JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Lipid Disorders in Children and Adolescents
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Lipid screening in childhood and adolescence can lead to early dyslipidemia diagnosis. The long-term benefits of lipid screening and subsequent treatment in this population are uncertain.

OBJECTIVE To review benefits and harms of screening and treatment of pediatric dyslipidemia due to familial hypercholesterolemia (FH) and multifactorial dyslipidemia.

DATA SOURCES MEDLINE and the Cochrane Central Register of Controlled Trials through May 16, 2022; literature surveillance through March 24, 2023.

STUDY SELECTION English-language randomized clinical trials (RCTs) of lipid screening; recent, large US cohort studies reporting diagnostic yield or screen positivity; and RCTs of lipid-lowering interventions.

DATA EXTRACTION AND SYNTHESIS Single extraction, verified by a second reviewer. Quantitative synthesis using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Health outcomes, diagnostic yield, intermediate outcomes, behavioral outcomes, and harms.

RESULTS Forty-three studies were included (n = 491 516). No RCTs directly addressed screening effectiveness and harms. Three US studies (n = 395 465) reported prevalence of phenotypically defined FH of 0.2% to 0.4% (1:250 to 1:500). Five studies (n = 142 257) reported multifactorial dyslipidemia prevalence; the prevalence of elevated total cholesterol level (≥200 mg/dL) was 7.1% to 9.4% and of any lipid abnormality was 19.2%. Ten RCTs in children and adolescents with FH (n = 1230) demonstrated that statins were associated with an 81- to 82-mg/dL greater mean reduction in levels of total cholesterol and LDL-C compared with placebo at up to 2 years. Nonstatin-drug trials showed statistically significant lowering of lipid levels in FH populations, but few studies were available for any single drug. Observational studies suggest that statin treatment for FH starting in childhood or adolescence reduces long-term cardiovascular disease risk. Two multifactorial dyslipidemia behavioral counseling trials (n = 934) demonstrated 3- to 6-mg/dL greater reductions in total cholesterol levels compared with the control group, but findings did not persist at longest follow-up. Harms reported in the short-term drug trials were similar in the intervention and control groups.

CONCLUSIONS AND RELEVANCE No direct evidence on the benefits or harms of pediatric lipid screening was identified. While multifactorial dyslipidemia is common, no evidence was found that treatment is effective for this condition. In contrast, FH is relatively rare; evidence shows that statins reduce lipid levels in children with FH, and observational studies suggest that such treatment has long-term benefit for this condition.

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Screening can identify abnormal lipid levels with genetic and nongenetic etiologies. Familial hypercholesterolemia (FH) is an autosomal codominant genetic disorder of cholesterol lipid metabolism associated with elevated levels of low-density lipoprotein cholesterol (LDL-C), which causes premature atherosclerosis and early cardiovascular morbidity and mortality.[1] Multifactorial dyslipidemia refers to dyslipidemias involving abnormal lipid levels that are not attributable to FH. Multifactorial dyslipidemia may be associated with environmental factors, such as lifestyle behaviors, with or without an inherited component from single-nucleotide variants with smaller additive effects.[2-4]

Therapies to reduce lipid levels in adulthood are well established,[5] and there is also a body of evidence for reducing lipid levels in children and adolescents with FH.[6] Evidence is uncertain, however, about when in the life span to begin screening for abnormal lipid levels. In 2016, the US Preventive Services Task Force (USPSTF) found insufficient evidence to assess the balance of benefits and harms of routine screening for any lipid disorders, including FH, in children and adolescents.[7] This systematic review updates the body of evidence on screening for dyslipidemia in children and adolescents and was used to update the prior USPSTF recommendation.

Methods

Scope of Review

Figure 1 shows the analytic framework, key questions (KQs) that guided the systematic review, and the contextual questions intended to provide additional background information. In addition to systematic review of the KQs, this review looked for evidence about the association between lipid-related outcomes in childhood and adolescence and adult health outcomes and the optimal timing of statin treatment initiation in FH. Additional methodological details, analyses, results for other lipid outcomes in treatment trials other than total cholesterol and LDL-C (high-density lipoprotein cholesterol [HDL-C], triglycerides, non–HDL-C), as well as treatment trials of fibrates and supplements, are available in the full evidence report.[9]

Data Sources and Searches

MEDLINE and the Cochrane Central Register of Controlled Trials were searched for relevant English-language articles published after the search dates for the prior reviews of lipid disorders in children and adolescents previously conducted for the USPSTF (January 1, 2016, to May 16, 2022) (eMethods in Supplement).[6,10] All studies in the prior reviews were evaluated,[6,10] as well as reference lists of related systematic reviews. ClinicalTrials.gov was searched for relevant ongoing trials. Active surveillance was conducted through March 24, 2023, via article alerts and targeted journal searches to identify major studies that might affect the conclusions of the review or understanding of the evidence. One new study was identified[11]; however, it did not substantively change the review's interpretation of findings or conclusions and is not addressed further.

Study Selection

Two independent reviewers screened titles, abstracts, and full-text articles against a priori eligibility criteria (eTable 1 in the Supplement). Eligible studies included children and adolescents 20 years and younger. Populations with homozygous FH, those already being followed up for dyslipidemia, or those with diagnoses associated with secondary dyslipidemia were excluded, as were populations with an established family history of FH.

