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Lipid Screening in Childhood for Detection of Multifactorial Dyslipidemia: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background. For purposes of this report, multifactorial dyslipidemia refers to dyslipidemias involving elevated total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) that are not familial hypercholesterolemia (FH). There is evidence that elevated TC and LDL-C concentrations in childhood, and especially adolescence, are associated with markers of atherosclerosis in young adults.

Purpose. We conducted this systematic evidence review on the benefits and harms of screening adolescents and children for multifactorial dyslipidemia to support the U.S. Preventive Services Task Force (USPSTF) in updating its previous recommendation.

Data sources. We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and PubMed for trials published between 1 January 2006 and 31 December 2014 relevant to all key questions (KQs) posed by the USPSTF. We supplemented our searches with reference lists from existing systematic reviews, cohort studies, suggestions from experts, and ongoing trials registered in Clinicaltrials.gov.

Study Selection. Investigators independently evaluated 7,137 abstracts and 537 articles against *a priori* inclusion criteria. Investigators also independently critically appraised each study using design-specific quality criteria based on USPSTF methods. Only fair- or good-quality studies that met the *a priori* criteria were chosen for each key question. Differences between investigators were resolved by consensus.

Data Extraction and Analysis. One investigator abstracted data from 16 included studies into evidence tables, and a second reviewer verified the accuracy of these data. We qualitatively summarized the evidence regarding screening for multifactorial dyslipidemia and its treatment.

Results. We found no direct evidence for an effect of screening children on adult health outcomes (KQ1), on intermediate health outcomes (KQ2), on the harms of screening (KQ4), or on the effect of treatment on adult health outcomes (KQ5). Studies met the inclusion criteria for four key questions:

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

Neither selective nor universal screening of children for multifactorial dyslipidemia has been evaluated in randomized controlled trials (RCTs). Fair evidence indicates that a screening total cholesterol (TC) concentration of 200 mg/dL (the National Cholesterol Education Program's [NCEP] recommended cut point for high TC) has a positive predictive value of 77 percent for a diagnosis of multifactorial dyslipidemia. Recent nationally representative prevalence estimates suggest a simulated diagnostic yield of 5.4 percent for 8-to-12-year-olds and of 6.5 percent for 13-to-17-year-olds. Simulated diagnostic yields ranged between 4 percent and 12 percent for different age and body mass index (BMI) subgroups. Based on large, recent U.S. studies, the highest diagnostic yield appears to be in obese children (12.3%), in children aged 9 to 11 years (7.2%), and in adolescents aged 16 to 19 years (7.2%). The Coronary Artery Risk Detection in Appalachian Communities study was conducted in the same age group recommended by the

National Heart, Lung, and Blood Institute expert panel for universal testing, so the diagnostic yields of 5.8 percent, 8.9 percent, and 12.3 percent for healthy weight, overweight, and obese 10- and-11-year-olds are reasonable estimates of what might be seen for those subgroups if screening 9-to-11-year-olds were more widely adopted.

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

We identified only one RCT of a dietary intervention, so the body of evidence on this question is fair at best. This trial provided good quality evidence of a modest effect of dietary counseling for a low-fat, low-cholesterol diet on lipid levels in children aged 8 to 10 years with mild-to-moderate dyslipidemia. After 1 year of relatively intensive counseling, mean differences between groups compared to baseline were a decrease of 6 mg/dL in mean TC and a decrease of 5 mg/dL in mean LDL-C; both differences were statistically significant. Both between-group differences were reduced to about 3 mg/dL at year 3, and by year 5, were no longer statistically significant. Adherence to the diet during the intervention was good, and some evidence indicated that diet quality improved in children in the intervention group.

A small, 4-week RCT of flaxseed found no cholesterol-lowering effect. We found no evidence to support any other type of treatment for multifactorial dyslipidemia, including nutritional supplements or medications.

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

Dietary changes made by children in the intervention group of the Dietary Intervention Study in Children (DISC) did not adversely affect children's nutritional status, growth, or development.

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

In a single, high-quality longitudinal study that included data on adolescents and young adults from the National Health and Nutrition Examination Survey (NHANES), TC concentration at age 12 to 39 years was not associated with death before age 55 years. The study did find that very high TC concentrations (at or above 240 mg/dL) were significantly associated with premature death in women only, although this estimate was based on a small number of deaths. The subgroup of females with concentrations this high is likely dominated by individuals who have familial hypercholesterolemia (FH), for whom premature coronary heart disease (CHD) deaths are expected. The meaning of this finding is unclear because of the small number of deaths in this subgroup.

Limitations.

Screening (KQ3)

The availability of confirmatory testing for only one of the included studies required that the diagnostic yield be estimated from simulations. The screening evidence draws heavily from epidemiologic studies rather than screening trials. The prevalence of elevated cholesterol concentrations across broad age ranges, as is often reported, is less meaningful than age-group

specific rates given the known variation by age. Only one school-based study was relevant to the primary care setting. The use of the fixed NCEP thresholds for defining elevated TC and LDL-C concentrations makes the prevalence of dyslipidemia (and diagnostic yield) difficult to interpret because they do not account for variability by age and sex. Finally, incomplete tracking of lipid concentrations between childhood, adolescence, and adulthood is another limitation of this body of evidence. Multifactorial dyslipidemia in children and adolescents under age 20 years is likely to resolve in the young adult years; thus, the importance of dyslipidemia identified in childhood or adolescence for health in adulthood is unclear.

Screening trials for detecting multifactorial dyslipidemia that include confirmatory testing are needed. Many studies were excluded because they used cut points for cholesterol concentrations that were lower than accepted cut points. Even the accepted, fixed NCEP 1992 cut points for LDL-C and TC concentrations may be inadequate because they may over- or under-identify children and adolescents, depending on age and sex. We found no trials that compared either universal or selective screening to no screening. Data on prevalence and diagnostic yield in racially or ethnically diverse populations of children are lacking. No studies addressed harms of screening.

Treatment (KQ6 and KQ7)

The DISC trial selected children with lower levels of hyperlipidemia, making it difficult to generalize results to children with TC concentrations above 200 mg/dL or LDL-C concentrations above 130 mg/dL. This trial also targeted 8-to-10-year-olds, so the impact of dietary intervention on adolescents is unknown. The intensity of the counseling intervention limits the generalizability of this treatment to primary care settings, where trained nutritional counselors may not be part of the health care team. Finally, the clinical importance of the small impact on cholesterol levels in the 1 to 3 years of the study time frame is unclear.

The evidence regarding treatment has several gaps. We found only one high-quality RCT of dietary intervention for children with multifactorial dyslipidemia. Larger RCTs with long-term followup are needed. Rigorous trials of dietary supplements and medications to reduce levels of atherogenic lipids in children and adolescents are also needed. Our search revealed no trials of statins in this population. The treatment studies reviewed for inclusion also relied on various TC and LDL-C cut points, often below the standard NCEP thresholds. Few studies followed participants for a year or longer.

Outcomes (KQ8)

Outcomes for adolescents were not reported separately from those for young adults. The single included study for KQ8 reported all-cause and endogenous-cause mortality, but not cardiovascular mortality, an outcome which would be more closely linked to the causal pathway. Long-term followup cohort studies of children are needed to better understand the association between pediatric dyslipidemia and adult myocardial infarction and stroke.

Conclusions. We found no direct evidence for an effect of cholesterol screening on intermediate or health outcomes. Only one study provided a diagnostic yield for TC screening (5.8%). Simulated diagnostic yields in data from large U.S. population-based studies show variation in

TC concentrations by age and BMI. There were no studies of diagnostic yield in selective screening and no studies on the harms of screening.

No evidence was found for an effect of treatment on health outcomes in adulthood (myocardial infarction and stroke). Dietary counseling may lower TC and LDL-C concentrations by 5-to-7 mg/dL over 3 years, but this intervention was relatively intensive and the effect on lipids dissipates by 5 years. No studies of lipid lowering medications met the inclusion criteria. There is fair evidence of the safety of dietary intervention in 8-to-10-year-olds.

In one longitudinal study using NHANES data combined for both sexes, neither very high nor moderately increased TC concentrations in 12-to-39-year-olds was independently associated with death before age 55 years.

Research needs include randomized trials of screening strategies with confirmatory testing and long-term followup, as well as rigorous RCTs of promising medications, supplements, and dietary interventions with long-term followup. Long-term follow up of pediatric cohorts is needed to better establish the long-term health risks conferred by elevated concentrations of TC and LDL-C. Although not the focus of this systematic review, our findings support a re-examination of the commonly accepted, fixed NCEP thresholds indicating elevated TC and LDL-C concentrations and a reconsideration of age- and sex-specific thresholds.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BMI	body mass index
CARDIA	Coronary Artery Risk Development in Young Adults (study)
CARDIAC	Coronary Artery Risk Detection in Appalachian Communities (study)
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CIMT	carotid intima medial thickness
CMS	Centers for Medicare and Medicaid Services
DISC	Dietary Intervention Study in Children
dL	deciliter
EPC	Evidence-based Practice Center
FH	familial hypercholesterolemia
HDL-C	high density lipoprotein cholesterol
HR	hazard ratio
KQ(s)	key question(s)
LDL-C	low density lipoprotein cholesterol
mg	milligram(s)
MI	myocardial infarction
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NHBLI	National Heart, Lung, and Blood Institute
non-HDL-C	TC minus HDL-C, a measure that includes LDL-C as well as other atherogenic lipoproteins (very low and intermediate density lipoproteins)
NR	not reported
PDAY	Pathobiological Determinants of Atherosclerosis in Youth (study)
PPV	positive predictive value
RCT	randomized controlled trial
RH	relative hazard
SD	standard deviation
TC	total cholesterol
TG	triglycerides
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VLDL	very low density lipoprotein cholesterol

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Chapter 1. Introduction

Scope and Purpose

The Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic evidence review to support the United States Preventive Services Task Force (USPSTF) in updating its 2007 recommendation on screening for lipid disorders in children.

Pediatric dyslipidemias are a heterogeneous set of conditions that include several monogenic disorders as well as dyslipidemias caused by a variety of factors, both genetic and environmental. On the basis of public input on the draft review research plan, the USPSTF decided to conduct two separate systematic reviews: one on screening for familial hypercholesterolemia (FH) and a second on screening for elevated concentrations of atherogenic lipoproteins, which we refer to as multifactorial dyslipidemia.

The two reviews were conducted by the same Evidence-based Practice Center (EPC) using a search strategy that produced one body of potential evidence encompassing both FH and multifactorial dyslipidemias. The evidence was assessed sequentially for each review's set of Key Questions (KQs). These two concurrent systematic reviews will allow the USPSTF to simultaneously consider both bodies of evidence when evaluating the preventive health benefits of screening children and adolescents for dyslipidemias involving elevated concentrations of low-density lipoprotein cholesterol (LDL-C) or total cholesterol (TC).

This review focuses on dyslipidemias involving elevated LDL-C or TC that are not FH, referred to in this report as multifactorial dyslipidemia. It reviews the evidence for benefits and harms of screening and treatment of multifactorial dyslipidemia in children and youth aged 0 to 20 years.

Cholesterol and Dyslipidemia in Childhood and Adolescence

Cholesterol concentrations in healthy children vary with age. The distribution of TC and LDL-C concentrations, for example, are bimodal in childhood. They start very low at birth, increase slowly in the first 2 years of life, peak prior to puberty, and decrease by 10 percent to 20 percent or more during adolescence before rising again during late adolescence and young adulthood.¹ Concentrations of TC and LDL-C are generally higher in girls than in boys. The peak in girls precedes that in boys by about 1 year, reflecting maturational differences.

Lipid disorders are defined according to population norms. The Lipid Research Clinics prevalence studies² used population distributions to determine age- and sex-specific cut points for TC and LDL-C concentrations.^{3,4} The National Heart, Lung, and Blood Institute (NHLBI) and American Academy of Pediatrics have adopted the National Cholesterol Education Program (NCEP) recommendation for fixed cutoff values to define dyslipidemia in children: TC \geq 200mg/dL and LDL-C \geq 130mg/dL.² These cut points are commonly used in published studies and widely accepted in clinical practice. We will use these in the current review, although, as noted below, fixed thresholds that ignore cholesterol variations by age and sex may be problematic.

The National Cholesterol Education Program’s recommended cut points define dyslipidemia in children

Category	Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)
Acceptable	less than 170	less than 110
Borderline	170 to 199	110 to 129
High	200 or greater	130 or greater

Abbreviations: mg/dL = milligram(s) per deciliter, LDL = low-density lipoprotein

Condition Definition

For purposes of this report, LDL-C concentrations of 130 mg/dL or greater or TC concentrations greater than 200 mg/dL not due to FH are referred to as “multifactorial dyslipidemia” and are the focus of the current review. Elevations in TC and LDL-C concentrations in children and adolescents are of concern because of the role of these lipids in cardiovascular disease in adults and in atherogenesis even at young ages. Non-high density lipoprotein cholesterol (non-HDL-C, which is the difference between TC concentration and the HDL-C concentration) has emerged as the best marker of atherogenic risk in adults; however, few screening studies have relied on non-HDL-C in pediatric populations.

Extremely high LDL-C and TC concentrations are seen in FH, which is the subject of the companion systematic evidence review commissioned by the USPSTF. In the accompanying systematic review, FH is defined using any one of several established diagnostic criteria, all of which include a combination of elevated lipid concentrations, physical findings, family history, or genetic tests.

Children and adolescents with a variety of renal, infectious, hepatic, inflammatory and storage disorders, types 1 and 2 diabetes, and several other syndromes are also at risk for experiencing elevated LDL-C or TC concentrations. These secondary dyslipidemias are beyond the scope of this review.

Multifactorial dyslipidemia in children and adolescents may be associated with environmental factors, such as a high-fat diet, with or without inherited susceptibility. Elevated LDL-C and TC concentrations appear to be associated with measures of adiposity, such as body mass index (BMI)^{5-7,8} and waist circumference.^{5,6} Overweight and obesity, now present in nearly a third of U.S. children aged 2 to 19 years,⁹ are associated with poor nutrition and physical inactivity, each of which may be independently associated with childhood dyslipidemia. However, the strongest association of BMI is with triglyceride concentrations, which are not part of the definition of multifactorial dyslipidemia. Some evidence indicates that higher rates of physical activity are associated with lower LDL-C concentrations,¹⁰ and sedentary activity may be correlated with TC concentrations.¹¹

A family history of dyslipidemia or premature cardiovascular disease is a risk factor for childhood dyslipidemia. Even apart from a monogenic condition with high penetrance, such as FH, there are a number of genetic variations with incomplete penetrance that contribute to multifactorial dyslipidemia¹². In the U.S., dyslipidemia is experienced disproportionately by adults with Hispanic ethnicity¹³ and those of Asian ancestry.¹⁴

The prevalence of elevated total cholesterol in children aged 8 to 17 years is 7.8 percent, according to National Health and Nutrition Examination Survey (NHANES) data from 2011 to 2012.⁸ The most recent national prevalence estimate (NHANES 2007 to 2010) of elevated LDL-C concentrations in adolescents is 7.4 percent.¹⁵ However, these NHANES data rely on a single lipid test. Within-person variability of lipid concentrations is considerable, such that repeat

testing is required to reliably categorize children according to the NCEP ranges of acceptable, borderline, or high.¹⁶ Therefore, these figures overestimate the true prevalence of these dyslipidemias in the population.

Multifactorial dyslipidemia is a risk factor, not a disease. The definition of multifactorial dyslipidemia is based on pediatric norms, not on actual risks associated with specific TC or LDL-C concentrations. It is unclear to what extent elevated lipid concentrations at ages younger than 18 to 20 years confer future disease risk.

Natural History and Disease Burden

Dyslipidemia, Atherosclerosis, and Adult Coronary Heart Disease

Cholesterol is a lipid that is a vital component of cell membranes and plays a role in synthesis of steroid hormones, vitamin D, and bile acids. Humans absorb dietary cholesterol and also synthesize it *de novo*. Diet and genetics both affect blood cholesterol concentrations, as do other environmental factors. Cholesterol synthesis and absorption vary greatly in the general population. Plasma cholesterol concentrations are the sum of intestinal absorption and hepatic synthesis minus net biliary excretion and cell use. Three classes of lipoproteins transport cholesterol in the serum: LDL-C, high-density lipoproteins (HDL-C), and very low density lipoproteins (VLDL-C). Total cholesterol is comprised of 60 percent to 70 percent LDL-C, 20 percent to 30 percent HDL-C, and 10 percent to 15 percent VLDL-C.

The burden of hypercholesterolemia is related to its link to atherosclerosis and coronary heart disease (CHD). LDL-C is the primary atherogenic lipoprotein and is the primary target of cholesterol-lowering therapy in adults. Some forms of VLDL-C are precursors to LDL-C and also promote atherosclerosis. HDL-C concentrations are inversely related to the risk for coronary heart disease. When elevated, LDL-C accumulates in blood vessels, contributing to plaque formation, which occurs in stages, starting with fatty streaks and progressing to fibrous plaques. Non-HDL-C provides an estimate of atherogenic particles including LDL-C, VLDL-C, lipoprotein a and intermediate-density lipoprotein.¹⁷ In adults, elevations in TC, LDL-C and non-HDL-C are risk factors for atherosclerotic cardiovascular disease, specifically CHD,¹⁷ which may lead to sudden coronary death and myocardial infarction (MI). The association of triglyceride levels with CHD is unclear and for this reason, our definition of multifactorial dyslipidemia excludes triglycerides. Other risk factors for CHD in adults are age, male sex, hypertension, smoking, diabetes, obesity, physical inactivity, an atherogenic diet, and family history of early CHD.

The prevalence of CHD increases with age and is higher in men than in women of the same age.¹⁸ In 2010, the overall age-adjusted prevalence of CHD was 6.0 percent in the United States. Age-specific prevalence was 1.2 percent in 18-to-44-year olds, 7.1 percent in 45-to-64-year olds, and 19.8 percent in age 65 years and older.¹⁸ Coronary heart disease is the leading cause of death in the United States.^{19, 20}

Identifying and treating dyslipidemia in adults over age 40 years is common clinical practice in the United States. The USPSTF recommends screening adults for dyslipidemia, with specific recommendations depending on age, sex, and risk factors.²¹ This recommendation is currently being updated.

Association Between Dyslipidemia in Childhood and Adolescence and Atherosclerosis

Multifactorial dyslipidemia in childhood and adolescence is a risk factor for future atherosclerosis. Several longitudinal studies have found associations between childhood lipid concentrations and measures of atherosclerosis. Studies of 204 individuals in the Bogalusa cohort who died between age 2 and 39 years showed a positive association between ante mortem LDL-C and TC concentrations and atherosclerosis at autopsy, as assessed by the presence of fatty streaks and fibrous plaques in the aorta and coronary arteries.^{22, 23} Data from the Muscatine study showed that LDL-C concentrations at ages 8 to 18 years predicted carotid intima medial thickness (CIMT) at ages 33 to 42 years.²⁴ A followup of the Bogalusa cohort found that LDL-C concentrations at age 5 to 17 years predicted CIMT at ages 16 to 19 years.²⁵ In the Young Finns study, LDL^{26, 27} and ApoB/ApoA-1²⁸ concentrations in adolescence (age 12 to 18 years) were associated with CIMT in adulthood.

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, a large cross-sectional autopsy study of 15-to-34-year-olds who died of external causes, found the extent of fatty streaks to be positively associated with post-mortem LDL-C plus VLDL-C concentrations and negatively associated with HDL-C concentrations.²⁹ In that same study, high non-HDL cholesterol and low HDL cholesterol concentrations were associated with more extensive fatty streaks and raised lesions in the abdominal aorta and right coronary artery.³⁰ In contrast, a cross-sectional U.S. study of 599 children and adolescents found that CIMT was not correlated with LDL-C concentrations when controlling for obesity.³¹

In the Coronary Artery Risk Development in Young Adults study (CARDIA, not to be confused with the more recent CARDIAC study [Coronary Artery Risk Detection in Appalachian Communities]), lipid concentrations at baseline (in the mid 1980s) and at age 20 years were positively associated with CIMT and coronary calcium Hounsfield units at age 20 years.^{32, 33} Exposure to non-optimal lipid concentrations in young adulthood is associated with atherosclerotic changes later in life. One prospective cohort study of 2,824 people age 18 to 30 years with non-optimal concentrations of LDL-C (defined as >100 mg/dL) at baseline found that cumulative exposure to higher LDL-C or lower HDL-C concentrations was associated with markers of atherosclerosis 2 decades later.³³

Tracking of Dyslipidemia Over Childhood and Adolescence

Another important aspect of the natural history of multifactorial dyslipidemia in youth is the incomplete tracking of lipid concentrations between childhood, adolescence, and adulthood. Many studies have documented correlation of lipid measurements across the pediatric and young adult age span.³⁴ Tracking to adulthood is highest for 12-to-18-year-olds.³⁵ However, dyslipidemia identified in childhood or adolescence imperfectly predicts adult lipid concentrations.³⁴ For example, the Muscatine study measured TC concentrations yearly for 6 years in a longitudinal cohort of almost 9,000 children and adolescents in Iowa. Although TC measurements were well correlated across the years, children in the highest quintile of the TC distribution had only about a 30 percent probability of being in the highest TC quintile 6 years later.³⁶ Magnussen and colleagues studied three large longitudinal study populations using two different sets of cut points: the fixed NCEP cut point and age- and sex-specific cut points derived from NHANES data. They estimated a positive predictive value of only 32.9% (NCEP) and 37.3% (NHANES) for LDL-C elevations in adolescence in predicting elevated LDL-C 15 to 20

years later,³⁷ indicating that adolescent measurement inaccurately identifies adults with dyslipidemia.

In summary, there is evidence that elevated LDL-C and TC concentrations in childhood, and especially adolescence, are associated with markers of atherosclerosis in young adults. However, the association between multifactorial dyslipidemia in childhood and clinical CHD is unknown, and it is difficult to predict which dyslipidemic youth will continue to have elevated cholesterol concentrations in young adulthood.

