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Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia

Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Familial hypercholesterolemia (FH) is characterized by elevated cholesterol concentrations early in life. Untreated FH is associated with premature cardiovascular disease in adulthood.

OBJECTIVE To systematically review the evidence on benefits and harms of screening adolescents and children for heterozygous FH for the US Preventive Services Task Force (USPSTF).

DATA SOURCES MEDLINE, the Cochrane Central Register of Controlled Trials, and PubMed were searched for studies published between January 1, 2005, and June 2, 2015; studies included in a previous USPSTF report were also searched. Surveillance was conducted through April 8, 2016.

STUDY SELECTION Fair- and good-quality studies in English with participants 0 to 20 years of age.

DATA EXTRACTION AND SYNTHESIS Two investigators independently reviewed abstracts and full-text articles and extracted data into evidence tables. Results were qualitatively summarized.

MAIN OUTCOMES AND MEASURES Myocardial infarction and ischemic stroke in adulthood; lipid concentrations and atherosclerosis in childhood; diagnostic yield of screening; any harm of screening or treatment.

RESULTS Based on 2 studies (n = 83 241), the diagnostic yield of universal screening for FH in childhood is 1.3 to 4.8 cases per 1000 screened. There was no eligible evidence on the benefits or harms of FH screening in childhood. Eight placebo trials of statin drugs (n = 1071, 6-104 weeks) found low-density lipoprotein cholesterol (LDL-C) decreases of 20% to 40%; 1 trial (n = 214) showed a 2.01% decrease in carotid intima-media thickness with statins, compared with 1.02% with placebo (P = .02). Three placebo trials of bile acid–sequestering agents (n = 332, 8-52 weeks) showed LDL-C reductions of 10% to 20%. In 1 trial (n = 248), ezetimibe with simvastatin resulted in greater LDL-C reductions compared with simvastatin alone at 33 weeks (mean, −54.0% [SD, 1.4%] vs −38.1% [SD, 1.4%]). One trial of ezetimibe monotherapy (n = 138) showed mean LDL-C decreases of 28% (95% CI, −31% to −25%) from baseline and negligible change with placebo at 12 weeks. Eighteen studies found statins generally well tolerated. One observational study found lower, but still normal, dehydroepiandrosterone sulfate concentrations in statin-treated males with FH at 10-year follow-up. Bile acid–sequestering agents were commonly associated with adverse gastrointestinal symptoms and poor palatability. There was no eligible evidence on the effect of FH treatment on myocardial infarction or stroke in adulthood.

CONCLUSIONS AND RELEVANCE Screening can detect FH in children, and lipid-lowering treatment in childhood can reduce lipid concentrations in the short term, with little evidence of harm. There is no evidence for the effect of screening for FH in childhood on lipid concentrations or cardiovascular outcomes in adulthood, or on the long-term benefits or harms of beginning lipid-lowering treatment in childhood.

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder of lipoprotein metabolism characterized by highly elevated total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) concentrations early in life. The estimated prevalence of heterozygous FH is 1 in 200 to 1 in 500 in North America and Europe and higher for populations with known founder effects.[1] Long-term exposure to elevated serum cholesterol is associated with atherosclerotic burden,[2-5] and untreated FH has been associated with increased relative risk of coronary heart disease (CHD) events and CHD mortality.[6-8] The excess relative CHD mortality risk is highest between ages 20 and 39 years, a group with very low baseline CHD mortality, and decreases with age.[6,7]

Familial hypercholesterolemia is treatable, asymptomatic in childhood and adolescence, and may be underdiagnosed in children.[9,10] The disorder is diagnosed through a combination of elevated lipid concentrations, physical findings, and genetic testing (eTables 1-3 in the Supplement).[6,11,12] Screening for elevated lipids is currently the most viable population-based screening option; incomplete penetrance of the gene variants that cause FH[13,14] limits the benefit of genetic screening for FH outside of cascade screening within affected families.

Primary care–based screening could identify presymptomatic children with FH through elevated TC and LDL-C concentrations, which can be 2 to 3 times higher in children with FH than in unaffected children.[11] Lipid-lowering treatment before clinically significant atherosclerosis develops could reduce future CHD risk in adulthood. However, in 2007 the US Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against routine screening for any lipid disorders, including FH in infants, children, or adolescents up to age 20 years (I recommendation).[4,15] The purpose of this evidence report was to assist the USPSTF in updating its previous recommendations on screening children and adolescents for FH.

Methods

Scope of Review

The Agency for Healthcare Research and Quality commissioned 2 systematic evidence reviews to support the USPSTF in updating its 2007 recommendation statement on screening for lipid disorders in childhood. This review focuses on benefits and harms of screening for and treatment of heterozygous FH in children and youth aged 0 to 20 years. A separate systematic review to update the 2007 USPSTF recommendations on multifactorial dyslipidemia addresses screening children and adolescents for other dyslipidemias involving elevated concentrations of LDL-C or TC that are not FH.[16] This evidence review focuses exclusively on heterozygous FH.