For KQ1, randomized clinical trials (RCTs) and controlled clinical trials comparing universal or selective serum lipid screening with no screening were used to evaluate the effectiveness of screening with nonfasting or fasting serum lipid tests typically ordered in primary care. Cascade screening was excluded because this represents a case-finding approach as opposed to population screening. For KQ2, large, recent US cohort studies were used for assessing diagnostic yield of screening. Studies reporting positive predictive value of a first elevated screening lipid result for a second confirmatory test were sought; however, no included studies used a confirmatory test, and thus studies reporting screen positivity based on a single lipid test were accepted. Author-defined thresholds for abnormal lipid levels were used. For KQ4, RCTs of treatments for dyslipidemia including drugs, behavioral counseling, and supplements were used to assess benefits. Outcomes for treatment benefits included health outcomes (myocardial infarction, ischemic stroke, cardiovascular disease [CVD] mortality, or all-cause mortality); the intermediate outcomes of serum lipid concentrations (total cholesterol, LDL-C, HDL-C, triglycerides, or non–HDL-C), atherosclerosis markers (carotid intima-media thickness, calcium score, or pathological findings), and body mass index (BMI); and behavioral outcomes (physical activity, sedentary behavior, or dietary intake). For KQ3 (screening harms) and KQ5 (treatment harms), RCTs, controlled clinical trials, and nonrandomized studies of interventions were accepted.

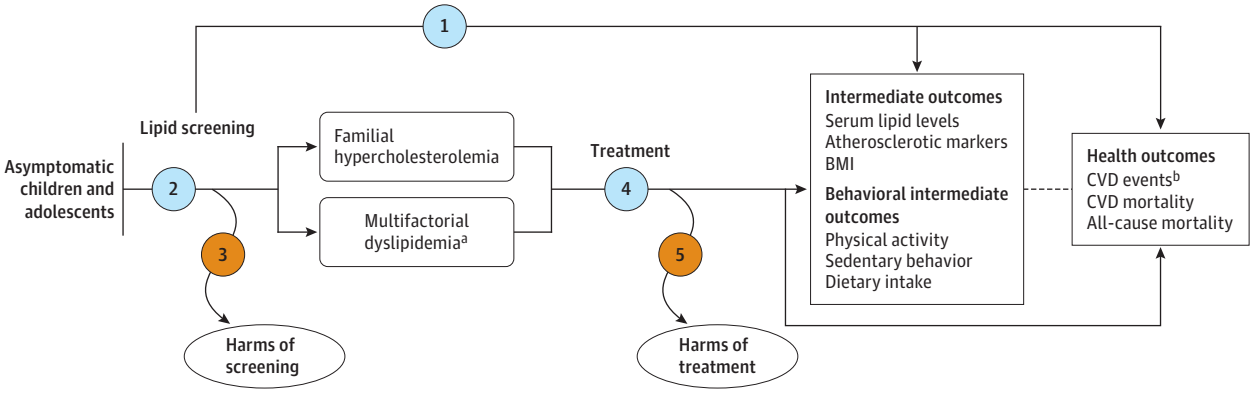
Data Extraction and Quality Assessment

Two reviewers independently applied USPSTF design-specific criteria to critically appraise each study (eTable 2 in the Supplement).[8] Each study was assigned a rating of "good," "fair," or "poor." Discordant ratings were resolved by consensus. Poor-quality studies were excluded. One reviewer extracted data into standardized evidence tables and a second reviewer checked the tables for accuracy.

Data Synthesis and Analysis

All results were synthesized separately for FH and multifactorial dyslipidemia. Evidence related to the prevalence of FH and multifactorial dyslipidemia (KQ2) were synthesized narratively and summarized in tables. For treatment studies (KQ4 and KQ5), results were synthesized by intervention. Only statins had a sufficient number of contributing studies for quantitative pooling; other interventions were summarized narratively and in tables. The random-effects restricted maximum likelihood method with the Knapp-Hartung correction was applied in meta-analyses for statins because of either high statistical heterogeneity (commonly $I^2 > 50\%$) or small number of trials to be pooled.[12,13] For pooling statin studies with multiple randomized groups with differing statin intensity, we selected the group receiving the highest-intensity dose. Statin intensity categorizations were based on 2018 guidelines for the management of cholesterol levels in adults,[14] because intensity categorizations are not established for pediatric populations.

Figure 1. Analytic Framework: Screening for Lipid Disorders in Children and Adolescents



Key questions

1. Does screening for familial hypercholesterolemia (FH) or multifactorial dyslipidemia in asymptomatic children and adolescents delay or reduce the incidence of health outcomes (eg, CVD events or mortality) or improve intermediate outcomes (eg, serum lipid levels and atherosclerotic markers) in children, adolescents, or adults?
2. What is the diagnostic yield or serum lipid screening for FH or multifactorial dyslipidemia in children and adolescents?
3. What are the harms of screening for FH or multifactorial dyslipidemia in children and adolescents?
4. Does treatment of FH or multifactorial dyslipidemia with behavioral interventions, lipid-lowering medications, or both in children and adolescents delay or reduce the incidence of health outcomes (eg, CVD events or mortality) or improve intermediate outcomes (eg, serum lipid levels and atherosclerotic markers) in children, adults, or both?
5. What are the harms of treatment of FH or multifactorial dyslipidemia in children and adolescents?

Contextual questions

1. What is the association between childhood and adolescent intermediate outcomes (lipids, atherosclerosis markers) and adult health outcomes (adult CVD events, mortality)?
2. What is the optimal timing of statin treatment initiation in FH?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a health outcome that immediately follows an intermediate outcome. For more details see the USPSTF Procedure Manual.[8] BMI indicates body mass index; CVD, cardiovascular disease.

[a] Defined as dyslipidemia not due to familial hypercholesterolemia.

[b] Defined as myocardial infarction or ischemic stroke.