Screening for Multifactorial Dyslipidemia

Rationale for Screening

In the absence of routine screening, elevated TC and LDL-C concentrations are unlikely to be detected in most children and adolescents. The rationale for screening children and adolescents for dyslipidemia is to identify affected children, interrupt the atherosclerotic process, reduce cholesterol burden over the long term, and prevent or delay cardiovascular events in adulthood through dietary modification or lipid-lowering therapy.

Screening strategies proposed for multifactorial dyslipidemia have included both selective and universal screening. Selective screening may be based on a family history of dyslipidemia or premature cardiovascular disease or on other risk factors, such as overweight or obesity. Family-history-based screening has been recommended by several expert guidelines.^{3, 38} The most recent NHLBI expert recommendations advocate universal screening (at 9 to 11 years and again at 17 to 21 years) as well as selective screening at other ages.³⁹

Laboratory Studies

Total cholesterol may be measured with fasting or non-fasting serum testing. Concentrations of LDL-C may be calculated with the Friedewald formula⁴⁰: $LDL-C = TC - (Triglyceride \div 5) - HDL$. Because the calculation depends on triglyceride concentration, an accurate calculated LDL-C concentration requires a fasting blood draw. Direct LDL-C measurement does not require fasting.³⁴ There is evidence, however, that fasting and non-fasting LDL-C concentrations do not differ substantially.⁴¹ Recent screening recommendations for childhood dyslipidemia have included guidelines for using either LDL-C or non-HDL-C.³⁹

Evolution of Clinical Practice Guidelines in the United States

This evidence review comes after more than two decades of efforts to arrive at an effective approach to screening for and treating dyslipidemia. Most of these efforts have targeted both multifactorial dyslipidemia as well as FH. In some cases, they have also addressed hypertriglyceridemia. Below is a chronological summary of the major U.S. expert opinion guidelines and evidence-based recommendations for identifying and treating dyslipidemia in childhood and adolescence, with a focus on elevated TC and LDL-C concentrations.

National Cholesterol Education Program, 1992

In 1992, the NCEP, a program of the NHLBI, convened an expert panel of representatives from the American Academy of Pediatrics, the American Academy of Family Practice, the American College of Cardiology, the American Dietetic Association, and other professional organizations. The panel recommended against universal screening, citing several reasons: many children with elevated lipid concentrations in childhood are not dyslipidemic as adults; the health

benefit and safety of lipid-lowering treatments was unknown; and universal screening could lead to over-use of these drugs in children.² The panel recommended selective screening based on a family history of premature coronary heart disease, first with TC concentrations and second, if TC concentrations were elevated, obtaining a fasting lipid panel (repeated if abnormal).

The NCEP used cut points derived from the Lipid Research Clinics data but opted to use a single set of thresholds across the pediatric age range. A fasting lipid panel was recommended for children with a TC concentration greater than 200 mg/dL on initial screening, or with an average TC concentration greater than 170 mg/dL on repeat testing. Children and adolescents with LDL-C concentrations greater than 130 were counseled to begin a low-fat, low-cholesterol diet (NCEP Step II diet; **Table 1**), with the goal of reducing LDL-C concentrations to below 130 mg/dL. For children aged 10 and older who had attempted the Step II diet for 6 to 12 months and who continued to have high LDL-C concentrations, the panel recommended considering treatment with bile sequestering agents. The LDL-C cut points defining dyslipidemia were 190 mg/dL or, in the presence of risk factors, greater than 160 mg/dL. The NCEP cautioned against the use of HMG CoA reductase inhibitors (statins) and other agents that had not been well studied in children at that time.

U.S. Preventive Services Task Force, 2007

In the years following the 1992 NCEP recommendation, numerous studies documented the low sensitivity of screening based on family history.³⁴ Some experts began to advocate for universal screening.⁴² In 2007, the USPSTF found insufficient evidence to recommend for or against routine screening for lipid disorders in infants, children, adolescents, or young adults up to age 20, and cited a lack of evidence on the long-term efficacy and harms of treatment for dyslipidemia in this age group.^{34,43}

American Academy of Pediatrics, 2008

In 2008, the American Academy of Pediatrics Committee on Nutrition updated an earlier recommendation and continued to advocate for selective screening of children age 2 to 10 years who had a family history of dyslipidemia or premature coronary heart disease, and unknown family history, or other cardiovascular disease risk factors (such as overweight, hypertension, tobacco use, or diabetes).⁴⁴ This statement proposed age- and sex-specific cut points to define dyslipidemia that were derived from the Lipid Research Clinics prevalence study.⁴ Nutritional and physical activity counseling were recommended for most children. The Committee recommended that treatment with bile sequestering agents, statins, cholesterol absorption inhibitors, or fibrates be considered for those 8 years and older who had 1) LDL-C concentrations greater than 190 mg/dL, 2) LDL-C concentrations greater than 160 mg/dL with family history of CHD, and cardiac risk factors or 3) LDL-C concentrations greater than 130 mg/dL and diabetes.

National Heart Lung and Blood Institute, 2011

In 2011, the most recent guideline on this topic was issued by the NHLBI expert panel on cardiovascular health and risk reduction in children and adolescents.³⁹ The panel issued recommendations for screening and treating dyslipidemia, including elevated LDL-C and TC concentrations. (The panel's recommendations on hypertriglyceridemia are not discussed here.) Despite noting the age- and sex-variations in LDL-C and TC concentrations, the panel recommended continued use of the 1992 fixed NCEP cut points. The panel recommended universal

screening with a fasting lipid panel at ages 9 to 11 years (coinciding with the pre-pubertal peak in LDL-C and TC concentrations) and at ages 17 to 21 years. The recommendations also included selective screening based on family history and risk factors at ages 2 to 8 years and at 12 to 16 years (**Table 2**). The recommendations call for a two-step screening, in which children with an initial fasting LDL-C concentration greater than 130 mg/dL undergo a second fasting LDL-C measurement; the two measurements are averaged, and children with values above 130 mg/dL are treated for dyslipidemia. For all children and adolescents in this category, the panel recommended the CHILD-2 diet, increasing physical activity, reducing screen time, and consideration of the use of plant stanols and sterols and psyllium.

In addition, the panel recommended treating different groups of children and adolescents with statins, depending on age, LDL-C concentration, family history, and other risk factors. For example, children age 10 years and older with an LDL-C concentration of 190 mg/dL or greater, regardless of family history or risk factors, would be considered for statin treatment. Statins were also to be considered in 8-or-9-year-olds with LDL-C concentrations persistently greater than 190 mg/dL who were unresponsive to the CHILD-2 diet in the presence of family history or risk factors. Children older than 10 years with an LDL-C concentration greater than 160 mg/dL or greater than 130 mg/dL with a family history or various combinations of risk factors (e.g., hypertension, obesity, tobacco use, and low HDL-C concentration) would also be candidates for statin treatment. The panel recommended reassessing LDL-C measurements after 6 to 12 months of dietary or medication treatment.

Current Clinical Practice in the United States

Rates of dyslipidemia screening in children and adolescents have been historically low. The frequency of lipid testing at well child visits, as documented in the National Ambulatory Medical Care Survey, was 2.5 percent in 1995 and 3.2 percent in 2010.⁴⁵ Claims data from health plans indicate that pharmacologic treatment of 8-to-20-year-olds with lipid-lowering agents is rare.⁴⁶

Limitations of Fixed Threshold Values for Dyslipidemia

All recent U.S. clinical guidelines for dyslipidemia screening in youth have relied on fixed thresholds proposed by the NCEP in 1992. However, normal cholesterol concentrations vary with age and sex throughout childhood. Thus, these cut points (TC \geq 200 mg/dL and LDL-C \geq 130 mg/dL) may both over-identify and under-identify dyslipidemia in children and adolescents, compared with those identified by age- and sex-specific cut points.

Two research groups have explored the impact of fixed cut points on prevalence estimates. Each group applied lambda mu sigma growth curve methods to NHANES data^{1, 41} and to cross-sectional data from the Bogalusa Heart Study, the Muscatine Study, the Fels Longitudinal Study, and the Princeton Lipid Research Clinics Study.¹ These procedures generated smoothed age- and sex-specific curves for lipid concentrations for children from pre-school through older adolescence.^{1, 41} The curves peak in TC, LDL-C, and HDL-C concentrations at ages 8 to 12 years for boys and 7 to 11 years for girls. These curves show that the fixed NCEP cut points label many children as abnormal who fall within the 95th percentile in the middle childhood years. At many ages, the 90th percentile of the curve for TC exceeds the fixed cut point of 200 mg/dL. The 95th percentile for LDL-C exceeds the 130-mg/dL threshold at almost all ages; in fact, the 90th percentile for LDL-C exceeds the 130-mg/dL threshold at many ages.¹ NCEP and NHANES cut points perform comparably across the adolescent age range³⁷.

Previous USPSTF Recommendation

In 2007, the USPSTF found insufficient evidence to recommend for or against routine screening for lipid disorders in infants, children, or adolescents up to age 20 (I recommendation).³⁴ The 2007 recommendation referred to screening for all forms of dyslipidemia in childhood and adolescence and did not include recommendations specific to screening for multifactorial dyslipidemia. The 2007 evidence review found these evidence gaps relevant to screening children and adolescents for multifactorial dyslipidemia:

- Data on risk factors that could inform risk-based, selective screening approaches, including overweight and physical inactivity.
- Data from RCTs on alternative screening strategies and long-term followup data sufficient to assess the impact of childhood screening and treatment of dyslipidemia on cardiovascular events in adulthood.
- Long-term data on the efficacy and safety of statin treatment and non-drug interventions, such as exercise and dietary interventions.

Chapter 2. Methods

Overview

This systematic review was designed to complement the systematic review supporting the 2015 screening recommendation for familial hypercholesterolemia in children and adolescents. For this review, we adapted the analytic framework for dyslipidemia screening in children used by the 2007 USPSTF review to address the benefits and harms of primary-care-relevant screening and treatment of children and adolescents with multifactorial dyslipidemia. Multifactorial dyslipidemia, as defined above, is an elevation in the concentrations of TC or LDL-C from causes other than familial hypercholesterolemia.

Key Questions and Analytic Framework

Using the USPSTF's methods (**Appendix A**), we developed an analytic framework (**Figure 1**) and eight KQs.

Screening Key Questions (1 through 4)

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 dyslipidemia in asymptomatic children and adolescents improve intermediate outcomes (i.e., improve lipid concentrations or reverse or slow the 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 through 7)

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 (i.e., reduce lipid concentrations or reverse or slow the 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)

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

Intermediate outcomes in childhood and adolescence include lipid concentrations (TC, LDL-C, HDL-C, and non-high-density lipoprotein cholesterol; triglycerides) and atherosclerosis markers (CIMT, calcium score, and pathological findings).

Data Sources and Searches

We designed this review to extend the 2007 systematic review on lipid screening in children. We worked with a trained medical librarian to develop the appropriate search strategy (**Appendix A - Search Strategy**). Our search included results from: Agency for Healthcare Research and Quality, 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, MEDLINE and PubMed, and National Institute for Health and Clinical Excellence. On February 12, 2014, we conducted our original search for this review. The search was updated on June 13, 2014, and bridge searches were conducted on December 16, 2014 and June 2, 2015.

For the literature published before September 2005, we searched all publications cited in the 2007 USPSTF review. Although that review did not specifically address diagnostic yield (KQ3 in this review), several of their key questions addressed various aspects of screening. We conducted a focused search of the studies cited in the 2007 USPSTF review to identify any that met our criteria for KQ3. Also, because the 2007 USPSTF review did not have a key question on the association between screening and intermediate outcomes (KQ2 in this review) or on the association between intermediate outcomes in children and adolescents with multifactorial dyslipidemia and health outcomes in adulthood (KQ8 in this review), we supplemented our search of the 2007 USPSTF citations with a search of the 2011 NHLBI Expert Panel Report^{39, 47} and publications from large published cohort studies with longitudinal data (**Appendix D**). To ensure comprehensiveness of our search strategy, we reviewed the reference lists of included studies and relevant systematic reviews and meta-analyses to identify articles that were not identified in our literature searches. We also supplemented our database searches with suggestions from experts and searched Clinicaltrials.gov to identify relevant ongoing trials (**Appendix B**). A diagram illustrating our literature search is in **Appendix A Figure 1**.

Study Selection

Two investigators independently reviewed the title and abstracts of all identified articles to determine whether the study met the inclusion and exclusion criteria for design, population, screening, intervention, and outcomes (**Appendix A Table 1**). Two reviewers then independently evaluated 509 full-text articles against the complete inclusion and exclusion criteria (**Appendix A Table 2**). We resolved discrepancies through discussion and consultation with a third reviewer. Excluded studies and their reason for exclusion are listed in **Appendix C**.

For screening studies (KQs 1 through 4), we included studies of asymptomatic people age 0 to 20 years at screening. Populations already being followed for dyslipidemia or diagnoses associated with secondary dyslipidemia were excluded. Eligible screening interventions were defined as a lipid panel (fasting or non-fasting lipid measurement, TC or LDL-C alone or in combination with HDL) delivered in a universal or selective screening strategy. For the diagnostic yield question (KQ3), we initially required screening studies to include confirmatory testing and subsequent confirmed dyslipidemia. However, because of sparse evidence, we included studies of large U.S. populations and used single-test prevalence to simulate diagnostic yield. We excluded screening studies with modalities not relevant to screening in primary care practice.

For treatment studies (KQs 5 through 7), we included interventions using lipid-lowering drugs or lifestyle interventions, including diet or exercise. We focused on interventions targeting people age 0 to 20 years with multifactorial dyslipidemia at the beginning of the intervention. We accepted any class of lipid-lowering drug, including, but not limited to, statins and bile acid sequestrants. We excluded studies that focused on treating those with secondary dyslipidemia or monogenic dyslipidemia. We included all reported clinical and laboratory harms associated with all included interventions with evidence of benefit, as per KQ6. Harms associated with interventions for which there was no KQ6 evidence were excluded.

We included studies with dyslipidemic populations of different causes when outcome data for those with multifactorial dyslipidemia were presented separately. We limited studies of efficacy or effectiveness to fair-to-good-quality studies that were conducted in countries with a United Nations Human Development Index score of ≥ 0.9 ⁴⁸. Included intervention trials had to compare an intervention against a usual-care or control group.

Consistent with current USPSTF methods, health outcomes (KQ1, KQ5, and KQ8) were defined as those experienced by the patient. We considered the incidence of disease (i.e., of atherosclerosis or elevated lipid concentrations) to be intermediate outcomes (KQ2 and KQ6). We included trials, cohort studies, and observational studies that reported clinical or laboratory harms, but did not include case series or case reports.

Quality Assessment and Data Abstraction

Two reviewers independently appraised all articles that met the inclusion criteria for this review. The appraisal criteria were adapted from USPSTF's design-specific quality criteria (**Appendix A Table 1**). Topic-specific quality criteria were designed with the assistance of clinical experts. The final quality rating used in the evidence tables was based on quality guidelines from the procedure manual for USPSTF reviews. We rated studies as good, fair, or poor quality. In general, a good-quality study met all criteria well. A fair-quality study did not meet, or did not clearly meet, at least one criterion but also had no known issue that would invalidate its results. A poor-quality study had limitations that made inferences on a population difficult or unwarranted, such as lack of random assignment with biased assignment, unclear diagnostic criteria, unclear classification procedures, or missing baseline characteristics. We excluded poor studies from this review. Excluded studies and their reason for exclusion are listed in **Appendix C**.

One reviewer extracted data from all included studies rated as fair or good into a standard evidence table. A second reviewer checked the data for accuracy. The reviewers abstracted study characteristics (e.g., population, purpose, exposure, and outcomes of the study), study design elements (e.g., recruitment procedures, inclusion/exclusion criteria, duration of followup, and attrition), randomized controlled trial characteristics (e.g., setting, blinding, methods of measuring outcomes and exposures, duration, lipid concentrations), outcomes for screening studies (e.g., true positives, diagnostic yield, positive predictive values), intermediate outcomes (e.g., lipid concentrations, CIMT) and health outcomes (e.g., MI and stroke) and harms.

Data Synthesis and Analysis

The findings are summarized in tables 3 through 14. We used the positive predictive value (PPV) from a study included for KQ3 to simulate diagnostic yield in other studies that did not conduct confirmatory testing. For screening studies, data on all relevant subgroups are presented. For treatment studies, lipid concentrations were expressed as percent change from baseline or

difference from baseline. We did not combine data across studies for KQ6 because no two included studies used the same treatment. None of the key questions had a sufficient number of included studies to permit meta-analysis.

Expert Review and Public Comment

A draft research plan that included the analytic framework, key questions, and inclusion-exclusion criteria, was available for public comment from January 23, 2014 to February 19, 2014. This draft research plan was broadly focused on dyslipidemia in childhood and adolescence, not specifically on FH. As a result of public comment, we decided to conduct two complementary reviews: screening for FH and screening for multifactorial dyslipidemia in children and adolescents. The final version of the research plan was posted in January 2015. The draft version of this report was reviewed by four invited content experts. We compiled and addressed comments received during this time, as appropriate.

USPSTF Involvement

The authors worked with USPSTF liaisons to refine the inclusion criteria, address methodological decisions on applicable evidence, and resolve issues around scope for the final evidence synthesis. The Agency for Healthcare Research and Quality (AHRQ) funded this research under a contract to support the work of the USPSTF. AHRQ staff oversaw the project and assisted in external review of the draft evidence synthesis. AHRQ was not involved in study selection, quality assessment, or synthesis.

Chapter 3. Results

Literature Search

We reviewed 7,137 unique abstracts and excluded 6,600. We reviewed 537 full-text articles and excluded 521 (**Appendix C. Excluded Studies**). The remaining 16 articles are the body of evidence for this review. We included 4 screening studies (the source for 8 articles; **Table 3**) and 2 treatment studies (the source for 7 articles; **Table 4**). There was overlap between the two key questions on treatment: 2 studies (the source for 5 articles) were included for KQ6 and 1 study (the source for 5 articles) was included for KQ7. One of these studies and 3 of the articles were included for both KQ6 and KQ7. We included one study of association between intermediate and health outcomes (**Table 5**).

Results of Included Studies

KQ1: 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.

KQ2: Does screening for multifactorial dyslipidemia in asymptomatic children and adolescents improve intermediate outcomes (i.e., improve lipid levels or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

No studies were identified.

KQ3: What is the diagnostic yield of screening for multifactorial dyslipidemia in children and adolescents?

Description of Included Studies

One good-quality study in a large group practice in Ohio met all inclusion criteria.⁴⁹ This study was also included in the 2007 USPSTF review. Several screening studies were excluded because they did not conduct confirmatory testing of individuals who screened positive. Diagnostic yield is the number of true positive results divided by the total number of individuals screened. This means that individuals screening positive needed to undergo a second test to differentiate true from false positive results. Among studies with confirmatory testing, several screened children using various definitions of dyslipidemia that did not meet our inclusion criteria, such as relying only on non-fasting concentrations, using a lower TC threshold in the 170 to 185 mg/dL range,⁵⁰⁻⁵³ and including elevated triglyceride and decreased HDL-C concentrations along with TC and LDL-C concentrations in the definition of dyslipidemia.⁵⁴

Given the dearth of studies meeting our criteria, we searched for large, recent U.S. studies that reported results of lipid screening—using a TC concentration of 200 mg/dL or greater, an LDL-C concentration of 130 mg/dL or greater, or both—on a single occasion. We reviewed several such population-based studies that had initially been excluded and chose three to include in this review. These studies provide a population-based prevalence of screening yield for

elevated TC and LDL-C concentrations in children and adolescents in different demographic and risk factor subgroups. In addition to offering contextual information, the prevalence of elevated TC concentrations can be combined with the positive predictive value from the older Ohio study to compute a simulated diagnostic yield: screening yield \times positive predictive value of the initial screen = diagnostic yield.

The three included screening studies (7 publications) using a single lipid test were:

1. The National Health and Nutrition Examination Survey (NHANES). This survey is conducted in consecutive 2-year cycles on a national sample selected with a multi-stage, stratified sampling design. NHANES is designed to produce results representative of the civilian, non-institutionalized U.S. population. Four good-quality published reports used data from NHANES surveys conducted between 1999 and 2012 to describe the epidemiology of elevated TC and LDL-C concentrations in U.S. children and adolescents and among different subgroups.^{8, 15, 55, 56}
2. West Virginia Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Program. Two publications report 2003 to 2008 TC and LDL-C data from this statewide screening program targeting 5th graders.^{7, 57}
3. A retrospective analysis of electronic health records from three large U.S. health systems (in California, Colorado, and Minnesota) reported on the frequency of pediatric lipid screening and also provided data on the prevalence of elevated TC and LDL-C concentrations in a sample of almost 30,000 children and adolescents.⁵⁸

There were no studies that used non-HDL-C to screen children or adolescents for multifactorial dyslipidemia. All of the included studies were published after the 2007 USPSTF review on this topic.

Included Populations

The Ohio study⁴⁹ (**Table 6**) screened 6,500 3-to-18-year-olds (mean age 6.4 years) receiving care at a large pediatric group practice between 1986 and 1988. No exclusion criteria were stated, so the study population may have included children with known primary or secondary dyslipidemia. Refusal rate was not reported. The authors described the population as “largely white, middle class.”

NHANES is based on a nationally representative sample. The overall response rate among people selected to take part in NHANES was 77 percent.⁵⁹ In 2011 to 2012, the survey oversampled Asians (30.5%), and the 1999 to 2006 data appear to reflect an oversampling of Blacks (40.0%) and Mexican Americans (34.4%), with Whites representing only 25.5 percent of sample. The four NHANES publications included here focused on overlapping age ranges, with the lower limit at age 6 to 8 years and the upper limit at 17 to 19 years. These publications have partially overlapping populations; however, only data from non-overlapping NHANES samples are shown in **Table 7**, **Table 8**, and **Table 9**. Individuals were not excluded from analyses for a diagnosis of primary or secondary dyslipidemia.

