediatr. 2014;164(3):572–6.
40. DeSantes K, Dodge A, Eickhoff J, Peterson AL. Improving universal pediatric lipid screening. J Pediatr. 2017;188:87–90.
41. Allen-Tice C, Steinberger J, Murdy K, Zierhut H. Pediatric cholesterol screening practices in 9- to 11-year-olds in a large midwestern primary care setting. J Clin Lipidol. 2020;14(2):224–30.
42. Valle CW, Binns HJ, Quadri-Sheriff M, Benuck I, Patel A. Physicians' lack of adherence to national heart, lung, and blood institute guidelines for pediatric lipid screening. Clin Pediatr (Phila). 2015;54(12):1200–5.
43. Zachariah JP, McNeal CJ, Copeland LA, Fang-Hollingsworth Y, Stock EM, Sun F, et al. Temporal trends in lipid screening and therapy among youth from 2002 to 2012. J Clin Lipidol. 2015;9(5 Suppl):S77-87.
44. Stempel H, Dodge A, Marriott E, Peterson AL. Referral patterns and cascade screening for familial hypercholesterolemia in a pediatric lipid clinic. J Pediatr. 2016;178:285–7.
45. Wu X, Pang J, Wang X, Peng J, Chen Y, Wang S, et al. Reverse cascade screening for familial hypercholesterolemia in high-risk Chinese families. Clin Cardiol. 2017;40(11):1169–73.

46 Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al. 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):2146–57.

47. Peterson AL, DeLine J, Korcarz CE, Dodge AM, Stein JH. Phenotypic variability in atherosclerosis burden in an old-order amish family with homozygous sitosterolemia. JACC: Case Rep. 2020;2(4):646–50.

48. Liebeskind A PA, Wilson DP. Sitosterolemia in the pediatric population. In: Feingold KR, Anawalt B, Boyce A, et al, editors. Endotext [Internet] South Dartmouth (MA): MDTextcom, Inc;2000-. Updated 2020 Jan 16.

49. Patel AM, Brautbar A, Desai NK, Wilson DP. Severe hypercholesterolemia and liver disease in a 3-year old. J Clin Lipidol. 2016;10(3):650–3.

50. Freedman DS, Byers T, Sell K, Kuester S, Newell E, Lee S. Tracking of serum cholesterol levels in a multiracial sample of preschool children. Pediatrics. 1992;90(1):80–6.

51. Ashraf AP, Kohn B, Wilson DP. Improving long-term outcomes of youth with lipid abnormalities—expanding the role of pediatric endocrinologists. J Clin Endocrinol Metab. 2019;104(10):4421–6.

52. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, 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. 2019;73(24):e285–e350.

53. Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, Ballantyne CM, et al. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018;72(6):662–80.

54 Musunuru K, Hershberger RE, Day SM, Klinedinst NJ, Landstrom AP, Parikh VN, et al. Genetic testing for inherited cardiovascular diseases: a scientific statement from the American Heart Association. Circ Genom Precis Med. 2020;13(4):e000067.

55.• Brown EE, Sturm AC, Cuchel M, Braun LT, Duell PB, Underberg JA, et al. Genetic testing in dyslipidemia: a scientific statement from the National Lipid Association. J Clin Lipidol. 2020;14(4):398–413. **Informative discussion of pros and cons of genetic testing in individuals with dyslipidemia. This publication provides relevant guidelines for clinical practice.**

56. Ethical and Policy Issues in Genetic Testing and Screening of Children. Pediatrics. 2013;131(3):620–2.

57. Ribas SA, Paravidino VB, Brandão JM, Santana da Silva LC. The Cardiovascular Health Integrated Lifestyle Diet (CHILD) lowers LDL-cholesterol levels in Brazilian dyslipidemic pediatric patients. J Am Coll Nutr. 2021:1–8.

58. Daniels SR, Couch SC. 25 - Lipid disorders in children and adolescents. In: Sperling MA, editor. Sperling Pediatric Endocrinology. 5th ed. Philadelphia: Elsevier; 2021. p. 1004–21.

59. Williams LA WD. Nutritional management of pediatric dyslipidemia. In: Feingold KR, Anawalt B, Boyce A, et al., editors Endotext [Internet] South Dartmouth (MA): MDTextcom, Inc;2000-. 2020.

60. Daniels SR, Couch SC. CHAPTER 23 - Lipid disorders in children and adolescents. In: Sperling MA, editor. Pediatric Endocrinology (Fourth Edition); 2014. p. 1015–34.e1.

61. Watts GF, Gidding S, Wierzbicki AS, Toth PP, Alonso R, Brown WV, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol. 2014;171(3):309–25.

62. Anagnostis P, Vaitsi K, Kleitsioti P, Mantsiou C, Pavlogiannis K, Athyros VG, et al. Efficacy and safety of statin use in children and adolescents with familial hypercholesterolaemia: a systematic review and meta-analysis of randomized-controlled trials. Endocrine. 2020;69(2):249–61.

63. deGoma EM, Ahmad ZS, O'Brien EC, Kindt I, Shrader P, Newman CB, et al. Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States. Circ Cardiovasc Genet. 2016;9(3):240–9.