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REVIEW

Is Family History for the Management of Cardiovascular Health in Youth Still Relevant in Clinical Practice?

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Abstract

Purpose of Review Family history of premature cardiovascular disease is a strong predictor of individual cardiovascular risk. However, family history is not always available and not always reliable. Roughly 80% of health outcomes are influenced not by genetic risk but by societal factors, including adverse health behaviors and environment. Furthermore, in the present age of genetic testing, laboratory evaluations, and imaging, a key question remains: *What is the contemporary relevance of family history screening in the management of cardiovascular disease in youth?*

Recent Findings Knowledge of an individual's family history can help clinicians identify not only inherited risk but also familial clustering of unhealthy behaviors and environmental adversity contributing to enhanced cardiovascular disease risk in youth. For those at greatest risk, prevention strategies can be applied sooner and more conservatively.

Summary Integrating family history into clinical practice is crucial for cardiovascular risk assessment and for optimizing outcomes, but, in some cases, is more reflective of social factors.

Keywords Family history · Cardiovascular · Hypertension · Hyperlipidemia · Social determinants of health

Introduction/Background

Cardiovascular disease (CVD) remains the leading cause of death in the United States [1]. Atherosclerosis is a complex process that involves many genetic loci, as well as multiple environmental and behavioral risk factors [2]. National organizations such as the American Academy of Pediatrics (AAP), American Heart Association (AHA),

2 Sentence article summary: Family history represents a composite of genetic, environmental, and behavior-related risks. Reliance on family history as an indicator of genetic risk alone, without consideration of the potential role of the social determinants of health, is cotemporally insufficient.

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and National Lipid Association (NLA) recommend family history as a key component of the cardiovascular health (CVH) assessment in youth [3–6]. CVD risk in offspring is reported to be inversely related to the age of the parent at the time of the index CVD event. According to epidemiologic studies, the earlier the onset of CVD in the family, the greater the risk of CVD in the offspring [7]. The association of a positive family history with increased CVD risk has been confirmed for men, women, and across all racial and ethnic groups [7, 8]. Pediatric guidelines recommend obtaining a screening family history of CVD as early as 2 years of age, including a family history of CVD in parents, grandparents, aunts, and uncles [7]. Premature CVD is defined by most guidelines as a history of myocardial infarction, treated angina, percutaneous coronary catheter interventional procedure, coronary artery bypass surgery, stroke, or sudden cardiac death ≤ 55 y in men and ≤ 65 y in women [7]. Repeat family history screening is recommended at each non-urgent healthcare visit between 5 and 21 years [7]. It is thought that youth with a family history of coronary heart disease (CHD) have early onset preclinical findings of CHD, including increased carotid intima-media thickness (cIMT) and impaired endothelial function [7]. In addition, adult guidelines recommend the incorporation of family history screening for premature CHD when considering initiation of statin therapy during mid-adulthood and when considering the timing of additional imaging, such as coronary artery calcium (CAC) scoring [6].

Reliance on a family history of CVD in a parent assumes that the parent has undergone screening or is aware of the results [7, 9]. However, family history is not always available, nor is it reliable [7]. When a clinician encounters a patient with little to no available family history, such as an adopted child, it is important to place greater emphasis on the patient's personal medical and social history. This includes a comprehensive review of past illnesses and chronic conditions and aspects of their lifestyle, including diet, exercise, and environmental exposures and risk factors, to recommend appropriate screening tests and preventive measures.

Acknowledgment of the challenges in obtaining a family history of CVD led to revisions in screening recommendations for lipid disorders in youth [9]. Now, regardless of family history (or lack thereof), routine screening for inherited forms of hyperlipidemia is recommended as early as 9 years of age [6, 7].

Families also have the potential to co-populate within environments and adopt similar health behaviors. "Socioecological models place individuals within families and depict family settings as the most intimate context of health and social influence" [10]. Thus, family history may represent not only a genetic risk for CVD but also a composite of environmental and behavioral-related risk.

When we consider the CVD inequities experienced by many minority populations, greater risk may be "neither natural nor inevitable" but the result of social structures and policies that confer privilege to one group while "subjugating another group" to lesser advantage, perpetuating disparity [11, 12]. In this case, clustering of disease within geographies (e.g., neighborhood) may be considered in addition to the inclusion of family history when assessing CVD risk.