Using USPSTF methods, an analytic framework and 8 key questions (KQs) were developed to assess the benefits of screening for and treatment of FH in childhood for intermediate outcomes in childhood, health outcomes in adulthood, the harms of screening and treatment, and the diagnostic yield of screening (**Figure 1**).

Complete discussion of the methods, including search strategy, inclusion and exclusion criteria, all excluded studies, and quality rating criteria, are available in the full report available at http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lipid-disorders-in-children-screening1.[18]

Data Sources and Searches

A literature search was conducted using several databases, including MEDLINE and PubMed, BMJ Clinical Evidence, Canadian Agency for Drugs and Technologies in Health, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment (Centre for Reviews and Dissemination), Institute for Clinical Systems Improvement, Institute of Medicine, and National Institute for Health and Clinical Excellence. The search strategies are listed in the eMethods in the Supplement.

The search included studies published January 1, 2005, or later. The original search was on February 12, 2014, and was updated on June 13, 2014, December 16, 2014, and June 2, 2015. Since June 2015, we continued to conduct ongoing surveillance through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on April 8, 2016.

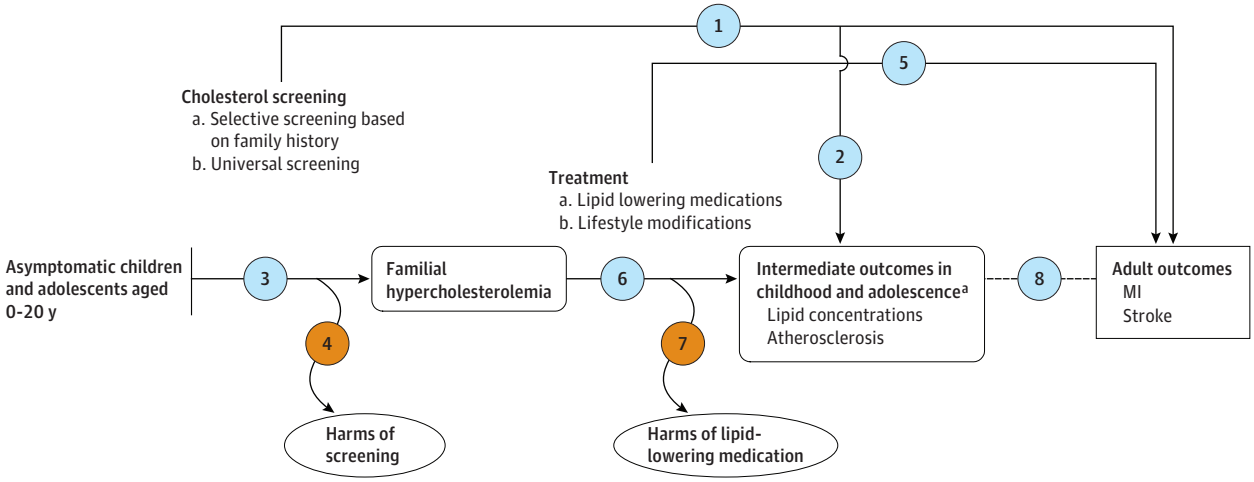
All studies included in the previous USPSTF evidence report[4] were reviewed, along with the reference lists of several reports, including the 2011 National Heart, Lung, and Blood Institute Expert Panel Report,[19] publications from large cohort studies with longitudinal data, and studies included in relevant systematic reviews and meta-analyses. Relevant articles were solicited from expert reviewers and ClinicalTrials.gov was searched to identify relevant ongoing trials.

Study Selection

All study selection procedures used dual independent review. The titles and abstracts were reviewed, followed by the full text of all potentially relevant citations, against the a priori inclusion and exclusion criteria for design, population, screening, intervention, outcomes, and setting. Discrepancies were resolved through discussion. For screening studies (KQ1-4), studies of asymptomatic children and adolescents aged 0 to 20 years at screening were included. Acceptable screening interventions were lipid panel (fasting or nonfasting lipid measurement, TC or LDL-C alone or in combination with high-density lipoprotein cholesterol [HDL-C]) delivered in a universal or selective screening strategy. Screening studies that focused on genetic screening alone or cascade screening (which involves case-finding among relatives of people with confirmed FH) were excluded because those screening approaches are not relevant to screening for FH in primary care. Screening studies of populations with known dyslipidemia, a diagnosis associated with secondary dyslipidemia, or a documented family history of FH were excluded. Only screening studies that reported the number of children with probable or definite FH were included.

