JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Lipid Screening in Childhood and Adolescence for Detection of Multifactorial Dyslipidemia

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

Paula Lozano, MD, MPH; Nora B. Henrikson, PhD, MPH; Caitlin C. Morrison, MPH; John Dunn, MD, MPH; Matt Nguyen, MPH; Paula R. Blasi, MPH; Evelyn P. Whitlock, MD, MPH

IMPORTANCE Multifactorial dyslipidemia, characterized by elevated total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C), is associated with dyslipidemia and markers of atherosclerosis in young adulthood. Screening for dyslipidemia in childhood could delay or reduce cardiovascular events in adulthood.

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

DATA SOURCES MEDLINE, 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 evidence report and reference lists of relevant studies and ongoing trials were also searched. Surveillance was conducted through April 9, 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 Outcomes included dyslipidemia (TC≥200 mg/dL or LDL-C≥130 mg/dL) and atherosclerosis in childhood; myocardial infarction and ischemic stroke in adulthood; diagnostic yield (number of confirmed cases per children screened); and harms of screening or treatment. Simulated diagnostic yield was calculated as initial screening yield × positive predictive value from a study with confirmatory testing.

RESULTS Screening of children for multifactorial dyslipidemia has not been evaluated in randomized clinical trials. Based on 1 observational study (n = 6500) and nationally representative prevalence estimates, the simulated diagnostic yield of screening for elevated TC varies between 4.8% and 12.3% (higher in obese children [12.3%] and at the ages when TC naturally peaks—7.2% at age 9-11 years and 7.2% at age 16-19 years). One good-quality randomized clinical trial (n = 663) found a modest effect of intensive dietary counseling for a low-fat, low-cholesterol diet on lipid levels at 1 year in children aged 8 to 10 years with mild to moderate dyslipidemia; mean between-group difference in TC change from baseline was −6.1 mg/dL (95% CI, −9.1 to −3.2 mg/dL; $P < .001$). Between-group differences dissipated by year 5. The intervention did not adversely affect nutritional status, growth, or development over the 18-year study period. One observational study (n = 9245) found that TC concentration at age 12 to 39 years was not associated with death before age 55 years.

CONCLUSIONS AND RELEVANCE The diagnostic yield of lipid screening varies by age and body mass index. No direct evidence was identified for benefits or harms of childhood screening or treatment on outcomes in adulthood. Intensive dietary interventions may be safe, with modest short-term benefit of uncertain clinical significance.

JAMA. 2016;316(6):634-644. doi:10.1001/jama.2016.6423

Editorial page 589

Related articles pages 625 and 645

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 660

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

Author Affiliations: Group Health Research Institute, Kaiser Permanente Research Affiliates Evidence-based Practice Center, Seattle, Washington (Lozano, Henrikson, Morrison, Dunn, Nguyen, Blasi); Kaiser Permanente Center for Health Research, Kaiser Permanente Research Affiliates Evidence-Based Practice Center, Portland, Oregon (Whitlock).

Corresponding Author: Paula Lozano, MD, MPH, Group Health Research Institute, 1730 Minor Ave, Ste 1600, Seattle, WA 98101 (lozano.p@ghc.org).

Elevations in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are precursors to atherosclerosis and coronary heart disease. Identifying and treating dyslipidemia in adults older than 40 years is common clinical practice in the United States.[1] Total cholesterol and LDL-C concentrations in healthy children vary with age: they are low at birth, increase until age 2 years, peak before puberty, decrease during adolescence, and increase again during late adolescence and young adulthood.[2] Total cholesterol and LDL-C concentrations are generally higher in girls and peak about 1 year earlier than in boys.[2]

Childhood dyslipidemia is commonly defined as TC≥200 mg/dL or LDL-C≥130 mg/dL using fixed cut points derived from population norms.[3] (To convert TC and LDL-C to millimoles per liter, multiply by 0.0259.) Childhood dyslipidemia is typically multifactorial, with the exception of lipid disorders of genetic etiology characterized by very high lipid concentrations, such as familial hypercholesterolemia. Multifactorial dyslipidemia may be associated with environmental and behavioral factors[4,5] as well as obesity,[6-8] with or without inherited susceptibility.

Dyslipidemia in childhood and adolescence is not a disease but is a risk factor for atherosclerosis and may contribute to coronary heart disease in adulthood.[9] However, lipid measurement in youth imperfectly identifies adults with dyslipidemia; elevated LDL-C in adolescence (age 12-18 years) has a positive predictive value of only 32.9% to 37.3% for dyslipidemia 15 to 20 years later[10] and lower for children younger than age 12 years.[11]

Screening youths for dyslipidemia may have the potential to identify affected youths, reduce long-term cholesterol burden through intervention, and prevent or delay cardiovascular events in adulthood. However, in 2007 the US Preventive Services Task Force (USPSTF) found insufficient evidence (I recommendation) to recommend for or against routine selective or universal lipid screening of children or adolescents.[12] The purpose of this evidence report was to assist the USPSTF in updating its previous recommendations on screening children and adolescents for multifactorial dyslipidemia, defined as elevations in TC or LDL-C not due to familial hypercholesterolemia.

Methods

Scope of Review

The Agency for Healthcare Research and Quality (AHRQ) commissioned 2 systematic evidence reviews to support the USPSTF in updating its 2007 recommendation statement on screening for lipid disorders in children. This review focuses on benefits and harms of screening for and treatment of multifactorial dyslipidemia in children and youths aged 0 to 20 years. A separate systematic review updated the 2007 USPSTF recommendations on heterozygous familial hypercholesterolemia.[13]

Using USPSTF methods,[14] an analytic framework and 8 key questions (KQs) were developed to assess evidence of the effect of screening and treatment on intermediate outcomes, adult health outcomes, and harms; the diagnostic yield of screening; and the association between intermediate outcomes in childhood and adult health outcomes (**Figure 1**). Adult health outcomes of interest were myocardial infarction (MI) and ischemic stroke. Intermediate outcomes included lipid concentrations (TC, LDL-C, high-density lipoprotein cholesterol [HDL-C], non–HDL-C, and triglycerides) and atherosclerosis markers (carotid intima-medial thickness, calcium score, and autopsy findings).