The CARDIAC study recruited 5th-grade students from schools in all 55 West Virginia counties. The racial-ethnic distribution was 93 percent White, 3 percent Black, 2 percent bi-racial, and less than 1 percent each Asian, Hispanic, and Other.^{7, 57} No exclusion criteria are stated, so the study population may have included children with known primary or secondary dyslipidemia.

The health system study included 3-to-19-year-olds enrolled in three large health systems in California, Colorado, and Minnesota. The racial-ethnic distribution for girls was 38.8 percent

White, 9.9 percent Black, 6.5 percent Asian, 19.8 percent Hispanic, 1.5 percent other, and 23.5 percent missing. The distribution for boys was similar. Individuals with known primary or secondary dyslipidemia were excluded.

All included studies had approximately equal numbers of boys and girls.

Included Interventions

The Ohio and CARDIAC studies were designed as population-based screening trials; both used a universal screening approach. The Ohio study drew a non-fasting blood sample from children and adolescents who presented for well child care. Those with non-fasting TC concentrations of 200 mg/dL or greater were asked to return to the clinic for a fasting lipid profile. An LDL-C concentration of 130 mg/dL or higher was considered to be elevated. Children and adolescents with elevated LDL-C received counseling and were referred to a nutritionist. No further work-up or diagnostic evaluation for children these children is described.

In CARDIAC, parents of all 5th-grade students in West Virginia were asked to participate in a cardiac risk-factor assessment including the collection of anthropometric data, blood pressure measurements, an exam for acanthosis nigricans, and a fasting lipid panel, including TC, LDL-C, HDL-C, and triglyceride (TG) concentrations. Survey staff based in schools disseminated information to parents, obtained parent consent and child assent, and conducted screenings. Parents were asked to complete a five-item family history questionnaire about premature coronary heart disease, defined as first- or second-degree relatives who had experienced MI, coronary bypass surgery, angioplasty or stent, or coronary death before age 55. Children with TC concentrations of 200 mg/dL or greater, or with LDL-C concentrations of greater than 130 mg/dL were considered screen-positive. Families received a health report with the results of screening, interpretations of the findings, and follow-up care recommendations.

In contrast to the Ohio and CARDIAC screening trials, NHANES and the health system study were designed to determine population-based prevalence. Thus, the actual screening approaches described should not be considered to be directly applicable to primary care settings, but the blood tests and cut points are relevant to primary care. NHANES participants were interviewed at home and invited to attend a mobile examination center, where they underwent examinations and provided a blood sample. Participants of all ages provided non-fasting samples for TC testing. In addition, 12-to-19 year olds also provided fasting samples for LDL-C testing.

All NHANES publications included in this review used the NCEP cut points of 200 mg/dL for TC and 130 mg/dL for LDL-C.³⁸ One of the NHANES publications⁵⁵ also used as cut points the Lipid Research Clinic's age- and sex-specific 95th percentile values for TC and LDL-C.⁴⁴ The health system study collected laboratory data on TC and fasting LDL-C from laboratory data in the electronic health record. This study also used the NCEP cut points.

Quality

Four publications from three studies were rated as fair quality,^{7, 49, 57, 58} and four publications from a single study (NHANES) were rated as good quality.^{8, 15, 55, 56} The major limitations for the fair-quality studies were non-generalizable populations, inappropriately addressed non-independence of observations, and the use of non-fasting lipid concentrations. Three articles were excluded for quality, 40 for study design issues, and 24 for screening method (**Appendix C. Excluded Studies**).

Overall Results and Summary of Findings

The 1989 Ohio study used non-fasting TC concentrations to screen children and adolescents universally. At a cut point of 200 mg/dL, this screening approach had a positive predictive value of 77 percent and a diagnostic yield of 5.8 percent. We then sought more recent estimates of the prevalence of elevated TC concentrations in U.S. children for simulating the expected diagnostic yield of this test. From the literature, we identified prevalence estimates for elevated TC concentrations (and standard errors or confidence intervals) for the overall population and for relevant subgroups. We applied the positive predictive value of 77 percent and obtained simulated diagnostic yields ranging from 4.8 percent to 12.3 percent (**Table 9**).

Detailed Results

The Ohio Practice-based Study

The Ohio practice-based study screened 6,500 children and adolescents presenting for care. The prevalence of elevated non-fasting TC concentrations was 8.5 percent. Of these children, 88 percent returned for a second screen after 1 to 6 weeks, and 77 percent of these had a fasting LDL-C concentration of 130 mg/dL or more (i.e., PPV=77%). The diagnostic yield was 5.8 percent. The authors do not report prevalence by subgroups, such as age or BMI categories.

The Ohio study met all our inclusion criteria, but it is older and limited to a single pediatric practice. Therefore, we analyzed three large U.S. studies. All lacked confirmatory testing and so did not report diagnostic yield. However, they did provide point estimates (and two provided confidence intervals) of the prevalence of elevated TC in the U.S. population and relevant subgroups. We estimated diagnostic yield by combining these more current estimates of the prevalence of elevated TC with the PPV from the older Ohio study. Of note, these studies report data on the prevalence of both TC and LDL-C abnormalities. Although the simulation requires TC as the initial test, we also present LDL data from these studies here to provide additional context for LDL-C elevations.

The National Health and Nutrition Examination Survey

Of the four included NHANES studies, three reported the prevalence of elevated TC concentrations^{8, 15, 55} and three on the prevalence of elevated LDL-C concentrations.^{15, 55, 56} Favorable (decreasing) trends in TC were seen between 1988 and 1994 and between 2011 and 2012.^{8, 15} Age- and sex-specific mean lipid concentrations were consistent with other studies: mean TC concentrations varied with age, rising from age 3 years until age 8 to 10 years, dropping during puberty, and then rising again at ages 15 to 17 years.⁵⁵ This trajectory was similar for both sexes, although boys lagged behind girls by 1 to 2 years. The highest rates of elevated TC concentrations by age group were found in ages 9 to 11 years (9.4%) and 16 to 19 years (9.4%).¹⁵ Despite this association with age, differences in age-specific prevalence of elevated TC concentrations were not statistically significant in any of the NHANES studies (**Table 7**).^{8, 15, 55}

Of the three publications that reported the prevalence of elevated LDL-C concentrations, two have entirely overlapping samples (from the 1999 to 2006 NHANES cycles), so we report LDL-C data from the one with an analysis of BMI subgroups and exclude the other from **Table 8**.⁵⁵ Favorable trends in LDL-C were seen between the 1988 to 1994 survey and the 2007 to 2010 survey.¹⁵ The highest age-specific rate of elevated LDL-C concentrations was reported in 18-to-19-year-olds.⁵⁶ Again, despite this association with age, differences in age-specific prevalence

were not statistically significant in any of the NHANES studies.^{15, 55, 56} The prevalence of elevated LDL-C concentrations was significantly greater in children with obesity (BMI above the 95th percentile for age and sex) than in healthy weight children (prevalence ratio, 2.5; 95% CI, 1.6 to 3.8). A similar but non-significant association was found for overweight children (BMI between the 85th and 95th percentile for age and sex; prevalence ratio, 1.4; 95% CI, 0.8 to 2.5; **Table 8**).

One of these NHANES studies⁵⁵ also estimated the number of adolescents who would meet the criteria for pharmacotherapy, as recommended by the NHLBI consensus panel; that is, LDL-C concentrations greater than 190 mg/dL, or greater than 160 mg/dL with 2 risk factors, or greater than 130 mg/dL with diabetes. Among 12-to-17-year olds, 0.8 percent meet these criteria for lipid-lowering medications. Of these, about half had LDL-C concentrations above 190 mg/dL, a concentration consistent with FH.⁵⁵

The CARDIAC Study

The West Virginia CARDIAC study screened 23,263 5th-grade students (ages 10 to 11 years) statewide between 2003 and 2008^{7, 57} for several cardiac risk factors. Of all eligible children, 24.6 percent had fasting lipid profiles available for analysis. The prevalence of elevated TC concentrations (200 mg/dL or greater) was 10.7 percent.⁷ (Neither of the two publications on this trial reported confidence intervals for prevalence estimates.) Point estimates were 7.5 percent for children with a BMI below the 85th percentile, 11.5 percent for overweight children (between the 85th and 95th percentiles), and 16.0 percent for obese children (above the 95th percentile). Elevated LDL-C (greater than 130 mg/dL) was reported in 8.7 percent of children.⁷

A second publication from this same study examined the prevalence of elevated LDL-C concentrations in children with and without a family history of premature coronary heart disease, defined as first- or second-degree relatives who had experienced MI, coronary bypass surgery, angioplasty or stent, or coronary death before age 55 years. Point estimates for the prevalence of elevated LDL-C concentrations were 8.3 percent with a family history and 9.5 percent without (**Table 7** and **Table 8**).⁵⁷

The Health System Study

In this retrospective analysis of automated medical records, children aged 3 to 19 years with at least one clinic visit in the period from 2007 through 2010 were included.⁵⁸ Out of the initial cohort (N=301,080), 29,360 (9.8%) had at least one TC measurement on record. The first TC or LDL-C measurement was used in the analyses (**Table 7** and **Table 8**). The highest point estimates for both TC and LDL-C measurements were in 9-to-11-year olds and 17-to-19-year-olds, compared with 3-to-8 year olds and 12-to-16 year olds. Elevated TC concentrations increased with BMI. The percentage of children and adolescents with elevated TC measurements was 10.7 percent in the obese group, 8.6 percent in the overweight group, and 6.7 percent in healthy weight group. The 95% confidence intervals did not overlap. A similar association was found for LDL-C measurements, although the confidence intervals for overweight and obese children overlapped a little.

Simulating the Prevalence of Dyslipidemia

Combining point estimates of the prevalence of elevated TC concentrations in participants from the NHANES^{8, 15} and CARDIAC studies⁷ with the PPV of an initial TC screen derived from the Ohio study, we simulated a range of diagnostic yields (**Table 9**).⁴⁹ For this simulation,

we selected TC estimates from the two NHANES publications that provided the most recent and age-specific data. Because of the variability across age groups, we did not use an overall population estimate. In addition, the BMI category-specific data from the CARDIAC study highlighted the greater prevalence of TC elevations in obese children. The highest estimated diagnostic yield was for obese 10-to-11-year-olds (12.3%).⁷ Across the age categories reported in the 2007 to 2010 NHANES publication, the prevalence (and projected diagnostic yield) rose and fell, reflecting the known biological trajectory of TC.¹⁵

KQ4: What are harms of screening for multifactorial dyslipidemia in children and adolescents?

No studies were identified.

KQ5: 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.

KQ6: Does treatment of multifactorial dyslipidemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

Description of Included Studies

We included two treatment trials (five publications)⁶⁰⁻⁶⁴, one good and one fair-quality in children and adolescents with elevated TC and LDL-C concentrations (**Table 4**). One of these trials⁶² was included in the 2007 USPSTF childhood dyslipidemia review, and one was published in 2013.⁶⁰ The Dietary Intervention Study in Children (DISC) was an RCT of a modified Step II diet² with a multi-year intervention and long-term followup. One report of this trial was published after the 2007 review.⁶⁴ Although the DISC trial enrolled children with lower LDL-C concentrations than stipulated in our inclusion criteria, we included it because it is the largest published high-quality trial of dietary intervention to lower cholesterol concentrations in children with mild-to-moderate dyslipidemia. The other trial was a small, short-term study of a dietary supplement (flaxseed) in children with moderate-to-severe dyslipidemia.⁶⁰ No studies meeting the inclusion criteria evaluated the effect of interventions for childhood dyslipidemia on atherosclerosis outcomes, and none evaluated the effect of drugs on intermediate outcomes in children with multifactorial dyslipidemia. No studies meeting the inclusion criteria evaluated interventions targeting primarily HDL-C or triglyceride concentrations.

Included Populations

The two trials included 32 and 663 participants (**Table 4**). Trial participants were drawn from somewhat different age groups. The DISC trial included children aged 8 to 10 years, whereas the flaxseed trial recruited children aged 8 to 18 years (mean, 13.2 years; SD, 2.3 years).⁶⁰ Girls and boys were well represented in both trials. The dietary trial was conducted in the United States⁶¹ and the other in Canada.⁶⁰ In DISC, 86.6 percent of participants were White.⁶¹ The flaxseed trial did not report race. The DISC trial recruited participants by screening asymptomatic children

recruited from schools, health plans, and primary care clinics.⁶¹ The flaxseed trial derived its participants from a tertiary care lipid clinic.⁶⁰

Dyslipidemia was defined using elevated fasting lipid concentrations in both trials, but the trials differed with regard to degree of dyslipidemia. The flaxseed trial was the only one that met the pre-determined inclusion criteria of abnormal LDL-C or TC concentrations, as defined by the NCEP criteria. This trial required children to have elevated fasting serum LDL-C concentrations (135 to 193 mg/dL) on a single occasion. The dietary trial had lower cut points for LDL-C and TC values, representing mild-to-moderate elevations.⁶¹ As described in the Methods section, the DISC trial was included despite not meeting these inclusion criteria because this large, high-quality diet trial with good retention and long-term followup was likely to provide useful information, given the lack of other large studies and the lack of any other dietary trials.

In the DISC trial, asymptomatic children were recruited from primary care sites. Lipid concentrations were measured on three occasions and compared to percentiles from the Lipid Research Clinic study.⁶⁵ Children were initially selected on the basis of a non-fasting TC concentration greater than 175 mg/dL. Children with fasting LDL-C concentration between the 70th and 99th percentiles for age and sex were offered a second fasting LDL-C test at the next visit. Children met the dyslipidemia criterion if the average of the two LDL-C measurements was between the 80th and 98th percentiles for age and sex. This criterion put many of the DISC participants below the NCEP definitions of high TC (200 mg/dL) and LDL-C (130 mg/dL) concentrations. Thus, the DISC trial consisted of children with moderately elevated LDL-C concentrations. In addition, DISC also excluded children with triglyceride concentrations above 200 mg/dL or HDL-C concentrations below 30 mg/dL.

The flaxseed trial differed from the DISC trial in several other respects. It required participants to have a first-degree relative with a history of hypercholesterolemia or premature atherosclerotic cardiovascular disease, and participants had to have adhered to the National Cholesterol Education Program Step II diet for a minimum of 6 months before enrollment. Thus, these participants had a family history of dyslipidemia and more severe elevations that did not respond to a low-fat diet. Although not identified as having FH, and therefore excluded from the concurrent review on screening for FH,⁶⁶ these 32 children have a more severe phenotype than those who participated in the DISC trial.

Children and youth with illnesses known to cause secondary hyperlipidemia or taking any lipid-lowering medications were excluded from both trials. The DISC trial excluded children with any sign of puberty at baseline. The flaxseed trial excluded children with known allergies to flaxseed.

Mean lipid concentrations in the DISC trial were close to the 95th percentile of the Lipid Research Clinics population for this age group, in accordance with the studies' inclusion criteria. The mean TC and LDL-C concentrations were somewhat higher in the flaxseed trial, which also included older children, so these lipid concentrations represented a greater degree of elevation relative to age-specific norms.

Included Interventions

The DISC trial evaluated a modified NCEP Step II diet delivered using a family-based counseling approach (**Table 1**). The initial intervention period lasted three years. During the first 6 months, participants had 11 group visits and 2 individual family visits. In the subsequent 2.5-year maintenance phase, group and individual visits tapered to monthly and then quarterly, with monthly telephone contacts in between. Parents of control group participants received written

educational materials about a heart-healthy diet and were informed of their child's baseline cholesterol concentrations. The trial was later extended beyond the initial 3 years, and participants in the intervention group continued to receive dietary counseling, albeit at a lower intensity, for about 8 years.⁶³ Finally, a subset of female participants was assessed again 9 years after the conclusion of the study, during which time no intervention was delivered.⁶⁴ Outcomes were evaluated at 1, 3, and 5 years after randomization, at the end of the trial (about 8 years after randomization), and again 9 years after the end of the trial (about 17 years after assignment).

The flaxseed intervention consisted of 30 g per day of ground flaxseed delivered through specified quantities of specially prepared muffins and bread. The control group received placebo muffins and bread with whole wheat flour instead of flaxseed.⁶⁰ Outcomes were assessed at the end of the 4-week intervention.

Quality

The flaxseed trial was rated as fair quality⁶⁰ and the DISC trial as good quality.^{61-64, 67, 68} The major limitations for the flaxseed study were the small sample size, 4-week duration, and recruitment from a tertiary care clinic. One trial was excluded for poor quality, and 50 studies were excluded for not being RCTs (**Appendix C. Excluded Studies**).

Overall Results

The two RCTs in children and adolescents with multifactorial dyslipidemia that met our inclusion criteria evaluated different treatments. Details from these studies are discussed below (**Table 4**). A low-fat dietary counseling intervention lowered mean LDL-C and TC concentrations relative to the control group 1 and 3 years later. This effect diminished with time.^{64, 67} A small, fair-quality trial of flaxseed found no effect on TC or LDL-C concentrations after 4 weeks.⁶⁰

Detailed Results

Effect on Lipid Concentrations

One good-quality RCT evaluated the effect of a modified NCEP Step II diet with behavioral counseling to reduce moderately elevated LDL-C concentrations in 663 children. Mean (SD) baseline fasting TC concentration for DISC participants was 200 (14.6) mg/dL and 200 (14.6) mg/dL for the intervention and control groups, respectively. Mean (SD) fasting LDL-C concentrations were 130.6 (12.2) mg/dL and 130.5 (11.6) mg/dL for the intervention and control groups, respectively (**Table 10**). Mean baseline HDL-C and TG concentrations were in the normal range. Intervention and control groups were otherwise similar at baseline.

This study was initially planned as a 3-year RCT, with a 6-month intensive intervention phase followed by 2.5 years of a lower-intensity maintenance phase. After DISC was extended to follow participants to age 18 years, intervention and annual assessments continued. Youth were last assessed at age 18 years (15.3%) or, because of funding constraints, at a closeout visit before age 18 years (84.7%).⁶³ An additional 19 participants (3%) who had initially declined to continue returned for a closeout visit. The age-18 and closeout visits were combined in all analyses and were referred to as "last visit" or Year 7; 580 of the original 663 DISC participants, or 87.5 percent, were assessed at Year 7. Mean (SD) age at Year 7 was 17.0 (0.91) years.⁶³ Retention varied across DISC time points, ranging from 94.0 percent at Year 3 to 78.7 percent at Year 5. An ancillary funded study (DISC06) recruited women who had taken part in DISC as children

and adolescents to undergo a single assessment 9 years after the end of DISC (18 years after randomization). The DISC06 followup study examined a series of biomarkers related to breast cancer risk as well as certain metabolic measurements.⁶⁴

Attendance at all study contacts (individual and group sessions as well as phone calls) was recorded. Attendance was highest in the first year, with participants attending a mean of 96 percent of the 19 total contacts. By year 5, attendance had dropped to a mean of 72 percent of about 4 contacts, and in the final year of the initial trial (about 8 years after randomization), intervention participants attended a mean of 1.3 contacts per year.

Adherence to dietary recommendations was assessed using 24-hour dietary recall instrument administered by trained certified dietitians on 3 non-consecutive days within 2 weeks of the clinic visit. At baseline, dietary intake of cholesterol, fat (total, saturated, monounsaturated, and polyunsaturated), protein, carbohydrate, and energy did not differ significantly between groups. Mean (SD) total fat intake (as a percentage of energy intake) in the intervention group was 28.5 (5.8) percent at year 1 and 28.6 (5.8) percent at year 3. These values were both consistent with the recommended fat intake for the DISC diet (28%) and significantly lower than the mean total fat intake for control subjects of 33.1 (5.5) percent at year 1 and 33.0 (4.7) percent at year 3 ($p < 0.001$ for adjusted mean differences at both time points). Mean intake of cholesterol, fat subtypes (saturated, monounsaturated, and polyunsaturated), and energy was significantly lower in the intervention group than in the control group at year 1 for all measures, except polyunsaturated fat and at year 3 for all measures ($p < 0.001$ for all adjusted differences, except that energy intake at year 1 had $p = 0.004$ and polyunsaturated fat intake at year 3 had $p = .03$). Protein and carbohydrate intake was significantly higher in the intervention group than in the control group at both year 1 and year 3 ($p < 0.001$ for all adjusted mean differences, except that protein intake at year 1 had $p = 0.001$).

To minimize regression to the mean, two fasting blood samples were analyzed for lipid concentrations 1 month apart, once at baseline and again at year 3. Single lipid measurements were obtained at years 1, 5, and 7. Concentrations of TC, HDL-C, and TG were measured with standard methods, and LDL-C concentration was calculated.

Decreases in LDL-C and TC relative to the control group were seen in participants randomized to the dietary intervention (**Table 10, Figure 2, Figure 3**). These were statistically significant only at years 1 and 3. The mean adjusted differences between groups were greatest 1 year after randomization (-6.1 mg/dL for TC and -4.8 mg/dL for LDL-C; $p < 0.001$) and were smaller, but still statistically significant, at year 3. The groups did not differ significantly at Year 5 (LDL-C and TC), year 7 (LDL-C and TC), or Year 18 (LDL-C only).

