U.S. Preventive Services Task Force

Screening for Lipid Disorders in Children and Adolescents: Recommendation Statement

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This summary is one in a series excerpted from the Recommendation Statements released by the USPSTF. These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at http://www.uspreventiveservicestaskforce.org/.

This series is coordinated by Sumi Sexton, MD, Associate Deputy Editor.

A collection of USPSTF recommendation statements published in *AFP* is available at http://www.aafp.org/afp/uspstf.

Summary of Recommendation and Evidence

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents 20 years or younger *(Table 1)*. **I statement.**

Rationale

IMPORTANCE

Dyslipidemia, a genetic or multifactorial disorder of lipoprotein metabolism, is defined by elevations in levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (non–HDL-C), triglycerides, or some combination thereof, as well as lower levels of HDL cholesterol (HDL-C). Elevations in levels of TC, LDL-C, and non–HDL-C are associated with risk of cardiovascular disease in adults, as are lower levels of HDL-C and, to a lesser extent, elevated triglyceride levels.

Heterozygous familial hypercholesterolemia occurs in approximately 1 of every 200 to 500 persons in North America and Europe and is more prevalent among populations with known founder effects (up to 1 of 100 persons).[1-3] Familial hypercholesterolemia is variably defined in the literature but generally includes highly elevated LDL-C levels (e.g., ≥ 190 mg/dL), genetic mutation, or both.

Alternatively, dyslipidemia can be a multifactorial disorder, with both polygenic and environmental causes, including obesity. Multifactorial dyslipidemia is defined by elevations in levels of LDL-C (≥ 130 mg/dL [to convert LDL-C values to mmol/L, multiply by 0.0259]), TC (≥ 200 mg/dL [to convert TC values to mmol/L, multiply by 0.0259]), or both that are not attributable to familial hypercholesterolemia.[4-6] Obesity is associated with slight elevations in LDL-C; it is more strongly related to elevated triglycerides and lower HDL-C.

Recent estimates from the National Health and Nutrition Examination Survey (NHANES) indicate that 7.8% of children aged 8 to 17 years have elevated levels of TC (≥ 200 mg/dL), and 7.4% of adolescents aged 12 to 19 years have elevated LDL-C (≥ 130 mg/dL).[1,4,5]

The rationale for screening for lipid disorders in children and adolescents is that early identification and treatment of elevated levels of LDL-C could delay the atherosclerotic process and thereby reduce the incidence of premature ischemic cardiovascular events in adults.

DETECTION

The USPSTF found inadequate evidence on the quantitative difference in diagnostic yield between universal and selective screening for familial hypercholesterolemia or multifactorial dyslipidemia.

BENEFITS OF EARLY DETECTION AND TREATMENT

The USPSTF found inadequate direct evidence on the benefits of screening for familial hypercholesterolemia or multifactorial dyslipidemia.

Familial Hypercholesterolemia. The USPSTF found adequate evidence from short-term trials (≤ 2 years) that pharmacotherapy interventions result in substantial reductions in levels of LDL-C and TC in children with familial hypercholesterolemia. One short-term pharmacotherapy trial reported a reduction in carotid intima-media thickness. The USPSTF found inadequate evidence to address whether treatment with short-term pharmacotherapy leads directly to a reduced incidence of premature cardiovascular

Table 1. Screening for Lipid Disorders in Children and Adolescents: Clinical Summary of the USPSTF Recommendation

Population	Asymptomatic children and adolescents 20 years or younger
Recommendation	No recommendation. Grade: I (insufficient evidence)
Risk assessment	Multifactorial dyslipidemia is associated with risk factors such as environmental factors (e.g., obesity) and currently unidentified genetic factors. Familial hypercholesterolemia is an autosomal dominant disorder caused by a genetic mutation.
Screening tests	Total cholesterol may be measured with fasting or nonfasting serum testing. Serum LDL-C levels may be calculated using the Friedewald formula. Direct LDL-C measurement does not require fasting. Other recent guidelines on screening for dyslipidemia in children have recommended measuring either LDL-C or non–HDL-C levels.
Treatment and interventions	Interventions for dyslipidemia include lifestyle modification (e.g., changes in diet and physical activity) and pharmacotherapy (e.g., statins, bile acid-sequestering agents, or cholesterol absorption inhibitors). The appropriate age at which to start statin use is subject to debate. The long-term benefits and harms of statin use in children and adolescents are unknown.
Balance of benefits and harms	The USPSTF concludes that the current evidence is insufficient and that the balance of benefits and harms of screening for lipid disorders in asymptomatic children and adolescents 20 years or younger cannot be determined.
Other relevant USPSTF recommendations	The USPSTF recommends that clinicians screen for obesity in children 6 years or older and offer them or refer them to a comprehensive, intensive behavioral intervention (B recommendation). The USPSTF found insufficient evidence on screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood (I statement). These recommendations are available on the USPSTF website (http://www.uspreventiveservicestaskforce.org).