Familial hypercholesterolemia and other monogenic conditions were excluded from this review, as were renal, infectious, hepatic, inflammatory, and storage disorders, types 1 and 2 diabetes, and several other syndromes that confer secondary risk of elevated LDL-C or TC. Detailed study methods and a list of excluded studies, including reasons, are listed in the full report (http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lipid-disorders-in-children-screening1).[16]

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 included studies published January 1, 2005, or later. The original search was conducted on February 12, 2014, and updated on June 13, 2014, December 16, 2014, and June 2, 2015. After 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 9, 2016, and identified no new relevant studies. The search strategies are listed in the eMethods in the Supplement.

All studies included in the previous USPSTF evidence report[9] were reviewed along with the reference lists of several reports, including the 2011 National Heart, Lung, and Blood Institute expert panel report,[17] publications from large cohort studies with longitudinal data, and studies included in other relevant systematic reviews and meta-analyses. Relevant articles were solicited from expert reviewers, and ClinicalTrials.gov was searched to identify relevant ongoing trials.

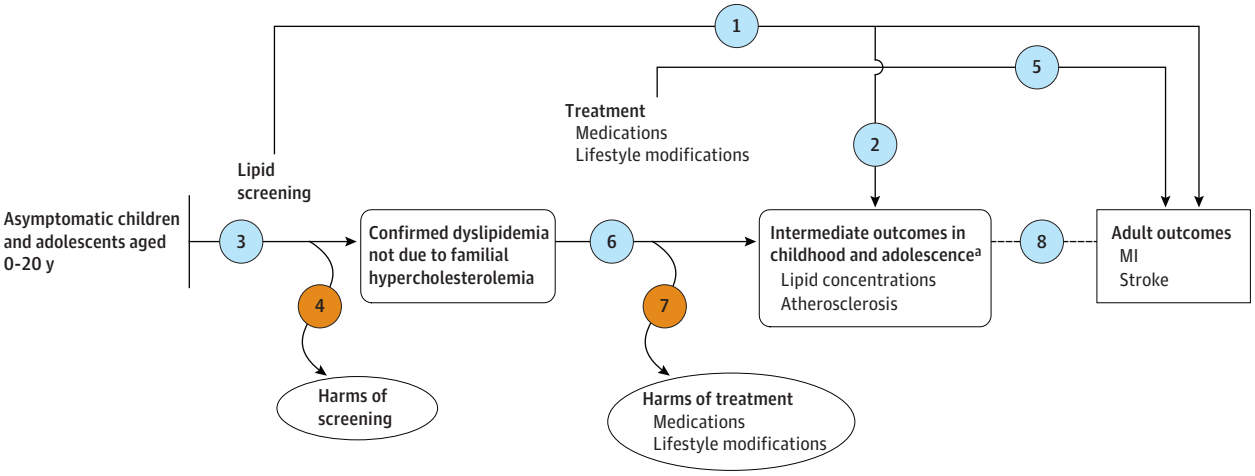
Study Selection

All study selection procedures used dual independent review. The title 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.

The screening population of interest was asymptomatic people aged 0 to 20 years. Eligible screening interventions were defined as a lipid panel (fasting or nonfasting lipid measurement, TC or LDL-C alone or in combination with HDL-C) delivered in a universal or selective screening strategy. Although non–HDL-C was not among the included screening interventions, no studies were excluded that screened youth using non–HDL-C. Screening studies with modes not relevant to primary care practice were excluded.

The treatment population of interest was people with multifactorial dyslipidemia (ideally screen detected) aged 0 to 20 years who were treated with lipid-lowering drugs or lifestyle interventions. All reported clinical and laboratory harms

Figure 1. Analytic Framework



Screening key questions

1. Does screening for multifactorial dyslipidemia in asymptomatic children and adolescents delay or reduce the incidence of MI or stroke in adulthood?
2. Does screening for multifactorial dyslipidema in asymptomatic children and adolescents improve intermediate outcomes (ie, improve lipid concentrations or reverse or slow progression of atherosclerosis) in childhood and adolescence?
3. What is the diagnostic yield of screening for multifactorial dyslipidemia in children and adolescents?
4. What are the harms of screening for multifactorial dyslipidemia in children and adolescents?

Treatment key questions

5. Does treatment of multifactorial dyslipidemia 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 multifactorial dyslipidemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (ie, reduce lipid concentrations or reverse or slow progression of atherosclerosis) in childhood and adolescence?
7. What are the harms of treatment of multifactorial dyslipidemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents?

Outcomes key question

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

MI indicates myocardial infarction. 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. Dashed line indicates an association between an intermediate outcome and a health outcome. Further details are available from the USPSTF procedure manual.[15]

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

associated with interventions that had any evidence of treatment benefit were included.

Studies of efficacy or effectiveness were limited to fair- or good-quality randomized clinical trials that were conducted in countries with a United Nations Human Development Index[18] greater than 0.9. Studies conducted in very high Human Development Index countries are more likely to be applicable to US settings. Trials, cohort studies, and observational studies that reported clinical or laboratory harms were included; case series and case reports were excluded.

Simulation of Diagnostic Yield

For the diagnostic yield question (KQ3), screening studies initially were required to include confirmatory testing to allow calculation of proportion of persons screened who were confirmed cases. However, because only 1 Ohio-based study met all inclusion criteria for KQ3, studies were included if they involved large US populations and reported results of lipid screening (using a TC concentration of ≥200 mg/dL, an LDL-C concentration of ≥130 mg/dL, or both on a single occasion to define dyslipidemia). Combining the

prevalence of elevated TC concentrations with the positive predictive value from the Ohio study allowed for computation of a simulated diagnostic yield (initial screening yield × positive predictive value of the initial screen = diagnostic yield).