For treatment studies (KQ5-7), interventions using lipid-lowering drugs or lifestyle interventions were included, focusing on interventions targeting people aged 0 to 20 years who had a diagnosis of FH at the beginning of the intervention (ideally screen-detected). Any class of lipid-lowering drug was accepted, including, but not limited to, 3-hydroxy-3-methyl-glutaryl

Figure 1. Analytic Framework and Key Questions



Screening key questions

1. Does screening for familial hypercholesterolemia in asymptomatic children and adolescents delay or reduce the incidence of myocardial infarction (MI) or stroke in adulthood?
   a. Selective screening based on family history
   b. Universal screening
2. Does screening for familial hypercholesterolemia in asymptomatic children and adolescents improve intermediate outcomes (ie, reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?
   a. Selective screening based on family history
   b. Universal screening
3. What is the diagnostic yield of appropriate screening tests for familial hypercholesterolemia in children and adolescents?
   a. Selective screening based on family history
   b. Universal screening
4. What are the harms of screening for familial hypercholesterolemia in children and adolescents?

Treatment key questions

5. Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents delay or reduce the incidence of adult MI and stroke events?
6. Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (Ie, reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in children and adolescents?
7. What are the harms of treatment of familial hypercholesterolemia with medications in children and adolescents?

Outcomes key question

8. What is the association between intermediate outcomes in childhood and adolescence and future incidence or timing of adult MI and stroke events?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions (KQs) 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. Dashed line indicates an association between an intermediate outcome and a health outcome. Further details are available from the USPSTF procedure manual.[17]

[a] Intermediate outcomes include lipid levels (total and low-density lipoprotein cholesterol) and atherosclerosis markers (carotid intima-media thickness, calcium score, pathological findings).

coenzyme A reductase inhibitors (statins) and bile acid–sequestering agents. Studies that focused on treating those with secondary dyslipidemia or monogenic dyslipidemia other than FH were excluded. Treatment studies focusing on apheresis and revascularization were excluded, as those treatments are reserved for persons with homozygous FH. All reported clinical and laboratory harms associated with lipid-lowering drugs were included.

Studies with mixed dyslipidemic populations were included when the outcome data for participants with FH were presented separately. Studies in which the researchers specifically identified participants with FH using any specified and accepted criteria were included. Studies of efficacy or effectiveness were limited to fair- to good-quality randomized clinical trials that were conducted in countries with a United Nations Human Development Index[20] greater than 0.9. Studies conducted in very high Human Development Index countries are more likely to be applicable to US settings. Included intervention trials had to compare an intervention against a usual care or control group.

Health outcomes (KQ1, KQ5, and KQ8) were defined as those experienced by the patient. Atherosclerosis (carotid intima-media thickness [CIMT], calcium score, or autopsy findings) and TC or LDL-C concentrations were considered to be intermediate outcomes (KQ2 and KQ6). Trials, cohort studies, and observational studies that reported clinical or laboratory harms were included; case series and case reports were excluded.

Data Extraction and Quality Assessment

Two reviewers independently critically appraised articles meeting inclusion criteria as good, fair, or poor in accordance with USPSTF guidance (eTable 4 in the Supplement).[21] Topic-specific quality criteria were designed with the assistance of clinical experts. Studies were rated as good, fair, or poor quality in accordance with USPSTF procedures. In general, a good-quality study met all quality criteria. A fair-quality study failed to meet at least 1 criterion but had no known issue that would invalidate its results. Poor-quality studies were those with important limitations that could invalidate study findings and were excluded from this review.

One reviewer (N.B.H., C.C.M., or M.N) extracted data from all included fair and good studies into a standard evidence table. A second reviewer (C.C.M., M.N., or P.R.B.) checked the data for accuracy. The reviewers abstracted study characteristics, study design elements, randomized trial characteristics, outcomes for screening studies, intermediate outcomes and health outcomes, and harms.

Data Synthesis and Analysis

Data were qualitatively summarized in the evidence tables with respect to each key question. For KQ6, the 6 studies were summarized in a plot of mean differences across statins by percent change from baseline of TC, LDL-C, and HDL-C concentrations. When trials reported standard errors or confidence intervals for the primary outcome, the reported results were used to compute standard deviations. For 1 trial with 3 groups randomly assigned to different doses of a statin,[22] weighted means and standard deviations were used to combine reported results into a single intervention effect for the study. Variability in drug, dosage, and intended duration of treatment precluded pooling data across studies.

Results

A total of 6753 unique abstracts and 375 full-text articles were reviewed (eFigure in the Supplement). Of these, 27 articles met all inclusion and quality criteria: 2 screening studies, 13 treatment studies, and 18 studies (24 publications) of treatment harms. Twelve studies (12 publications) were included for both KQ6 and KQ7. No relevant studies were found on adult health outcomes, intermediate outcomes, or harms of FH screening.

Screening and Health Outcomes

Key Question 1. Does screening for familial hypercholesterolemia in asymptomatic children and adolescents delay or reduce the incidence of myocardial infarction (MI) or stroke in adulthood?

No studies were identified on either universal or selective screening strategies.

Key Question 2. Does screening for familial hypercholesterolemia in asymptomatic children and adolescents improve intermediate outcomes (ie, reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

No studies were identified on either universal or selective screening strategies.