NOTE: *For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, go to http://www.uspreventiveservicestaskforce.org/.*

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; USPSTF = U.S. Preventive Services Task Force.

disease (e.g., myocardial infarction or stroke). The USPSTF found inadequate evidence on the association between changes in intermediate lipid outcomes or noninvasive measures of atherosclerosis in children and adolescents and incidence of or mortality from relevant adult health outcomes.

Multifactorial Dyslipidemia. The USPSTF found inadequate evidence on the benefits of lifestyle modification or pharmacotherapy interventions in children and adolescents with multifactorial dyslipidemia to improve intermediate lipid outcomes or atherosclerosis markers or to reduce incidence of premature cardiovascular disease.

HARMS OF EARLY DETECTION AND TREATMENT

The USPSTF found inadequate evidence to assess the harms of screening for familial hypercholesterolemia or multifactorial dyslipidemia. The USPSTF found inadequate evidence to assess the long-term harms of treatment of familial hypercholesterolemia in children or adolescents. Long-term evidence on the treatment of familial

hypercholesterolemia was limited to 1 study of statins. Short-term statin use was generally well tolerated in children and adolescents with familial hypercholesterolemia, with transient adverse effects (such as elevated liver enzyme levels). Treatment with bile acid-sequestering agents was commonly associated with gastrointestinal symptoms and poor palatability. The USPSTF also found inadequate evidence to assess the harms of treatment of multifactorial dyslipidemia in children or adolescents. One trial of a low-fat, low-cholesterol dietary intervention in children with multifactorial dyslipidemia showed no harms.

USPSTF ASSESSMENT

The USPSTF concludes that the current evidence is insufficient and that the balance of benefits and harms of screening for lipid disorders in asymptomatic children and adolescents 20 years or younger cannot be determined.

Clinical Considerations

PATIENT POPULATION UNDER CONSIDERATION

This recommendation applies to asymptomatic children and adolescents 20 years or younger without a known diagnosis of a lipid disorder.

SUGGESTIONS FOR PRACTICE REGARDING THE I STATEMENT

Potential Preventable Burden. Heterozygous familial hypercholesterolemia is an autosomal dominant disorder caused primarily by mutations in the LDL receptor (*LDLR*) gene (NCBI Entrez Gene 3949) that causes severe elevations in levels of LDL-C, resulting in early atherosclerotic lesions. Children with familial hypercholesterolemia can have TC and LDL-C levels 2 to 3 times higher than those of unaffected children. Familial hypercholesterolemia is generally asymptomatic in childhood and adolescence and is rarely associated with cardiovascular events in the first 2 decades of life.[1] The burden of familial hypercholesterolemia is attributable to premature cardiovascular events in adulthood resulting from long-term exposure to elevated serum cholesterol levels and atherosclerosis.

Studies conducted before statin use became common suggest that familial hypercholesterolemia is associated with a cumulative incidence of ischemic heart disease in 1 of 6 men and 1 of 10 women by age 40 years. By age 50 years, 25% of women and 50% of men with untreated familial hypercholesterolemia will experience clinical cardiovascular disease.[5] Coronary artery disease occurs in 50% of men by age 50 years and 30% of women by age 60 years.[7,8] Mortality from coronary artery disease is greater in adults younger than 60 years with familial hypercholesterolemia. Among adults surviving to age 60 years, the risk of coronary heart disease approaches that of the general population.[1,9]

Multifactorial dyslipidemia is defined by elevated levels of LDL-C (≥ 130 mg/dL) or TC (≥ 200 mg/dL) that are not attributable to familial hypercholesterolemia.[2] Several longitudinal studies have documented an association between childhood lipid levels in this range and measures of atherosclerosis in adulthood.[1] Studies show that tracking lipid levels from childhood and adolescence to adulthood cannot predict which individuals will have elevated LDL-C or TC as adults.[2] In addition, the association between multifactorial dyslipidemia in childhood and adolescence and clinical cardiovascular disease in adulthood is unknown.