Statistical heterogeneity among pooled studies was evaluated using standard χ^2tests and the magnitude of heterogeneity was estimated using the I^2 statistic. Due to the limited number of trials (<10) for pooled analyses of statins, assessment of small-study effects and publication bias were not performed.[15,16]

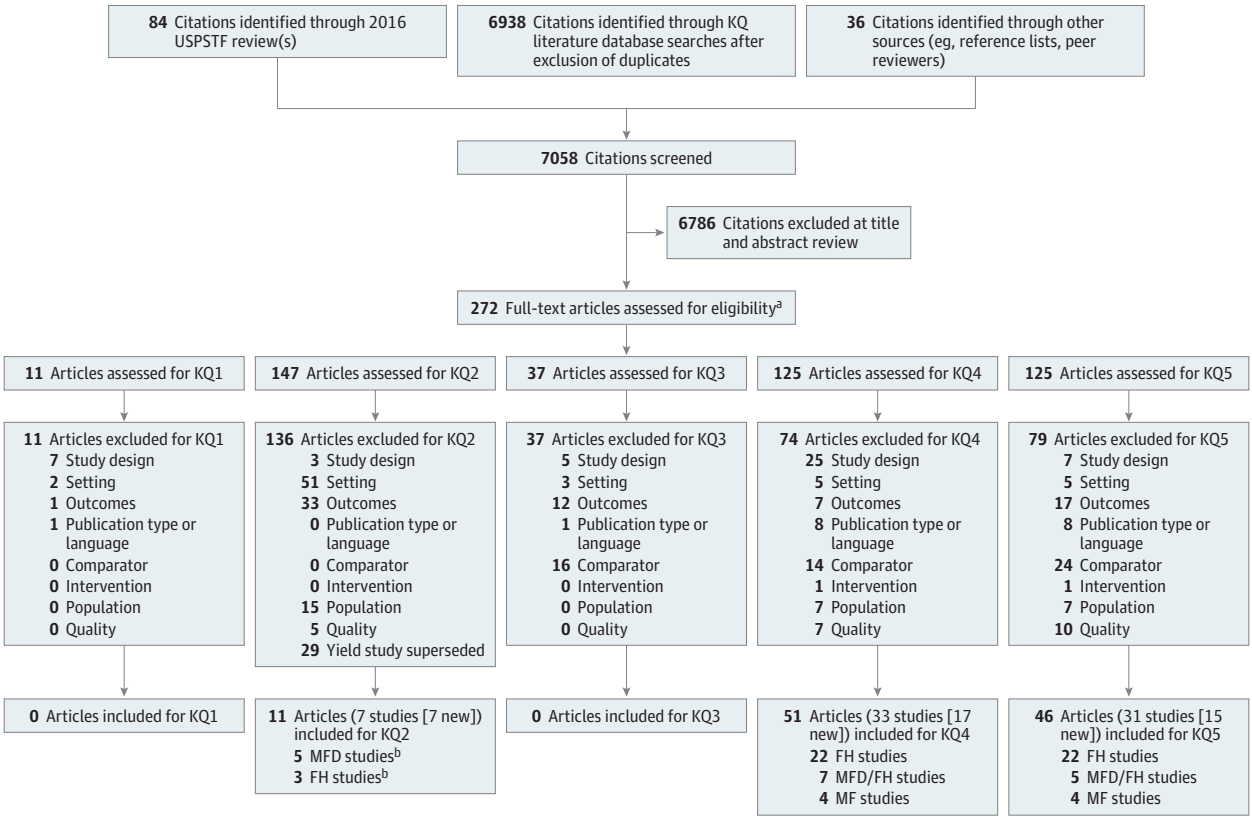
All quantitative analyses were performed using Stata version 16.1 (StataCorp). All significance testing was 2-sided, and results were considered statistically significant at $P < .05$.

The aggregate strength of evidence was assessed for each KQ using the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[17] based on the number, quality, and size of studies and the consistency and precision of results.

Results

Two reviewers evaluated 7058 abstracts and 272 full-text articles for KQ eligibility (**Figure 2**). Overall, 43 studies (65 publications) met inclusion criteria for this systematic review.[18-83] Thirteen of these studies evaluated the benefits of supplement interventions and 10 reported on the harms of supplement interventions. These studies were small, of short duration, and had few contributing studies for any one supplement. Evidence was generally insufficient and these interventions are not addressed further; additional details are available in the full report.[9]

Figure 2. Literature Search Flow Diagram: Screening for Lipid Disorders in Children and Adolescents



Reasons for exclusion: Study design: Study did not use an included design. Setting: Study was not conducted in a country relevant to US practice. Outcomes: Study did not have relevant outcomes or had incomplete outcomes. Comparator: Study included a comparator group that was not included. Intervention: Study used an excluded intervention or screening approach. Population: Study was not conducted in an average-risk population. Quality: Study did not meet criteria for fair or good quality. Yield study superseded: Publication evaluated for KQ2 (yield) was superseded by another publication that was more contemporary, comprehensive, or more relevant. FH indicates familial hypercholesterolemia; KQ, key question; MFD, multifactorial dyslipidemia.

[a] Studies may appear in more than 1 KQ.

[b] One study reports both FH and MFD populations.

Screening Benefits and Harms

KQ1. Does screening for familial hypercholesterolemia (FH) or multifactorial dyslipidemia in asymptomatic children and adolescents delay or reduce the incidence of health outcomes (eg, CVD events or mortality) or improve intermediate outcomes (eg, serum lipid levels and atherosclerotic markers) in children, adolescents, or adults?

No studies met inclusion criteria for this KQ.

Diagnostic Yield

KQ2. What is the diagnostic yield of serum lipid screening for FH or multifactorial dyslipidemia in children and adolescents?

No studies performed a confirmatory lipid or genetic test; thus, the evidence on lipid screening for identifying FH or multifactorial dyslipidemia is limited to the prevalence of single positive screening test results rather than the diagnostic yield as defined by confirmatory testing.

Familial Hypercholesterolemia

A summary of the evidence related to familial hypercholesterolemia is provided in **Table 1**. Three fair-quality US studies (n = 395 465) including the National Health and Nutrition Examination Survey (NHANES),[82] a Texas blood donor program,[81] and the West Virginia Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) study,[72] reported the prevalence of FH (eTables 3 and 4 in the Supplement). Using diagnostic criteria exclusively based on lipid levels (LDL-C ≥190 mg/dL or total cholesterol ≥270 mg/dL [to convert LDL-C and total cholesterol values to mmol/L, multiply by 0.0259]), prevalence ranged from 0.2% to 0.4% (1:250 to 1:500). One study showed that targeted screening in persons with a family history of hypercholesterolemia would miss many cases of children with LDL-C levels of 160 mg/dL or greater (prevalence in those with family history, 1.2%; prevalence in those without family history, 1.7%).[70]

Multifactorial Dyslipidemia

A summary of the evidence related to multifactorial dyslipidemia is provided in **Table 2**. Five fair-quality studies (n = 142 257), including NHANES,[23] HEALTHY,[25] the Study of Latino Youth,[22] Poudre Valley Health System Healthy Hearts Club,[24] and CARDIAC,[72] reported the prevalence of multifactorial dyslipidemia (eTables 5 and 6 in the Supplement). Lipid abnormalities were common, being generally more common for the parameters of HDL-C and triglycerides.