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 in the Supplement).[14] Poor-quality studies were those with important limitations that could invalidate study findings and were excluded from this review.

For all included articles, data were abstracted into evidence tables, including study characteristics, study design elements, test characteristics for screening studies, intermediate and adult health outcomes, and harms, including all relevant subgroups where available.

Data Synthesis and Analysis

Summary tables of study characteristics, population characteristics, intervention characteristics, and outcomes were created separately for each KQ. For treatment studies, lipid concentrations were expressed as percent change or difference from baseline. Data were not combined across treatment studies. No KQs had a sufficient number of included studies to permit meta-analysis.

Results

A total of 7137 unique abstracts and 537 full-text articles were reviewed (eFigure in the Supplement). Of these, 16 articles were included. These include 4 screening studies (8 articles),[7,8,19-24] 2 treatment studies (5 articles),[25-29] 1 study (5 articles) on treatment harms,[27-31] and 1 study (1 article) of association between intermediate and adult health outcomes.[32] Three articles were included for both KQ6 and KQ7.

Screening and Health Outcomes

Key Question 1. Does screening for multifactorial dyslipidemia in asymptomatic children and adolescents delay or reduce the incidence of MI or stroke in adulthood?

No studies were identified.

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

No studies were identified.

Diagnostic Yield of Screening

Key Question 3. What is the diagnostic yield of screening for multifactorial dyslipidemia in children and adolescents?

Three fair-quality studies[7,19,23,24] and 1 good-quality study (the National Health and Nutrition Examination Study [NHANES])[8,20-22] met the inclusion criteria (**Table 1**). Only 1 study used confirmatory testing to establish dyslipidemia.[19] In a large pediatric group practice setting, 6500 people aged 3 to 18 years (mean, 6.4 years) presenting for well child care between 1986 and 1988 provided a nonfasting blood sample. Those with nonfasting TC concentrations of 200 mg/dL or greater returned for a fasting lipid profile. The prevalence of elevated nonfasting TC concentrations was 8.5%. Of these, 88% returned for a second screen after 1 to 6 weeks, and 77% of these had a fasting LDL-C concentration of 130 mg/dL or more (positive predictive value = 77%). The diagnostic yield was 5.8%.

The positive predictive value of 77% for screening for elevated TC concentrations from the confirmatory testing study was combined with data from large recent studies to simulate population-based diagnostic yields. Three large population-based studies that used only a single lipid test (without confirmatory testing) and had screening yields of 8% to 11% were used for this purpose.[7,8,20]

Three studies reported the prevalence of elevated lipid concentrations by age and body mass index (BMI) subgroups. These studies defined healthy weight as BMI in less than the 85th percentile for age and sex, overweight as BMI between the 85th and 95th percentile for age and sex, and obese as BMI in the 95th percentile or higher for age and sex.

NHANES is a nationally representative sample survey.[34] All 4 of the NHANES articles[8,20-22] included adolescents; 2 included children as young as 6 to 8 years. All used the National Cholesterol Education Program (NCEP) cut points of 200 mg/dL for TC and 130 mg/dL for LDL-C.[3] Participants provided nonfasting blood samples for TC testing; 12- to 19-year-olds also provided fasting blood samples for LDL-C testing. The highest rates of elevated TC were in those aged 9 to 11 years (9.4%; 95% CI, 7.3%-11.6%) and 16 to 19 years (9.4%; 95% CI, 7.0%-11.8%)[20]; there were no significant differences in age-specific prevalence.[8,20,22] Prevalence of elevated LDL-C was higher in children with obesity (14.2%; 95% CI, 10.2%-19.6%) than in healthy-weight children (prevalence ratio, 2.5; 95% CI, 1.6-3.8).[21]

The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project screened 23 263 West Virginia fifth-grade students statewide between 2003 and 2008[7,24] for elevated lipid concentration and family history of early coronary heart disease or hypercholesterolemia. After a nonfasting screening test, the prevalence of elevated TC (≥200 mg/dL) was 10.7% (7.5% for children with healthy weight, 11.5% for overweight children, and 16.0% for obese children).[7] Prevalence of elevated LDL-C (≥130 mg/dL) was 8.7% overall[7] (8.3% in those with a family history of early coronary heart disease and 9.5% in those without).[24]

In a study of 3- to 19-year-olds enrolled in 3 large health systems in California, Colorado, and Minnesota,[23] elevated TC concentrations using NCEP criteria were increased significantly with BMI: 10.7% (95% CI, 10.2%-11.3%) in the obese group, 8.6% (95% CI, 7.8%-9.4%) in the overweight group, and 6.7% (95% CI, 6.2%-7.1%) in the healthy-weight group. A similar association was found for LDL-C measurements.

Simulated diagnostic yields ranged between 4.8% and 12.3% for different age and BMI subgroups. The highest diagnostic yields appear to be in obese children (12.3%) and at the ages when TC naturally peaks (children aged 9-11 years, 7.2%; adolescents aged 16-19 years, 7.2%).[20] The subgroup with the highest estimated diagnostic yield was obese children aged 10 to 11 years (12.3%).[7]

Harms of Screening

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

No studies were identified.