Potential Harms. Most children with elevated lipid levels of a multifactorial origin will not progress to a clinically important lipid disorder or develop premature cardiovascular disease and are therefore subject to overdiagnosis. Screening could result in the labeling of children with a "nondisease," parental or child anxiety, or unnecessary or harmful testing and treatment. The adverse effects of long-term use of lipid-lowering pharmacotherapy and lifestyle modification (including diet and physical activity) have not been adequately studied.

Current Practice. Generally, screening rates for dyslipidemia in children and adolescents seen in primary care have been low. According to the National Ambulatory Medical Care Survey, 2.5% of well-child visits included lipid testing in 1995, and 3.2% included it in 2010.[10] Claims data from health insurance plans report rare use of lipid-lowering pharmacotherapy in 8- to 20-year-olds. Among more than

13 million children, 665 children initiated lipid-lowering pharmacotherapy between 2005 and 2010, for an overall incidence rate of 2.6 prescriptions per 100,000 person-years (95% CI, 0.1 to 2.7).[11]

SCREENING TESTS

Normal lipid level values for children and adolescents are currently defined by population distributions of lipid levels from the Lipid Research Clinics Prevalence Study, which was conducted in the 1970s.[2,12] In 1992, the National Cholesterol Education Program (NCEP) proposed fixed threshold values to define dyslipidemia in children (TC ≥ 200 mg/dL, LDL-C ≥ 130 mg/dL, or both). These values are slightly lower than the 95th percentile observed in the Lipid Research Clinics Prevalence Study for both boys and girls at nearly all ages, although there are some age-related variations in adolescence.[2,13]

Cholesterol levels vary by sex and age throughout childhood. Total cholesterol levels increase from birth, stabilize at approximately age 2 years, peak before puberty, and then decline slightly during adolescence.[2,14] The accepted cutoff values for elevated LDL-C and TC may overidentify or underidentify children and adolescents, depending on age and sex.[2] Abnormal lipid levels in youth are based on population distributions, not associations with health outcomes. It is unclear to what degree elevated lipid levels in children and adolescents 20 years or younger are associated with future disease risk.

Elevated lipid levels track modestly into adulthood, making it difficult to predict which children and adolescents will continue to have elevated cholesterol levels as adults.[2,15,16] Longitudinal studies suggest that elevated LDL-C levels in adolescence predict elevated LDL-C 15 to 20 years later, with a positive predictive value of 32.9% to 37.3% and lower predictive values among younger children.[17]

Levels of TC may be measured with fasting or nonfasting serum testing. Serum (or plasma) TC and HDL-C levels do not change appreciably according to a fasting or nonfasting state. Serum LDL-C levels may be calculated using the Friedewald formula (LDL-C = TC − [triglycerides/5] − HDL-C). Because accurate calculation depends on triglyceride levels, serum testing requires a fasting state. Direct measurement of LDL-C does not require fasting and is preferred when triglyceride levels are greater than 400 mg/dL.[2] Recent guidelines on screening for dyslipidemia in children recommend measuring either LDL-C or non–HDL-C levels.[18]

Screening strategies for dyslipidemia in clinical practice include selective or universal screening. Selective screening is based on family history of dyslipidemia or premature cardiovascular disease. Universal screening is based only on age. Cascade screening is a common screening strategy for familial hypercholesterolemia in other countries. Cascade screening involves case-finding among relatives of patients with confirmed familial hypercholesterolemia and testing for genetic variants identified in the first affected relative (i.e., the proband). However, the U.S. health system does not currently have the infrastructure to implement cascade screening.[2]

There are no universally accepted criteria for the diagnosis of familial hypercholesterolemia. Studies of children and adolescents with familial hypercholesterolemia use several different diagnostic criteria. All of the criteria use a combination of elevated lipid levels, physical findings, family history, or genetic tests to establish the diagnosis.[1]

TREATMENT OF DYSLIPIDEMIA

Interventions for dyslipidemia include lifestyle modification (e.g., changes in diet and physical activity) and pharmacotherapy (e.g., statins, bile-acid sequestering agents, or cholesterol absorption inhibitors).