Table 1. Familial Hypercholesterolemia: Summary of Evidence

Intervention	No. of included studies (No. of participants)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of screening						
Universal or selective screening	0	NA	NA	NA	Insufficient	NA
KQ2: Yield						
Universal or selective screening	3 (n = 395 465) New: 3	Diagnostic yield: No studies reported true diagnostic yield, as there were no screening studies with genetic testing Prevalence: Using thresholds of LDL-C ≥190 mg/dL or total cholesterol ≥270 mg/dL, FH prevalence was 0.20% to 0.42% (1:250 to 1:500) Targeted screening based on family history would miss a substantial proportion of cases	Diagnostic yield: NA Prevalence: reasonably consistent; reasonably precise	No genetic or family history criteria; lipid values are used as a proxy for FH	Insufficient for diagnostic yield Low for prevalence	US children and adolescents with most evidence for ages 10 y or older; applicability to various recruitment settings and geographic locations
KQ3: Harms of screening						
Universal or selective screening	0	NA	NA	NA	Insufficient	NA
KQ4: Benefits of treatment						
Statin	10 (n = 1230) New: 1	Total cholesterol: 7 studies (n = 706); MD in change, −82.1 mg/dL (95% CI, −101.1 to −63.2); I^2 = 83.0% LDL-C: 8 studies (n = 742); MD in change, −81.3 mg/dL (95% CI, −97.6 to −65.0); I^2 = 81.6% Total cholesterol and LDL-C effects appear dose-related	Consistent; reasonably precise	Heterogeneity of statin drugs and intensity Short-term follow-up (one 2-y trial but all other trials <6 mo) No health outcomes Small sample sizes (range, 50-214)	Moderate for benefit	Children and adolescents aged 6-18 y with FH defined using various diagnostic criteria
Bile acid sequestrants	3 (n = 332) New: 0	Total cholesterol: MD in change, −22.1 to −40.6 mg/dL LDL-C: MD in change, −13.2 to −45.9 mg/dL Variation in effect by dose	Reasonably consistent; reasonably precise	Different formulations of bile acid sequestrants Short duration (8-52 wk) No health outcomes	Low for benefit	Children and adolescents aged 6-17 y with FH
Ezetimibe	1 (n = 138) New: 0	Total cholesterol: MD in change, −64.0 mg/dL (95% CI, −81.1 to −46.9) LDL-C: MD in change, −63.0 mg/dL (95% CI, −79.5 to −46.5)	Consistency NA; reasonably precise	Short duration (12 wk) No health outcomes	Low for benefit	Children aged 6-11 y with FH
PCSK9 inhibitor	1 (n = 158) New: 1	LDL-C: MD in change, −68.6 mg/dL (95% CI, −83.1 to −54.0)	Consistency NA; reasonably precise	Short duration (24 wk) No health outcomes	Low for benefit	Children and adolescents aged 10-17 with FH
Drug combination (simvastatin + ezetimibe)	1 (n = 248) New: 0	Compared with single drug: Total cholesterol: MD in change, −40.1 mg/dL (95% CI, −51.1 to −29.2) LDL-C: MD in change, −37.5 mg/dL (95% CI, −48.0 to −27.0)	Consistency NA; reasonably precise	Short duration (33 wk) No health outcomes	Low for benefit	Children and adolescents aged 10-17 y with FH

(continued)

Table 1. Familial Hypercholesterolemia: Summary of Evidence (continued)

Intervention	No. of included studies (No. of participants)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
Behavioral counseling	1 (n = 21) New: 1	Lipids: no difference Physical activity outcomes: overlapping confidence intervals for intervention vs control Dietary outcomes: mixed results	Consistency NA; imprecise	Very small trial Short duration (12 wk) No health outcomes	Insufficient	Low-intensity diet and physical activity intervention for patients aged 10-18 y with FH
KQ5: Harms of treatment						
Statin	12 (n = 1476 in trials, 10 336 in NRSI harms-only studies) New: 3 (1 RCT, 2 NRSI)	Transaminitis >3× ULN: 0%-4.5% (intervention) vs 0%-1.9% (control), but largest trial (n = 214) with 2-y follow-up reported no cases in the statin group and 2 cases of AST >3× ULN in the control group In the 10-y observational follow-up of this trial, transaminitis at this threshold was similarly rare (ALT: 1 case of >3× ULN elevation in the statin group; AST: 1 case of >3× ULN each in the statin and control group) CK ≥10× ULN: 0 in 2 trials and up to 4.5% (intervention) vs 1.7% (control) but 1 trial's 10-y observational follow-up reported no instances of elevated CK 1 NRSI (n = 943) reported ALT elevations of >3× ULN, with a frequency of 4.4% in the statin group and 1.5% in the control group over 3.5 y of observation 1 NRSI (n = 9393) showed no difference in new diabetes diagnoses over 9 y Six trials (n = 931) and 1 NRSI (n = 309) reported no significant differences between Tanner stages or other hormonal adverse events	Inconsistent; imprecise	Most trials were short-term and small with few events, leading to imprecise estimates Clinical importance of transient elevations in these laboratory values is unknown	Low for reversible liver and musculoskeletal laboratory abnormalities Insufficient for new-onset diabetes Low for no growth or hormonal harms	Short-term harms
Bile acid sequestrants	3 (n = 332) New: 0	Similar rates of total adverse events in intervention and control groups	Relatively consistent, imprecise	Different formulations, few events Short duration (8-52 wk)	Low for minimal harm	Children and adolescents aged 6-17 y with FH
Ezetimibe	1 (n = 138) New: 0	Similar rates of total adverse events in intervention and control groups	Consistency NA, imprecise	Single trial Short duration (12 wk) Few events	Insufficient	Children aged 6-11 y with FH
PCSK9 inhibitor	1 (n = 158) New: 1	Similar rates of total adverse events in intervention and control groups	Consistency NA, imprecise	Single trial Short duration (24 wk) Few events	Insufficient	Children and adolescents aged 10-17 with FH
Drug combination (simvastatin + ezetimibe)	1 (n = 248) New: 0	Similar rates of total adverse events in intervention and control groups	Consistency NA, imprecise	High total adverse events in both the intervention and the control group Short duration (33 wk)	Insufficient	Children and adolescents aged 10-17 y with FH
Behavioral counseling	0	NA	NA	NA	Insufficient	NA