Diagnostic Yield of Screening

Key Question 3. What is the diagnostic yield of appropriate screening tests for familial hypercholesterolemia in children and adolescents?

Two fair-quality studies of universal screening for FH in school settings were identified. The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project was a school-based screening program aimed at identifying the prevalence of obesity, dyslipidemia, hypertension, glucose intolerance, and other cardiac risk factors in West Virginia fifth-grade students aged 10 to 11 years. Between 1998 and 2012, 81 156 (42.1%) of eligible children were screened, and 12 204 (25.7%) of the approximately 47 487 children with fasting lipid profiles had at least 1 abnormal lipid value. Children with LDL-C concentrations greater than 155 mg/dL (to convert LDL-C values to mmol/L, multiply by 0.0259) or TC concentrations greater than 260 mg/dL (to convert TC values to mmol/L, multiply by 0.0259) plus DNA evidence of an LDL-C receptor mutation in a first- or second-degree relative were considered to have "probable FH." The program reported that 107 children participating had "probable FH," for a diagnostic yield of 1.3 cases per 1000 screened.[23]

A Danish school-based study of first-grade school children aged 6 to 8 years measured apolipoproteins as a screening test for FH, along with family history questionnaires from parents.[24] From a sample of 2085, this study identified 10 participants with laboratory results and a family history consistent with FH, suggesting a diagnostic yield of 4.8 per 1000.[24]

Harms of Screening

Key Question 4. What are the harms of screening for familial hypercholesterolemia in children and adolescents?

No studies were identified.

Benefits of Treatment of Familial Hypercholesterolemia

Key Question 5. Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents delay or reduce the incidence of adult MI and stroke events?

No studies were identified.

Key Question 6. Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (ie, reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

Thirteen fair- or good-quality treatment trials of lipid-lowering medication in children with FH aged 6 to 18 years met our inclusion criteria. No eligible studies evaluated lifestyle modifications or dietary supplements. None of the studies reported treating screening-detected participants. Mean baseline TC concentrations ranged from 260 to 320 mg/dL. Mean baseline LDL-C ranged from 198 to 254 mg/dL. Mean baseline HDL-C ranged from 42 to 50 mg/dL (to convert HDL-C values to mmol/L, multiply by 0.0259). Mean baseline triglcerides ranged from 62 to 110 mg/dL (to convert triglyceride values to mmol/L, multiply by 0.0113).

Statins

Three of 8 statin trials were longer than 6 months: 2 were of 48 weeks' duration,[25,26] and 1 lasted 104 weeks.[27] All 8 trials reported decreases in LDL-C concentrations from baseline, with mean decreases ranging from 23 to 57 mg/dL. Dose-response relationships were demonstrated for pravastatin[22] and rosuvastatin.[28] The greatest effect on LDL-C was for rosuvastatin,[28] for which participants who received the highest dose (20 mg/d) experienced a 50% decrease (least squares means) in LDL-C from baseline (absolute difference, −120 mg/dL), compared with a 1% decrease among controls ($P < .001$; absolute difference, −2 mg/dL). All trials also showed decreases in TC of 20% to 30% from baseline, compared with placebo. The effects of statins on HDL-C were mixed. One trial of pravastatin found a 2.01% decrease in CIMT after 104 weeks (absolute difference, −0.010 mm [95% CI, −0.019 to −0.001]), compared with a 1.02% increase in the control group (absolute difference, 0.005 mm [95% CI, −0.003 to 0.013]) ($P = .02$).[27] No study assessed the effect of statins on calcium score or pathologic findings.

Six randomized clinical trials (RCTs) of statins reporting means and standard deviations for percent change are summarized graphically (**Figure 2**). Intervention effects are presented as the mean difference between groups with 95% confidence intervals.

Surveillance of newly published literature identified 1 additional statin study.[29] This 12-week placebo-controlled RCT compared 1, 2, and 4 mg of pitavastatin in 106 children and adolescents aged 6 to 17 years, of whom 103 had FH. Efficacy findings were generally consistent with those for other statins identified in the systematic review.

Nonstatin Medications

Five RCTs of nonstatin medications in children and adolescents with FH met the inclusion criteria: 3 of bile acid–sequestering agents and 2 of ezetimibe. All trials reported decreases in LDL-C concentrations from baseline. A good-quality trial of colestipol found a mean LDL-C reduction of 19.5% after 8 weeks (absolute difference, −50.7 mg/dL), compared with a 1% decrease in the control group (absolute difference, −4.64 mg/dL).[30] One fair-quality RCT of cholestyramine found an 18.6% reduction in LDL-C after 1 year of treatment, compared with a 1.5% increase in the control group.[31] One good-quality 8-week RCT of colesevelam[32] found a decrease in least-squares mean LDL-C of 10% (95% CI, −14.1% to −5.9%) at the higher of 2 doses (absolute difference, −24.1 mg/dL), compared with a least squares mean increase of 2.5% (95% CI, −1.50 to 6.50) in the control group (absolute difference, 2.0 mg/dL). A lower dose resulted in a smaller nonsignificant reduction. One good-quality RCT[33] reported a mean LDL-C decrease of 54.0% in participants who received ezetimibe and simvastatin (absolute difference, −122.2 mg/dL), compared with a 38.1% decrease in the simvastatin-only group at 33 weeks (absolute difference, −84.7 mg/dL). A good-quality RCT of ezetimibe monotherapy reported a 28% reduction (95% CI, −25% to −31%) in LDL-C in the treatment group (absolute difference, −60 mg/dL), compared with negligible change in the placebo group.[34]

