Screening for Lipid Disorders in Children and Adolescents: Recommendation Statement

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.

Homozygous 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). 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. 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). 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 direct 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 (<7 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 adequate evidence to address whether treatment with short-term pharmacotherapy leads directly to a reduced incidence of premature cardiovascular
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

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

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic children and adolescents 20 years or younger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>No recommendation.</td>
</tr>
<tr>
<td>Grade</td>
<td>I (insufficient evidence)</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>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.</td>
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<tr>
<td>Screening tests</td>
<td>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.</td>
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<tr>
<td>Treatment and interventions</td>
<td>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.</td>
</tr>
<tr>
<td>Balance of benefits and harms</td>
<td>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.</td>
</tr>
<tr>
<td>Other relevant USPSTF recommendations</td>
<td>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 (<a href="http://www.uspreventiveservicestaskforce.org">http://www.uspreventiveservicestaskforce.org</a>).</td>
</tr>
</tbody>
</table>

**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.
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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. 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. Coronary artery disease occurs in 50% of men by age 50 years and 30% of women by age 60 years. 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.

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. Several longitudinal studies have documented an association between childhood lipid levels in this range and measures of atherosclerosis in adulthood. 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. In addition, the association between multifactorial dyslipidemia in childhood and adolescence and clinical cardiovascular disease in adulthood is unknown.

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. 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/S] − 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. 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). 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).

This recommendation statement was first published in JAMA. 2016;316(6):625-633 [published correction appears in JAMA. 2016;316(10):1116].


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. Public Health Service.

REFERENCES