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CK, creatine kinase; DHA, docosahexaenoic acid; FDA, US Food and Drug Administration; FH, familial hypercholesterolemia; KQ, key question; LDL-C, low-density lipoprotein cholesterol; MD, mean difference; NA, not applicable; NRSI, nonrandomized controlled study of intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized clinical trial; ULN, upper limit of normal.
SI conversion factors: To convert LDL-C and total cholesterol values to mmol/L, multiply by 0.0259.

Table 2. Multifactorial Dyslipidemia: Summary of Evidence

Intervention	No. of included studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of screening						
Universal or selective screening	0	NA	NA	NA	Insufficient	NA
KQ2: Yield						
Universal or selective screening	5 (n = 142 257) New: 5	Diagnostic yield: No studies reported true diagnostic yield, as there were no screening studies with confirmatory testing Prevalence: ≥1 Abnormal lipid value: 19.2% (NHANES [n = 4381]) Total cholesterol ≥200 mg/dL: 7.1% (NHANES) to 9.4% (PVHS) (3 studies [n = 75 551]) LDL-C ≥130 mg/dL: 6.4% (NHANES) to 7.4% (CARDIAC) (2 studies [n = 56 824]) HDL-C <40 mg/dL: 12.1% (NHANES) to 22.2% (PVHS) (4 studies [n = 72 320]) Triglycerides ≥130 mg/dL: 10.2% (NHANES) (1 study [n = 2045]) Non-HDL-C ≥145 mg/dL: 6.4% (NHANES) and 13.0% (PVHS) (2 studies [n = 16 150])	Diagnostic yield: NA Prevalence: Consistent; reasonably precise for total cholesterol and LDL-C but imprecise for other measures	No confirmatory testing NHANES represents only national sample and included most recent years of 2016; fasting and nonfasting samples Prevalence varies by population characteristics	Insufficient for diagnostic yield of screening tests Moderate that abnormal lipid values are common	US children and adolescents aged 6-19 y Overall prevalence lower in national data set (NHANES) compared with other geographically focused recruitment settings
KQ3: Harms of screening						
Universal or selective screening	0	NA	NA	NA	Insufficient	NA
KQ4: Benefits of treatment						
Behavioral counseling	2 (n = 934) New: 1	One 7-y trial (DISC) of a high-intensity dietary intervention showed statistically significant reductions in total cholesterol and LDL-C (MD in change, −3.3 mg/dL for total cholesterol and LDL-C) at 3 y that were not sustained at 7-y follow-up One low-intensity dietary 10-wk intervention with up to 1 y of follow-up: statistically significant reduction in LDL-C (MD in change, −6.7 mg/dL) at 3 mo not sustained at 1-y follow-up Both trials reported that interventions were associated with improved dietary intake outcomes, which were attenuated at longer follow-up	Consistent, reasonably precise	Heterogeneous dietary interventions with variable intensity, duration, and follow-up	Low for no long-term benefit	Children aged 4-10 y
KQ5: Harms of treatment						
Behavioral counseling	2 (n = 934) New: 1	No harmful effects identified in growth (BMI, weight, height), development (Tanner stage), nutritional outcomes (serum ferritin, red cell folate, zinc, albumin), or psychological outcomes (anxiety, depression, behavior) One trial (DISC) reported better depression outcomes in the intervention group	Consistent, reasonably precise	Heterogeneous dietary interventions with variable intensity, duration, and follow-up	Low for no harms	Children aged 4-10 y

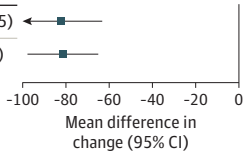
Abbreviations: BMI, body mass index; CARDIAC, Coronary Artery Risk Detection in Appalachian Communities; DISC, Dietary Intervention Study in Children; KQ, key question; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MD, mean difference; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; non-HDL-C, non–high-density lipoprotein cholesterol; PVHS, Poudre Valley Health System study; RCT, randomized clinical trial.

SI conversion factors: To convert LDL-C, total cholesterol, HDL-C, and non–HDL-C values to mmol/L, multiply by 0.0259; triglyceride values to mmol/L, multiply by 0.0113.

Figure 3. Familial Hypercholesterolemia: Statin Intervention Trials—Meta Plot of Total Cholesterol and Low-Density Lipoprotein Results (Key Question 4)

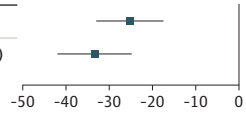
A Mean difference in change

Lipid	No. of studies (No. of observations)	Mean baseline, mg/dL		Mean difference in change (95% CI)
		Intervention	Control	
Total cholesterol	7 (706)	291.3	292.1	-82.14 (-101.12 to -63.15)
LDL-C	8 (742)	230.0	228.0	-81.28 (-97.58 to -64.99)



B Mean percent change

Lipid	No. of studies (No. of observations)	Mean baseline, mg/dL		Mean percent change (95% CI)
		Intervention	Control	
Total cholesterol	5 (526)	295.8	292.2	-25.26 (-33.0 to -17.52)
LDL-C	6 (577)	232.0	230.2	-33.39 (-41.99 to -24.79)



LDL-C indicates low-density lipoprotein cholesterol.