Finally, with the advent of coronary artery imaging, genetic testing, and biomarker indicators of increased CVD risk (e.g., Lp(a)), the question remains: *What is the contemporary utility of family history screening for assessing CVD risk in youth?*

Overall Cardiovascular Health

In 2010, the AHA defined CVH as a positive construct designed to promote and maintain health [13]. Updated in 2022 and now known as AHA's "Life's Essential Eight" (AHA LE8), the factors that define CVH include body mass index, blood pressure, cholesterol, glucose, smoking, physical activity, diet, and sleep [14]. Maintaining optimal CVH has been associated with significant health benefits, including a reduction in all-cause mortality, CVD events [15], and stroke [16].

Individuals who maintain optimal CVH through the age of 50 years can decrease their likelihood of CVD events. Unfortunately, despite strong evidence supporting the health benefits of optimal CVH, CVH in adults and children is suboptimal [17]. The benefits of optimal CVH are felt to be independent of family history according to cumulative incidence data. Behaviors such as smoking are associated with earlier onset of CVD and a two times cumulative incidence of CVD. Increasing blood pressure and total cholesterol are associated with an increased lifetime risk for CVD and shorter median survival. With each additional CVD-related risk, median survival declines [18]. Family history may influence the presence of CVD risk factors, but management of CVD risk may be what is most important to one's CVH and CVD status over time. Furthermore, as it has been found that early prenatal and childhood exposures influence CVH, that these early exposures influence CVH trajectories and CVD risk, early disease recognition and intervention of CVD risk may be more important than family history assessment alone [19].

Guidelines support elicitation of a positive family history of early CHD as most useful for identifying children at risk for accelerated atherosclerosis [7]. We propose that a positive family history should elicit supportive action,

including educating the patient about family/personal risk for early heart disease as well as careful assessment of individual risk. However, as highlighted in AHA LE8, social determinants of health (SDoH) and environment need to be considered [14]. SDoH include social and economic factors that impact the conditions in which we live and grow and that account for the majority of health outcomes [20].

Hypertension

Hypertension is prevalent in 4–6% of youth and predominantly primary in origin [21]. Heritability of a condition is defined as "the proportion of observed variation attributed to an inherited genetic factor" versus an environmental factor. Studies of heritability suggest that primary HTN in children and adolescents is not definitively due to genetics, and that "highly correlated" environmental risk factors cannot be excluded [22]. In support of this conclusion, we have previously published results from a statewide analysis that assessed the relationship between environmental factors such as high levels of neighborhood deprivation and hypertension diagnosis in youth. We found that higher levels of neighborhood deprivation are associated with a 61% greater odds of hypertension diagnosis in youth [23].

Only 15–20% of cases of hypertension in youth are secondary [24, 25]. Screening for secondary causes is recommended if there is a family history of congenital renal disease [7]. Patient characteristics used to distinguish primary from secondary hypertension in youth, include, age under 6 years (sensitivity range: 0.25–0.36, specificity range of 0.86–0.88), weight in the 10th percentile or lower for age (sensitivity 0.27, specificity 0.94), history of prematurity (sensitivity 0.17 to 0.33, specificity 0.86–0.94), and positive family history of secondary hypertension (sensitivity 0.46; specificity 0.90) [3, 25]. Genetic causes are rare and due to abnormalities in aldosterone, deoxycorticosterone, cortisol, inappropriate sodium retention, catecholamines, and blood vessels [26]. Monogenic causes of hypertension, such as Liddle syndrome, are even rarer and can be genetically confirmed via identification of a gain of function variant in the epithelial Na + channel (ENaC) and suspected in youth with hypertension, hypokalemia, metabolic alkalosis, suppressed plasma renin and aldosterone levels [27].

Although many genome-wide association studies (GWAS) have identified loci linked to hypertension, the majority of these genetic variants do not affect protein-coding sequences [28]. Further work in this area is needed if we are to conclude that a significant burden of primary hypertension in youth is related to genetic predisposition.