Table 1. Included Studies by Key Question

Source	Study Family[a]	Quality[b]	Country	No.	Study Design	Age, Mean (Range), y	Population and Setting Intervention (for Trials)	Outcomes Assessed	Dates of Data Collection
Screening Studies (KQ3)									
Garcia and Moodie,[19] 1989		Fair	US (Ohio)	6500	Cross-sectional	6.4 (3-18)	White, middle-class children presenting for well child care at large group practice; 100% of population was white	Nonfasting blood sample followed by fasting lipid profile if TC≥200 mg/dL; LDL-C ≥130 mg/dL was considered elevated	1986-1988
Kit et al,[8] 2015	NHANES	Good	US	13 172	Cross-sectional	NR (8-17)	Nationally representative US sample; female participants ranged from 741/1558 (47.6%) in 2009-2010 to 1173/2333 (50.3%) in 2001-2002[c]	Single lipid assessment; nonfasting TC≥200 mg/dL or fasting LDL-C≥130 mg/dL were considered elevated	1999-2012
Kit et al,[20] 2012	NHANES	Good	US	16 116	Cross-sectional	NR (6-19)	Nationally representative US sample; female participants ranged from 2009/4205 (47.8%) in 2007-2010 to 2954/5759 (51.3%)[c]	Single lipid assessment; nonfasting TC≥200 mg/dL or fasting LDL-C≥130 mg/dL were considered elevated	1988-2010
CDC,[21] 2010	NHANES	Good	US	3125	Cross-sectional	NR (12-19)	Nationally representative US sample; female participants: 1491 (47.7%)[c]	Single lipid assessment; nonfasting TC≥200 mg/dL or fasting LDL-C≥130 mg/dL were considered elevated	1996-2006
Ford et al,[22] 2009	NHANES	Good	US	9868	Cross-sectional	NR (6-17)	Nationally representative US sample; female participants: 4907 (49.7%)[c]	Single lipid assessment; nonfasting TC≥200 mg/dL or fasting LDL-C≥130 mg/dL were considered elevated	1999-2006
Margolis et al,[23] 2014		Fair	US	29 360	Retrospective analysis of automated medical records	NR (3-19)[d]	Youths with ≥1 visit during the study period in 3 large US health systems Female participants: 15 404 (52.5%); race/ethnicity for female participants included white: 5974 (38.8%); Asian: 1008 (6.5%); black: 1521 (9.9%); Hispanic: 3044 (19.8%); other: 237 (1.5%); and missing: 3620 (23.5%); comparable race/ethnicity distribution for male participants	First TC measurement on record; ≥200 mg/dL was considered elevated	2007-2010
Ice et al,[7] 2011 Ritchie et al,[24] 2010	CARDIAC Project	Fair	US (West Virginia)	23 263	Cross-sectional	10.84 (NR)	Fifth-grade students in all 55 counties of West Virginia; population was 53.2% female; race/ethnicity included white (93%); biracial (2%); black (3%); and Asian, Hispanic, and other (<1% each)	Cardiac risk factor assessment with 1-time fasting lipid panel (TC, LDL-C, HDL-C, and TG); family history of premature coronary heart disease before age 55 y (assessed by parent survey); TC≥200 mg/dL or LDL-C≥130 mg/dL were considered elevated	2003-2008

(continued)

Table 1. Included Studies by Key Question (continued)

Source	Study Family[a]	Quality[b]	Country	No.	Study Design	Age, Mean (Range), y	Population and Setting Intervention (for Trials)	Outcomes Assessed	Dates of Data Collection
Treatment Studies (KQ6, KQ7)									
Wong et al,[25] 2013[e]		Fair	Canada	32 (16 intervention; 16 control)	Randomized clinical trial	13 (8-18)	Youths receiving care at specialty lipid clinic with fasting serum LDL-C 135-193 mg/dL, first-degree family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease, and adherence to NCEP Step II diet; female participants: 15 (46.9%); intervention group received 30 g/d of ground flaxseed via specially prepared muffins and bread; control group received placebo muffins and bread	LDL-C, TC, and TG assessed at 4 wk	2009-2010
DISC,[26] 1993 DISC,[27] 1995 Obarzanek et al,[30] 1997 Lavigne et al,[31] 1999 Obarzanek et al,[28] 2001 Dorgan et al,[29] 2011	DISC	Good	US	663 (334 intervention; 329 control)	Randomized clinical trial	Boys: 9.7 (8-10); girls: 9.0 (8-10)	Prepubertal children with LDL-C≥80th to <98th percentiles for age and sex recruited from public and private elementary schools; female participants: 301 (45.4%); race/ethnicity included white: 574 (86.6%); black: 56 (8.4%); and other: 33 (5.0%); intervention group received modified NCEP Step II diet delivered via family-based counseling approach (years 0-3) followed by lower-intensity dietary counseling (years 4-8); control group received feedback to parent about child's baseline cholesterol concentration, written heart-healthy diet materials	LDL-C, TC, and potential harms evaluated at 1, 3, 5, 7-8, and 18 y after randomization	1987-2008
Outcomes Study (KQ8)									
Saydah et al,[32] 2013		Good	US	9245	Prospective study of NHANES participants with 12-18 y follow-up	26.1 (12-39)	Population was 50.4% female; race/ethnicity included non-Hispanic white (77.2%); non-Hispanic black (14.7%); and Mexican American (8.1%); baseline mean lipid values were: TC, 182.0 (SE, 0.82); HDL-C, 50.4 (SE, 0.37); non-HDL-C, 131.6 (SE, 0.90) mg/dL	Mortality from endogenous and all causes before age 55 y	1988-1994 to 2006

Abbreviations: CARDIAC, Coronary Artery Risk Detection in Appalachian Communities; CDC, Centers for Disease Control and Prevention; DISC, Dietary Intervention Study in Children; HDL-C, high-density lipoprotein cholesterol; KQ, key question; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; NHANES, National Health and Nutrition Examination Survey; NR, not reported; TC, total cholesterol; TG, triglycerides.

[a] Articles in the same study family use the same study population or same data source to describe multiple results.

