JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Lipid Disorders in Children and Adolescents
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Elevations in levels of total, low-density lipoprotein, and non–high-density lipoprotein cholesterol; lower levels of high-density lipoprotein cholesterol; and, to a lesser extent, elevated triglyceride levels are associated with risk of cardiovascular disease in adults.

OBJECTIVE To update the 2007 US Preventive Services Task Force (USPSTF) recommendation on screening for lipid disorders in children, adolescents, and young adults.

EVIDENCE REVIEW The USPSTF reviewed the evidence on screening for lipid disorders in children and adolescents 20 years or younger—1 review focused on screening for heterozygous familial hypercholesterolemia, and 1 review focused on screening for multifactorial dyslipidemia.

FINDINGS Evidence on the quantitative difference in diagnostic yield between universal and selective screening approaches, the effectiveness and harms of long-term treatment and the harms of screening, and the association between changes in intermediate outcomes and improvements in adult cardiovascular health outcomes are limited. Therefore, the USPSTF concludes that the balance of benefits and harms cannot be determined.

CONCLUSIONS AND RECOMMENDATION 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. (I statement)

JAMA. 2016;316(6):625-633. doi:10.1001/jama.2016.9852

Editorial page 589

Author Audio Interview at jama.com

Related articles pages 634 and 645

CME Quiz at jamanetworkcme.com

Related articles at jamacardiology.com jamainternalmedicine.com jamapediatrics.com

Author/Group Information: The USPSTF members are listed at the end of this article.

Corresponding Author: Kirsten Bibbins-Domingo, PhD, MD, MAS (chair@uspstf.net).

The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

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 (I statement) (**Figure 1**).

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 (eg, ≥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

Figure 1. US Preventive Services Task Force Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

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

Figure 2. Screening for Lipid Disorders in Children and Adolescents: Clinical Summary

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 (eg, 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 (eg, changes in diet and physical activity) and pharmacotherapy (eg, 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).

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

U.S. Preventive Services TASK FORCE

JAMA

LDL-C indicates low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol; USPSTF, US Preventive Services Task Force.

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 disease (eg, 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 (**Figure 2**).

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 (ie, the proband). However, the US 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 (eg, changes in diet and physical activity) and pharmacotherapy (eg, 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).

Other Considerations

Research Needs and Gaps

Randomized trials of screening programs are needed to assess the benefits and harms of combined screening and treatment programs for familial hypercholesterolemia in children and adolescents. For both familial hypercholesterolemia and multifactorial dyslipidemia, long-term, controlled treatment trials of lipid-lowering medications, supplements, dietary interventions, or combinations thereof are needed to assess harms, as well as effectiveness to improve intermediate and health outcomes in adulthood.[1,2] These trials should be conducted in racially and ethnically diverse US populations. In the absence of randomized clinical trials (RCTs) of screening programs, treatment studies in patients with screen-detected multifactorial dyslipidemia would be informative. In addition, longitudinal studies would help to understand the association between intermediate outcomes in childhood and adolescence and premature myocardial infarction and stroke in adulthood.[1,2] With these studies, it may be possible to consider age- and sex-specific (rather than fixed) cutoff values to define thresholds for abnormal levels of TC and LDL-C.[2]

There is doubt that long-term RCTs of statin use in children and adolescents with familial hypercholesterolemia can be feasibly and ethically conducted. The feasibility of conducting such trials may increase with use of intermediate outcomes that predict coronary heart disease.[2,22]

Discussion

Burden of Disease

Data from the 2011-2012 NHANES estimate the prevalence of elevated TC levels in children aged 8 to 17 years as 7.8%, and data from the 2007-2010 NHANES estimate the prevalence of elevated LDL-C levels in adolescents as 7.4%.[4,5] These are likely overestimates of the true prevalence of dyslipidemia because of within-person variability. Repeat testing in an individual is necessary to reliably identify children and adolescents with elevated lipid levels.[2,4,5,12]

Much attention has been directed at screening for dyslipidemia in childhood and adolescence because atherosclerosis starts in youth; lipid levels in youth are associated with the extent of atherosclerosis in adulthood; familial hypercholesterolemia is associated with premature ischemic cardiovascular disease; short-term treatment of familial hypercholesterolemia with statins substantially lowers LDL-C levels and, based on 1 study, improves measures of atherosclerosis; abnormal lipid levels in adulthood have been strongly associated with the risk of coronary heart disease events; and early identification and intervention with cholesterol-lowering therapy in certain populations of adults can prevent such events.