Persons with primary hypertension often have overweight/obesity, do not have physical examination findings consistent with a secondary cause of hypertension, and sometimes have poor diet, limited physical activity, and evidence of psychosocial stress [3]. Consistent with these factors, family history may suggest environmental and behavioral level risk increasing a youth's predisposition toward these factors, contributing to hypertension risk. To promote CVH and reduce the risk of heart disease associated with hypertension in children, lifestyle interventions play a pivotal role. One crucial aspect is adherence to the Dietary Approaches to Stop Hypertension (DASH) diet [29–32], which emphasizes the consumption of fruits, vegetables, low-fat dairy, whole grains, lean proteins, nuts, and limited sodium intake. Research suggests that this dietary pattern not only lowers blood pressure (BP) in adults but also benefits children by fostering healthier cardiovascular profiles [33].

Alongside dietary modifications, engagement in exercise, weight management and complementary medicine interventions may be beneficial. Moderate to vigorous aerobic exercise for at least 30 to 60 min, three to five days per week, has been shown to effectively lower BP in children [34]. Weight management strategies are essential [3]. Likewise, complementary medicine interventions, such as mindfulness-based stress reduction programs, breathing awareness meditation, and yoga, show promise in reducing BP levels in hypertensive children and adolescents [35].

Weight Management and Obesity

Approximately 20% of youth have obesity [1, 36]. Children with at least 1 parent with obesity are at greater risk for obesity [7]. However, obesity is multifactorial in origin. Risk begins with prenatal exposure, early sources of nutrition (e.g., absence of breastfeeding), early-life feeding patterns (e.g., early introduction of solids), and lifestyle [37]. A positive family history of obesity may suggest a shared genetic susceptibility to obesity.

There are 3 reported subtypes of genetic causes of obesity: [1] rare syndromic Mendelian, [2] rare non-syndromic (monogenic) Mendelian obesity, and [3] polygenetic [38]. Hyperphagia from early childhood, along with developmental delays, obesity onset under 5 years of age, early onset of peak height velocity, and the presence of syndromic features, may suggest a genetic and inherited cause for obesity. The familial presence of severe obesity alone or "severe obesity resulting in metabolic and bariatric surgery" may also be suggestive of a genetic susceptibility [36]. Twin, family, and adoption studies have estimated that obesity is heritable in 40 to 70% of cases, suggesting

genetic differences in response to the obesogenic environment [39].

However, obesity risk factors are "embedded in the socioecological and environmental fabric of children's lives" [36]. We know that social factors such as neighborhood deprivation are associated with a greater risk of obesity in youth [12, 40]. A family history of obesity may represent a "shared environment, social factors, and stress" that contribute to the risk. Family history may represent a shared lifestyle and early life exposure that, if not causal, is at least a disease-modifying risk [36]. In fact, a family history of obesity may reflect behavioral, environmental, and even cultural factors that contribute to one's risk, such as "What are the cultural norms and practices surrounding food consumption?" [41]. Finally, factors such as family dietary practices may intersect with policy (e.g., food marketing and availability) to contribute to risk [41].

Sleep Disorders

Sleep is a universal need and a requirement for biological functioning. Unfortunately, poor sleep has been identified as an independent predictor of CVD [42, 43]. Sleep is the most recent addition to the definition of CVH as described by AHA LE8 [14]. Its influence on all-cause mortality and cardiometabolic health, along with improved techniques to measure sleep health, are reasons for its inclusion in the updated CVH definition [14]. Sleep disorders include sleep apnea, narcolepsy, nightmare distress, sleep paralysis, and psychiatric sleep disorders. An additional disorder is rapid eye movement (REM) sleep behavior disorder (RBD) [44]. REM sleep disorder can be identified with 90% sensitivity and 90% specificity in an answer to the question: "Do (or did) any of your family members 'act out' their dreams at night? (e.g., punching, kicking, or flailing during sleep while dreaming)" [44]. Periodic limb movement disorder (PLMD) is rare, with an estimated prevalence of 0.3% [45]. Another potential genetic cause of sleep disorder in youth is Prader Willi syndrome (PWS) [46]. PWS is also rare and can be distinctly identified without reliance on family history, as these patients often have a history of hypotonia and feeding difficulties early in life, developmental delays, endocrinopathies, and behavioral concerns [46].