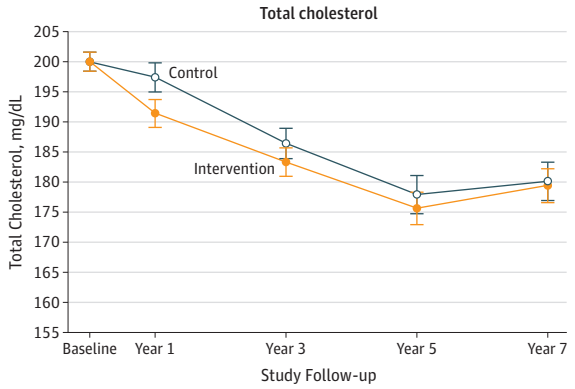
[b] Quality was assessed using criteria developed by the US Preventive Services Task Force[14] and the Newcastle-Ottawa Scale.[33]

[c] Sample weights were used to obtain prevalence estimates representative of the civilian noninstitutionalized US population.

[d] This study does not report mean age. The age distribution for the cohort is: 3-5 years, 2.7%; 6-8 years, 6.8%; 9-11 years, 15.4%; 12-16 years, 41.6%; and 17-19 years, 33.4%.[23]

[e] This study was evaluated for KQ6 only.

Figure 2. Effect of a Dietary Intervention on Mean Total Cholesterol in Children Aged 8 to 10 Years at Baseline in the Dietary Intervention Study in Children[28]



No. of participants					
Intervention	334	315	320	268	283
Control	329	303	303	254	265

Error bars indicate 95% CIs. To convert total cholesterol to millimoles per liter, multiply by 0.0259. The numbers of participants in each study group contributing data at each time point are shown below the graph. Median follow-up was 7.2 years (range, 6.5-9.3 years). Mean age of study participants was 9.5 years at baseline and 17.0 years at year 7; mean age was not reported at other time points. In this same study, low-density lipoprotein cholesterol showed a similar pattern to total cholesterol over time in both study groups.

Benefits of Treatment of Multifactorial Dyslipidemia

Key Question 5. Does treatment of multifactorial dyslipidemia 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 multifactorial dyslipidemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (ie, improve lipid levels or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

No studies meeting the inclusion criteria evaluated the effect of medications on intermediate outcomes in children or adolescents with multifactorial dyslipidemia. For lifestyle modification, 1 good-quality trial (4 articles)[26-29] and 1 fair-quality treatment trial (1 article)[25] were included (Table 1). A 4-week trial tested the effect of flaxseed supplementation of 30 g/d delivered through specially prepared muffins and bread. The control group received placebo muffins and bread.[25] Compared with placebo, flaxseed was associated with non–statistically significant lower TC concentrations (relative change of −4%; 95% CI, −10% to 2%; $P = .20$) and LDL-C concentrations (relative change of −5%; 95% CI, −12% to 2%; $P = .15$). Flaxseed also was associated with lower HDL-C concentrations relative to placebo (mean change, −15%; 95% CI, −24% to −6%; $P = .001$).

The Dietary Intervention Study in Children (DISC) was a randomized clinical trial of a modified NCEP Step II (low-fat, low-cholesterol) diet[3] with a multiyear intervention and long-term follow-up of children with LDL-C between the 80th and 98th percentiles for age and sex (aged 8-10 years at baseline; n = 663). During the first 6 months, participants had group visits and individual family visits, followed by a 2.5-year maintenance phase to support adoption of the low-fat diet. Parents of control-group participants received feedback about the child's cholesterol concentration and educational materials. Children in the intervention group received dietary counseling at a lower intensity until about 8 years after randomization.[28] A subset of 230 female participants was assessed again as adults, about 18 years after randomization.[29]

Adherence to the diet during the intervention period was good,[27] and the children in the intervention group had improved dietary quality.[35] Small, statistically significant decreases in LDL-C and TC relative to the control group were seen in participants randomized to the dietary intervention at years 1 and 3. Adjusted mean between-group differences in change from baseline at 1 year were −6.1 mg/dL (95% CI, −9.1 to −3.2 mg/dL; $P < .001$) for mean TC and −4.8 mg/dL (95% CI, −7.4 to −2.2 mg/dL; $P < .001$) for mean LDL-C. The groups did not differ significantly at year 5 (LDL-C and TC),[30] year 7 (LDL-C and TC),[28] or year 18 (LDL-C)[29] (**Figure 2**).

Harms of Treatment of Multifactorial Dyslipidemia

Key Question 7. What are the harms of treatment of multifactorial dyslipidemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents?

Only DISC was included for treatment harms (Table 1). Weight, height, and BMI were assessed at baseline and annually through the final visit in the original study and (for the subset of 230 women) at year 18.[28,29] Skin-fold thickness and mid arm, waist, and hip circumferences were measured at several points. Sexual maturation was evaluated at every visit through year 5 or until the participant reached Tanner stage 5. Age at menarche was recorded for female participants at year 7 and at year 18. Blood pressure was measured at baseline, year 1, year 3, and year 18. Laboratory measures and macronutrient and micronutrient intake were measured at several time points. Psychosocial assessments[31] were performed at year 3 to assess social emotional development, depression/anxiety, academic development, and eating disorders. DISC identified no harms of a modified NCEP Step II dietary intervention with behavioral counseling in children with multifactorial dyslipidemia.

Relationship Between Intermediate Outcomes and Adult Health Outcomes

Key Question 8. What is the association between intermediate outcomes in childhood and adolescence and future incidence of MI and stroke events in adults?