Screening in children and adolescents may identify those with undiagnosed familial hypercholesterolemia or multifactorial dyslipidemia. However, the clinical health benefits and risks among children and adolescents identified with and treated for dyslipidemia have not been sufficiently studied, making the role of screening in children and adolescents uncertain.

Scope of Review

To update its 2007 recommendation,[23] the USPSTF commissioned 2 systematic evidence reviews on screening for lipid disorders in children and adolescents 20 years or younger. The USPSTF decided to conduct 2 separate reviews based on public comment on the draft research plan—1 on screening for familial hypercholesterolemia and 1 on screening for multifactorial dyslipidemia. The review on familial hypercholesterolemia focused on heterozygous familial hypercholesterolemia. Homozygous familial hypercholesterolemia and secondary causes of dyslipidemia (such as diabetes, nephrotic syndrome, or hypothyroidism) were outside the scope of the review.

Accuracy of Screening Tests

Familial Hypercholesterolemia

The review identified 2 fair-quality studies of universal screening for familial hypercholesterolemia. Both studies took place in school settings. The first study, the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) project, was a universal screening program (n = 81 156) in West Virginia schools intended to identify the prevalence of cardiac risk factors, such as obesity, dyslipidemia, hypertension, and glucose intolerance.[24] The second study was a Danish screening study (n = 2085) that measured apolipoprotein levels as a screening test for familial hypercholesterolemia. No studies on selective screening for familial hypercholesterolemia were identified.[1,25]

The CARDIAC project reported a diagnostic yield of about 1.3 cases per 1000 persons screened when familial hypercholesterolemia was diagnosed based on an LDL-C level greater than 155 mg/dL, a TC level greater than 260 mg/dL, or both, plus DNA evidence of a genetic mutation in a first- or second-degree relative.[24] The Danish study identified 10 children based on laboratory testing and a family history consistent with familial hypercholesterolemia, for a diagnostic yield of 4.8 cases per 1000 persons screened.[1,25]

Multifactorial Dyslipidemia

No studies on selective screening for multifactorial dyslipidemia were identified. No studies screened for multifactorial dyslipidemia by measuring levels of non–HDL-C.

An Ohio study (n = 6500) used a nonfasting TC threshold level of 200 mg/dL or greater to universally screen for multifactorial dyslipidemia in children and adolescents. The prevalence of elevated nonfasting TC was 8.5%. After confirmatory testing using a fasting LDL-C threshold level of 130 mg/dL or greater, the positive predictive value was 77% and the diagnostic yield was 5.8%.[2,26]

Population-based studies suggest that approximately 8% to 11% of children and adolescents would screen positive using the NCEP nonfasting TC threshold level of 200 mg/dL or greater. Point estimates of the prevalence of elevated TC from 3 large, population-based US studies were combined with the positive predictive value derived from the Ohio study to simulate diagnostic yield (screening yield × positive predictive value of the initial screening). Simulated diagnostic yield ranged from 4% to 12% for different subgroups based on age and body mass index. Subgroups with the highest diagnostic yield were children with obesity (12.3%) and overweight (8.9%), children aged 9 to 11 years (7.2%), and adolescents aged 16 to 19 years (7.2%).[2]

Effectiveness of Early Detection and Treatment

Familial Hypercholesterolemia

No direct evidence was found that reported on selective or universal screening and intermediate or health outcomes in children and adolescents with familial hypercholesterolemia.

Thirteen randomized, blinded trials (n = 1789) examined the effectiveness of lipid-lowering pharmacotherapy in children and adolescents. No evidence on the effectiveness of dietary supplements or lifestyle interventions on intermediate outcomes in children with familial hypercholesterolemia was found. The 13 fair- to good-quality trials included 8 trials of statins, 3 trials of bile acid–sequestering agents, and 2 trials of a cholesterol absorption inhibitor.[1]

Trials included 54 to 248 participants whose ages ranged from 6 to 18 years (mean age range, 12-15 years). Both sexes were well represented. In trials reporting race/ethnicity, the majority of trial participants were white. The trials were conducted in countries with a high Human Development Index (>0.9). Participants were patients at tertiary care lipid clinics. Trial duration ranged from 6 weeks to 2 years, with most lasting less than 1 year. All trials excluded participants with homozygous familial hypercholesterolemia, secondary dyslipidemia, or use of medications that could affect lipid levels. Familial hypercholesterolemia was defined on the basis of elevated fasting lipid levels and family history, using various standard criteria.[1]