One fair-quality, double-blind 4-week RCT evaluated flaxseed supplementation against placebo.⁶⁰ Mean (SD) fasting lipid concentrations for participants at baseline were: TC, 208 (30) mg/dL; LDL-C, 138 (25) mg/dL; HDL-C, 49 (12) mg/dL; and TG, 112 (47) mg/dL (**Table 11**). Differences between intervention and control groups at baseline were not statistically significant, except for HDL-C, which was higher in the flaxseed group ($p = 0.05$; **Table 11**). Outcomes were compared between groups after 4 weeks of receiving baked goods with flaxseed or placebo (whole wheat). One patient was lost to followup; analyses were conducted based on intent-to-treat. Daily logs and an accounting of unconsumed foods revealed a mean (SD) of 80 (18) percent adherence to the dietary supplement in the placebo group and 85 (12) percent in those receiving flaxseed. Flaxseed was associated with lower, but not statistically significant, TC and LDL-C concentrations relative to placebo (4% and 5%, respectively; **Table 11**). The decrease in HDL-C in the intervention group was 15 percent greater than the decrease in the placebo group

($p=0.001$). The relative difference between groups in change in TG was 26 percent ($p=0.02$; increase in intervention group compared to placebo).

Effect on Atherosclerosis Markers

No studies assessed the effect on atherosclerosis markers treating dyslipidemia in children with multifactorial dyslipidemia.

There were too few studies of any one treatment to allow for exploration of heterogeneity or publication bias.

KQ7: What are the harms of treatment of multifactorial dyslipidemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents?

Description of Included Studies

One RCT, the DISC trial, included in KQ6, met all inclusion criteria for assessing potential harms of treating children and adolescents with elevated TC or LDL-C concentrations (**Table 4**). This trial yielded five good-quality publications with harms data; one was published after the 2007 USPSTF review.⁶⁴ Also, as mentioned above, the DISC trial was included, despite the fact that its LDL-C requirement was lower than our inclusion criterion, because of its potential contribution to understanding the impact of dietary intervention to lower cholesterol concentrations in children with mild-to-moderate dyslipidemia. Studies reporting on treatments that had at least some evidence of effectiveness were considered for inclusion for KQ7. We excluded the flaxseed trial included in KQ6 because the intervention had no benefit.⁶⁰

Included Populations

The DISC trial cohort is described above under KQ6.

Included Interventions

The DISC modified Step II diet and family-based counseling approach are described above under KQ6.

Assessment of Harms

The DISC participants' anthropometric measurements (weight, height, BMI) were assessed at baseline and annually through the final visit in the original study (referred to here as "year 7," although the actual time after randomization ranged from 6.5 to 9.3 years.⁶³ Anthropometrics were measured again at the 2006-2008 followup (referred to here as "year 18").⁶⁴ In addition, measurement of skin fold thicknesses in various locations and of mid-arm, waist, and hip circumferences was taken at baseline, year 1, and year 3. Waist circumference was also measured at year 18. Sexual maturation was evaluated at every visit through year 5 or until the participant reached Tanner Stage 5. Age at menarche was recorded for females at year 7 and at year 18. Blood pressure was measured at baseline, year 1, year 3, and year 18.

Serum concentrations, measured at baseline, year 1, and year 3, consisted of albumin, zinc, copper, ferritin, red blood cell folate, retinol, tocopherol, carotenoids, vitamin E, and hemoglobin. Serum glutamic pyruvic transaminase, chemistry panel, fasting blood glucose, and fatty acid distribution in cholesterol esters were also measured at baseline and were scheduled to be measured at either 6 months or 24 months; however, no results were reported past baseline. In

addition, ferritin, folate, retinol, and zinc were measured at year 7, and blood glucose was measured at year 18.

Diet was assessed with three random, 24-hour dietary recalls at all time points through year 7 to estimate the intake of fats, cholesterol, protein, and carbohydrate. The intake of vitamins A, C, B6, E, B12 and calcium, magnesium, phosphorous, thiamine, niacin, riboflavin, folate, iron, and zinc was monitored at these time points to warn of possible deficiencies.

Psychosocial assessments⁶⁸ were done at year 3 and included: the Child Behavior Checklist (internalizing, externalizing, social competency, thought problems, anxiety/depression, aggression/conduct subscales, and total score), State-Trait Anxiety Inventory, Child Depression Inventory, Woodcock-Johnson Psychoeducational Battery (mathematics and reading achievement) and the Family Environment Scale (cohesion, conflict, intellectual/cultural orientation, moral religious orientation, and achievement orientation subscales). Medical history collected from parents at baseline and years 1 and 3 included questions about whether a doctor had told them in the past 12 months that their child had anorexia or bulimia and whether the child had expressed suicidal thoughts or behavior.

Quality

The DISC trial was rated as good quality. One trial of a dietary intervention was excluded for poor quality⁶⁹ (**Appendix C. Excluded Studies**). Other trials were excluded because they were not RCTs.

Overall Results

The DISC trial revealed no harms of a modified Step II dietary intervention with behavioral counseling in children with multifactorial dyslipidemia. Details regarding the different types of harms assessed at the various time points are discussed below (**Table 12**).

Detailed Results

The DISC trial reported no harms of the dietary intervention at any time point. Growth and adiposity were similar in the two study groups at all times,^{62, 63, 67, 68} with the exception of a lower waist-to-hip ratio in the intervention group noted at year 1 only.⁶² Mean systolic and diastolic blood pressures did not differ between groups at years 1 and 3. Sexual maturation or age-of-menarche was also similar in both groups through year 7. Biochemical analyses, including blood micronutrients, did not differ between groups, with the exception of an unexpected benefit of higher mean retinol concentration in the intervention group at year 3 (0.4 µg/dL greater than control; p=0.04) and again at year 7 (2.4 µ/dL greater than control; p=0.02). The difference was not significant at year 1.⁶³ The only significant difference between groups for nutrient intake was that mean daily zinc intake was lower in the intervention group (-0.5 mg vs +0.6 mg; adjusted mean difference, -0.6 mg, p=0.03).⁶² The adjusted mean difference was no longer significant at year 3, and no other significant differences in intake of vitamins or nutrients were reported at any time period.

Psychosocial measures at 3 years were largely similar between groups.⁶⁸ The proportions with elevated scores on the Child Behavior Checklist Internalizing and Externalizing subscales and on the Total Behavior Problem score were similar, as was the proportion with elevated anxiety scores on the State-Trait Anxiety Inventory and the proportion with low (≤the 25th percentile) scores on mathematics and reading performance on the Woodcock-Johnson Psychoeducational Battery. The only difference in psychosocial outcomes between groups was

for depression, where the odds ratio of the treatment group was 0.24 (95% CI, 0.09 to 0.65) for scoring above the cut point indicating depression on the Child Depression Inventory ($p < 0.005$).

Means of all psychosocial measurements were also compared between groups using linear regression adjusting for baseline values of age, sex, household income, and number of parents in the household. An interaction term for treatment group \times sex was entered into separate models. Across a large number of comparisons, some statistically significant differences were found, some favoring the control group and some the intervention group. Individual differences between groups were not clinically significant.

At the year-18 follow up (i.e., ages 25 to 29 years), the groups did not differ significantly in mean height, weight, BMI, adiposity, or reproductive characteristics among the women (the men were not included in this follow-up observational study).⁶⁴ Frequency of metabolic syndrome did not differ between groups. However, both systolic blood pressure and fasting plasma glucose concentrations were significantly lower in the treatment group (mean systolic blood pressure, 107.7 mm Hg vs 110.0 mm Hg, $p = 0.03$; fasting plasma glucose, 87.0 mg/dL vs 89.1 mg/dL, $p = 0.01$). Substituting percent body fat (obtained by dual-energy X-ray absorptiometry from 215 participants) for BMI in models that included non-dietary variables did not materially alter these results.

Three random, non-consecutive, 24-hour dietary recall surveys were collected from each subject, and analyzed for intake of sodium, calcium, potassium, and magnesium (in addition to analyses of fatty acid, fiber, and calorie intake); nutrient intake was not significantly different between groups, although intake of dietary fiber was higher in the intervention group and intake of saturated fatty acids was lower in the intervention group. Alcohol intake was significantly higher in the treatment group (4.0 drinks/week vs. 2.5 drinks/week in controls ; $p = 0.05$). Leisure physical activity in the past year did not differ significantly between groups.

KQ8: What is the association between intermediate outcomes in childhood and adolescence and future incidence of MI and stroke events in adults?

Included Studies

One study met the inclusion criteria for KQ8, although the sample included adults and children (age range, 12 to 39 years), and data were not reported by age subgroups.⁷⁰ The aim of the study was to identify any associations between mortality before age 55 and several cardiovascular risk factors: lipid and hemoglobin A1C (glycosylated hemoglobin) concentrations, smoking, adiposity, and blood pressure. We included this study for its potential to provide useful evidence about the association between elevated TC concentrations in adolescents and young adults and mortality before age 55 years in the absence of any other included evidence.

Included Population

This study identified a cohort of 9,245 NHANES participants between 1988 through 1994 age 12 to 39 years at the time of the survey. Half the participants were female, mean (SE) age was 26.1 years (0.17) 77.2 percent were non-Hispanic white, 14.7 percent non-Hispanic black, and 8.1 percent Mexican American. Participants whose race or ethnicity was classified as something other than these three categories were excluded from analysis. Baseline mean TC concentration was 182.0 (SE 0.82), and 28.5 percent of participants had concentrations greater

than 200 mg/dL, consisting of 20.9 percent with concentrations between 200 and 239 mg/dL and 7.6 percent with concentrations greater than 240 mg/dL.

Included Interventions

Lipid concentrations and baseline data were obtained as per NHANES procedures, outlined above as part of KQ3.

Included Outcomes

Outcomes of interest were death before age 55 from all causes and death before age 55 from endogenous causes only (i.e., from diseases and self-inflicted injury, but not from accidents or homicides). Vital status was assessed using National Death Index data from 1988 through 2006. The followup period was 12 to 18 years.

Quality

The included study was considered to provide fair-quality evidence for KQ8, primarily because its age range was broader than our a priori inclusion criteria. No studies were excluded for poor quality.

Summary of Findings

At the end of the study, 283 participants (3.1%) had died. Leading causes of death for the 12-to-19-year-olds were accidents, self-inflicted injuries, circulatory diseases, and cancer. Proportional hazards models were adjusted for sex, race-ethnicity, and chronic disease status. Risk for death before age 55 was associated with central obesity (relative hazard [RH], 2.39), smoking (RH, 1.86), and elevated hemoglobin A1c concentrations (RH, 3.81). Elevated TC concentrations were not significantly associated with a relative hazard for death before age 55 years (all causes and endogenous causes) when both sexes were included in the same analysis. Secondary analyses by sex (**Table 13**) found that for females, only a very high TC concentration (≥ 240 mg/dL) was associated with a greater risk of death before 55 (RH, 2.58; 95% CI, 1.31 to 5.08), although a moderately high TC concentration (200 to 239 mg/dL) did not confer risk (RH, 0.77; 95% CI 0.36 to 1.62). The authors urge caution in interpreting the finding because it is based on fewer than 90 deaths among female participants. There were no significant associations for males.

Chapter 4. Discussion

Findings from the systematic review of lipid screening for detecting multifactorial dyslipidemia are discussed here. The reader is reminded that screening for detecting FH is the focus of the companion report.

Screening

Summary of Evidence

We found no direct evidence for the effect of screening for multifactorial dyslipidemia on intermediate or health outcomes or on the harms of screening. No RCTs tested screening programs for multifactorial dyslipidemia, either selective or universal.

There is fair evidence that TC screening with a cut point of 200 mg/dL has a PPV of 77 percent for multifactorial dyslipidemia. Recent nationally representative prevalence estimates suggest a simulated diagnostic yield of 5.4 percent for 8-to-12 year olds and 6.5 percent for 13-to-17-year-olds. Simulated diagnostic yield ranges between 4 percent and 12 percent for different age and BMI subgroups. Based on large, recent U.S. studies, the highest diagnostic yield appears to be in obese children (12.3%), in children aged 9 to 11 years (7.2%), and in adolescents aged 16 to 19 years (7.2%). The CARDIAC study was conducted in the same age group that the NHLBI expert panel recommends for universal testing, so the diagnostic yields of 5.8 percent, 8.9 percent, and 12.3 percent for healthy weight, overweight, and obese 10-to-11-year-olds provide reasonable estimates of what might be seen for those subgroups if screening 9-to-11-year-olds were more widely adopted.

The prevalence of elevated TC and LDL-C concentrations (on which diagnostic yields were calculated) were consistent across three large recent U.S. studies. The NHANES studies show a gradual decrease in the prevalence of elevated concentrations of TC and LDL-C in recent years. However, prevalence estimated from a single lipid test overestimates the true prevalence of dyslipidemia because two tests are needed to appropriately classify children according to the NCEP ranges of acceptable, borderline, or high cholesterol concentrations.¹⁶

Limitations of the Body of Evidence

The fact that only one of the included studies performed confirmatory testing of hypercholesterolemia required that we simulate diagnostic yield. The screening evidence draws heavily from epidemiologic studies rather than screening trials. The prevalence of cholesterol elevations across broad age ranges, as is often reported, is less meaningful than age-group specific rates, given the variation of TC concentrations by age.

Only one school-based study⁷ was relevant to the primary care setting. The use of the fixed NCEP thresholds for TC and LDL-C concentrations make the prevalence of dyslipidemia (and diagnostic yield) difficult to determine because these thresholds ignore age and sex variability. There were no studies using non-HDL-C as a screening test. Finally, incomplete tracking of lipid concentrations from childhood, through adolescence, and into adulthood³⁴ is a current limitation of the evidence. Multifactorial dyslipidemia detected in people under age 20 years is likely to resolve in young adulthood³⁷; thus, dyslipidemia identified in childhood or adolescence has unclear significance for adult health.

Evidence Gaps

There are several gaps in the evidence regarding potential benefit and harms of screening for multifactorial dyslipidemia. We found no data on potential benefits of screening such as reducing atherosclerosis. There is a need for screening trials for detection of multifactorial dyslipidemia in childhood and adolescence using both primary and confirmatory testing. Many studies were excluded because they used cut points below accepted cut points (e.g., an LDL-C concentration of 175 or 180 mg/dL rather than 200 mg/dL). Even the accepted, fixed 1992 NCEP cut points for elevated LDL-C and TC concentrations may be inadequate because they may over- or under-identify children and adolescents with high TC concentrations, depending on age and sex. We found no trials that compared screening (universal or selective approaches) to no screening. There was also a lack of data on prevalence and diagnostic yield in racially and ethnically diverse populations of children.

We found no studies of the harms of screening children and adolescents for multifactorial dyslipidemia. The 2007 USPSTF review reported that harms of screening for childhood dyslipidemia in general were poorly reported, but none of the studies in that review met our criteria. In fact, screening for dyslipidemia in children and adolescents has several potential harms. The fixed NCEP cut points likely over-identify children in the age groups currently targeted for screening (ages 9 to 11 years). Even if the 95th percentiles of age- and sex-adjusted norms for specific populations are used as thresholds, up to 5 percent of the population will be identified as having some degree of biochemical abnormality. However, dyslipidemia is a risk factor, not a disease. The association between elevated TC or LDL-C concentrations in youth and current or future disease is unknown. At least some identified individuals may never progress to develop clinically important lipid concentrations or cardiovascular disease. Such “non-disease” could result in subtle harms, such as labelling a child as “sick” or causing parent or child anxiety. In some cases, screening may lead to unnecessary or even harmful additional testing and treatment.⁷¹ The 2011 NHLBI consensus panel recommends that statin therapy be considered in children age 10 years and older with various combinations of LDL-C concentrations exceeding specific cut points, family history, and risk factors.³⁹ However, statins have unknown benefits and harms in children and adolescents with multifactorial dyslipidemia. In one NHANES study, as many as 0.8 percent of adolescents met the NHLBI indications for statin therapy.⁵⁵ Depending on the proportion of children and adolescents with FH among those with elevated LDL-C concentrations, screening could result in some being started inappropriately on lipid-lowering medications.

Treatment

Summary of Evidence

No direct evidence was found for an effect of treatment on health outcomes.

This review identified only one RCT of a dietary intervention (the DISC Study), so the body of evidence is fair at best. This RCT provided good-quality evidence of a modest effect of dietary counseling for a low-fat, low-cholesterol diet on lowering lipid concentrations in children with mild-to-moderate dyslipidemia. After 1 year of relatively intensive intervention, mean differences between groups compared to baseline were a decrease of 6 mg/dL in mean TC and a decrease of 5 mg/dL in mean LDL-C; both differences were statistically significant. Both between-group differences shrank to about 3 mg/dL at Year 3 and by Year 5, were no longer

statistically significant. Adherence to the diet during the intervention period was good,⁶² and there is evidence that the children in the intervention group had improved dietary quality.⁷²

Dietary changes made by children in the treatment group in the DISC study did not adversely affect their nutritional status, growth, or development. This finding is consistent with data from the Special Turku Coronary Risk Factor Intervention Project, which found that a preventive dietary intervention (consisting of counseling for a low-saturated fat, low-cholesterol diet) begun in infancy had no adverse effect on growth or maturation through age 14 years.⁷³

A small, 4-week RCT of flaxseed found no effect on TC concentrations. There was no evidence to support any other type of treatment for multifactorial dyslipidemia, including nutritional supplements or medications.

The 2007 USPSTF review included the DISC trial but not the more recent flaxseed RCT.

Limitations of the Evidence

The DISC trial enrolled children with milder hyperlipidemia, making it difficult to generalize results to children with TC concentrations above 200 mg/dL or LDL-C above 130 mg/dL. This trial also targeted 8-to-10-year-olds, so the impact of a dietary intervention on adolescents is unknown. The intensity of the counseling intervention limits the generalizability of this treatment to primary care settings where trained nutritional counselors may not be part of the health care team. Finally, the clinical importance of the small impact on cholesterol concentrations in the 1-to-3-year time frame is unclear. The flaxseed RCT included children with a family history of dyslipidemia and although they were not identified as having FH, it is possible that some of the participants could have met FH criteria.

Evidence Gaps

We found only one high quality RCT of dietary intervention for multifactorial dyslipidemia in children. There is a need for other large, RCTs with long-term followup. Rigorous trials of dietary supplements and medications to reduce concentrations of atherogenic lipids in children and adolescents are also lacking. Several trials that did not meet our inclusion criteria examined supplements, such as psyllium/soluble fiber, niacin, polyunsaturated fatty acid, *Bifidobacterium*, glucomannan, red yeast extract, and plant stanols. Our search revealed few studies of medications for children or adolescents with multifactorial dyslipidemia. We excluded a trial of ezetimibe (an inhibitor of intestinal cholesterol absorption) for lack of a control group⁷⁴ and found no trials of statins in this population. It should be noted that the current guidelines do not recommend the use of lipid-lowering medications to treat multifactorial dyslipidemia in children and adolescents. The treatment studies reviewed for inclusion also relied on various TC and LDL-C cut points, often below the standard NCEP thresholds. Few studies followed participants for a year or longer.

Outcomes

Summary of Evidence

A single high-quality, longitudinal study that included adolescents and young adults from the NHANES found no association between TC concentrations and death before age 55 years when both sexes were combined. The study did find that very high TC concentrations (at or above 240 mg/dL) was significantly associated with premature death in women only, although the authors caution that this estimate was based on a small number of deaths. The subgroup of females with

TC concentrations above 240 mg/dL may well be dominated by individuals who have FH, for whom premature CHD deaths are expected. The importance of this finding is unclear, given the small number of deaths in this subgroup. (This study was published after the 2007 USPSTF review).

Limitations of the Body of Evidence

In this single included study (NHANES), outcomes for adolescents were not reported separately from those for young adults. Because the 12-to-20-year-olds only reached age 30 to 38 years (in the 1988 NHANES survey) or 24 to 32 years (in the 1994 NHANES survey), the findings were weighted toward mortality outcomes for the 21-to-39-year-olds. This issue might have been more of a limitation if there had been positive findings. In that case, an association for the overall cohort might have been driven by the 20-to-39-year-olds. However, given the largely negative findings, this is only a minor limitation. Another limitation is that this study reported all-cause and endogenous cause mortality, but not cardiovascular mortality, an outcome that is more closely linked to the causal pathway.

Evidence Gaps

Long-term followup studies of pediatric cohorts are needed to better understand the association between cholesterol concentrations in children and adolescents with multifactorial dyslipidemia and adult health outcomes.

Conclusions

We found no direct evidence of effect of TC screening on intermediate or health outcomes. Only one study provided a diagnostic yield for TC screening (5.8%). Simulated diagnostic yields in data from large, U.S. population-based studies show variation in TC by age and BMI. There were no studies of the diagnostic yield of selective screening, and no studies on the harms of screening.

No evidence was found supporting an effect of treatment on health outcomes in adulthood (MI and stroke events). Dietary counseling may lower TC and LDL-C concentrations by 5 to 7 mg/dL over 3 years, but this intervention was relatively intensive, and the effect on lipids dissipated over 5 years. No studies of lipid-lowering medications met the inclusion criteria. There is fair evidence of the safety of dietary interventions.

In one longitudinal study using NHANES data, neither very high nor moderately increased TC concentrations in 12-to-39-year-olds was independently associated with death before age 55 years (when males and females were combined).

Research needs include randomized trials of screening strategies with confirmatory testing and longitudinal followup, as well as rigorous treatment RCTs of promising medications, supplements, and dietary interventions with long-term followup. Long-term followup studies of pediatric cohorts, including racially and ethnically diverse cohorts, are needed to better establish the long-term health risks conferred by elevated TC and LDL-C concentrations. Although not the focus of this systematic review, our findings support a re-examination of the commonly accepted fixed NCEP threshold TC and LDL-C concentrations that define dyslipidemia and a reconsideration of age- and sex-specific cut points.