Duration and quality of sleep are important in youth [47]. Among students, 73% report an average of < 8 of hours of sleep per school night [48]. It is estimated that 34% of youth had a sleep disorder during COVID-19 [49]. Furthermore, 1–6% of all children have obstructive sleep apnea (OSA), which can result in shorter sleep duration and has been associated with hypertension, arrhythmia, impaired ventricular contractility, and elevated right heart pressure in children and adolescents [50].

A systematic review and meta-analysis suggest that 46% of the variability in sleep duration and 44% of the variability in sleep quality is genetically determined and that this genetic determination has a stronger influence as one ages [51]. However, poor sleep health and fewer hours of sleep are also associated with obesity, hypertension, and insulin sensitivity [52]. According to a systematic review, childhood adversity is also associated with sleep apnea, narcolepsy, nightmare distress, sleep paralysis, and psychiatric sleep disorders [53]. Additional risk factors for poor sleep duration include poor sleep hygiene, delayed sleep–wake phase disorder, and media use. Insufficient sleep due to adolescent sleep patterns and daytime obligations, electronic media, caffeine, declines in mental health, and prescribed psychotropic medications have been identified as a significant health risk in this population [54].

Obtaining a sleep history, which includes average hours of sleep per night [47], timing and pattern of sleep routine, sleep efficiency, and impact on daytime alertness, is an important component of the CVH assessment. Identifying and managing poor sleep health, including obstructive sleep apnea, may help improve overall CVH. Like hypertension and obesity, behaviors within a family may indicate a greater risk for a sleep-related disorder in youth. Interventions that address the individual, as well as the family's shared risk factors (e.g., obesity) and sleep behaviors, may be beneficial [48].

Blood Sugar Levels and Type 2 Diabetes Mellitus

Maintaining stable blood sugar levels is crucial for maintaining CVH. CVD is the most prevalent cause of mortality and morbidity in diabetic populations [55]. High blood sugar levels, as seen in diabetes, can damage blood vessels, leading to atherosclerosis and increasing the risk of heart disease, stroke, and other cardiovascular complications [56]. Studies have reported several factors, including increased oxidative stress, inflammation, coagulability, endothelial dysfunction, and autonomic neuropathy in patients with diabetes, which may directly contribute to the development of CVD [56].

Genetics plays a role in susceptibility to both cardiovascular complications and diabetes, as both can be inherited. Individuals with a family history of diabetes may be more prone to developing insulin resistance and metabolic syndrome, both of which increase the risk of CVD [57]. Current guidelines recommend evaluation for type 2 DM in children ≥ 10 years of age (or at onset of puberty) with at least overweight status, signs of insulin resistance (e.g., acanthosis nigricans), reported use of obesogenic psychotropic medication, polycystic ovarian syndrome, or a family

history of T2DM or gestational diabetes. Repeat testing is recommended every 2 years [7].

However, shared lifestyle factors within families, such as diet and activity levels, can influence the development of diabetes. Although genetic risk may play a role, the influence of environment and behavior that cluster within families may contribute to the familial risk of T2DM. Like obesity, cultural norms related to food consumption and the environment need to be considered when assessing the risk for T2DM in youth.

Cholesterol Levels

Approximately 20% of youth have abnormal cholesterol levels [1]. Guidelines are available defining acceptable, borderline, and high cholesterol levels in pediatric patients [6, 7]. There is ample evidence of an association between cholesterol level and risk of cardiovascular morbidity and mortality. Cholesterol, being a modifiable risk factor, has been associated with the highest risk for CHD [58]. Low-density lipoprotein cholesterol (LDL-C) has been demonstrated by many epidemiological and interventional studies to be a major contributor to the formation of atherosclerotic plaque [59, 60].

Recommendations for screening and treatment of a lipid disorder in youth are influenced by family history. Screening is advised beginning at age 2 years if there is a family history of early CVD or significant primary hypercholesterolemia [6]. Furthermore, amongst youth with dyslipidemia, the presence of a family history of premature CHD has been proposed as a reason to consider initiation of statin therapy before 10 years of age [7].