Harms of Treatment of Familial Hypercholesterolemia

Key Question 7. What are the harms of treatment of familial hypercholesterolemia with medications in children and adolescents?

Statins

There were 13 studies (19 articles) on harms of statins, including 1492 children and adolescents. Intervention durations ranged from 8 to 12 weeks, to 2 years. One trial provided 10-year follow-up data on a cohort of people who had begun statins in childhood as an RCT. No severe, permanent harms of statins were reported, and reported treatment adverse events usually did not differ significantly compared with placebo and were generally not believed to be associated with medication use (eTables 5 and 6 in the Supplement).[21,22,25-28,35-48] Statins were generally well tolerated, although reversible elevations of liver enzyme concentrations, creatine kinase concentrations, or both were noted in some studies. At 10 years, statin continuation and adherence was high; people treated with statins had lower dehydroepiandrosterone sulfate (DHEAS) levels than their unaffected siblings. Mean DHEAS levels were 8.4 (SD, 3.0) μmol/L among statin-treated males and 5.6 (SD, 3.2) μmol/L among statin-treated females, compared with 12.9 (SD, 4.9) μmol/L among unaffected male siblings and 6.8 (SD, 3.9) μmol/L among unaffected female siblings. Because the DHEAS levels were still within normal range, the finding is of unclear clinical significance.[39,40]

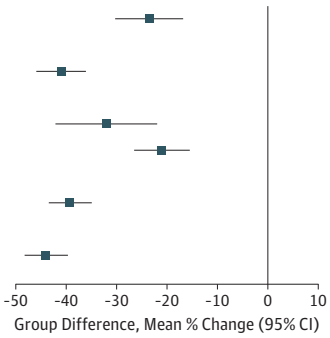
Systemic, immunologic, and pain-related adverse events were reported sporadically. Muscle pain occurred at similar frequencies in treatment and placebo groups. Six of 11 studies assessing liver transaminase and creatine kinase concentrations found no abnormalities. Detected abnormalities were usually transient, resolving either spontaneously or after medication withdrawal. Of 10 studies assessing the effect of statin use on growth and pubertal development in children or adolescents, none suggested an important association between statin use and growth and development.[22,25-28,37,38,41,42,44]

The pitavastatin trial[29] identified through literature surveillance found DHEAS levels decreased by 10.3% in the 4-mg dose group over the 12-week trial period (mean change, −10.4 μg/dL [SD, 19.1] from a baseline of 101.0 μg/dL [SD, 97.3]; $P = .01$). The clinical significance of this effect is difficult to assess with the data provided. Other safety findings were generally consistent with those in the systematic review of other statins.

Figure 2. RCTs Showing Effect of Statins on Mean Percent Change in LDL, Total, and HDL Cholesterol Levels (Key Question 6)

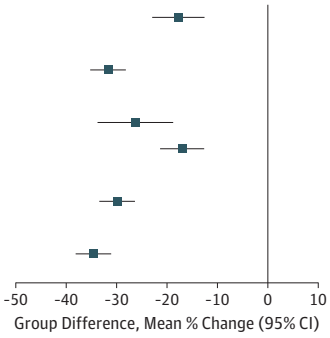
A LDL-Cholesterol

Study	Study Duration, wk	Placebo No. of Patients	Placebo Mean % Change (SD)	Statin No. of Patients	Statin Mean % Change (SD)	Group Difference, Mean % Change (95% CI)
Pravastatin						
Knipscheer et al,[22] 1996	12	18	-3 (13)	53	-27 (10)	-24 (-30 to -17)
Simvastatin						
de Jongh et al,[25] 2002	48	56	0 (10)	83	-41 (19)	-41 (-46 to -36)
Lovastatin						
Clauss et al,[42] 2005	24	18	5 (17)	33	-27 (20)	-32 (-42 to -22)
Stein et al,[26] 1999	48	49	-4 (14)	61	-25 (16)	-21 (-27 to -16)
Atorvastatin						
McCrindle et al,[44] 2003	26	47	0 (13)	140	-40 (13)	-39 (-44 to -35)
Rosuvastatin						
Avis et al,[28] 2010	12	46	0 (13)	130	-44 (12)	-44 (-48 to -40)