Statin trials included pravastatin, simvastatin, lovastatin, atorvastatin, and rosuvastatin. The studies reported statistically significant reductions in LDL-C levels from baseline, with most effect sizes ranging from 20% to 40% compared with placebo. Because of the variability in medication, dosage, and duration of treatment, data were not pooled across trials.[1]

Dose response was seen in 2 trials of pravastatin and rosuvastatin.[1] The greatest effect on levels of LDL-C was in a trial of rosuvastatin. In that trial—the only statin trial that reported treatment target levels—only 12% to 41% of participants reached the target LDL-C level of less than 110 mg/dL, with greater effects at higher doses. Participants who received the highest dose (20 mg/d) had a 50% reduction (least squares mean estimate) in LDL-C from baseline, compared with 1% in the control group ($P < .001$). The effects of statins on HDL-C were mixed, with some trials reporting minimal improvement and others showing no change. Trials that evaluated TC levels found reductions of 20% to 30% from baseline compared with placebo. One trial of pravastatin reported a 2.0% reduction in carotid intima-media thickness in the treatment group, compared with a 1.0% increase in the control group. The mean change in carotid intima-media thickness differed significantly between groups ($P = .02$).[1] No trials assessed the effect of statins on pathologic findings or coronary calcium scores.

Three trials of bile acid–sequestering agents (colesevelam, cholestyramine, and colestipol) reported more modest effects on levels of LDL-C and TC, with similar effect sizes across trials. The trial of colesevelam showed a dose response. Only 3.2% to 7.9% of participants reached the target LDL-C level of 110 mg/dL or less, with greater effects at higher doses.[1]

One drug, an intestinal cholesterol absorption inhibitor (ezetimibe, studied in 2 RCTs), also showed smaller effects on levels of LDL-C in a trial of combination therapy with simvastatin. Ezetimibe reduced LDL-C by 54% compared with a 38% reduction using simvastatin alone. In a trial assessing ezetimibe monotherapy compared with placebo, ezetimibe reduced LDL-C by 28% (95% CI, −31 to −25) from baseline compared with a negligible change in the placebo group.[1]

No evidence was found on lifestyle modification alone or dietary supplements as treatment for familial hypercholesterolemia in children or adolescents. No evidence was found on the effectiveness of interventions in childhood or adolescence on cardiovascular outcomes in adulthood. There was also a lack of evidence on the association between intermediate outcomes in childhood or adolescence and health outcomes in adulthood among those with familial hypercholesterolemia.[1]

Multifactorial Dyslipidemia

No direct evidence was found that evaluated selective or universal screening and intermediate or health outcomes in children and adolescents with multifactorial dyslipidemia.[2]

There is also a lack of evidence on the effectiveness of treatment in childhood on adult health outcomes. However, 2 trials addressed the effectiveness of treatment on intermediate outcomes in children with multifactorial dyslipidemia.[2]

A good-quality trial, the Dietary Intervention Study in Children (n = 663), evaluated a modified NCEP Step II diet (low fat and low cholesterol) delivered using an intensive multiyear, family-based counseling intervention in children aged 8 to 10 years.[27] Trial participants had a mean baseline LDL-C level of 131 mg/dL, which is near the minimum threshold for dyslipidemia. Outcomes were evaluated at 1, 3, and 5 years after randomization, at the end of the trial (about 8 years after randomization), and 9 years after the end of the trial (about 17 years after randomization). The intervention resulted in statistically significant reductions in mean LDL-C and TC in the intervention vs control groups at 1 and 3 years. The mean adjusted between-group difference was greatest in year 1 (TC, −6.1 mg/dL; LDL-C, −4.8 mg/dL; $P < .001$) and smaller but still statistically significant in year 3 (TC, −3.3 mg/dL [$P = .04$]; LDL-C, −3.3 mg/dL [$P = .02$]). However, the groups did not differ significantly at years 5, 7, or 18.[2,27]

A small fair-quality trial (n = 32) of flaxseed supplementation (30 g/d) in children aged 8 to 18 years with moderate to severe dyslipidemia found no effect at 4 weeks on levels of TC or LDL-C.[2,28]