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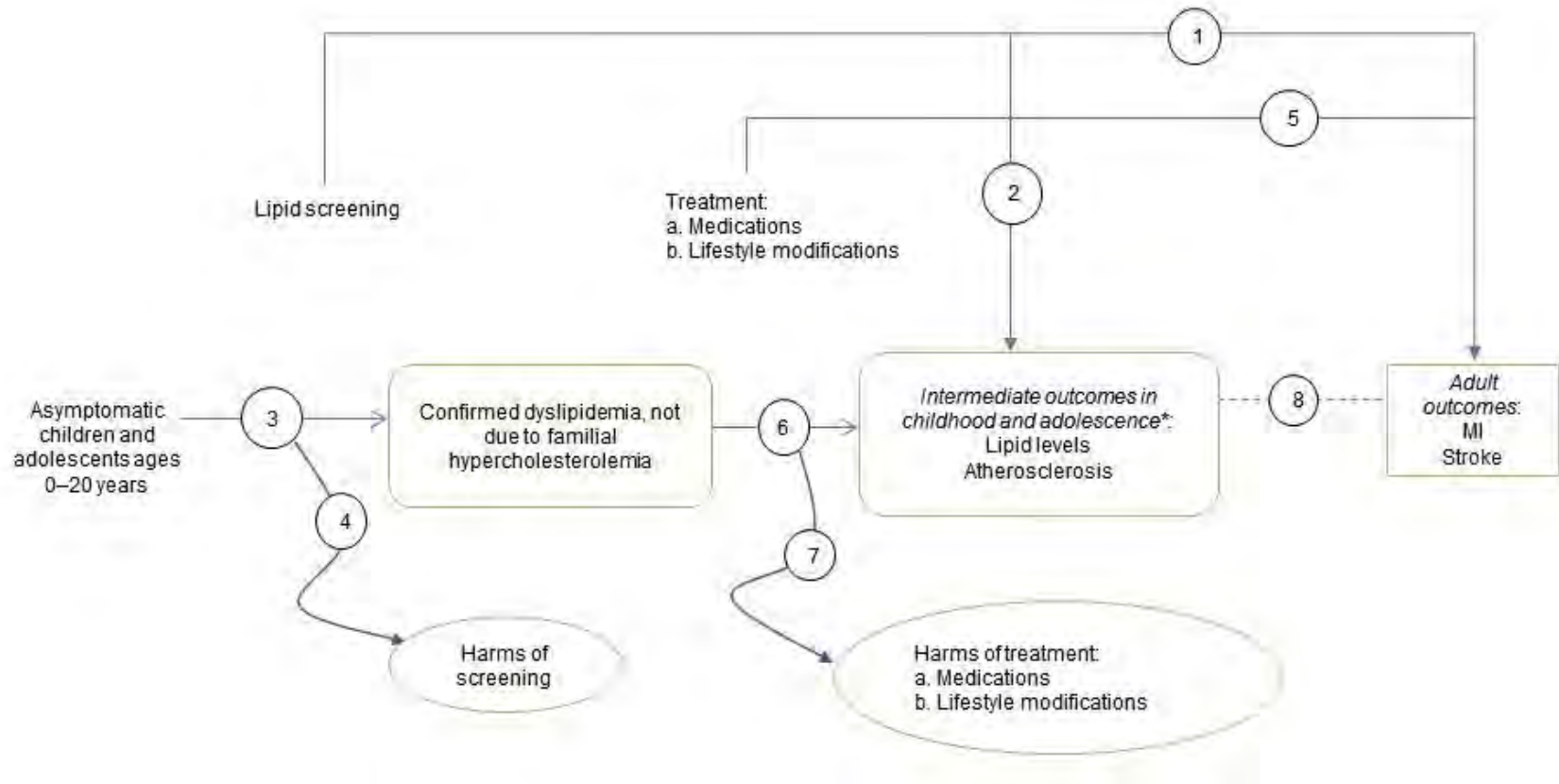
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Figures and Tables

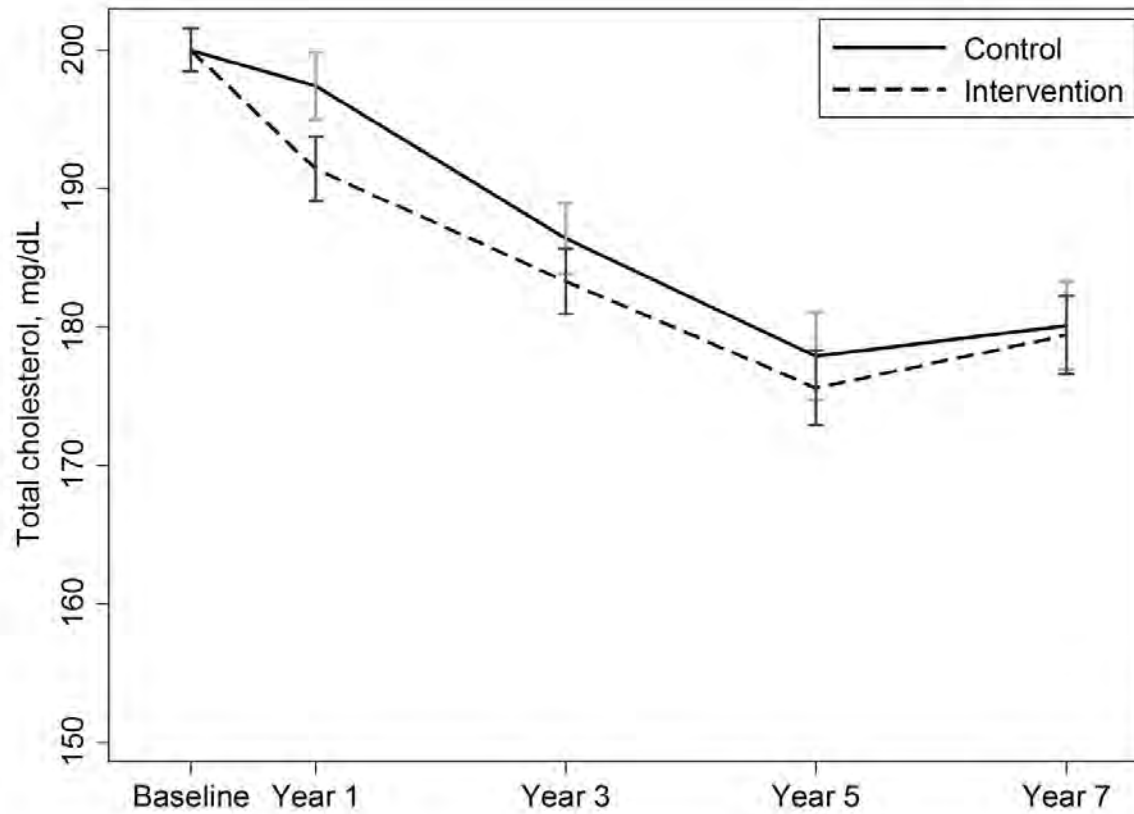
Figure 1. Analytic Framework



Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

*Intermediate outcomes include lipid levels (total, LDL, HDL, and non-HDL cholesterol; triglycerides) and atherosclerosis markers (carotid intima-media thickness, calcium score, pathological findings).

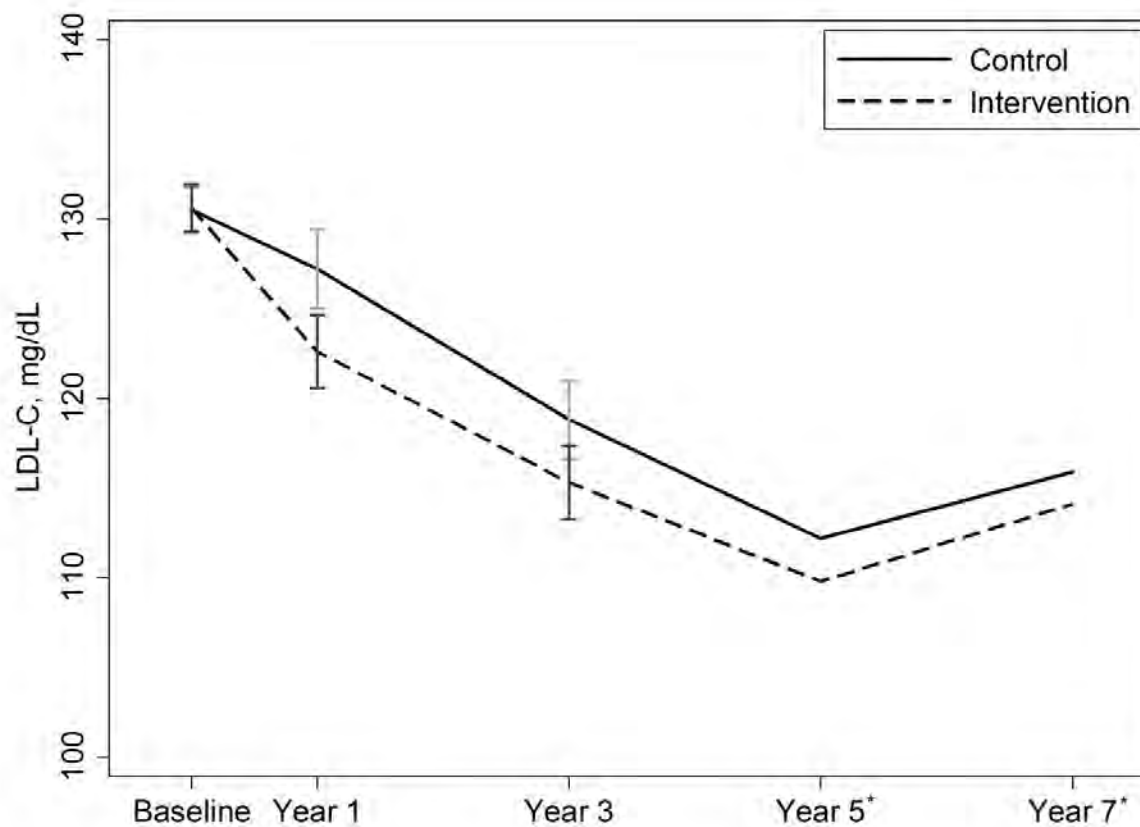
Figure 2. Results from DISC Study: Mean Total Cholesterol



Abbreviations: DISC = Dietary Intervention Study in Children, mg/dL = milligram(s) per deciliter

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.

Figure 3. Results from DISC Study: Mean LDL Cholesterol



Abbreviations: DISC = Dietary Intervention Study in Children, mg/dL = milligram(s) per deciliter, LDL-C = low density lipoprotein cholesterol

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.

*Years 5 and 7 have no error bars because the articles did not report standard deviations for mean LDL levels

Table 1: Comparison of recommended diets for treatment of dyslipidemia in children and adolescents

Diet and Year Published	NCEP ² Step 1 [†] 1992	NCEP ² Step 2 [†] 1992	DISC Trial ^{6†} 1993	NHLBI ⁷⁵ CHILD-1 2011	NHLBI ⁷⁵ CHILD-2-LDL 2011
Target population Age	Children and adolescents >2 years	Children and adolescents >2 years	8-10 years	2-21 years	2-21 years
Target population LDL-C	110-129 mg/dL	≥130 [†]	Moderately elevated LDL-C	Dyslipidemia or other risk factors [*]	LDL-C≥130 mg/dL
Goal of diet	LDL<110 mg/dL	LDL<110 mg/dL, ideally (or LDL<130 mg/dL)	LDL-C reduction	Cardiovascular risk reduction	LDL-C<130 mg/dL
Nutrients (percent of calories)					
Total fat	≤30%	≤30%	28%	25-30%	25-30%
Saturated fat	<10%	<7%	<8%	8-10%	≤7%
Polyunsaturated fat	<10%	≤10%	9%	Combined poly- and mono-unsaturated fats ≤20%	-
Monounsaturated fat	Remaining fat calories	Remaining fat calories	11%		~10%
Protein	~15-20%	~15-20%	14%	-	-
Carbohydrate	~55%	~55%	58%	-	-
Cholesterol (daily intake)	<300 mg/day	<200 mg/day	75mg/1000kcal maximum 150 mg/day	<300 mg/day	<200 mg/day
Other	Calories for normal growth and development	-	Encourage fiber	Avoid trans fats Encourage fiber	Avoid trans fats Encourage fiber

Abbreviations: NCEP=National Cholesterol Education Program; DISC = Dietary Intervention Study in Children, NHLBI = National Heart, Lung, and Blood Institute, CHILD = Cardiovascular Health Integrated Lifestyle Diet, LDL-C = low density lipoprotein cholesterol, mg = milligram(s), kcal = kilocalorie(s)

^{*}Other risk factors identified by NHLBI Consensus Panel include high-risk medical conditions that might ultimately require more intensive dietary change as well as obesity positive family history of early cardiovascular disease, , primary hypertension, diabetes or exposure to smoking in the home

[†]NCEP recommends that children and adolescents with LDL-C ≥130 start on Step 1 diet and if LDL-C ≥110 mg/dL after 3 months, advance to Step 2 diet.

Table 2: Recommendations for lipid assessment from NHLBI Expert Panel Report³⁹

Age	Recommendation	Grade ⁺	Recommendation Level [†]
Birth-12 months	No lipid screening	C	<i>Recommend</i>
2-8 years	No routine lipid screening Measure fasting lipid profile (FLP) x 2; [‡] average results [§] if:	B	<i>Recommend</i>
	<ul style="list-style-type: none"> Parent, grandparent, aunt/uncle, or sibling with myocardial infarction (MI), angina, stroke, coronary artery bypass graft (CABG)/stent/ angioplasty at <55 years in males, <65 years in females 	B	<i>Strongly Recommend</i>
	<ul style="list-style-type: none"> Parent with TC ≥240 mg/dL or known dyslipidemia 	B	<i>Strongly Recommend</i>
	<ul style="list-style-type: none"> Child has diabetes, hypertension, BMI ≥95th percentile or smokes cigarettes 	B	<i>Strongly Recommend</i>
	<ul style="list-style-type: none"> Child has a moderate- or high-risk medical condition[§] 	B	<i>Strongly Recommend</i>
9-11 years	Universal screening	B	<i>Strongly Recommend</i>
	<ul style="list-style-type: none"> Non-FLP: Calculate non-HDL-C: Non-HDL-C = TC - HDL-C** Non-HDL ≥145 mg/dL, HDL <40 mg/dL → FLP x 2, lipid algorithms in NHLBI report[§] OR FLP: LDL-C ≥130 mg/dL, non HDL-C ≥145 mg/dL HDL-C <40 mg/dL, TG ≥100 mg/dL if <10 years; ≥130 mg/dL if ≥10 years → Repeat FLP after 2 weeks but within 3 months → lipid algorithms in NHLBI report[§] 		
12-16 years	No routine screening^{††} Measure FLP x 2; [‡] average results, if new knowledge of:	B	<i>Recommend</i>
	<ul style="list-style-type: none"> Parent, grandparent, aunt/uncle or sibling with MI, angina, stroke, CABG/stent/angioplasty, sudden death at <55 years in males, <65 years in females 	B	<i>Strongly Recommend</i>
	<ul style="list-style-type: none"> Parent with TC ≥240 mg/dL or known dyslipidemia 	B	<i>Strongly Recommend</i>
	<ul style="list-style-type: none"> Patient has diabetes, hypertension, BMI ≥85th percentile or smokes cigarettes 	B	<i>Strongly Recommend</i>
	<ul style="list-style-type: none"> Patient has moderate- or high-risk medical condition[§] 	B	<i>Strongly Recommend</i>

Age	Recommendation	Grade*	Recommendation Level†
17-21 years	<p>Universal screening once in this time period</p> <p>Non-FLP: Calculate non-HDL-C: Non-HDL-C = TC - HDL-C[§]</p> <p>17-19 years: Non-HDL \geq145 mg/dL, HDL <40 mg/dL → FLP x 2, lipid algorithms in NHLBI report[§] OR FLP: LDL-C \geq130 mg/dL, non HDL-C \geq145 mg/dL HDL-C <40 mg/dL, TG \geq130 mg/dL → Repeat FLP after 2 weeks but within 3 months → lipid algorithms in NHLBI report[§]</p> <p>20-21 years: Non-HDL-C \geq190 mg/dL, HDL-C <40 mg/dL** → FLP x 2;‡ average results → <i>Adult Treatment Panel III (ATP III)</i> management algorithm[§] OR FLP: LDL-C \geq160 mg/dL, non HDL-C \geq190 mg/dL HDL-C <40 mg/dL, TG \geq150 mg/dL → Repeat FLP after 2 weeks but within 3 months, average results → <i>ATP III</i> management algorithm[§]</p>	B	<i>Recommend</i>

Abbreviations: NHLBI = National Heart, Lung, and Blood Institute, FLP=fasting lipid profile, CABG = coronary artery bypass graft, TC = total cholesterol, mg/dL = milligram(s) per deciliter, BMI = body mass index, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, MI = myocardial infarction, ATP=Adult Treatment Panel

*Grades reflect the findings of the evidence review.

†Recommendation levels reflect the consensus opinion of the Expert Panel.

‡Interval between FLP measurements: after 2 weeks but within 3 months

§Refer to NHLBI Expert Panel Report³⁹ for interpretation of results, lipid algorithms, and/or management of results

**Disregard TG and LDL-C in nonfasting samples

††Lipid screening is not recommended for those ages 12-16 years because of significantly decreased sensitivity and specificity for predicting adult LDL-C levels and significantly increased false-negative results in this age group. Selective screening is recommended for those with the clinical indications outlined

Table 3. Included screening studies

Type of study	Study, year Quality Country	Number screened	Study design	Age, years Mean (SD)	Age range	% Female	Race/Ethnicity	Population and setting	Dates of data collection	Included for Key Question
<i>Study with confirmatory testing</i>	Garcia 1989 ⁴⁹ Fair U.S.A (OH)	6,500	Cross-sectional	6.4 (NR)	3-18	NR	100% White	White, middle-class children being seen for well-child visits at a large, pediatric, group practice.	1986-1988	3
<i>Study without confirmatory testing - NHANES</i>	Kit 2015 ⁵ Good U.S.A	13,172	Cross-sectional	NR	8-17	47.6%-50.3% (range across time periods)	Sample weights were used to obtain prevalence estimates representative of the civilian non-institutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1999-2012	3
	Kit 2012 ¹⁵ Good U.S.A	16,116	Cross-sectional	NR	6-19	48.2-49% (range across time periods)	Sample weights were used to obtain prevalence estimates representative of the civilian non-institutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1988-1994, 1999-2002, 2007-2010	3
	CDC 2010 ⁵⁶ Good U.S.A	3,125	Cross-sectional	NR	12-19	48%	Sample weights were used to obtain prevalence estimates representative of the civilian non-institutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1999-2006	3
	Ford 2009 ⁵⁵ Good U.S.A	9,868 [*]	Cross-sectional	NR	6-17 [*]	49.7% [*]	Sample weights were used to obtain prevalence estimates representative of the civilian non-institutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1999-2006	3

Type of study	Study, year Quality Country	Number screened	Study design	Age, years Mean (SD)	Age range	% Female	Race/Ethnicity	Population and setting	Dates of data collection	Included for Key Question
Studies without confirmatory testing – other large U.S. studies	Margolis 2014⁵⁸ Fair U.S.A	29,360	Cross-sectional	NR [†]	3-19	52.4%	Girls (n=15,404): White: 38.8% Asian: 6.5% Black: 9.9% Hispanic: 19.8% Other: 1.5% Missing: 23.5% (male distribution comparable)	Children and adolescents with ≥1 visit during the study period in 3 large U.S. health systems	2007- 2010	3
	CARDIAC Ice 2011⁷ Ritchie 2010⁵⁷ Fair U.S.A (WV)	23,263	Cross-sectional	10.84 (0.76)	NR	53.2%	93% Caucasian 2% Bi-racial 3% Black <1% each Asian, Hispanic and Other	Fifth grade students in all 55 counties of West Virginia, Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project	2003 - 2008	3

Abbreviations: SD = Standard deviation, OH = Ohio, NR = Not reported, NHANES = National Health and Nutrition Examination Survey

*Represents population for whom TC data were available. The article also includes LDL-C data on 2,724 adolescents ages 12-17 (48.6% female).

[†]This study does not report mean age. The age distribution for the cohort is: 3-5 y: 2.7%; 6-8 y: 6.8%; 9-11 y: 15.4%; 12-16 y: 41.7%; 17-19 y: 33.4%⁵⁸.