Statins, or 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors, have been widely adopted for use in adults with hypercholesterolemia, because these drugs are effective at reducing cardiovascular events in high-risk adults. As a result of their efficacy in adults, statins are one of the first-line medications considered for use in children and adolescents with hypercholesterolemia.[2,19]

The appropriate age at which to start statin use in children with familial hypercholesterolemia is subject to debate. Some experts recommend starting statin use at age 8 or 10 years; others, concerned with adverse effects, recommend initiating use

at age 20 years.[2] The long-term effects of statin use in children and adolescents are unknown.

USEFUL RESOURCES

The USPSTF recommends that clinicians screen for obesity in children 6 years or older and offer them or refer them to a comprehensive, intensive behavioral intervention (B recommendation).[20] The USPSTF found insufficient evidence on screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood (I statement).[21] These recommendations are available on the USPSTF website (http://www.uspreventiveservicestaskforce.org).

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The "Other Considerations," "Discussion," "Update of Previous USPSTF Recommendation," and "Recommendations of Others" sections of this recommendation statement are available at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lipid-disorders-in-children-screening1.

The USPSTF recommendations are independent of the U.S. government. They do not represent the views of the Agency for Healthcare Research and Quality, the U.S. Department of Health and Human Services, or the U.S. Public Health Service.

REFERENCES

1. Lozano P, Henrikson NB, Dunn J, et al. *Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: A Systematic Evidence Review for the U.S. Preventive Services Task Force.* Evidence synthesis no. 141. AHRQ publication no. 14-05204-EF-2. Rockville, Md.: Agency for Healthcare Research and Quality; 2016.
2. Lozano P, Henrikson NB, Morrison CC, et al. *Lipid Screening in Childhood for Detection of Multifactorial Dyslipidemia: A Systematic Evidence Review for the US Preventive Services Task Force.* Evidence synthesis no. 140. AHRQ publication no. 14-05204-EF-1. Rockville, Md.: Agency for Healthcare Research and Quality; 2016.
3. Lozano P, Henrikson NB, Dunn J, et al. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;316(6):645-655.
4. Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, Ogden CL. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. *JAMA Pediatr.* 2015;169(3):272-279.
5. Kit BK, Carroll MD, Lacher DA, Sorlie PD, DeJesus JM, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. *JAMA*. 2012;308(6):591-600.
6. Lozano P, Henrikson NB, Morrison C, et al. Lipid screening in childhood and adolescence for detection of multifactorial dyslipidemia: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;316(6):634-644.
7. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. *Lancet*. 1969;2(7635):1380-1382.
8. Stone NJ, Levy RI, Fredrickson DS, Verter J. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation.* 1974;49(3):476-488.
9. Setia N, Verma IC, Khan B, Arora A. Premature coronary artery disease and familial hypercholesterolemia: need for early diagnosis and cascade screening in the Indian population. *Cardiol Res Pract*. 2012;2012:658526.
10. Vinci SR, Rifas-Shiman SL, Cheng JK, Mannix RC, Gillman MW, de Ferranti SD. Cholesterol testing among children and adolescents during health visits. *JAMA*. 2014;311(17):1804-1807.
11. Joyce N, Wellenius GA, Dore DD, Newburger JW, Zachariah JP. Patterns of lipid lowering therapy among children ages 8-20 years. *J Pediatr.* 2015;167(1):113-119.e1.
12. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind BM. Lipid and lipoprotein distributions in white children ages 6-19 yr: the Lipid Research Clinics Program Prevalence Study. *J Chronic Dis.* 1981;34(1):27-39.
13. Cook S, Auinger P, Huang TT. Growth curves for cardiometabolic risk factors in children and adolescents. *J Pediatr.* 2009;155(3):S6.e15-26.
14. 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.
15. Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, Nelson HD. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. *Pediatrics.* 2007;120(1):e189-e214.
16. Clarke WR, Schrott HG, Leaverton PE, Connor WE, Lauer RM. Tracking of blood lipids and blood pressures in school age children: the Muscatine study. *Circulation.* 1978;58(4):626-634.
17. Magnussen CG, Raitakari OT, Thomson R, et al. Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. *Circulation.* 2008;117(1):32-42.
18. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128(suppl 5):S213-S256.
19. Eiland LS, Luttrell PK. Use of statins for dyslipidemia in the pediatric population. *J Pediatr Pharmacol Ther.* 2010;15(3):160-172.
20. US Preventive Services Task Force. Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. *Pediatrics.* 2010;125(2):361-367.
21. US Preventive Services Task Force. Screening for primary hypertension in children and adolescents: U.S. Preventive Services Task Force recommendation statement. *Pediatrics*. 2013;132(5):907-914. ■