One fair-quality longitudinal study (n = 9245) of adolescents and young adults (aged 12 to 39 years) from the NHANES evaluated the association between mortality before age 55 years and several cardiovascular risk factors, including lipid levels. In multivariate models, neither highly elevated TC (≥240 mg/dL) nor moderately increased TC (200-239 mg/dL) was independently associated with death (all causes and endogenous causes) when both sexes were combined. Extremely elevated TC (≥240 mg/dL) was associated with a greater risk of death (endogenous causes) before age 55 years (relative hazard ratio, 2.58 [95% CI, 1.31 to 5.08]) in females only. However, this estimate was based on a small number of deaths.[29] In addition, this study did not report on cardiovascular mortality, an outcome more closely linked to the causal pathway.

A good-quality trial suggests that a low-fat, low-cholesterol diet combined with intensive counseling has a modest effect on levels of LDL-C in children and adolescents with multifactorial dyslipidemia,[2,27] but the effect dissipates with time. No evidence was found on dietary supplements for the treatment of multiple dyslipidemia in children or adolescents. No evidence was found on the effectiveness of interventions in childhood or adolescence on cardiovascular outcomes in adulthood. There was also a lack of evidence on the association between intermediate outcomes in childhood or adolescence and health outcomes in adulthood among those with multiple dyslipidemia.[2]

Potential Harms of Screening and Treatment

Familial Hypercholesterolemia

No studies reported on the harms of screening for familial hypercholesterolemia in children and adolescents. Evidence was available from short-term trials of pharmacotherapy in children and adolescents with familial hypercholesterolemia. The USPSTF evaluated 18 fair- to good-quality trials (n = 2210) for the harms of treatment of familial hypercholesterolemia in children and adolescents, including 13 trials of statins, 3 trials of bile acid–sequestering agents, and 2 trials of a cholesterol absorption inhibitor (ezetimibe). Most were applicable to the US primary health care setting. Trial duration ranged from 8 weeks to 2 years.[1] Bile acid–sequestering agents were commonly associated with gastrointestinal symptoms and poor palatability. Statins were well tolerated; elevated liver enzyme levels, creatine kinase levels, or both were observed in some studies but were transient. Ten trials evaluated the effects of statin use on growth or sexual maturation and found no reported abnormalities. Ezetimibe was well tolerated in short-term trials.[1]

Overall, evidence of treatment harms was limited to only 1 long-term study. The study was a 10-year cohort follow-up of a 2-year trial of pravastatin followed by continued statin use over the intervening years. Sex hormone levels were measured in young adult siblings (mean age, 24 years). Young men with familial hypercholesterolemia had lower dehydroepiandrosterone sulfate levels (within normal ranges) compared with their unaffected siblings. However, this difference is of unknown clinical significance.[30]

Multifactorial Dyslipidemia

No studies were found that reported on the harms of screening for multifactorial dyslipidemia in children and adolescents.

The only trial that evaluated harms of treatment in children with multifactorial dyslipidemia was the Dietary Intervention Study in Children, which evaluated a dietary intervention combined with behavioral counseling in children with multifactorial dyslipidemia. This good-quality trial demonstrated no harms in anthropometric, laboratory, psychosocial, or sexual maturation measures during the trial or long-term follow-up (18 years), suggesting that low-fat, low-cholesterol dietary interventions may not be harmful in children.[2]

Estimate of Magnitude of Net Benefit

The USPSTF found inadequate evidence on the quantitative difference in diagnostic yield between universal and selective screening approaches. There is inadequate evidence on the effectiveness and harms of long-term treatment and the harms of screening. The USPSTF also found inadequate evidence on the association between changes in intermediate outcomes (eg, lipid levels or noninvasive measures of atherosclerosis) and improvements in adult cardiovascular health outcomes. Therefore, the USPSTF concludes that the evidence on the benefits and harms of screening for lipid disorders in children and adolescents 20 years or younger is insufficient and that the balance of benefits and harms cannot be determined.

How Does the Evidence Fit With Biological Understanding?

Left untreated, familial hypercholesterolemia leads to premature clinical atherosclerotic cardiovascular events in adulthood resulting from long-term exposure to elevated levels of serum cholesterol. Cardiovascular events rarely occur in the first 2 decades of life, typically taking place during the fourth decade. Because of the lack of evidence on the long-term benefits and harms of pharmacotherapy, it is not known whether there is benefit to initiating treatment in childhood vs later in adolescence or adulthood. It is also not known if improvement in intermediate outcomes results in improvement in adult health outcomes.