Prevalence ranged from 7.1% to 9.4% for elevated total cholesterol level (≥200 mg/dL), 6.4% to 7.4% for elevated LDL-C (≥130 mg/dL), 12.1% to 22.2% for low HDL-C (<40 mg/dL), 8.0% to 17.3% for elevated triglycerides (using various thresholds), and 6.4% to 13.0% for elevated non–HDL-C (≥145 mg/dL) (to convert HDL-C and non–HDL-C values to mmol/L, multiply by 0.0259). Prevalence of any lipid abnormality in 6- to 19-year-olds was 19.2% based on NHANES data (2013-2016, n = 4381). Prevalence of abnormal lipid levels by population characteristics are shown in eFigures 1-3 in the Supplement.

Screening Harms

KQ3. What are the harms of screening for FH or multifactorial dyslipidemia in children and adolescents?

No studies met inclusion criteria for this KQ.

Treatment Benefit

KQ4. Does treatment of FH or multifactorial dyslipidemia with behavioral interventions, lipid-lowering medications, or both in children and adolescents delay or reduce the incidence of health outcomes (eg, CVD events or mortality) or improve intermediate outcomes (eg, serum lipid levels and atherosclerotic markers) in children, adults, or both?

Familial Hypercholesterolemia

A summary of the evidence related to familial hypercholesterolemia is provided in Table 1. No treatment trials reported long-term health outcomes. Twenty-two fair- to good-quality trials (n = 2257) examined the effectiveness of various lipid-lowering treatments for FH including pharmacotherapy, behavioral counseling, and dietary supplements. Trials were generally small and short-term. Overall, this body of evidence demonstrated that pharmacotherapy appears beneficial for total cholesterol and LDL-C outcomes, with the largest evidence available for statins; behavioral counseling was not effective.

Ten fair- to good-quality RCTs (n = 1230) of statins with follow-up for up to 2 years comprised the largest body of evidence addressing FH treatment, but only 1 trial is new in this update.[56-65] Pooled analyses demonstrated that statins were associated with an 81- to 82-mg/dL greater mean reduction in total cholesterol and LDL-C levels compared with placebo at up to 2 years' follow-up (total cholesterol: 7 studies [n = 706]; mean difference [MD] in change, −82.1 mg/dL [95% CI, −101.1 to −63.2]; I^2 = 83.0%; LDL-C: 8 studies [n = 742]; MD in change, −81.3 mg/dL [95% CI, −97.6 to −65.0]; I^2 = 81.6%) (**Figure 3**; eFigures 4 and 5 in the Supplement). One good-quality and 2 fair-quality bile acid sequestrant trials (n = 332) demonstrated that treatment was associated with a significantly greater reduction in total cholesterol level compared with placebo.[78-80] Total cholesterol reductions ranged from −22.1 mg/dL to −40.6 mg/dL and LDL-C reductions from −13.2 mg/dL to −45.9 mg/dL at 8 weeks (eFigures 6 and 7 in the Supplement). One good-quality ezetimibe trial (n = 138) showed a statistically significant reduction in total cholesterol (MD in change, −64.0 mg/dL [95% CI, −81.1 to −46.9]) and LDL-C (MD in change, −63.0 mg/dL [95% CI, −79.5 to −46.5]) (eFigures 6 and 7 in the Supplement).[75]

One new good-quality trial of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (n = 158) demonstrated that evolocumab was associated with a statistically significant 68.6-mg/dL reduction in LDL-C level (95% CI, −83.1 to −54.1) (eFigure 7 in the Supplement).[69] One trial of combination drug therapy of a statin plus ezetimibe compared with a statin alone (n = 248) showed that the 2-drug intervention was associated with a greater reduction in total cholesterol level (MD in change, −40.1 mg/dL [95% CI, −51.1 to −29.2]) and LDL-C (MD in change, −37.5 mg/dL [95% CI, −48.0 to −27.0]) compared with the single-drug intervention control group at 33 weeks (eFigures 6 and 7 in the Supplement).[76]

One very small, fair-quality behavioral counseling trial in an FH population (n = 21) tested a low-intensity diet and exercise counseling intervention of a single in-person 60-minute individual session with a dietitian and 4 follow-up sessions via email or telephone over a 12-week period.[73] The trial reported no statistically significant improvement in lipid levels (MD in LDL-C, −13.9 mg/dL [95% CI, −32.0 mg/dL to 4.2 mg/dL]) (eFigure 7 in the Supplement), overlapping confidence intervals for physical activity

outcomes, and mixed results for dietary outcomes (eTable 7 in the Supplement).[73]

Multifactorial Dyslipidemia

A summary of the evidence related to multifactorial dyslipidemia is provided in Table 2. There were no included trials of drug interventions in child and adolescent populations with multifactorial dyslipidemia. There were 2 fair- to good-quality behavioral counseling trials (n = 934); both focused on dietary changes.[18,83] Overall, this body of evidence showed that behavioral counseling interventions were associated with nonsustained, short-term reductions in levels of total cholesterol and LDL-C, with some improvements in dietary intake. The first trial, in which intervention continued throughout a mean follow-up of 7.4 years, evaluated an intensive intervention of 19 individual sessions with a case manager and 31 group sessions led by dietitians, behaviorists, and health educators.[83] The second trial was a 10-week, low-intensity intervention RCT with 1 year of follow-up and included 2 intervention groups. The first group received a home-based, social cognitive theory–based intervention with 10 audiotape story books with accompanying picture books, child activity books, and a parent manual to be reviewed over 10 weeks; the second intervention group received a child-parent in-person 45- to 60-minute counseling session with a pediatric registered dietitian and home print materials with access to the dietitian by phone with any questions after the session.[18] These 2 trials demonstrated statistically significant 3- to 6-mg/dL greater reductions in levels of total cholesterol and LDL-C and improvements in dietary intake outcomes in the intervention group compared with the control group during the first follow-up for each trial, but findings did not persist at the second follow-up (eTables 8 and 9 in the Supplement). No treatment trials reported long-term health outcomes.