One good-quality study met the inclusion criteria (Table 1).[32] This study identified a cohort of 9245 NHANES participants aged 12 to 39 years and measured deaths before age 55 years through linkage with the National Death Index. Total cholesterol concentrations were greater than 200 mg/dL in 28.5% of the cohort and greater than 240 mg/dL in 7.6%. At the end of the study, 283 participants (3.1%) had died. Moderately elevated TC concentrations (200-239 mg/dL) were not significantly associated with a relative hazard (RH) for death before age 55 years for male participants (RH for all causes, 0.75 [95% CI, 0.42-1.37]; RH for endogenous causes, 0.71 [95% CI, 0.34-1.51]) or for female participants (RH for all causes, 1.39 [95% CI, 0.71-2.70]; RH for

Table 2. Summary of Evidence by Key Question

Key Question	Study Design	No. of Studies	No. of Observations	Summary of Findings	Consistency	Applicability	Major Limitations	Overall Quality
Key question 1: Screening and adult health outcomes	NA	0	0	NA	NA	NA	NA	NA
Key question 2: Screening and intermediate outcomes	NA	0	0	NA	NA	NA	NA	NA
Key question 3: Screening diagnostic yield	Cross-sectional	4 (8 articles)	78 792[a]	The 1 study that included confirmatory testing found a diagnostic yield of 5.8%. Data from studies using a single test found simulated diagnostic yields of 4.8%-12.3%.	Taken together, results are internally consistent.	All studies were conducted in US settings. Two were in US primary care settings and are most directly applicable. One study was conducted in a school-based setting and is likely relevant to primary care. NHANES data may not have direct relevance to primary care.	In non-NHANES studies, populations were almost exclusively white. Only 1 study included confirmatory testing (n = 6500), all others used a single test, so true diagnostic yield not available.	Fair
Key question 4: Screening harms	NA	0	0	NA	NA	NA	NA	NA
Key question 5: Treatment in childhood and health outcomes	NA	0	0	NA	NA	NA	NA	NA
Key question 6: Treatment in childhood and intermediate outcomes	RCT; longitudinal follow-up of 1 trial cohort to 18 y after randomization	2 (5 articles)	695	The diet study found lower LDL-C and TC levels at 1-y and 3-y follow-up in the intervention group. On longitudinal follow-up of the trial cohort, treatment effects were attenuated. The study of flaxseed supplementation found no effect on lipid levels at 4 wk.	NA (different interventions)	The diet study is likely applicable to a US setting if the relatively high intensity of dietary counseling could be replicated in primary care. The flaxseed study has limited applicability to a primary care setting.	In larger study (diet), cutoffs used to define dyslipidemia were lower than evidence report criteria. Smaller study (flaxseed) had a small sample size (n = 32) and was limited to high-risk population in tertiary care setting.	Fair
Key question 7: Treatment harms	RCT; longitudinal follow-up of trial cohort to 18 y after randomization	1 (5 articles)	663	No harms reported at any point during trial or long-term follow-up for anthropometric, laboratory, psychosocial, or maturation measures.	NA (1 study)	DISC is likely applicable to a US setting if the relatively high intensity of family counseling could be replicated in primary care.	Cutoffs used to define dyslipidemia were lower than evidence report criteria.	Fair
Key question 8: Association of childhood intermediate outcomes and adult health outcomes	Longitudinal analysis of NHANES data	1	9245	At follow-up, 283 people were deceased before age 55 y. Leading causes of death for age 12-19 y at baseline were unintentional or self-inflicted injury, circulatory causes, and cancer. In multivariate models, neither very high TC (≥240 mg/dL) nor moderately increased TC (200-239 mg/dL) was independently associated with death combining sexes. For females only, very high TC was associated with greater risk of death before age 55 y (relative hazard, 2.58; 95% CI, 1.31-5.08).	NA (1 study)	NHANES data may not have direct relevance to primary care.	Outcomes in children within total study population (aged 12-39 y) were not reported separately.	Fair

Abbreviations: DISC, Dietary Intervention Study in Children; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; RCT, randomized clinical trial; TC, total cholesterol.

[a] The number of observations of 78 792 is an estimate because the 4 NHANES articles included for KQ3 have overlapping populations.

endogenous causes, 0.77 [95% CI, 0.36-1.62]). A very high TC concentration (≥240 mg/dL) was associated with a greater risk of death due to endogenous causes (RH, 2.58; 95% CI, 1.31-5.08) in female participants only.

Discussion

Screening strategies proposed for dyslipidemia have included both selective and universal screening. Several expert groups recommend screening based on family history, primarily for detecting familial hypercholesterolemia.[3,17,36,37] A 2011 guideline from the National Heart, Lung, and Blood Institute recommended universal screening at age 9 to 11 years and again at age 17 to 21 years, with selective screening at other ages.[17] Elevated LDL-C and TC concentrations are associated with higher BMI[6-8,38] and waist circumference,[6,38] suggesting a rationale for selective screening. However, BMI is most strongly associated with elevated triglyceride concentration, which, not being atherogenic, is not included in the definition of multifactorial dyslipidemia. Current rates of dyslipidemia screening in children and adolescents are low, estimated between 2.5% and 3.2%.[39] Current guidelines do not recommend lipid-lowering medications to treat multifactorial dyslipidemia in youths,[17] and pharmacologic treatment of 8- to 20-year-olds with lipid-lowering agents is rare.[40]

This evidence report found that in population-based studies, 8% to 11% of children and adolescents screened positive at the fixed NCEP cut point of 200 mg/dL or higher on a single TC test, with higher rates in obese children and, to a lesser extent, in overweight children. After confirmatory testing, screening is estimated to result in diagnostic yields ranging from 4.8% to 12.3%, with higher yields in higher BMI subgroups, if screening is widely adopted (**Table 2**). However, no direct evidence was found for the effect of screening for multifactorial dyslipidemia on dyslipidemia and atherosclerosis in childhood or on MI and ischemic stroke in adulthood.

No evidence was found on the harms of screening for multifactorial dyslipidemia in childhood. Because the majority of dyslipidemias identified in childhood do not develop clinically important lipid elevations or cardiovascular disease,[10,41] such "nondisease" could result in harms, such as labeling a child as sick, parent or child anxiety, and unnecessary or harmful testing and treatment. Furthermore, the NCEP cut points are derived from population distributions,[3] not from associations between lipid concentrations and clinical outcomes, as they are for adults. Although widely accepted, these fixed cut points may overidentify children in the age groups currently targeted for screening, who naturally experience peaks in TC and LDL-C concentrations.