Table 4. Included treatment studies

Study, year Quality	N	Study design	Age, years Mean (SD)	Age range	% Female	Race	Population and setting	Dates of data collection	Included for key question(s)
Wong 2013⁶⁰ Fair Canada	32	Randomized controlled trial	IG: 13 (2) CG: 13 (3)	8 – 18	46.9%	NR	Children receiving care at a specialty lipid clinic. Inclusion criteria: fasting serum LDL-C levels 135-193mg/dL, first-degree family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease, and compliance with the National Cholesterol Education Program Step II diet.	2009 – 2010	6
DISC 1993⁶¹ DISC 1995⁶² Obarzanek 1997⁶⁷ Lavigne 1999⁶⁸ Obarzanek 2001⁶³ Dorgan 2011⁶⁴ Good U.S.A	663	Randomized controlled trial	Boys: 9.7 Girls: 9.0	8 – 10	45.4%	White: 86.6%* Black: 8.4%* Other:5.0%*	Prepubertal boys and girls aged 8-10 years with LDL-C levels ≥80th percentile and <98th percentile for age and sex. Participants were recruited from public and private elementary schools, health plans, and physician offices.	1987 - 1990	6 ⁶¹⁻⁶⁴ 7 ^{62-64, 67, 68}

Abbreviations: SD = Standard deviation, IG = intervention group, CG = control group, NR = Not reported, LDL-C = low density lipoprotein cholesterol, DISC = Dietary Intervention Study in Children

*Values taken from population described in DISC 1993 article⁶¹

Table 5. Included association study

Author, Year Quality Country	N	Percent female	Age Mean (SE) Age range	Race/Ethnicity % (SE)	Outcomes measured	Baseline lipid values Mean (SE)	Study design Followup period
Saydah 2013 ⁷⁰ Good U.S.A	9,245	50.4%	26.1 (.17) 12-39	Non-Hispanic white: 77.2% (1.19) Non-Hispanic black: 14.7% (0.98) Mexican American: 8.1% (0.76)	Death before age 55 years from all causes Death before age 55 years from endogenous causes	Total cholesterol: 182.0 (0.82) HDL cholesterol: 50.4 (0.37) Non-HDL cholesterol: 131.6 (0.90)	Prospective study of NHANES participants 12-18 years of followup (1988-1994 to 2006)

Abbreviations: SD = standard deviation, SE = standard error, NHANES = National Health and Nutrition Examination Survey

Table 6. Screening study of screening for dyslipidemia in childhood and adolescence that includes confirmatory testing (KQ3)

Study, year Quality Country	Number screened Age range	Setting Racial/ethnic	Universal vs. selective	Cut point for screening test	Screen positive N % of screened	Cut point for confirmatory test	Returned for confirmatory test N % of screen positive	PPV*	Diagnostic yield†
Garcia 1989 ⁴⁹ Good U.S.A	6,500 3-18	Large pediatric group practice in Ohio Described as white, middle class	Universal	Non-fasting TC≥200 mg/dL	552 8.5%	Fasting LDL-C≥130 mg/dL	487 88%	375 77%	5.8%

Abbreviations: KQ = key question, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, PPV = positive predictive value

*PPV: positive predictive value computed as true positive/ returned for confirmatory test

†Diagnostic yield = true positives divided by total screened

Table 7. Weighted prevalence of elevated TOTAL CHOLESTEROL concentration (TC≥200 mg/dL) by sex, age, race/ethnicity, BMI category, and family history among children and adolescents in large U.S. studies (KQ3)

Type of study	Study, Cohort Quality	N	Age range (years)	Total % (95% CI or SE)	Sex % (95% CI or SE)	Age % (95% CI or SE)	Race/ethnicity % (95% CI or SE)	BMI percentile % (95% CI or SE)
NHANES Studies [†]	Kit 2015 ⁸ 2011 to 2012 Good	1,482	8-17	7.8 (5.7-10.4)	Boys: 6.6 (4.5-9.1) Girls: 9.0 (5.4-13.8)	8-12 y: 7.0 (4.4-10.4) 13-17 y: 8.5 (5.2-12.9)	NH White: 7.0 (3.7-11.9) NH Black: 10.0 (8.3-11.8) Hispanic: 8.6 (6.0-11.8) NH Asian: 7.5 (3.7-13.1)	5th to <85th: 7.7 (5.3-10.8) 85th to <95th: 5.8 (2.7-10.9) ≥95th: 9.8 (5.9-15.1)
	Kit 2012 ¹⁵ 2007 to 2010 Good	4,205	6-19	8.1 (6.7-9.5)	Boys: 8.5 (6.7-10.3) Girls: 7.7 (5.9-9.5)	6-8 y: 7.7 (5.5-9.9) 9-11 y: 9.4 (7.3-11.6) 12-15 y: 6.2 (4.4-8) 16-19 y: 9.4 (7-11.8)	NH White: 8.1 (5.9-10.3) NH Black: 8.1 (6.2-10) Mexican American: 7.5 (5.1-9.9)	NR
	Ford 2009 ⁵⁵ 1999 to 2006 Good	9,868	6-17	9.6 (0.5)	Boys: 8.9 (0.8) Girls: 10.3 (0.6)	6-11 y: 10.6 (0.8) Boys: 9.3 (1.0) Girls: 12.0 (1.1) 12-17 y: 8.6 (0.5) Boys: 8.4 (0.9) Girls: 8.8 (0.7)	NH White: 9.3 (0.7) Boys: 8.1 (1.1) Girls: 10.6 (0.8) NH Black: 11.9 (0.6) Boys: 12.1 (0.8) Girls: 11.7 (0.9) Mexican American: 8.4 (0.5) Boys: 8.7 (0.7) Girls: 8.1 (0.7)	NR
Other studies	Margolis 2014 ⁵⁸ U.S. health systems 2007-2010 Fair	29,360	3-19	8.6 (NR)	Boys: 8.5 (8.0-8.9) Girls: 8.8 (8.4-9.3)	3-5 y: 5.8 (4.2-7.5) 6-8 y: 8.6 (7.4-9.8) 9-11 y: 10.6 (9.7-11.5) 12-16 y: 7.2 (6.7-7.6) 17-19 y: 9.8 (9.2-10.4)	White: 9.1 (8.6-9.7) Asian: 9.6 (8.4-10.8) Black: 7.6 (6.6-8.6) Hispanic: 8.2 (7.5-8.9) Other: 9.3 (6.6-12.0) Unknown: 8.3 (7.7-9.0)	<85th: 6.7 (6.2-7.1) 85 to <95th: 8.6 (7.8-9.4) ≥95th: 10.7 (10.2-11.3)
	CARDIAC Ice 2011 ⁷ WV screening 2003-2008 Fair	23,263	NR [†]	10.7 (NR)	NR	NR	NR	<85th: 7.5 (NR) 85 to <95th: 11.5 (NR) ≥95th: 16.0 (NR)

Abbreviations: TC = total cholesterol, BMI = body mass index, KQ = key question, NHANES = National Health and Nutrition Examination Survey, CI = confidence interval, SE = standard error, y = years, NH = Non-Hispanic, NR = not reported, CARDIAC = Coronary Artery Risk Detection in Appalachian Communities

*The included publications used data from overlapping cohorts back to 1999. Shown in this table are data only from the non-overlapping populations.

[†]This study did not report age range. The study population was fifth graders with a mean age of 10.84 (standard deviation 0.76)⁷

Table 8. Weighted prevalence of elevated LOW DENSITY LIPOPROTEIN CHOLESTEROL concentration (LDL≥130 mg/dL) by sex, age, race/ethnicity, BMI category, and family history, among children and adolescents in U.S. studies (KQ3)

Type of study	Study, Cohort	N*	Age range (years)	Total (%) (95% CI or SE)	Sex (%) (95% CI or SE)	Age category (%) (95% CI or SE)	Race/ethnicity (%) (95% CI or SE)	Prevalence by subgroups: BMI percentile (%) Family history (95% CI or SE)
NHANES studies	Kit 2012 ¹⁵ NHANES 2007-2010	996	12-19	7.4 (5.4-9.4)	Boys: 7.3 (4.5-10.1) Girls: 7.6 (5.3-9.9)	12-15 y: 5.6 (3.2-8.1) 16-19 y: 9.3 (6.4-12.1)	NH White: 7.8 (4.7-11) NH Black: 9.2 (5-13.4) Mexican American: 5.3 (2.3-8.4)	NR
	CDC 2010 ⁵⁶ NHANES 1999-2006	3,125	12-19	7.5 (NR)	Boys: 8.4 (6.4-11.0) Girls: 6.8 (5.1-9.0)	12-13 y: 7.3 (5.0-10.6) 14-15 y: 6.9 (4.4-10.6) 16-17 y: 5.2 (3.4-8.0) 18-19 y: 11.4 (8.3-15.5)	NH White: 7.7 (5.9-10.0) NH Black: 8.9 (7.3-10.8) Hispanic: 5.4 (4.1-7.0)	BMI: <5th to <85th: 5.8 (4.3-7.8) 85th to <95th: 8.4 (5.4-12.8) ≥95th: 14.2 (10.2-19.6)
	Ford 2009 ⁵⁵ NHANES 1999-2006	2,724	12-17	6.6 (0.6)	Boys: 7.3 (1.1) Girls: 5.8 (0.8)	NR	NH White: 6.4 (1.0) Boys: 7.7 (1.7) Girls: 5.1 (1.3) NH Black: 8.1 (1.0) Boys: 8.5 (1.1) Girls: 7.6 (1.5) Mexican American: 6.2 (0.9) Boys: 6.5 (1.1) Girls: 5.9 (1.1)	NR
Other studies	CARDIAC Ritchie 2010 ⁵⁷ Ice 2011 ⁷ WV screening program 2003-2008	23,263	NR [†]	8.7 (NR)	NR	NR	NR	BMI [‡] <85th: 6.0 (NR) 85 to <95th: 10.2 (NR) ≥95th: 12.9 (NR) Family history [§] Yes: 8.3(NR) No: 9.5 (NR)
	Margolis 2014 ⁵⁸ U.S. health systems 2007-2010	9,750	3-19	8.0	Boys: 7.8 (7.0-8.6) Girls: 8.2 (7.5-9.0)	3-5y: 6.8 (1.6-12.1) 6-8y: 7.4 (4.8-9.9) 9-11y: 8.1 (6.6-9.7) 12-16y: 7.6 (6.7-8.4) 17-19y: 8.5 (7.7-9.3)	White: 8.4 (7.7-9.2) Asian: 8.5 (5.7-11.3) Black: 6.9 (5.2-8.6) Hispanic: 6.8 (5.6-7.9) Other: 10.3 (5.8-14.8) Unknown: 8.5 (7.1-9.8)	BMI <85th: 5.6 (5.0-6.3) 85 to <95th: 9.1 (7.7-10.6) ≥95th: 10.4 (9.4-11.4)

Abbreviations: LDL-C = low density lipoprotein cholesterol, BMI = body mass index, KQ = key question, NHANES = National Health and Nutrition Examination Survey, CI = confidence interval, SE = standard error, y = years, NH = Non-Hispanic, NR = not reported, CARDIAC = Coronary Artery Risk Detection in Appalachian Communities

*N reflects people with fasting lipid levels, may differ from overall number of observations reported in Table 3 and Table 7

[†]This study did not report age range. The study population was fifth graders with a mean age of 10.84 (standard deviation 0.76)⁷

[‡]BMI data are reported in Ice 2011.

[§]Family history data are reported in Ritchie 2010. Family history refers to first or second degree relative with premature cardiovascular or hypercholesterolemia.

Table 9. Simulated diagnostic yield for Total Cholesterol as a screening test for dyslipidemia in children and adolescents, by subgroups based on age and BMI, using estimates from two large U.S. studies (KQ3)

Study, Cohort	Age (years) and BMI subgroups		Screen positive, single test (%)	95% CI lower	95% CI upper	Estimated diagnostic yield* at 77% PPV
Kit 2015 ⁸ NHANES 2011-2012	8-12		7.0	4.4	10.4	5.4
	13-17		8.5	5.2	12.9	6.5
Kit 2012 ¹⁵ NHANES 2007-2010	6-8		7.7	5.5	9.9	5.9
	9-11		9.4	7.3	11.6	7.2
	12-15		6.2	4.4	8.0	4.8
	16-19		9.4	7.0	11.8	7.2
Ice 2011 ⁷ West Virginia screening program CARDIAC 2003-2008	NR [†]	<85th percentile	7.5	NR	NR	5.8
		85th to <95th percentile	11.5	NR	NR	8.9
		≥95th percentile	16.0	NR	NR	12.3

Abbreviations: NHANES = National Health and Nutrition Examination Survey, BMI = body mass index, CI = confidence interval, PPV = positive predictive value, CARDIAC = Coronary Artery Risk Detection in Appalachian Communities, NR = not reported

*Diagnostic yield calculated as true positives / number screened. True positive rate was not available for these studies as no confirmatory tests were done, so this column represents an estimated diagnostic yield based on the one included study that included a confirmatory test and had a PPV of 77%.⁴⁹

[†]This study did not report age range. The study population was fifth graders with a mean age of 10.84 (standard deviation 0.76)⁷

Table 10. Effect of dietary intervention on TC and LDL-C (mg/dL) in children and adolescents: Results of the Dietary Intervention Study in Children (DISC) trial at five time points (KQ6)^{*}

Time point	Intervention in preceding time period	N [†]	Age, years mean (SD)	Adherence (attendance at visits)	TC mean (SD)	TC adjusted mean difference [‡] (95% CI)	LDL-C mean (SD)	LDL-C adjusted mean difference [‡] (95% CI)
Baseline	--	IG: 334 CG: 329	IG: 9.5 (.74) CG: 9.5 (.70)	--	IG: 200 (14.6) CG: 200 (14.6)	--	IG: 130.6 (12.2) CG: 130.5 (11.6)	--
Year 1	0 to 6 months: 6 weekly, then 5 biweekly group sessions and 2 individual sessions with nutritionist 7 months - 1 year: 4 group and 2 individual sessions	IG: 315 CG: 303	NR	6 mo: 96% 12 mo: 91%	IG: 191.4 (20.9) CG: 197.4 (21.4)	-6.1 (-9.1, -3.2) p<.001	IG: 122.6 (18.2) CG: 127.2 (19.4)	-4.8 (-7.4 to -2.2) p<.001
Year 3	Years 2 and 3: group and individual maintenance sessions 4 to 6 times per year, with monthly phone contact	IG: 320 CG: 303	NR	89%	IG: 183.3 (21.5) CG: 186.4 (22.3)	-3.3 (-6.4, -0.2) p=.04	IG: 115.3 (18.7) CG: 118.8 (19.4)	-3.3 (-6.0 to -0.6) p=.02
Year 5	Years 4 – 7: 2 group events and 2 individual visits annually, phone contact as needed	IG: 268 CG: 254	NR	72%	IG: 175.6 (22.4) CG: 177.9 (25.7)	-2.6 (-6.3, 1.2) p=.18	IG: 109.8 (NR) CG: 112.2 (NR)	-2.7 (NR) p=.11
Year 7	NR	IG:283 CG:265	IG: 17.0 (.88) CG: 17.0 (.93)	1.3 mean contacts per year	IG: 179.4 (24.1) CG: 180.1 (26.3)	-1.1 (-5.0, 2.8) p=.59	IG: 114.1 (NR) CG: 115.9 (NR)	-2.0 (NR) p=.25
Year 18	none	230 women [§] IG: 118 CG: 112	IG: 27.3 (1.0) CG: 27.2 (1.1)	N/A	NR	NR	IG: 119.9 (27.8) CG: 118.1 (24.3)	NR ^{**}

Abbreviations: DISC = Dietary Intervention Study in Children, KQ = key question, SD = standard deviation, TC = total cholesterol, CI = confidence interval, LDL-C = low density lipoprotein cholesterol, IG = intervention group, CG = control group, mo = month, NR = not reported, N/A = not applicable

^{*}Data in this table come from four articles about the DISC trial: DISC 1993⁶¹, DISC 1995⁶², Obarzanek 2001⁶³, and Dorgan 2011⁶⁴

[†]663 children were randomized. All analyses through the Year 7 were conducted as intent-to-treat. Numbers of participants assessed at each time point are shown in this column.

[‡]Year 1, Year 3, and Year 5 outcomes were adjusted for baseline value and sex. Outcomes at Year 7 were adjusted for baseline value, sex, and age at Year 7. Adjusted mean difference for TC and LDL-C were not reported at Year 18.

§230 women who had participated in the DISC trial as children were recruited for a followup assessment 9 years after the termination of the DISC trial. 260 (86.4%) of the 301 females originally randomized were screened; 30 were excluded due to pregnancy or breastfeeding.

** Adjusted mean difference not reported. P-value testing difference between LDL-C means reported $p = 0.62$ (not significant)

Table 11. Effect of dietary supplement on lipid levels (mg/dL) in children and adolescents (KQ6)

Author, Year Quality Country	N (IG/CG) Percent female	Age (y), Mean (SD) Range	Treatment RCT duration		TC	LDL-C	HDL-C	Triglycerides
Wong 2013 ⁶⁰ Fair Canada	32 16/16 46.9%	IG: 13 (2) CG: 13 (3) 8 – 18	Flaxseed supple- mentation 4 weeks	Baseline lipid concentrations Mean (SD)	IG: 214 (25) CG:202 (34)	IG: 141 (22) CG:134 (27)	IG: 53 (12) CG: 44 (12)	IG: 104 (39) CG:119 (54)
				Relative difference (% change) in intervention group compared to control group Mean (95% CI) P value	-4% (-10%, 2%) .20	-5% (-12%, 2%) .15	-15% (-24%, -6%) .001	26% (4%, 48%) .02

Abbreviations: mg/dL = milligram(s) per deciliter, KQ = key question, IG = intervention group, CG = control group, y = year, RCT = randomized controlled trial, SD = standard deviation, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, CI = confidence interval

Table 12. Harms of dietary intervention on TC and LDL-C (mg/dL) in children and adolescents (KQ7)

Author, Year Quality	N IG/CG Percent female	Adverse effects assessed systematically	Adverse effects reported	Unexpected benefits
DISC, 1995⁶² Obarzanek, 1997⁶⁷ Lavigne 1999⁶⁸ Obarzanek, 2001⁶³ Dorgan, 2011⁶⁴ Good	663 334/329 45.4%	All time points (baseline, years 1, 3, 5, and 7[*]): <u>Anthropometric measures:</u> Height, weight, BMI <u>Dietary assessment:</u> 24-hour recall Baseline, years 1, 3, and 7[*] only: <u>Laboratory studies:</u> Ferritin, retinol, zinc, red blood cell folate Baseline, years 1, 3, and 5 only: <u>Clinical:</u> Tanner staging Baseline, years 1 and 3 only: <u>Laboratory studies:</u> albumin, beta carotene, hemoglobin, vitamin E, copper, tocopherol <u>Clinical:</u> Blood pressure <u>Anthropometrics:</u> skinfold thickness, waist circumference Baseline and year 3 only: <u>Psychosocial:</u> Various instruments [†] , history of anorexia, bulimia, suicidality Year 5 and Year 7[*] only: age at menarche	No significant differences between treatment groups reported	Compared to control group, intervention group had improved depression score at year 3 (lower adjusted mean score on Child Depression Inventory) p = 0.31
	230 118/112 100%	Year 18[‡] (Post-trial year 9): <u>Anthropometric measures:</u> Height, weight, BMI, waist circumference <u>Clinical:</u> blood pressure <u>Laboratory studies:</u> fasting glucose, adiposity (DXA scan) <u>Dietary assessment:</u> 24-hour recall	No significant differences between treatment groups reported	Compared to control group, intervention group had: Lower mean systolic blood pressure (p = 0.03) Lower mean fasting plasma glucose (p = 0.01) Lower mean VLDL (p = 0.07)

Abbreviations: TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, mg/dL = milligram(s) per deciliter, KQ = key question, DISC = Dietary Intervention Study in Children, IG = intervention group, CG = control group, BMI = body mass index, DXA = dual-energy x-ray absorptiometry, VLDL = very low density lipoprotein cholesterol

*“Year 7” refers to the final follow up visit in the original study (1997); actual time-since-enrollment ranged from 7-to-9 years

†Instruments include: Achenbach Child Behavior Checklist, Spielberger State-Trait Anxiety Inventory for Children, Kovacs Child Depression Inventory, Family Environment Scale (Moos), Woodcock-Johnson Psycho-Educational Battery

‡ “Year 18” refers to the follow up study performed in 2006-2008 (approximately 18 years following original enrollment of study subjects in 1988-1990)

Table 13. Association[†] between elevated TC and non-HDL-cholesterol and the risk for death before age 55 from all causes and from endogenous causes among participants aged 12 to 39 years during NHANES III, with followup from 1988 to 2006 (KQ8)⁷⁰

	Males	Males	Females	Females
	Risk of death before age 55 (all cause)[†] RH (95% CI)	Risk of death before age 55 (endogenous causes)[†] RH (95% CI)	Risk of death before Age 55 (all cause)[†] RH (95% CI)	Risk of death before age 55 (endogenous)[†] RH (95% CI)
Total cholesterol ≥200 mg/dL	(reference)	(reference)	(reference)	(reference)
200–239 mg/dL	0.75 (0.42–1.37)	0.71 (0.34–1.51)	1.39 (0.71–2.70)	0.77 (0.36–1.62)
≥240 mg/dL	0.83 (0.32–2.14)	1.01 (0.36–2.85)	2.46 (1.31–4.65)	2.58 (1.31–5.08)
Non-HDL cholesterol ≥130 mg/dL	(reference)	(reference)	(reference)	(reference)
130–144	2.03 (0.98–4.23)	2.00 (0.81–4.92)	0.72 (0.20–2.59)	0.46 (0.10–2.14)
≥144	1.10 (0.64–1.91)	0.85 (0.42–1.71)	2.00 (1.11–3.62)	1.95 (0.97–3.90)

Abbreviations: TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, NHANES = National Health and Nutrition Examination Survey, KQ = key question, mg/dL = milligram(s) per deciliter, RH = relative hazard, CI = confidence interval

*Associations are expressed as relative hazards. Proportional hazards models for each variable separately with age as the time scale adjusted for race/ethnicity and history of chronic disease (self-report of cardiovascular disease, diabetes, and/or cancer).

[†]Other variables measured: blood pressure and cotinine levels. Variables with statistically significant relationships with all cause death: males (none); females (blood pressure, hypertension, and cotinine levels 10-99 and ≥100). Variables with statistically significant relationships with endogenous causes of death: males: (none); females (blood pressure, hypertension, and cotinine levels 10-99 and ≥100).

Table 14. Summary of evidence table

Key Question	Studies (k), Observations (n)	Design	Major limitations	Consistency	Applicability	Overall quality	Summary of findings
KQ1 (screening & health outcomes)	no studies	N/A	N/A	N/A	N/A	N/A	N/A
KQ2 (screening & intermediate outcomes)	no studies	N/A	N/A	N/A	N/A	N/A	N/A
KQ3 (screening diagnostic yield)	k=4 (8 publications) n=78,792*	Cross-sectional	In non-NHANES studies, populations were almost exclusively white. Only one study included confirmatory testing (n=6,500); all others used a single test so true diagnostic yield is not available	Taken together the results are internally consistent.	All studies were conducted in U.S. settings. Two were in U.S. 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.	Fair	The one 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% to 12.3%.
KQ4 (screening harms)	no studies	N/A	N/A	N/A	N/A	N/A	N/A
KQ5 (treatment in childhood & health outcomes)	no studies	N/A	N/A	N/A	N/A	N/A	N/A
KQ6 (treatment in childhood & intermediate outcomes)	k=2 (5 publications) n=695	RCT Longitudinal followup of one trial cohort to 18 years post-randomization	In the larger study (diet) the cutoffs used to define dyslipidemia were lower than our criteria. The smaller study (flaxseed) had a small sample size (n=32) and was limited to a high-risk population in a tertiary care setting.	N/A – different interventions	The diet study is likely applicable to a U.S. 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.	Fair	The diet study found lower LDL-C and TC levels at 1 and 3 year followup in the intervention group. On longitudinal followup of the trial cohort the treatment effects were attenuated. The study of flaxseed supplementation found no effect at 4 weeks on lipid levels.