Treatment Harms

KQ5. What are the harms of treatment of FH or multifactorial dyslipidemia in children and adolescents?

Familial Hypercholesterolemia

A summary of the evidence related to familial hypercholesterolemia is provided in Table 1. Overall, harms reported in pharmacotherapy trials were similar in the intervention and control groups; however, most studies were relatively short-term and small with few events, leading to imprecise estimates. Further, the clinical importance of transient elevations in laboratory values was unknown.

In the 9 statin studies reporting transaminitis of 3 times or more the upper limit of normal, this outcome occurred in 0% to 4.5% in intervention groups and 0% to 1.9% in control groups (eFigure 8 in the Supplement).[47,56-58,60,63-65,75] The largest trial (n = 214) with 2-year follow-up reported no cases in the statin group and only 2 cases of aspartate aminotransferase levels more than 3 times the upper limit of normal in the control group.[56] In the 10-year observational follow-up of this trial, transaminitis at this threshold was similarly rare (alanine aminotransferase: 1 case of >3 times elevation in the statin group; aspartate aminotransferase: 1 case of >3 times elevation each in the statin and control group).[55] Abnormal creatine kinase level of 10 times or greater the upper limit of normal was reported as zero in 2 trials[57,63] and up to 4.5% in the statin groups and up to 1.7% in the control groups (eFigure 9 in the Supplement).[60,65] One trial's 10-year observational follow-up reported no instances of elevated creatine kinase level in participants taking statins and in 2 siblings without FH not taking statins.[55]

Two observational studies evaluated statin harms in populations with dyslipidemia, without specification of the type of dyslipidemia. One fair-quality observational study evaluated the association of statins and new-onset diabetes (n = 9393), showing no difference in new diabetes diagnoses over up to 9 years' follow-up in individuals taking statins compared with controls. One fair-quality observational study (n = 943) reported alanine aminotransferase levels more than 3 times the upper limit of normal, with a frequency of 4.4% in the statin group and 1.5% in the control group over 3.5 years of observation.

In the statin trials, no significant differences between Tanner stages[56-58,67] or other hormonal adverse events like abnormal levels of adrenocorticotropic hormone,[59] cortisol,[59] dehydroepiandrosterone sulfate,[55] follicle-stimulating hormone,[55] or thyrotropin[59] were reported in the RCTs or in longer observational follow-up (eTables 10 and 11 in the Supplement). Harms in the 3 bile acid sequestrant trials (n = 332) were similar in the intervention and control groups; however, the trials were generally small with few events, and significance testing was not reported.[78-80] Harms in the ezetimibe trial (n = 138),[75] PCSK9 inhibitor trial (n = 158),[69] and combination statin plus ezetimibe vs statin trial (n = 248)[76] showed similar rates of total adverse events in the intervention and control groups. The diet and physical activity counseling intervention did not mention harms.[73]

Multifactorial Dyslipidemia

A summary of the evidence related to multifactorial dyslipidemia is provided in Table 2. Overall, behavioral counseling interventions do not appear to be associated with important harms (eTables 12 and 13 in the Supplement).[18,83] The 2 behavioral counseling trials in children with multifactorial dyslipidemia (n = 934) reported no adverse effects in terms of growth and Tanner staging[83]; nutrient adequacy in ferritin, retinol, zinc, or albumin[83]; and psychosocial outcomes[18,83] in the dietary intervention group compared with the control group.

Contextual Questions

Contextual question details are reported in the eDiscussion and eFigure 10 in the Supplement. Contextual question 1 focuses on the indirect evidence linking childhood lipid levels to adult health outcomes. Robust evidence suggests that abnormal lipid levels in childhood and young adulthood are highly associated with adult CVD events. For example, the 35-year follow-up from the i3C Consortium (n = 38 589) reported hazard ratios for a fatal CVD event in adulthood of 1.30 (95% CI, 1.14-1.47) per unit increase in the *z* score for total cholesterol in childhood.[84]

Meta-analysis of 6 US-based cohort studies demonstrated the independent association between exposure to high lipid levels in young adulthood (age 18-39 years) and later CVD events, taking into account exposure to elevated lipid levels in later adulthood (≥40 years). In this study, exposure to LDL-C levels 100 mg/dL or higher in young adulthood was associated with an adjusted hazard ratio of 1.64 (95% CI, 1.27-2.11) for coronary heart disease, compared with LDL-C levels lower than 100 mg/dL in young adulthood.[85] Similarly, a mendelian randomization study of 9 single-nucleotide variants in an LDL-C gene suggested that lower

LDL-C levels throughout the life span are associated with substantially lower incidence of coronary heart disease in adulthood.[86]

Studies of lipid values over the life course show that it is common but not inevitable for high lipid levels in childhood to persist into adulthood.[84,87-90] There is robust evidence supporting the association between adult lipid levels and adult health outcomes from observational evidence and statin treatment trials.[5,86,91-93]

Contextual question 2 addresses the optimal timing of statin initiation in FH. In summary, there is no direct comparative effectiveness evidence to determine the exact age to start statin treatment for heterozygous FH, but earlier initiation is supported by indirect observational evidence. Markers of atherosclerosis are evident as early as age 8 years in children with FH compared with unaffected siblings or healthy controls; these subclinical atherosclerotic markers include higher carotid intima-media thickness, endothelial dysfunction, and arterial stiffness.[94-97]