Evidence from 1 trial suggests that moderately dyslipidemic 8- to 10-year-olds following a low-fat, low-cholesterol diet experience a small decrease in lipid levels without evidence of harms (Table 2). The study diet closely resembled current macronutrient recommendations for children with LDL-C concentrations of 130 mg/dL or higher.[17] The small beneficial effect of a low-fat, low-cholesterol diet did not persist beyond 3 years and was consistent with the natural decrease in LDL-C concentration seen in early adolescence. The relatively high intensity of the counseling intervention limits its generalizability to primary care settings, in which trained nutritional counselors may not be part of the health care team. In addition, the clinical importance of the small effect on cholesterol concentrations in a 3-year period is unclear. A randomized clinical trial of flaxseed supplementation found no effect on TC concentrations; this trial included children with a family history of dyslipidemia, so it is possible that some of the participants could have met criteria for familial hypercholesterolemia.

Despite the clear link between lipid concentrations and coronary heart disease in adults, the association between elevated TC or LDL-C concentrations in youth and cardiovascular disease in adulthood is poorly understood. A single longitudinal study of adolescents and young adults from the NHANES database found no association between TC concentrations and death before age 55 years when men and women were combined but did find that women who had an extremely high TC concentration (≥240 mg/dL) at age 12 to 39 years had a greater risk of death before age 55 years. This subgroup is likely dominated by women with familial hypercholesterolemia, among whom premature coronary heart disease deaths are expected. The meaning of this finding is unclear because of the small number of deaths in this subgroup and because it represents both adolescence and young adulthood.

Research Needs

Large randomized clinical trials of lifestyle interventions with long-term follow-up would provide evidence to inform recommendations for management of children and youth with multifactorial dyslipidemia. Rigorous trials of dietary supplements and medications to reduce concentrations of atherogenic lipids in children and adolescents would also improve the body of evidence.

Evidence for the effect of screening in childhood on health outcomes in adulthood is notably lacking and could be provided by large trials of both universal and selective screening strategies that use accepted cut points defining dyslipidemia, perform confirmatory testing, and include racially and ethnically diverse populations. Pediatric studies that screen for abnormal non–HDL-C or apolipoprotein B concentrations, which have emerged as strong markers of atherogenic risk in adults,[42-44] could also be useful. Long-term follow-up studies of pediatric cohorts into adulthood would provide evidence that would aid the understanding of the association between cholesterol concentrations in children with multifactorial dyslipidemia and adult health outcomes.

Although cut points for defining dyslipidemia in childhood are not a primary focus of this review, the findings suggest that the current commonly accepted fixed cut points are imprecise given the normal, predictable, and well-documented fluctuations in lipid levels that occur during childhood and adolescence. Reexamination of cut points that more precisely reflect the fluctuations of lipids during childhood and their implications for screening may be warranted.

Limitations

This review identified no screening studies with follow-up to adulthood and only 2 randomized clinical trials of different

dietary interventions. The larger trial targeted 8- to 10-year-olds, so the effect of a dietary intervention on adolescents with dyslipidemia remains unknown. There was no evidence to support any other type of treatment for multifactorial dyslipidemia. This evidence report excluded familial hypercholesterolemia, which is addressed in a companion review.[13] However, it is worth noting that the 2 conditions are detected with the same screening test.

Conclusions

The diagnostic yield of lipid screening varies by age and BMI. No direct evidence was identified for benefits or harms of childhood screening or treatment on outcomes in adulthood. Intensive dietary interventions may be safe, with modest short-term benefit of uncertain clinical significance.

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, Morrison, Dunn, Whitlock.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lozano, Henrikson, Morrison, Nguyen.
Critical revision of the manuscript for important intellectual content: All authors.
Obtained funding: Lozano, Whitlock.
Administrative, technical, or material support: Lozano, Henrikson, Morrison, Nguyen, Blasi.
Study supervision: Lozano, Henrikson.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This research was funded by AHRQ under a contract to support the USPSTF.

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight; reviewed the report to ensure that the analysis met methodological standards; and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings.

Additional Contributions: We gratefully acknowledge the following individuals for their contributions to this project: the AHRQ staff; the USPSTF; David Grossman, MD, MPH, Group Health Research Institute, and Bruce Psaty, MD, PhD, University of Washington, for their feedback on the research plan; and the Evidence-Based Practice Center staff members, Smyth Lai, MLS, Christel Kratohvil, Gabrielle Gundersen, BA, Sarah Kotowski, PhD, Brittany Burda, MPH, Caitlyn Senger, MPH, Tracy Beil, MS, and Aaron Scrol, MA. USPSTF members, expert consultants, and peer reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 4 content experts (Stephen R. Daniels, MD, PhD, University of Colorado School of Medicine and Children's Hospital Colorado; Sarah De Ferranti, MD, MPH, Boston Children's Hospital; Patrick McBride, MD, MPH, University of Wisconsin School of Medicine and Public Health; and Alpo Vuorio, MD, Department of Medicine, University of Helsinki). Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF Recommendation Statement. It did not undergo additional peer review after submission to *JAMA*.

REFERENCES

1. Helfand M, Carson S. *Screening for Lipid Disorders in Adults: Selective Update of 2001 US Preventive Services Task Force Review: Evidence Synthesis No. 49*. Rockville, MD: Agency for Healthcare Research and Quality; 2008. AHRQ publication 08-05114-EF-1.

2. Cook S, Auinger P, Huang TT. Growth curves for cardio-metabolic risk factors in children and adolescents. *J Pediatr*. 2009;155(3)(suppl 6): 6.e15-6.e26.

3. National Cholesterol Education Program. Highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89(3):495-501.

4. Gidding SS, Barton BA, Dorgan JA, et al. Higher self-reported physical activity is associated with lower systolic blood pressure: the Dietary Intervention Study in Childhood (DISC). *Pediatrics*. 2006;118(6):2388-2393.