However, the use of family history alone to identify familial cholesterol disorders, is estimated to miss ~ 30 to 60% of children with dyslipidemia [61] as most parents have either not had their levels checked, don't know them to be abnormal, or don't realize that even if they are treated, that they may carry a transmissible risk for disease [7]. Furthermore, family history of premature CVD is a risk-enhancing factor [6], but factor analysis to determine the relative contribution of this additional risk for a particular individual does not yet exist [62].

Amongst individuals with abnormal cholesterol levels, other CVD risk enhancers have been identified that can be measured via laboratory testing or imaging, including lipoprotein (a) (Lp(a)) [7] and coronary artery calcium (CAC) scoring. In adults, the CAC is known as a reliable test for estimating the risk of CHD; however, in small studies, CAC scores are not associated with a positive family history of CHD [63].

Routine measurement of serum lipid levels, beginning at age 9–11 years and repeated at 17–21 years, is now recommended for identifying children with hyperlipidemia [6, 7]. Reliance on family history alone would not capture all youth. Further, other independent measures of assessing CVD risk, aside from family history, including Lp(a) testing in youth and CAC scoring in adults, can be used.

Combined and Familial Combined

Combined dyslipidemia (CD) and familial combined hyperlipidemia (FCH) are both conditions characterized by abnormal levels of lipids in the blood. Individuals with CD and FCH share the same metabolic defect, which is overproduction of hepatic very low-density lipoprotein (VLDL), but there are key differences. CD is highly prevalent in youth and is associated with obesity. CD occurs in 30% to 60% of children and adolescents with obesity [64–66]. CD is primarily influenced by a complex of related cardiometabolic factors [67] contributing to the pathophysiology of CD. Visceral adiposity develops and initiates a cascade of reactions that result in CD, insulin resistance/T2DM, and non-alcoholic fatty liver disease (NAFLD) [67].

While both CD and FCH involve high levels of cholesterol and triglycerides, FCH specifically refers to a complex disorder, influenced by multiple genetic as well as environmental factors [68]. The estimated prevalence of FCH is 0.5% to 4% [68]. It is the most reported genetic dyslipidemia, and its presence is known to increase the risk of early atherosclerosis [69]. FCH was initially described as an autosomal dominant inherited lipid disorder. However, it was later found to have a multigenic and complex inheritance [69, 70]. Some of the key genes implicated in FCH include apolipoprotein B (ApoB), low density lipoprotein receptor (LDLR), proprotein convertase subtilisin/Kexin Type 9 (PCSK9), apolipoprotein E (APOE), and lipoprotein lipase (LPL) [71]. FCH is caused by an underlying pathophysiological mechanism characterized by hepatic overproduction of lipoprotein particles containing Apolipoprotein B-100, namely VLDL and LDL. This results in elevated levels of plasma total cholesterol, triglycerides, and ApoB. This oversaturates the ability of lipoprotein lipase to remove triglycerides. Furthermore, individuals with FCH exhibit reduced HDL-C levels and an increase in small dense LDL (sdLDL) and remnant lipoprotein particles [71].

Heterozygous Familial Hypercholesterolemia

In children, LDL-C $\geq$ 160 mg/dL and a family history of early atherosclerosis or elevated cholesterol in 1 parent is diagnostic of familial hypercholesterolemia [6]. It is estimated that the prevalence of heterozygous familial

hypercholesterolemia (HeFH) is 1 in 250 in the general population [72]. A genetically inherited disorder, it is associated with a 10–20-fold increased risk for early atherosclerotic disease and early death; this risk exists even in the absence of other cardiovascular risk factors [73]. Although familial hypercholesterolemia inheritance is complex and can involve polygenic mutations, monogenic mutations typically occur in the LDL receptor (LDL-R) gene, followed by lower proportion of disease associated with mutations in the (APO-B) or PCSK9 [74] genes [75].

HeFH remains underdiagnosed and undertreated, especially in the pediatric population [76]. Early identification and treatment of affected children, combined with rigorous familial screening practices (cascade screening) is crucial in the prevention of atherosclerotic CVD.