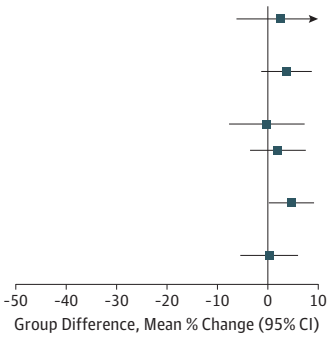
B Total cholesterol

Study	Study Duration, wk	Placebo No. of Patients	Placebo Mean % Change (SD)	Statin No. of Patients	Statin Mean % Change (SD)	Group Difference, Mean % Change (95% CI)
Pravastatin						
Knipscheer et al,[22] 1996	12	18	-2 (10)	53	-20 (8)	-18 (-23 to -13)
Simvastatin						
de Jongh et al,[25] 2002	48	56	1 (10)	83	-31 (12)	-32 (-35 to -28)
Lovastatin						
Clauss et al,[42] 2005	24	18	5 (12)	33	-22 (14)	-26 (-34 to -19)
Stein et al,[26] 1999	48	49	-3 (7)	61	-20 (16)	-17 (-21 to -13)
Atorvastatin						
McCrindle et al,[44] 2003	26	47	-1 (10)	140	-31 (12)	-30 (-33 to -26)
Rosuvastatin						
Avis et al,[28] 2010	12	46	0 (11)	130	-34 (10)	-35 (-38 to -31)



C HDL-cholesterol

Study	Study Duration, wk	Placebo No. of Patients	Placebo Mean % Change (SD)	Statin No. of Patients	Statin Mean % Change (SD)	Group Difference, Mean % Change (95% CI)
Pravastatin						
Knipscheer et al,[22] 1996	12	18	4 (16)	53	7 (16)	2.4 (-6 to 11)
Simvastatin						
de Jongh et al,[25] 2002	48	56	0 (15)	83	3 (15)	3.7 (-1 to 9)
Lovastatin						
Clauss et al,[42] 2005	24	18	3 (12)	33	3 (14)	-0.2 (-8 to 7)
Stein et al,[26] 1999	48	49	-1 (14)	61	1 (16)	2 (-4 to 7.5)
Atorvastatin						
McCrindle et al,[44] 2003	26	47	-2 (13)	140	3 (15)	5 (0.2 to 9)
Rosuvastatin						
Avis et al,[28] 2010	12	46	8 (18)	130	8 (14)	0.3 (-5.5 to 6)



LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

Nonstatins

Three short-term RCTs of 332 children with FH examined the harms of colesevelam,[32] cholestyramine,[31] and colestipol[30] (eTable 7 in the Supplement).[21,30-34] Abdominal pain, diarrhea, nausea, or vomiting were reported at similar rates in the treatment and placebo groups.[31,32] Cholestyramine and colestipol were associated with decreased vitamin D and folate concentrations compared with placebo,[30,31] and homocysteine was increased in children treated with cholestyramine.[30,31] No marked laboratory abnormalities were associated with colesevelam, although it is not clear which safety factors were measured. Unpalatability was noted with both colestipol and cholestyra-

mine; withdrawal due to unpalatability was similar in the cholestyramine treatment and placebo groups.

Two RCTs evaluated harms of ezetimibe in 373 children and adolescents with FH.[33,34] At 1 year, elevated alanine aminotransferase concentrations were slightly more likely with simvastatin plus ezetimibe (5%) compared with simvastatin alone (2%) and resolved with treatment discontinuation.[33] Ezetimibe monotherapy was not associated with serious adverse events or with different rates of adverse events compared with a control group at 12 weeks.[34]

Relationship Between Intermediate Outcomes and Adult Health Outcomes

Key Question 8. What is the association between intermediate outcomes in childhood and adolescence (lipid concentrations or atherosclerosis markers) and the future incidence or timing of adult MI and stroke events?

No studies were identified.

Discussion

Universal lipid screening approaches suggested a diagnostic yield of 0.13% to 0.48% for detecting FH in childhood,[23,24] but no direct evidence was found on the relationship between screening and FH outcomes in childhood or adulthood. A large body of fair- to good-quality RCT evidence suggests that lipid-lowering treatment of children with FH improves lipid levels up to 50% with few short-term harms (**Table**). No evidence was available to assess lifelong usage, and no direct evidence was found on the relationship between either lipid levels or treatment in childhood and MI or stroke outcomes in adulthood.

Screening

Consensus in the current debate on screening for dyslipidemia in childhood is that the primary benefit of screening is identifying children with FH, although a secondary, more controversial benefit may be identifying children with mild or moderate elevations in LDL-C concentrations.[19,49-54] Early identification of children and adolescents with FH, followed by pharmacotherapy and a low-fat, low-cholesterol diet, could plausibly slow atherosclerosis progression and reduce incidence or delay onset of CHD and stroke in adulthood. However, no evidence allows estimation of the benefits of screening. Screening for FH in childhood is not without potential harms. Children identified through screening may never experience clinically relevant lipid concentrations,[55] risking unnecessary labeling, parent or child anxiety, or unnecessary or harmful treatment. The current lack of evidence limits conclusions about the magnitude or severity of these potential harms.