Multifactorial dyslipidemia in childhood and adolescence is a risk factor for future atherosclerosis. Although elevated lipid levels can continue into adulthood, they do so inconsistently, making it difficult to predict which children and adolescents will have elevated cholesterol as adults. The relationship between dyslipidemia and coronary heart disease in adults has been well established; however, the association between multifactorial dyslipidemia in children and adolescents and future disease risk in adults is unknown.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from December 22, 2015, to January 25, 2016. The USPSTF reviewed all comments received. A few comments agreed with the insufficiency of the evidence; several comments disagreed with the recommendation. A few comments provided citations for related articles, and the USPSTF reviewed these for relevance to the current recommendation. The USPSTF added language to emphasize the burden of familial hypercholesterolemia and to clarify its diagnosis. The USPSTF also added language on the feasibility of research to the section on Research Needs and Gaps.

Update of Previous USPSTF Recommendation

This recommendation updates the 2007 USPSTF recommendation on screening for lipid disorders in children, adolescents, and

young adults. This recommendation is similar to the previous recommendation in that the evidence to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents remains insufficient.

Recommendations of Others

The National Heart, Lung, and Blood Institute's Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents[18] and the American Academy of Pediatrics' Bright Futures[31] recommend universal screening before adolescence (ages 9 to 11 years) and again after puberty (ages 17 to 21 years). Selective screening (eg, based on family history and other risk factors) is recommended for younger children starting at age 2 years. The American Academy of Family Physicians[32] states that there is insufficient evidence to recommend for or against routine screening for lipid disorders in infants, children, adolescents, or young adults (up to age 20 years). The UK National Screening Committee[33] indicates that there is insufficient evidence to recommend universal screening, although a project is currently under way to evaluate cascade screening.

ARTICLE INFORMATION

Authors/US Preventive Services Task Force (USPSTF) members: Kirsten Bibbins-Domingo, PhD, MD, MAS; David C. Grossman, MD, MPH; Susan J. Curry, PhD; Karina W. Davidson, PhD, MASc; John W. Epling Jr, MD, MSEd; Francisco A. R. García, MD, MPH; Matthew W. Gillman, MD, SM; Alex R. Kemper, MD, MPH, MS; Alex H. Krist, MD, MPH; Ann E. Kurth, PhD, RN, MSN, MPH; C. Seth Landefeld, MD; Michael LeFevre, MD, MSPH; Carol M. Mangione, MD, MSPH; William R. Phillips, MD, MPH; Maureen G. Phipps, MD, MPH; Michael P. Pignone, MD, MPH; Albert L. Siu, MD, MPH.

Affiliations of Authors/US Preventive Services Task Force (USPSTF) members: University of California, San Francisco (Bibbins-Domingo); Group Health Research Institute, Seattle, Washington (Grossman); University of Iowa, Iowa City (Curry); Columbia University, New York, New York (Davidson); State University of New York Upstate Medical University, Syracuse (Epling); Pima County Department of Health, Tucson, Arizona (García); Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts (Gillman); Duke University, Durham, North Carolina (Kemper); Fairfax Family Practice Residency, Fairfax, Virginia (Krist); Virginia Commonwealth University, Richmond (Krist); Yale University, New Haven, Connecticut (Kurth); University of Alabama at Birmingham (Landefeld); University of Missouri, Columbia (LeFevre); University of California, Los Angeles (Mangione); University of Washington, Seattle (Phillips); Brown University, Providence, Rhode Island (Phipps); University of Texas at Austin (Pignone); Mount Sinai School of Medicine, New York, New York (Siu); James J. Peters Veterans Affairs Medical Center, Bronx, New York (Siu).

Author Contributions: Dr Bibbins-Domingo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The USPSTF members contributed equally to the recommendation statement.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Bibbins-Domingo reported having consulted for the Institute for Clinical and Economic Review on the cost-effectiveness of a new class of lipid-lowering drugs. No other authors reported discosures. Authors followed the policy regarding conflicts of interest described at http://www.uspreventiveservicestaskforce.org/Page/Name/conflict-of-interest-disclosures. All members of the USPSTF receive travel reimbursement and an honorarium for participating in USPSTF meetings.

Funding/Support: The USPSTF is an independent, voluntary body. The US Congress mandates that the Agency for Healthcare Research and Quality (AHRQ) support the operations of the USPSTF.