Key Question	Studies (k), Observations (n)	Design	Major limitations	Consistency	Applicability	Overall quality	Summary of findings
KQ7 (treatment harms)	k=1 (5 publications) n=663	RCT Longitudinal followup of trial cohort to 18 years post-randomization	Cutoffs used to define dyslipidemia were lower than our criteria.	N/A – one study	The DISC study is likely applicable to a U.S. setting if the relatively high intensity of family counseling could be replicated in primary care.	Fair	No harms reported at any time point during the trial or on long-term followup for anthropometric, laboratory, psychosocial or maturation measures.
KQ8 (association: childhood intermediate outcomes & adult health outcomes)	k=1 n=9,245	Longitudinal analysis of NHANES data	Outcomes on children within the total study population (age 12-39) were not reported separately.	N/A – one study	NHANES data may not have direct relevance to primary care.	Fair	At followup 283 people were deceased before age 55. Leading causes of death for people age 12-19 at baseline were accident, self-inflicted injury, circulatory causes, and cancer. In multivariate models neither very high cholesterol (TC \geq 240 mg/dL) nor moderately increased TC (200-239 mg/dL) was independently associated with death, when both sexes were combined. For females only a very high cholesterol was associated with a greater risk of death before 55 (RH 2.58; 95% CI 1.31, 5.08).

Abbreviations: KQ = key question, N/A = not applicable, NHANES = National Health and Nutrition Examination Survey, RCT = randomized controlled trial, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, mg/dL = milligram(s) per deciliter, DISC = Dietary Intervention Study in Children, RH = relative hazard, CI = confidence interval

*N=78,792 is an estimate, as the four NHANES publications included for KQ3 have overlapping populations

Appendix A. Detailed Methods

Search Strategy

Sources searched:

Cochrane Central Register of Controlled Clinical Trials, via Wiley
Medline, via Ovid
PubMed, publisher-supplied

Key:

/ = MeSH subject heading
\$ = truncation
ti = word in title
ab = word in abstract
adj# = adjacent within x number of words
pt = publication type
* = truncation
ae = adverse effects
ci = chemically induced
de=drug effects
mo=mortality
nm = name of substance

Cochrane Central Register of Controlled Clinical Trials Issue 1 of 12, January 2014

#1 (hyperlipid*emia*:ti,ab,kw or dyslipid*emia*:ti,ab,kw or hypercholesterol*emia*:ti,ab,kw or hyperlipoprotein*emia*:ti,ab,kw or hypertriglycerid*emia*:ti,ab,kw or dysbetalipoprotein*emia*:ti,ab,kw)
#2 (familial next hypercholesterol*emi*):ti,ab,kw or (familial next hyperlipid*emi*):ti,ab,kw or (essential next hypercholesterol*emi*):ti,ab,kw or (familial near/3 apolipoprotein):ti,ab,kw
#3 "heterozygous fh":ti,ab,kw or "homozygous fh":ti,ab,kw
#4 (lipid next disorder*):ti,ab,kw or (lipid near/3 dysfunction*):ti,ab,kw
#5 (high or elevated or abnormal or aberr*):ti,ab,kw near/3 (cholesterol or lipid* or LDL*):ti,ab,kw
#6 (low or decrease* or deficien* or abnormal or aberr*):ti,ab,kw near/3 HDL*:ti,ab,kw
#7 (cholesterol or lipid* or lipoprotein* or LDL* or HDL*):ti,ab,kw near/3 (detect* or measure* or check* or assess* or analyz* or analys* or test* or panel* or profile*):ti,ab,kw
#8 (fasting or nonfasting or non-fasting):ti,ab,kw next (lipid* or lipoprotein* or cholesterol):ti,ab,kw
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 (child*:ti,ab,kw or adolesc*:ti,ab,kw or teen:ti,ab,kw or teens:ti,ab,kw or teenage*:ti,ab,kw or youth:ti,ab,kw or youths:ti,ab,kw or p*ediatic*:ti,ab,kw)
#11 #9 and #10 from 2007 to 2014, in Trials

MEDLINE

Dyslipidemia screening, screening harms

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 11, 2014>, Ovid MEDLINE(R) Daily Update <February 11, 2014>

Search Strategy:

-
- 1 Hyperlipidemias/
 - 2 Dyslipidemias/
 - 3 Hypercholesterolemia/
 - 4 Lipid Metabolism Disorders/
 - 5 Hyperlipoproteinemias/
 - 6 Hypertriglyceridemia/
 - 7 Hyperlipoproteinemia Type II/
 - 8 Hyperlipidemia, Familial Combined/
 - 9 Hypobetalipoproteinemias/
 - 10 Abetalipoproteinemia/
 - 11 hyperlipid?emia\$.ti,ab.
 - 12 dyslipid?emia\$.ti,ab.
 - 13 hypercholesterol?emia\$.ti,ab.
 - 14 hyperlipoprotein?emia\$.ti,ab.
 - 15 hypertriglycerid?emia\$.ti,ab.
 - 16 dysbetalipoprotein?emia\$.ti,ab.
 - 17 familial hypercholesterol\$emi*.ti,ab.
 - 18 familial hyperlipid?emi*.ti,ab.
 - 19 essential hypercholesterol?emi*.ti,ab.
 - 20 (familial adj3 apolipoprotein).ti,ab.
 - 21 heterozygous fh.ti,ab.
 - 22 homozygous fh.ti,ab.
 - 23 lipid disorder\$.ti,ab.
 - 24 or/1-23
 - 25 Cholesterol/bl
 - 26 Triglycerides/bl
 - 27 Lipoproteins/bl
 - 28 Cholesterol, HDL/
 - 29 Cholesterol, LDL/
 - 30 Apolipoprotein B-100/
 - 31 Apolipoprotein B 100.ti,ab.
 - 32 apob 100.ti,ab.
 - 33 apo b 100.ti,ab.
 - 34 ((high or elevated or abnormal or aberr\$) adj3 (cholesterol or lipid\$ or LDL\$)).ti,ab.
 - 35 ((low or decrease\$ or deficien\$ or abnormal or aberr\$) adj3 HDL\$).ti,ab.
 - 36 or/25-35
 - 37 Mass screening/

- 38 screen\$.ti,ab.
- 39 ((cholesterol or lipid\$ or lipoprotein\$ or LDL\$ or HDL\$) adj3 (detect\$ or measur\$ or check\$ or assess\$ or analyz\$ or analys\$ or test\$ or panel\$ or profile\$)).ti,ab.
- 40 (fasting adj (lipid\$ or lipoprotein\$ or cholesterol)).ti,ab.
- 41 (non-fasting adj (lipid\$ or lipoprotein\$ or cholesterol)).ti,ab.
- 42 37 or 38 or 39 or 40 or 41
- 43 (24 or 36) and 42
- 44 adolescent/ or child/ or young adult/
- 45 43 and 44
- 46 (child\$ or teen or teens or teenage\$ or adolescen\$ or youth or youths or young people or pediatric\$ or paediatric\$).ti,ab.
- 47 43 and 46
- 48 limit 47 to ("in data review" or in process or "pubmed not medline")
- 49 45 or 48
- 50 limit 49 to english language
- 51 limit 50 to yr="2007 -Current"
- 52 remove duplicates from 51

Dx yield/accuracy

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 11, 2014>, Ovid MEDLINE(R) Daily Update <February 11, 2014>

Search Strategy:

-
- 1 Hyperlipidemias/
 - 2 Dyslipidemias/
 - 3 Hypercholesterolemia/
 - 4 Lipid Metabolism Disorders/
 - 5 Hyperlipoproteinemias/
 - 6 Hypertriglyceridemia/
 - 7 Hyperlipoproteinemia Type II/
 - 8 Hyperlipidemia, Familial Combined/
 - 9 Hypobetalipoproteinemias/
 - 10 Abetalipoproteinemia/
 - 11 hyperlipid?emia\$.ti,ab.
 - 12 dyslipid?emia\$.ti,ab.
 - 13 hypercholesterol?emia\$.ti,ab.
 - 14 hyperlipoprotein?emia\$.ti,ab.
 - 15 hypertriglycerid?emia\$.ti,ab.
 - 16 dysbetalipoprotein?emia\$.ti,ab.
 - 17 familial hypercholesterol\$emi*.ti,ab.
 - 18 familial hyperlipid?emi*.ti,ab.
 - 19 essential hypercholesterol?emi*.ti,ab.
 - 20 (familial adj3 apolipoprotein).ti,ab.
 - 21 heterozygous fh.ti,ab.

22 homozygous fh.ti,ab.
 23 lipid disorder\$.ti,ab.
 24 or/1-23
 25 Cholesterol/bl
 26 Triglycerides/bl
 27 Lipoproteins/bl
 28 Cholesterol, HDL/
 29 Cholesterol, LDL/
 30 Apolipoprotein B-100/
 31 Apolipoprotein B 100.ti,ab.
 32 apob 100.ti,ab.
 33 apo b 100.ti,ab.
 34 ((high or elevated or abnormal or aberr\$) adj3 (cholesterol or lipid\$ or LDL\$)).ti,ab.
 35 ((low or decrease\$ or deficien\$ or abnormal or aberr\$) adj3 HDL\$).ti,ab.
 36 ((cholesterol or lipid\$ or lipoprotein\$ or LDL\$ or HDL\$) adj3 (detect\$ or measur\$ or check\$ or assess\$ or analyz\$ or analys\$ or test\$ or panel\$ or profile\$)).ti,ab.
 37 (fasting adj (lipid\$ or lipoprotein\$ or cholesterol)).ti,ab.
 38 (non-fasting adj (lipid\$ or lipoprotein\$ or cholesterol)).ti,ab.
 39 or/25-38
 40 "Sensitivity and Specificity"/
 41 "Predictive Value of Tests"/
 42 ROC Curve/
 43 False Negative Reactions/
 44 False Positive Reactions/
 45 Diagnostic Errors/
 46 "Reproducibility of Results"/
 47 Reference Values/
 48 Reference Standards/
 49 Observer Variation/
 50 Receiver operat\$.ti,ab.
 51 ROC curve\$.ti,ab.
 52 sensitivit\$.ti,ab.
 53 specificit\$.ti,ab.
 54 predictive value.ti,ab.
 55 accuracy.ti,ab.
 56 false positive\$.ti,ab.
 57 false negative\$.ti,ab.
 58 miss rate\$.ti,ab.
 59 error rate\$.ti,ab.
 60 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
 61 (24 or 39) and 60
 62 adolescent/ or child/ or young adult/
 63 61 and 62
 64 (child\$ or teen or teens or teenage\$ or adolescen\$ or youth or youths or young people or pediatric\$ or paediatric\$).ti,ab.

- 65 61 and 64
- 66 limit 65 to ("in data review" or in process or "pubmed not medline")
- 67 63 or 66
- 68 limit 67 to (english language and yr="2007 -Current")
- 69 remove duplicates from 68

Drug Tx Harms

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 5 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 11, 2014>, Ovid MEDLINE(R) Daily Update <February 11, 2014>

Search Strategy:

-
- 1 Hyperlipidemias/
 - 2 Dyslipidemias/
 - 3 Hypercholesterolemia/
 - 4 Lipid Metabolism Disorders/
 - 5 Hyperlipoproteinemias/
 - 6 Hypertriglyceridemia/
 - 7 Hyperlipoproteinemia Type II/
 - 8 Hyperlipidemia, Familial Combined/
 - 9 Hypobetalipoproteinemias/
 - 10 Abetalipoproteinemia/
 - 11 hyperlipid?emia\$.ti,ab.
 - 12 dyslipid?emia\$.ti,ab.
 - 13 hypercholesterol?emia\$.ti,ab.
 - 14 hyperlipoprotein?emia\$.ti,ab.
 - 15 hypertriglycerid?emia\$.ti,ab.
 - 16 dysbetalipoprotein?emia\$.ti,ab.
 - 17 familial hypercholesterol\$emi*.ti,ab.
 - 18 familial hyperlipid?emi*.ti,ab.
 - 19 essential hypercholesterol?emi*.ti,ab.
 - 20 (familial adj3 apolipoprotein).ti,ab.
 - 21 heterozygous fh.ti,ab.
 - 22 homozygous fh.ti,ab.
 - 23 lipid disorder\$.ti,ab.
 - 24 ((high or elevated or abnormal or aberr\$) adj3 (cholesterol or lipid\$ or LDL\$)).ti,ab.
 - 25 ((low or decrease\$ or deficien\$ or abnormal or aberr\$) adj3 HDL\$).ti,ab.
 - 26 or/1-25
 - 27 hypolipidemic agents/ or bezafibrate/ or butoxamine/ or clofenapate/ or clofibrate/ or clofibric acid/ or colestipol/ or fenofibrate/ or gemfibrozil/ or halofenate/ or meglutol/ or nafenopin/ or niacin/ or niceritrol/ or pyridinolcarbamate/ or simvastatin/ or triparanol/
 - 28 anticholesteremic agents/ or azacosterol/ or chitosan/ or cholestyramine resin/ or clofibrate/ or clofibric acid/ or lovastatin/ or meglutol/ or pravastatin/ or probucol/ or simvastatin/ or "trans-1,4-bis(2-chlorobenzaminomethyl)cyclohexane dihydrochloride"/
 - 29 hydroxymethylglutaryl-coa reductase inhibitors/ or lovastatin/

30 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor\$.ti,ab.
 31 hydroxymethylglutaryl coa reductase inhibitor\$.ti,ab.
 32 hydroxymethylglutaryl coa inhibitor\$.ti,ab.
 33 hydroxymethylglutaryl coenzyme a reductase.ti,ab.
 34 hydroxymethylglutaryl coenzyme a inhibitor\$.ti,ab.
 35 hmg coa reductase inhibitor\$.ti,ab.
 36 hmg coa inhibitor\$.ti,ab.
 37 atorvastatin.ti,ab.
 38 fluvastatin.ti,ab.
 39 lovastatin.ti,ab.
 40 pitavastatin.ti,ab.
 41 pravastatin.ti,ab.
 42 rosuvastatin.ti,ab.
 43 simvastatin.ti,ab.
 44 hypolipidemic\$.ti,ab.
 45 anticholesteremic\$.ti,ab.
 46 antilipidemic.ti,ab.
 47 statin\$.ti,ab.
 48 lipid lower\$.ti,ab.
 49 (treat\$ or therap\$ or medicat\$).ti.
 50 or/27-49
 51 ae.fs.
 52 "Drug-Related Side Effects and Adverse Reactions"/
 53 Mortality/
 54 Morbidity/
 55 Death/
 56 mo.fs.
 57 (harm or harms or harmful or harmed).ti,ab.
 58 (adverse adj (effect\$ or event\$ or outcome\$)).ti,ab.
 59 safety.ti,ab.
 60 overtreat\$.ti,ab.
 61 (death or deaths).ti,ab.
 62 drug-induced liver injury/
 63 drug-induced liver injury, chronic/
 64 Liver Neoplasms/ci
 65 Liver/de
 66 Liver failure/ci
 67 Liver failure, acute/ci
 68 (liver adj3 (injur\$ or dysfunction\$ or failure\$)).ti,ab.
 69 (Hepatic adj3 (injur\$ or dysfunction\$ or failure\$)).ti,ab.
 70 (transaminase adj3 (elevat\$ or abnormal\$ or dysfunction\$)).ti,ab.
 71 Liver enzyme\$.ti,ab.
 72 alanine transaminase.ti,ab.
 73 alanine aminotransferase.ti,ab.
 74 aspartate transaminase.ti,ab.
 75 aspartate aminotransferase.ti,ab.

- 76 (AST or ALT).ti,ab.
- 77 Muscular Diseases/ci
- 78 Myositis/
- 79 Myositis.ti,ab.
- 80 Dermatomyositis/
- 81 Dermatomyositis.ti,ab.
- 82 myositis ossificans.ti,ab.
- 83 Rhabdomyolysis/
- 84 rhabdomyolysis.ti,ab.
- 85 myotoxicity.ti,ab.
- 86 myopathy.ti,ab.
- 87 muscle enzyme\$.ti,ab.
- 88 (creatine adj3 (high or elevat\$ or abnormal\$)).ti,ab.
- 89 Myalgia/
- 90 myalgia.ti,ab.
- 91 or/51-90
- 92 26 and 50 and 91
- 93 adolescent/ or child/ or young adult/
- 94 92 and 93
- 95 (child\$ or teen or teens or teenage\$ or adolescen\$ or youth or youths or young people or pediatric\$ or paediatric\$).ti,ab.
- 96 92 and 95
- 97 limit 96 to ("in data review" or in process or "pubmed not medline")
- 98 94 or 97
- 99 limit 98 to english language
- 100 limit 99 to yr="2007 -Current"

Drug and lifestyle treatment efficacy

Database: Ovid MEDLINE(R) without Revisions <1996 to June Week 1 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 12, 2014>, Ovid MEDLINE(R) Daily Update <June 12, 2014>
 Search Strategy:

-
- 1 Hyperlipidemias/
 - 2 Dyslipidemias/
 - 3 Hypercholesterolemia/
 - 4 Lipid Metabolism Disorders/
 - 5 Hyperlipoproteinemias/
 - 6 Hypertriglyceridemia/
 - 7 Hyperlipoproteinemia Type II/
 - 8 Hyperlipidemia, Familial Combined/
 - 9 Hypobetalipoproteinemias/
 - 10 Abetalipoproteinemia/
 - 11 hyperlipid?emia\$.ti,ab.
 - 12 dyslipid?emia\$.ti,ab.

- 13 hypercholesterol?emia\$.ti,ab.
- 14 hyperlipoprotein?emia\$.ti,ab.
- 15 hypertriglycerid?emia\$.ti,ab.
- 16 dysbetalipoprotein?emia\$.ti,ab.
- 17 familial hypercholesterol\$emi*.ti,ab.
- 18 familial hyperlipid?emi*.ti,ab.
- 19 essential hypercholesterol?emi*.ti,ab.
- 20 (familial adj3 apolipoprotein).ti,ab.
- 21 heterozygous fh.ti,ab.
- 22 homozygous fh.ti,ab.
- 23 lipid disorder\$.ti,ab.
- 24 ((high or elevated or abnormal or aberr\$) adj3 (cholesterol or lipid\$ or LDL\$)).ti,ab.
- 25 ((low or decrease\$ or deficien\$ or abnormal or aberr\$) adj3 HDL\$).ti,ab.
- 26 or/1-25
- 27 hypolipidemic agents/ or bezafibrate/ or butoxamine/ or clofenapate/ or clofibrate/ or clofibric acid/ or colestipol/ or fenofibrate/ or gemfibrozil/ or halofenate/ or meglutol/ or nafenopin/ or niacin/ or niceritrol/ or pyridinolcarbamate/ or simvastatin/ or triparanol/
- 28 anticholesteremic agents/ or azacosterol/ or chitosan/ or cholestyramine resin/ or clofibrate/ or clofibric acid/ or lovastatin/ or meglutol/ or pravastatin/ or probucol/ or simvastatin/ or "trans-1,4-bis(2-chlorobenzaminomethyl)cyclohexane dihydrochloride"/
- 29 hydroxymethylglutaryl-coa reductase inhibitors/ or lovastatin/
- 30 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor\$.ti,ab.
- 31 hydroxymethylglutaryl coa reductase inhibitor\$.ti,ab.
- 32 hydroxymethylglutaryl coa inhibitor\$.ti,ab.
- 33 hydroxymethylglutaryl coenzyme a reductase.ti,ab.
- 34 hydroxymethylglutaryl coenzyme a inhibitor\$.ti,ab.
- 35 hmg coa reductase inhibitor\$.ti,ab.
- 36 hmg coa inhibitor\$.ti,ab.
- 37 atorvastatin.ti,ab.
- 38 fluvastatin.ti,ab.
- 39 lovastatin.ti,ab.
- 40 pitavastatin.ti,ab.
- 41 pravastatin.ti,ab.
- 42 rosuvastatin.ti,ab.
- 43 simvastatin.ti,ab.
- 44 hypolipidemic\$.ti,ab.
- 45 anticholesteremic\$.ti,ab.
- 46 antilipidemic.ti,ab.
- 47 statin\$.ti,ab.
- 48 lipid lower\$.ti,ab.
- 49 (treat\$ or therap\$ or medicat\$).ti.
- 50 or/27-49
- 51 diet/
- 52 diet, carbohydrate-restricted/
- 53 diet, fat-restricted/
- 54 diet, mediterranean/

- 55 diet, protein-restricted/
- 56 diet, reducing/
- 57 diet, vegetarian/
- 58 caloric restriction/
- 59 portion size/
- 60 Food habits/
- 61 Diet Therapy/
- 62 Soybean Proteins/
- 63 Fatty Acids, Omega-3/
- 64 Phytosterols/
- 65 Dietary Fiber/
- 66 Dietary Protein/
- 67 Dietary Carbohydrates/
- 68 Dietary Fats/
- 69 diet\$.ti,ab.
- 70 ((reduce\$ or reduction\$ or manipulat\$ or restrict\$) adj3 (fat\$ or carbohydrate\$ or cholesterol)).ti,ab.
- 71 low fat.ti,ab.
- 72 lowfat.ti,ab.
- 73 fiber.ti,ab.
- 74 omega 3 fatty acid\$.ti,ab.
- 75 n 3 polyunsaturated fatty acid\$.ti,ab.
- 76 n 3 fatty acid\$.ti,ab.
- 77 n 3 pufa.ti,ab.
- 78 soy\$ protein\$.ti,ab.
- 79 plant stanol\$.ti,ab.
- 80 esters.ti,ab.
- 81 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80
- 82 Exercise/
- 83 Exercise therapy/
- 84 Motor activity/
- 85 Physical fitness/
- 86 Plyometric Exercise/
- 87 Physical Conditioning, Human/
- 88 Running/
- 89 Jogging/
- 90 Swimming/
- 91 Walking/
- 92 Resistance training/
- 93 (exercise or exercising or exercises).ti,ab.
- 94 physical fitness.ti,ab.
- 95 physical conditioning.ti,ab.
- 96 (running or jog\$ or swim\$ or walk\$).ti,ab.
- 97 (lifestyle\$ or life style\$).ti,ab.
- 98 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97