Treatment

A large, good-quality body of trial evidence consistently suggests that the benefits of statin treatment outweigh the harms after 2 years of treatment in children and adolescents with definite FH. However, the long-term benefits and harms of lipid-lowering medications begun in childhood or adolescence remain poorly understood, especially in screen-detected populations. Most trials have been conducted in tertiary clinic populations, who may not accurately represent the experience of children and adolescents who would be identified from a screening program. Dietary counseling and exercise in the absence of medication have previously been shown to have limited effect in reducing LDL-C concentrations in children and adolescents with probable or definite FH.[56] No new studies were found of lifestyle treatment for FH in youth, but all medication trial protocols included a low-fat, low-cholesterol diet, so dietary modification is represented in the medication trial results.

Optimal age of statin initiation in children with FH is a matter of expert debate. In the absence of RCT or high-quality observational data comparing adult CHD outcomes in youth started on statins at different ages, the optimal age of statin initiation in children and adolescents with FH remains unclear. The best such evidence to date comes from observational 10-year follow-up of the cohort enrolled in a trial of pravastatin for children with FH in the Netherlands.[27,37,38] Younger age at treatment initiation and longer duration of statin exposure independently was associated with favorable CIMT values at 4.5 years[37] and 10 years.[38] However, the overall body of evidence on this issue is quite limited. Studies comparing the long-term incidence of MI or stroke in adults identified and successfully treated for FH from an earlier age with incidence in those identified in early or middle adulthood also might be informative. In 14 cohort studies in children or adolescents, no such evidence was found.[18]

When the aim of pharmacologic treatment is reducing disease risk rather than treating existing disease, only a low risk of harm is acceptable. The evidence about the short-term harms of pharmacologic treatment of children and adolescents with FH is fair to good, but only 1 observational study provided data at 10 years. Long-term studies of people initiating FH treatment in childhood are needed. For example, the report of a small increase in cancer risk among adults treated with ezetimibe[57] emphasizes the importance of long-term follow-up studies when potentially lifelong treatment is being considered in children and adolescents.

Outcomes

No direct evidence supports a link between lipid concentrations or measures of atherosclerosis in children and adolescents with FH and health outcomes in adulthood. Elevated LDL-C concentrations in adults is associated with MI and stroke.[14,58] The Simon Broome Register found excess CHD mortality in people with FH compared with the general population, with markedly elevated standardized mortality ratios in the group aged 20 to 39 years.[6] These data show the severity of the natural history of FH possible among adults referred to lipid clinics but do not allow estimation of the association between lipid concentrations or atherosclerosis in general-population youth and their risk of CHD in adulthood. Furthermore, children and adolescents with severely elevated LDL-C may have pathologic signs of atherosclerosis at earlier ages than do those of the same age with normal LDL-C concentrations,[3,59] but these signs have not been directly linked to the probability of CHD in adulthood.

Limitations

This review did not assess the evidence for the benefits of cascade screening in families of identified children with FH, an

Table. Overall Summary of Evidence by Key Question

Key Question	No. of Studies, Study Design	Participants, No.	Summary of Findings	Consistency	Applicability	Overall Quality
Screening						
Key question 1: Health outcomes in adulthood	0	0	No evidence on the effect of either selective or universal screening for FH on adult health outcomes or intermediate outcomes in childhood and adolescence.			
Key question 2: Intermediate outcomes	0	0				
Key question 3: Diagnostic yield of screening for FH	2 (prospective cohort)	n = 83 241	Using 2 different tests, the diagnostic yield of screening for FH ranged 0.13%-0.48%.	NA (different screening tests, different populations: United States and Denmark)	School-based setting is relevant to primary care. Limited applicability of findings from non-US population.	Fair
Key question 4: Adverse effects of screening	0	0	No evidence on harms of screening.			
Treatment						
Key question 5: Treatment and adult health outcomes	0	0	No evidence on effect of treatment in childhood or adolescence on adult health outcomes.			
Key question 6: Effect of treatment on intermediate outcomes	Statins: 8 RCTs Nonstatins: 5 RCTs	Statins: n = 1071 Nonstatins: n = 718	For statins, all trials reported statistically significant LDL-C decreases, with most effect sizes ranging from 20%-40%, compared with negligible changes with placebo. Dose response was seen in 2 studies. All 8 studies that evaluated effect on TC found decreases that were smaller than for LDL-C and consistent across studies. One trial reported decrease in CIMT. For nonstatins, all 5 trials (including bile acid-sequestering agents and ezetimibe) reported decreases in LDL-C ranging from 10%-27%.	Consistent treatment effects on LDL-C and TC across 5 different statins. Nonstatins (3 bile acid-sequestering agents and an inhibitor of cholesterol absorption) had more modest effects.	Studies applicable to youth with FH cared for in US primary care settings. Participants were recruited from tertiary clinics and were not screen-identified.	Good/fair: 3 studies had <80% retention
Key question 7: Harms of treatment	18 (12 RCTs, 3 observational studies, 2 open-label trials, 1 crossover RCT)	n = 2210[a]	Statins were generally well tolerated; adverse effects were transient. There was no reported effect on growth or maturation. One trial showed lower DHEAS in children with FH treated with pravastatin compared with unaffected siblings. Bile acid-sequestering agents were commonly associated with gastrointestinal symptoms and poor palatability.	Consistent findings of harms within class: statins, and bile acid-sequestering agents.	Good; most studies were applicable to US primary care setting.	Fair: Most studies were less than 2 y duration
Outcomes						
Key question 8: Association of intermediate outcomes and adult health outcomes	0	0	No evidence on the association between intermediate outcomes in childhood or adolescence and adult health outcomes in persons with FH.			