Role of the Funder/Sponsor: AHRQ staff assisted in the following: development and review of the research plan, commission of the systematic evidence review from an Evidence-based Practice Center, coordination of expert review and public comment of the draft evidence report and draft recommendation statement, and the writing and preparation of the final recommendation statement and its submission for publication. AHRQ staff had no role in the approval of the final recommendation statement or the decision to submit for publication.

Disclaimer: Recommendations made by the USPSTF are independent of the US government. They should not be construed as an official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We thank Iris Mabry-Hernandez, MD, MPH (AHRQ), who contributed to the writing of the manuscript, and Lisa Nicolella, MA (AHRQ), who assisted with coordination and editing.

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 US Preventive Services Task Force. Evidence Synthesis No. 141.* Rockville, MD: Agency for Healthcare Research and Quality; 2016. AHRQ Publication No. 14-05204-EF-2.

2. Lozano P, Henrikson NB, Dunn J, 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.* Rockville, MD: Agency for Healthcare Research and Quality; 2016. AHRQ Publication No. 14-05204-EF-1.

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*. doi:10.1001/jama.2016.6176.

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*. doi:10.1001/jama.2016.6423.

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, et al. Premature coronary artery disease and familial hypercholesterolemia: need for early diagnosis and cascade screening in the Indian population [published online October 27, 2011]. *Cardiol Res Pract*. doi:10.1155/2012/658526.

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.

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 cardio-metabolic risk factors in children and adolescents. *J Pediatr*. 2009;155(3):6.e15-6.e26.

14. National Cholesterol Education Program (NCEP). 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. Barton M; 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. Moyer VA; U.S. 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.

22. Vuorio A, Docherty KF, Humphries SE, Kuoppala J, Kovanen PT. Statin treatment of children with familial hypercholesterolemia—trying to balance incomplete evidence of long-term safety and clinical accountability: are we approaching a consensus? *Atherosclerosis*. 2013;226(2):315-320.

23. US Preventive Services Task Force. Screening for lipid disorders in children: US Preventive Services Task Force recommendation statement. *Pediatrics*. 2007;120(1):e215-e219.

24. Cottrell L, John C, Murphy E, et al. Individual-, family-, community-, and policy-level impact of a school-based cardiovascular risk detection screening program for children in underserved, rural areas: the CARDIAC Project [published online June 5, 2013]. *J Obes*. doi:10.1155/2013/732579.

25. Skovby F, Micic S, Jepsen B, et al. Screening for familial hypercholesterolaemia by measurement of apolipoproteins in capillary blood. *Arch Dis Child*. 1991;66(7):844-847.

26. Garcia RE, Moodie DS. Routine cholesterol surveillance in childhood. *Pediatrics*. 1989;84(5):751-755.

27. Obarzanek E, Hunsberger SA, Van Horn L, et al. Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC). *Pediatrics*. 1997;100(1):51-59.

28. Wong H, Chahal N, Manlhiot C, Niedra E, McCrindle BW. Flaxseed in pediatric hyperlipidemia: a placebo-controlled, blinded, randomized clinical trial of dietary flaxseed supplementation for children and adolescents with hypercholesterolemia. *JAMA Pediatr*. 2013;167(8):708-713.

29. Saydah S, Bullard KM, Imperatore G, Geiss L, Gregg EW. Cardiometabolic risk factors among US adolescents and young adults and risk of early mortality. *Pediatrics*. 2013;131(3):e679-e686.

30. Kusters DM, Avis HJ, de Groot E, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. *JAMA*. 2014;312(10):1055-1057.

31. American Academy of Pediatrics (AAP). Recommendations for Preventive Pediatric Health Care. https://www.aap.org/en-us/professional-resources/practice-support/Periodicity/Periodicity%20Schedule_FINAL.pdf. 2015. Accessed December 15, 2015.

32. American Academy of Family Physicians (AAFP). Clinical Preventive Service Recommendation: Lipid Disorders, Infants, Children, Adolescents, and Young Adults. http://www.aafp.org/patient-care/clinical-recommendations/all/lipid-disorders.html. 2007. Accessed December 15, 2015.

33. UK National Screening Committee (UK NSC). The UK NSC Recommendation on Familial Hypercholesterolaemia Screening in Children. http://legacy.screening.nhs.uk/familialhypercholesterolaemia-child. 2015. Accessed December 15, 2015.