5. Wong ND, Hei TK, Qaqundah PY, Davidson DM, Bassin SL, Gold KV. Television viewing and pediatric hypercholesterolemia. *Pediatrics*. 1992;90(1 pt 1): 75-79.

6. Raman A, Sharma S, Fitch MD, Fleming SE. Anthropometric correlates of lipoprotein profile and blood pressure in high BMI African American children. *Acta Paediatr*. 2010;99(6):912-919.

7. Ice CL, Murphy E, Cottrell L, Neal WA. Morbidly obese diagnosis as an indicator of cardiovascular disease risk in children: results from the CARDIAC Project. *Int J Pediatr Obes*. 2011;6(2):113-119.

8. Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, Ogden CL. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. *JAMA Pediatr*. 2015;169(3):272-279.

9. Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, Nelson HD. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. *Pediatrics*. 2007;120(1):e189-e214.

10. Magnussen CG, Raitakari OT, Thomson R, et al. Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. *Circulation*. 2008;117(1): 32-42.

11. Juhola J, Magnussen CG, Viikari JS, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. *J Pediatr*. 2011;159(4):584-590.

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

13. Lozano P, Henrikson NB, Dunn J, et al. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. doi:10.1001/jama.2016.6176.

14. Harris RP, Helfand M, Woolf SH, et al; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3)(suppl):21-35.

15. US Preventive Services Task Force. *US Preventive Services Task Force Procedure Manual*. Rockville, MD: US Preventive Services Task Force; 2015.

16. Lozano P, Henrikson NB, Morrison CC, et al. *Lipid Screening in Childhood for Detection of Multifactorial Dyslipidemia: A Systematic Evidence Review for the US Preventive Services Task Force*. Rockville, MD: Agency for Healthcare Research and Quality; 2016.

17. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213-S256.

18. United Nations Development Programme. Human Development Index: 2013 Rankings. http://hdr.undp.org/en/2013-report. Accessed July 14, 2016.

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

20. Kit BK, Carroll MD, Lacher DA, Sorlie PD, DeJesus JM, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. *JAMA*. 2012;308(6):591-600.

21. Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths—United States, 1999-2006. *MMWR Morb Mortal Wkly Rep*. 2010;59(2):29-33.

22. Ford ES, Li C, Zhao G, Mokdad AH. Concentrations of low-density lipoprotein

cholesterol and total cholesterol among children and adolescents in the United States. *Circulation*. 2009;119(8):1108-1115.

23. Margolis KL, Greenspan LC, Trower NK, et al. Lipid screening in children and adolescents in community practice: 2007 to 2010. *Circ Cardiovasc Qual Outcomes*. 2014;7(5):718-726.

24. Ritchie SK, Murphy EC, Ice C, et al. Universal vs targeted blood cholesterol screening among youth: the CARDIAC Project. *Pediatrics*. 2010;126(2):260-265.

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

26. DISC Collaborative Research Group. Dietary Intervention Study in Children (DISC) with elevated low-density-lipoprotein cholesterol: design and baseline characteristics. *Ann Epidemiol*. 1993;3(4):393-402.

27. Writing Group for the DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. *JAMA*. 1995;273(18):1429-1435.

28. Obarzanek E, Kimm SY, Barton BA, et al; DISC Collaborative Research Group. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: 7-year results of the Dietary Intervention Study in Children (DISC). *Pediatrics*. 2001;107(2):256-264.

29. Dorgan JF, Liu L, Barton BA, et al. Adolescent diet and metabolic syndrome in young women: results of the Dietary Intervention Study in Children (DISC) follow-up study. *J Clin Endocrinol Metab*. 2011;96(12):E1999-E2008.

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

31. Lavigne JV, Brown KM, Gidding S, et al. A cholesterol-lowering diet does not produce adverse psychological effects in children: 3-year results from the Dietary Intervention Study in Children. *Health Psychol*. 1999;18(6):604-613.

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

33. Wells GA, Shea B, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analysis*. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed July 14, 2016.

34. National Center for Health Statistics. *Analytic and Reporting Guidelines: the Third National Health and Nutrition Examination Survey (NHANES III) 1988-1994*. Hyattsville, MD: National Center for Health Statistics; 1996.

35. Van Horn L, Obarzanek E, Friedman LA, Gernhofer N, Barton B. Children's adaptations to a fat-reduced diet: the Dietary Intervention Study in Children (DISC). *Pediatrics*. 2005;115(6):1723-1733.

36. Daniels SR. Screening for familial hypercholesterolemia: what is the most effective strategy? *Nat Clin Pract Cardiovasc Med*. 2008;5(3):130-131.

37. Daniels SR, Greer FR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. *Pediatrics*. 2008;122(1):198-208.

38. Martínez-Gómez D, Eisenmann JC, Gómez-Martínez S, Veses A, Marcos A, Veiga OL. Sedentary behavior, adiposity and cardiovascular risk factors in adolescents: the AFINOS study. *Rev Esp Cardiol*. 2010;63(3):277-285.

39. Vinci SR, Rifas-Shiman SL, Cheng JK, Mannix RC, Gillman MW, de Ferranti SD. Cholesterol testing among children and adolescents during health visits. *JAMA*. 2014;311(17):1804-1807.

40. Joyce N, Wellenius GA, Dore DD, Newburger JW, Zachariah JP. Patterns of lipid lowering therapy among children ages 8-20 years. *J Pediatr*. 2015;167(1):113-9.e1.

41. Clarke WR, Schrott HG, Leaverton PE, Connor WE, Lauer RM. Tracking of blood lipids and blood pressures in school age children: the Muscatine study. *Circulation*. 1978;58(4):626-634.

42. Di Angelantonio E, Sarwar N, Perry P, et al; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302(18):1993-2000.

43. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes*. 2011;4(3):337-345.

44. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol*. 2009;53(4):316-322.