99 26 and (50 or 81 or 98)
 100 Hyperlipidemias/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention & Control, Therapy]
 101 Dyslipidemias/dh, dt, pc, th
 102 Hypercholesterolemia/dh, dt, pc, th
 103 Lipid Metabolism Disorders/dh, dt, pc, th
 104 Hyperlipoproteinemias/dh, dt, pc, th
 105 Hypertriglyceridemia/dh, dt, pc, th
 106 Hyperlipoproteinemia Type II/dh, dt, pc, th
 107 Hyperlipidemia, Familial Combined/dh, dt, pc, th
 108 Hypobetalipoproteinemias/dh, dt, pc, th
 109 Abetalipoproteinemia/dh, dt, pc, th
 110 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
 111 adolescent/ or child/ or young adult/
 112 110 and 111
 113 (child\$ or teen or teens or teenage\$ or adolescen\$ or youth or youths or young people or pediatric\$ or paediatric\$).ti,ab.
 114 110 and 113
 115 limit 114 to ("in data review" or in process or "pubmed not medline")
 116 112 or 115
 117 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/
 118 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
 119 Random\$.ti,ab.
 120 control groups/ or double-blind method/ or single-blind method/
 121 clinical trial\$.ti,ab.
 122 controlled trial\$.ti,ab.
 123 meta analy\$.ti,ab.
 124 117 or 118 or 119 or 120 or 121 or 122 or 123
 125 116 and 124
 126 limit 125 to (english language and yr="2007 -Current")
 127 remove duplicates from 126

PubMed search strategy [publisher-supplied references only], searched 2.12.2014

Search	Query
#11	Search #10 AND publisher[sb] Filters: Publication date from 2007/01/01 to 2014/12/31; English
#10	Search #8 AND #9
#9	Search child*[tiab] OR teen[tiab] OR teens[tiab] OR teenage*[tiab] OR adolescen*[tiab] OR youth[tiab] OR youths[tiab] OR "young people"[tiab] OR pediatric*[tiab] OR paediatric*[tiab]
#8	Search #1 or #2 or #3 or #4 or #5 or #6 or #7
#7	Search (fasting[tiab] or non fasting[tiab] OR nonfasting[tiab]) AND (lipid*[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab])
#6	Search (lipid[tiab] OR lipids[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab] OR LDL*[tiab] OR HDL*[tiab]) AND (detect*[tiab] OR measur*[tiab] OR check*[tiab] OR assess*[tiab] OR analyz*[tiab] OR analys*[tiab] OR test*[tiab] OR panel*[tiab] OR profile*[tiab])
#5	Search (lipid[tiab] OR lipids[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab] OR LDL*[tiab] OR HDL*[tiab]) AND (low[tiab] OR high[tiab] OR elevated[tiab] OR abnormal[tiab] OR aberr*[tiab])
#4	Search lipid disorder*[tiab] OR lipid dysfunction*[tiab]
#3	Search familial[tiab] AND apolipoprotein[tiab]
#2	Search familial hypercholesterolemia*[tiab] OR familial hypercholesterolaemia*[tiab] OR familial hyperlipidemi*[tiab] OR familial hyperlipidaemi*[tiab] OR essential hypercholesterolemi*[tiab] OR essential hypercholesterolaemi*[tiab] OR heterozygous fh[tiab] OR homozygous fh[tiab]
#1	Search (hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR dyslipidemia*[tiab] OR dyslipidaemia*[tiab] OR hypercholesterolemia*[tiab] OR hypercholesterolaemia*[tiab] OR hyperlipoproteinemia*[tiab] OR hyperlipoproteinaemia*[tiab] OR hypertriglyceridemia*[tiab] OR hypertriglyceridaemia*[tiab] OR dysbetalipoproteinemia*[tiab] OR dysbetalipoproteinaemia*[tiab])

Appendix A Table 1: Quality assessment criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the USPSTF methods ⁷⁶	<ul style="list-style-type: none"> • Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Were measurements equal, valid, and reliable? • Was there intervention fidelity? • Was there adequate adherence to the intervention? • Were outcome assessors blinded? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there evidence of selective reporting of outcomes? • Was the device calibration and/or maintenance reported?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS) ⁷⁷	<ul style="list-style-type: none"> • Was the cohort systematically selected to avoid bias? • Was eligibility criteria specified? • Were groups similar at baseline? • Was the outcome of interest not present at baseline? • Were measurements equal, valid, and reliable? • Were outcome assessors blinded? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate?

Abbreviations: USPSTF = U.S. Preventive Services Task Force

Appendix A Table 2. Inclusion and exclusion criteria

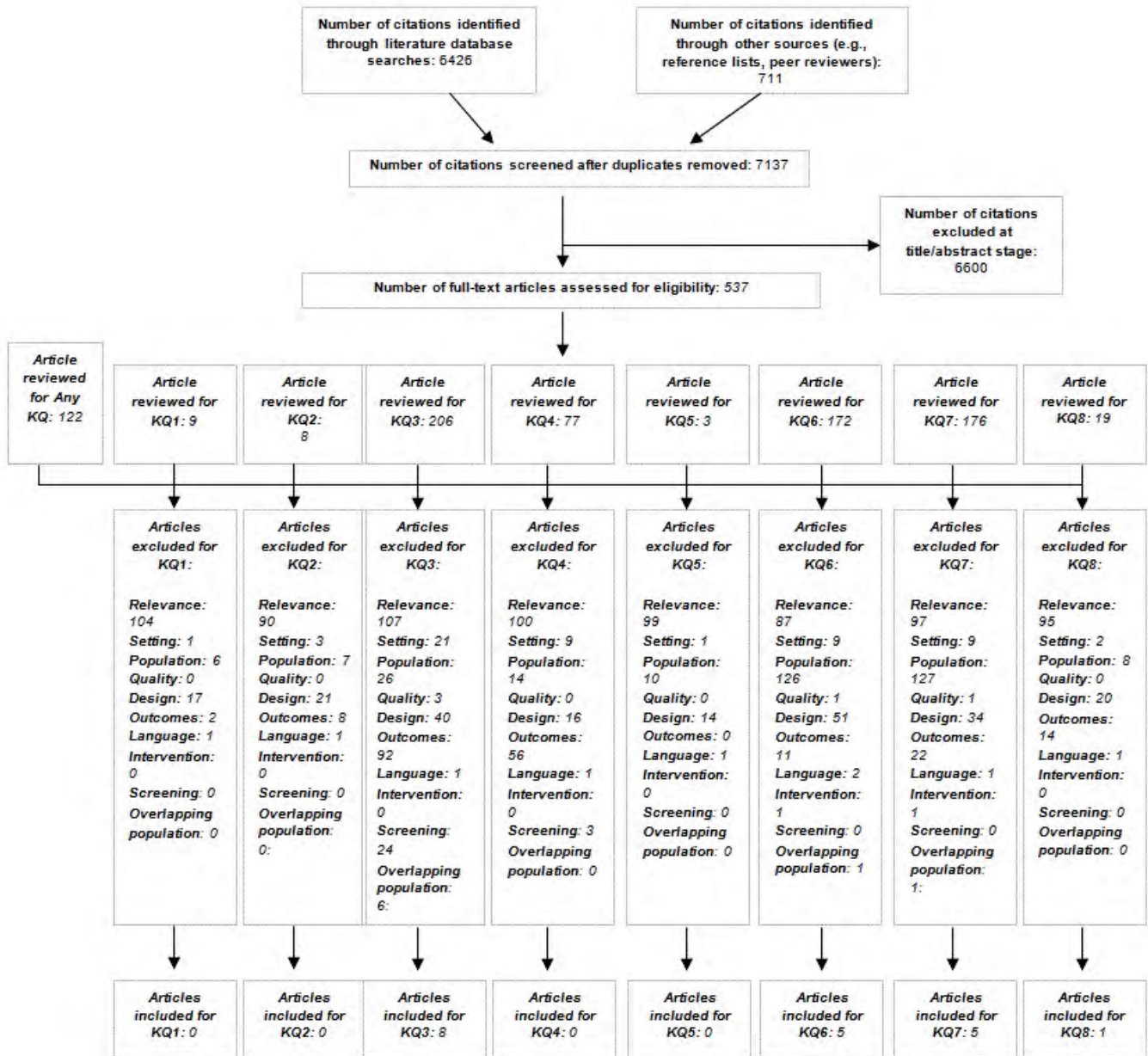
	Included	Excluded
Population	<p>All KQs: Children and adolescents ages 0 to 20 years</p> <p>KQs 1–4: Asymptomatic children and adolescents ages 0 to 20 years</p> <p>KQs 5–8: Children and adolescents ages 0 to 20 years with dyslipidemia not due to familial hypercholesterolemia</p>	<p>KQs 1–4: Children and adolescents with any of the following:</p> <ul style="list-style-type: none"> • Known dyslipidemia • Diagnosis associated with secondary dyslipidemia • Established family history of familial hypercholesterolemia <p>KQs 5–8: Children and adolescents with familial hypercholesterolemia</p>
Diseases	<p>KQs 5–8: Dyslipidemia, as defined by the National Cholesterol Education Program (i.e., ≥ 1 of the following lipid/lipoprotein values, measured either in a nonfasting state followed by fasting or by 2 fasting tests):</p> <ul style="list-style-type: none"> • Total cholesterol ≥ 200 mg/dL (5.2 mmol/L) • LDL cholesterol ≥ 130 mg/dL (3.4 mmol/L) • Non-HDL cholesterol ≥ 145 mg/dL (3.8 mmol/L) • HDL cholesterol < 40 mg/dL (1 mmol/L) • Triglycerides (ages 0 to 9 years) ≥ 100 mg/dL (1.1 mmol/L) • Triglycerides (ages 10 to 19 years) ≥ 130 mg/dL (1.5 mmol/L) <p>Abnormal values are >95th percentile, except for HDL cholesterol, which is <10th percentile. Non-HDL cholesterol includes LDL cholesterol, lipoprotein-a, intermediate-density lipoprotein, and very-low density lipoprotein</p>	<p>KQs 5–8:</p> <ul style="list-style-type: none"> • Familial hypercholesterolemia • Secondary dyslipidemia*
Screening interventions	<p>KQs 1–4:</p> <ul style="list-style-type: none"> • Lipid panel (fasting or nonfasting lipid measurement, total or LDL cholesterol alone or in combination with other lipid markers) • Comparison with no screening or usual care • Universal or selective screening strategy (e.g., screening based on body mass index) 	<p>KQs 1–4:</p> <ul style="list-style-type: none"> • Genetic screening alone • Cascade screening
Treatments	<p>KQs 5–7:</p> <ul style="list-style-type: none"> • Lipid-lowering medications • Lifestyle modifications, including diet or exercise 	<p>KQs 5–7: None</p>
Outcomes	<p>KQs 1, 5, 8:</p> <ul style="list-style-type: none"> • MI • Ischemic stroke <p>KQ3:</p> <ul style="list-style-type: none"> • Diagnostic yield (true positives/number screened) • Positive predictive value (true positives/true positives + false positives) <p>KQ4: All harms (e.g., false-positive or false-negative results, psychosocial effects, overdiagnosis)</p> <p>KQs 2, 6:</p> <ul style="list-style-type: none"> • Lipid levels (total, LDL, HDL, and non-HDL cholesterol; triglycerides) • Atherosclerosis markers (carotid intima–media thickness, calcium score, pathological findings) <p>KQ7: All harms from:</p> <ul style="list-style-type: none"> • Medications (e.g., adverse events, long-term safety, overtreatment) • Lifestyle modifications (e.g., nutritional, psychosocial) 	<p>KQs 1, 5, 8:</p> <ul style="list-style-type: none"> • Diabetes • Metabolic syndrome • Hypothyroidism • Renal failure • Obstructive liver disease • Nephrotic syndrome • Lipodystrophy • Other serum markers (e.g., apolipoprotein A1, C-reactive protein)
Study design	<p>KQs 1, 2: RCTs, CCTs, and systematic reviews</p> <p>KQ3: RCTs, CCTs, systematic reviews, and cohort</p>	<p>All KQs: Studies rated as poor quality</p> <p>KQs 1–3, 5, 6, 8: Qualitative studies, case</p>

	Included	Excluded
	studies KQs 4, 7: RCTs, CCTs, systematic reviews, cohort studies, observational studies, systematically selected case-series, and qualitative studies KQs 5, 6: RCTs and systematic reviews KQ8: RCTs, CCTs, systematic reviews, cohort studies, registry studies, long-term trial followup, high-quality case-control studies	reports, cost-effectiveness studies KQs 1, 2, 5, 6: Cohort studies KQs 4, 7: None
Settings	<ul style="list-style-type: none"> • Publication date of 2007 to present and studies included in prior USPSTF reviews on this topic • Conducted in countries with a Human Development Index score of ≥ 0.9, as defined by the United Nations 	Settings not generalizable to primary care

Abbreviations: KQ = key question, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, mg/dL = milligram(s) per deciliter, mmol/L = millimole per liter, MI = myocardial infarction, CCT = controlled clinical trial, RCT = randomized controlled trial, USPSTF = U.S. Preventive Services Task Force, HIV = human immunodeficiency virus

*Secondary causes of dyslipidemia include: renal (chronic renal disease, hemolytic uremic syndrome, nephrotic syndrome); infectious (acute viral or bacterial infections, HIV, hepatitis); hepatic (obstructive liver disease, cholestasis, biliary cirrhosis, Alagille syndrome); inflammatory (systemic lupus erythematosus, juvenile rheumatoid arthritis); storage (glycogen storage disease, Gaucher disease, cystine storage disease, Tay-Sachs disease, Niemann-Pick disease); and other (Kawasaki disease, anorexia nervosa, cancer, previous solid organ transplant, progeria, idiopathic hypercalcemia, Klinefelter syndrome, Werner syndrome, polycystic ovary syndrome, type 1 or 2 diabetes).

Figure 1: Literature flow diagram



Appendix B. Ongoing Studies

We identified one potentially relevant ongoing RCT through four registries: ClinicalTrials.gov (<http://clinicaltrials.gov>), Current Controlled Trials (<http://www.controlled-trials.com>), Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>) and the World Health Organization's International Clinical Trials Registry Platform (<http://www.who.int/ictrp>). We restricted our searches to dyslipidemia in children that met our inclusion criteria for any key question.

We found a study evaluating statins in obese teenagers with dyslipidemia that was completed in 2013 but whose results are not yet published.⁷⁸ The obese teenagers with dyslipidemia were randomly assigned to receive either 10 mg of atorvastatin every day for 1 year or placebo. The main endpoint was change in carotid intima media thickness. Lipid profiles were measured at baseline, 6 months, and 12 months after the intervention.

Appendix C. Excluded Studies

Table 1: Exclusion Codes

Code	Reason for Exclusion
E1	Not English
E2	Not original research in a peer-reviewed journal
E4	Ineligible SETTING (a) non-generalizable to primary care; (b) low HDI country
E5	Ineligible POPULATION
E6	Ineligible OUTCOMES
E7	Ineligible screening strategy
E8	Ineligible treatment
E9	Ineligible study design
E10	Study rated as poor quality
E11	Overlapping study population
E12	N/A

Abbreviations: HDI = Human Development Index, N/A = not applicable

*The exclusion code E3 was not used

- | | |
|---|---|
| <p>1. Abe Y, Okada T, Sugiura R, et al. Reference ranges for the non-high-density lipoprotein cholesterol levels in Japanese children and adolescents. <i>J Atheroscler Thromb.</i> 2015;22(7):669-75. PMID: 25739922. KQ3E6.</p> | <p>25381943. KQ1E13, KQ2E13, KQ3E5, KQ4E5, KQ5E13.</p> |
| <p>2. Abello F, Cagliero P, Giorgis M, et al. Lycopene supplementation in children affected by primary dyslipidaemia: Effects on lipid profile and oxidative stress. <i>High Blood Press Cardiovasc Prev.</i> 2012;(2):94. KQ6E13, KQ7E13.</p> | <p>6. Alavian SM, Motlagh ME, Ardalan G, et al. Hypertriglyceridemic waist phenotype and associated lifestyle factors in a national population of youths: CASPIAN Study. <i>J Trop Pediatr.</i> 2008;54(3):169-77. PMID: 18156644. KQ3E4.</p> |
| <p>3. Agirbasli M, Agaoglu NB, Orak N, et al. Sex hormones, insulin resistance and high-density lipoprotein cholesterol levels in children. <i>Horm Res Paediatr.</i> 2010;73(3):166-74. PMID: 20197668. KQ3E4, KQ4E4.</p> | <p>7. Ali MK, Bullard KM, Beckles GL, et al. Household income and cardiovascular disease risks in U.S. children and young adults: analyses from NHANES 1999-2008. <i>Diabetes Care.</i> 2011;34(9):1998-2004. PMID: 21868776. KQ3E6.</p> |
| <p>4. Akdim F, Tribble DL, Flaim JD, et al. Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidaemia. <i>Eur Heart J.</i> 2011;(21):2650-9. PMID: 21593041. KQ6E5, KQ7E5.</p> | <p>8. Amundsen AL, Ose L, Nenseter MS, et al. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia. <i>Am J Clin Nutr.</i> 2002;(2):. PMID: 12145004. KQ1E5, KQ2E13, KQ3E13, KQ4E13, KQ5E13.</p> |
| <p>5. Akyurek N, Atabek ME, Eklioglu BS, et al. Is there a relationship between cardiovascular risk factors and dehydroepiandrosterone sulfate levels in childhood obesity? <i>J Pediatr Endocrinol Metab.</i> 2014;28(42130):545-50. PMID:</p> | <p>9. Andersen GE, Brokhattingen K, Lous P. Familial hypobetalipoproteinaemia in 9 children diagnosed as the result of cord blood screening for hypolipoproteinaemia in 10,000 Danish newborns. <i>Arch Dis Child.</i> 1979;54(9):691-4. PMID: 229774. KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.</p> |
| | <p>10. Andersen GE, Lous P, Friis-Hansen B. Screening for hyperlipoproteinemia in</p> |

- 10,000 Danish newborns. Follow-up studies in 522 children with elevated cord serum VLDL-LDL-cholesterol. *Acta Paediatr Scand.* 1979;68(4):541-5. PMID: 223372. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
11. Andersen GE, Nielsen HG. Neonatal screening for hyperlipoproteinemia. Methods for direct estimation of cord serum VLDL + LDL. *Clin Chim Acta.* 1976;66(1):29-41. PMID: 177231. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
 12. Andersen LB, Riddoch C, Kriemler S, et al. Physical activity and cardiovascular risk factors in children. *Br J Sports Med.* 2011;45(11):871-6. PMID: 21791456. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
 13. Andersen LB, Wedderkopp N, Hansen HS, et al. Biological cardiovascular risk factors cluster in Danish children and adolescents: the European Youth Heart Study. *Prev Med.* 2003;37(4):363-7. PMID: 14507494. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
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 17. Avis HJ, Vissers MN, Wijburg FA, et al. The use of lipid-lowering drug therapy in children and adolescents. *Curr Opin Investig Drugs.* 2009;10(3):224-31. PMID: 19333879. **KQ6E9, KQ7E9.**
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 21. Ballantyne C, Gleim G, Liu N, et al. Effects of coadministered extended-release niacin/laropiprant and simvastatin on lipoprotein subclasses in patients with dyslipidemia. *J Clin Lipidol.* 2012;6(3):235-43. PMID: 22658147. **KQ6E5, KQ7E5.**
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- infarction. *J Cardiovasc Med (Hagerstown)*. 2011;12(7):482-6. PMID: 21519277. **KQ3E5, KQ4E5.**
25. Bassols J, Prats-Puig A, Gispert-Sauch M, et al. Increased serum IgG and IgA in overweight children relate to a less favourable metabolic phenotype. *Pediatr Obes*. 2013;9(3):232-8. PMID: 23554403. **KQ3E6.**
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41. Bell L, Davis E, Knuiman M, et al. Lipids in Australian children: cause for concern? 2005-2007 Busselton Health Study. *J Paediatr Child Health*. 2012;48(10):E172-7. PMID: 22998088. **KQ3E7.**
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65. Cagliero P, Marini E, Cena C, et al. The effects of probiotics supplementation on antioxidant activity in children affected by primary hyperlipidemia. *High Blood Press Cardiovasc Prev.* 2014;21(2):151-169. **KQ6E13, KQ7E13.**
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Appendix D. Cohort Studies

National Health and Nutritional Examination Survey (NHANES)
Bogalusa Heart Study
Pathobiological Determinants of Atherosclerosis in Youth (PDAY)
Muscatine Study
Princeton Lipid Research Clinics Follow-up Study
Cardiovascular Risk in Young Finns Study (Young Finns)
National Heart, Lung, and Blood Institute Growth and Health Study (NGHS)
Special Turku Coronary Risk Factor Intervention Project (STRIP)
Coronary Artery Risk Development in Young Adults Study (CARDIA)
Minnesota Children's Blood Pressure Study
Beaver County Lipid Study
Fels Longitudinal Study
National Children's Study (NIH)
Four Provinces study (4P)