Abbreviations: CIMT, carotid intima-media thickness; DHEAS, dehydroepiandrosterone sulfate; FH, familial hypercholesterolemia; KQ, key question; LDL-C, low density lipoprotein cholesterol; NA, not applicable; RCT, randomized clinical trial; TC, total cholesterol.

[a] Studies included for KQ7 involved 2210 patients, 2197 of whom had FH.

approach recommended in several countries.[10,60] Cascade screening was excluded from this review because of its limited relevance to current US primary care practice, but it may be a promising strategy for FH case-finding, especially as genetic testing evolves.[61]

The available literature is limited in volume, applicability, and relevance to determination of health outcomes. No published studies met the inclusion criteria for several key questions, notably the effect on health outcomes. Participants in the included statin trials were patients at tertiary care centers; none of the studies were conducted in screen-detected populations, and few were conducted in nonwhite populations. Furthermore, the age distribution of the statin studies as a whole was skewed to early adolescence, with a mean age of 12 to 15 years; 2 trials included children as young as 8 years. Thus, the bodies of evidence on screening (children aged 6 to 8 years) and on statin treatment (largely adolescents) are not aligned. No updated evidence was found on lifestyle interventions for FH or any trials comparing initiation of statins at different ages. The body of evidence on harms of pharmacotherapy also lacks long-term studies.

Future Research Needs

Randomized trials are needed to assess the benefits and harms of FH screening programs in children and adolescents. Future studies should describe screening programs in detail, including the follow-up and confirmatory testing of children who screen positive; screening and diagnostic criteria for FH; and the number of true positives.

Long-term statin trials are required to assess harms and effectiveness in improving health outcomes in adulthood and intermediate outcomes in youth. Treatment studies in screen-detected FH cases are essential in the absence of RCTs of screening programs. Further consideration of genetic mutation status in treatment response and outcomes for patients with FH may provide important data for personalizing treatment. Studies examining benefits and harms of lipid-lowering medication are needed in children with FH younger than 10 years. Treatment studies should systematically report adverse effects of treatment.

Understanding outcomes would be furthered by studies examining longitudinal data on persons with FH, with particular attention to characterizing those most likely to represent screen-detected cases, to elucidate the association between intermediate outcomes in youth and MI and stroke in adulthood.

Past FH screening recommendations have generated controversy, much of which centered on the advisability of accepting indirect evidence from short-term trials that lack outcomes beyond lipid concentrations.[50,51,53,54,62,63] Some experts have expressed skepticism that long-term RCTs of statins in youth with FH could be feasibly and ethically conducted,[64] while others have called for the conduct of RCTs as a public health priority.[65,66] Reaching agreement on acceptable surrogate end points, such as CIMT and other atherosclerosis measures,[66] may increase the feasibility of such a trial, allowing a shorter time frame, provided such end points are predictive of CHD.

Conclusions

Screening can detect FH in children, and lipid-lowering treatment in childhood can reduce lipid concentrations in the short term, with little evidence of harm. There is no evidence for the effect of screening for FH in childhood on lipid concentrations or cardiovascular outcomes in adulthood, or on the long-term benefits or harms of beginning lipid-lowering treatment in childhood.

ARTICLE INFORMATION

Author Contributions: Dr Lozano 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.
Study concept and design: Lozano, Henrikson, Dunn, Morrison, Whitlock.
Acquisition, analysis, or interpretation of data: Lozano, Henrikson, Dunn, Morrison, Nguyen, Blasi, Anderson, Whitlock.
Drafting of the manuscript: Lozano, Henrikson, Morrison.
Critical revision of the manuscript for important intellectual content: Lozano, Henrikson, Dunn, Nguyen, Blasi, Anderson, Whitlock.
Statistical analysis: Lozano, Anderson.
Obtained funding: Lozano.
Administrative, technical, or material support: Lozano, Henrikson, Morrison, Nguyen, Blasi.
Study supervision: Lozano, Henrikson.

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