Observational evidence further supports early treatment improvements in intermediate and health outcomes. At 10- to 20-year follow-up, carotid intima-media thickness progression rates converged in children with pathogenic variant–confirmed FH treated with statins and their unaffected siblings.[42,55] One compelling observation from a 20-year follow-up study of 214 treated patients from the statin trial by Wiegman et al[42,56] was that initiation of statins in adolescence was associated with an improved cumulative CVD-free survival at age 39 years. Participants with pathogenic variant–confirmed FH who started statins in youth (mean statin initiation age, 14.0 [SD, 3.1] years) had higher rates of CVD-free survival compared with their parents, for whom statins were not available until adulthood (99% v 74% CVD-free survival; hazard ratio, 11.8 [95% CI, 3.0-107.0] adjusted for sex, smoking status).[42]

Discussion

Summary

This review, performed since the previous systematic reviews for the USPSTF,[6,10] included the following new data: 7 studies of prevalence, 16 treatment trials, and 2 nonrandomized studies of interventions. Despite the inclusion of new evidence, the conclusions are similar to those of the prior reviews (Table 1 and Table 2). There is no direct evidence from population-based screening trials addressing the benefits and harms of pediatric lipid screening for intermediate, behavioral, or health outcomes.

Dyslipidemia is common in contemporary pediatric populations in the US, with a prevalence of 19.2% for any lipid abnormality and heterozygous FH prevalence (as defined by phenotype) estimated at 0.2% to 0.4% (1:250 to 1:500). The body of evidence on treatment benefit is strongest for statins in children and adolescents with FH, with pooled analysis showing beneficial effects on total cholesterol and LDL-C levels; these results were based on mostly small, short-term studies, with the longest trial lasting 2 years.

Most of the evidence for statin harms is from small, short-term studies. Limited longer-term evidence shows few withdrawals due to adverse events, slightly higher rates of liver and musculoskeletal laboratory elevations, and no significant differences in Tanner staging or hormonal adverse events between statin and placebo groups. These safety and efficacy findings are consistent with those from another recent systematic review[98] and from 1- to 20-year observational follow-up studies of children and adolescents taking statins.[99-107] Additional observational long-term reporting of health outcomes and statin safety (including diabetes, transaminitis) in those with FH for whom statins were initiated at various time points in childhood and adolescence would provide additional data for long-term benefits and harms. The nonstatin-drug trials show reductions in 1 or more lipid parameters and are generally associated with low withdrawals due to adverse events. There is scant evidence on behavioral counseling interventions in FH.

The body of evidence on treatment of multifactorial dyslipidemia is sparse, being limited to 2 behavioral counseling interventions showing modest short-term benefits in lipid levels that did not persist with longer follow-up. These results are consistent with short-term quality improvement projects in specialty settings that have shown that clinician advice targeting lifestyle modifications has shown promising results, especially for reductions in LDL-C levels.[107]

Single Screening Test Identifies Distinct Conditions

The natural history of FH and multifactorial dyslipidemia are quite different. While a single screening lipid panel identifies both conditions, FH is far less common and more prognostically severe. Further, the strength of the bodies of treatment literature are quite distinct for different dyslipidemias. Some observers have argued that the rationale for universal lipid screening in childhood is solely or primarily to identify those with FH because identifying FH has more potential benefit in reducing premature CVD events and death.[42] While the treatment evidence for multifactorial dyslipidemia is scant, some observers have suggested that early identification of any dyslipidemia could lead to earlier nonpharmacologic interventions or pharmacologic management for significantly elevated LDL-C levels and potentially improve health outcomes.[108] However, there is no direct evidence to suggest an effective lipid-lowering intervention for the nearly 20% of children and adolescents in whom screening would identify abnormal lipid levels.

Lipid screening may lead to additional benefits beyond identifying children with dyslipidemia, including discovery and treatment of secondary comorbid conditions (eg, diabetes, hypothyroidism) and identification and treatment of this condition in other family members via cascade testing. However, there is limited direct evidence about additional benefits of screening beyond the child.[70,109-112]

Other observers have surmised that screening and identification of dyslipidemia in children and adolescents with elevated BMI may make weight management interventions more effective; however, limited existing evidence does not support this hypothesis.[113,114] Behavioral counseling intervention trials in children with multifactorial dyslipidemia with and without elevated BMI are needed in addition to trials of behavioral counseling as an adjunct to pharmacotherapy in children with FH.

Limitations of the Literature and Future Research Needs

Familial hypercholesterolemia diagnostic criteria in yield studies were limited to lipid levels alone; this is inconsistent with treatment trial criteria, which also included genetic, family, or clinical history components in addition to lipid levels. Consistency in the use of FH criteria between screening studies and treatment studies would facilitate more direct interpretation of evidence to clinical practice.

Outcomes for treatment trials were limited to intermediate outcomes with insufficient follow-up periods to assess long-term health effects or harms. Obtaining such health outcome data may be quite difficult. To report on health outcomes for CVD events occurring in adulthood, these large cohort studies would need to be conducted over a period of decades while maintaining adequate follow-up.

Limitations

The accuracy of FH diagnostic criteria was not systematically reviewed; instead, this review accepted studies of FH as defined by study authors. Familial hypercholesterolemia is genetically heterogeneous, and the relationship between the FH genotype and FH phenotype as expressed by elevated LDL-C level is not straightforward.[115-118] Further, diagnosis of FH by genetic testing is rare in the US, further limiting the direct applicability of trials that use genetically confirmed FH to real-life practice, where FH is generally phenotypically defined. Furthermore, this review did not include other less common monogenic or polygenic dyslipidemias, so estimates of the positivity rates for screening may be an underestimate of familial dyslipidemias.

Conclusions

No direct evidence on the benefits or harms of pediatric lipid screening was identified. While multifactorial dyslipidemia is common, no evidence was found that treatment is effective for this condition. In contrast, FH is relatively rare; evidence shows that statins reduce lipid levels in children with FH, and observational studies suggest that such treatment has long-term benefit for this condition.

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Author Contributions: Dr Guirguis-Blake 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.
Concept and design: Guirguis-Blake, Evans, Coppola.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Guirguis-Blake, Evans, Coppola.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Guirguis-Blake, Redmond.
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Supervision: Guirguis-Blake, Evans.

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