In children, routine testing for FH is necessary to detect familial hypercholesterolemia [77]. Family history screening can also be used to identify the rarer, homozygous forms of the disease, homozygous FH (HoFH), as the AAP recommends obtaining a lipid profile as early as 2 years of age when there is a strong family history of high cholesterol or early atherosclerosis.

Cascade screening involves testing of all first-degree relatives of an affected individual. Family history assessment of a child's parents, grandparents, siblings, half-siblings, uncles, aunts, and cousins on both sides of the family is recommended. Due to the autosomal dominant pattern of inheritance of familial hypercholesterolemia, a parent with HeFH has a 50% chance of passing the gene to each child. This also means that all first-degree relatives of a person with familial hypercholesterolemia have a 50% chance of having familial hypercholesterolemia. If a relative is found to have familial hypercholesterolemia, then that relative's first-degree relatives are all tested, and so forth. Cascade screening, thus, allows for higher rates of detection of affected individuals [78, 79]. Genetic testing, when available, is useful to achieve a definitive diagnosis of familial hypercholesterolemia.

Lipoprotein(a)

A relative indication for Lp(a) measurement in children is a family history of premature CVD or a family history of a first-degree relative with elevated Lp(a) [6]. Lp(a) is an ApoB-containing lipoprotein that reaches adult levels by 2 years of age [80]. According to AHA/ACC lipid guidelines, elevated Lp(a) is a CVD risk modifier; an individual with elevated Lp(a) has a higher lifetime risk for CVD [6]. According to data from the Atherosclerosis Risk in Communities (ARIC) study, the odds of an individual developing premature CHD due to a positive family history of premature CHD (OR 1.17, 95% CI: 1.09–1.26) and the odds due to an elevated Lp(a) (OR 1.25, 95% CI: 1.12–1.40), are independent (interaction term, $p = 0.75$) [81]. Therefore, despite a known association between a family history of premature CHD and elevated Lp(a), each is an independent risk factor for premature CHD [81]. Thus, it is important to note that there is an independent but cumulative impact of elevated Lp(a) and family history of premature CHD on individual CHD outcome [81]. It is also important to note that currently, there are no Food and Drug Administration-approved treatments available for elevated Lp(a) in children and adolescents.

How can clinicians improve their ability to take a reliable history?

Improving the ability to take a reliable history involves a combination of honing communication skills, understanding the patient, and consistently applying a structured approach to cover all the necessary aspects of the history. Some examples include active listening, using open-ended questions, being aware of cultural differences that might affect communication and understanding, and the use of technology, which includes the use of pre-visit surveys and questionnaires/standardized forms that can be filled out prior to the patients visit allowing them to premeditate and research their histories prior to their visit.

Conclusion

Family history remains a key component of a comprehensive health assessment of future CVD risk, beginning in youth. Existing guidelines, which guide "what we should do," advocate for the inclusion of family history screening. Family history may not only reflect genetic predisposition but also greater behavioral risk for disease that exists within a family. Family history provides an illustration not only of a patient's genetic and biochemical makeup but also of family behaviors and shared environment often embedded in close social structures associated with health and disease. Identifying a family history of cardiovascular disease allows healthcare providers to implement preventive measures and screening protocols at an earlier age or more frequently. In the absence of family history or little to no available family history, it is important to place greater emphasis on the patient's personal medical and social history, including a comprehensive review of past illnesses and chronic conditions and aspects of their lifestyle, including diet, exercise, and environmental exposures and risk factors, to recommend appropriate screening tests and preventive measures. This early detection can help mitigate risk factors and potentially prevent or delay the onset of CVD. Screening family members with a history

of cardiovascular conditions can help identify individuals who may benefit from early intervention and treatment and provides valuable information for personalized risk assessment. Combining family history with other risk factors helps healthcare providers better understand an individual's overall risk profile and tailor preventive and treatment strategies accordingly. Education about the importance of accurate and complete family health information, but also recognition that family history may reflect shared environment and behavioral risk should also be part of routine care for children and adolescents. Armed with knowledge of their family health history and risk, individuals can make more informed decisions about their healthcare, including discussions with their healthcare providers about appropriate screening tests, medications, and lifestyle modifications.

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Declarations

Conflict of Interest The authors declare no competing interests.

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