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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 January 1, 2006 and December 31, 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 KQ. 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), intermediate health outcomes (KQ2), harms of screening (KQ4), or effect of treatment on adult health outcomes (KQ5). Studies met the inclusion criteria for four KQs.

KQ3. 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 TC concentration of 200 mg/dL (the National Cholesterol Education Program's [NCEP's] 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 6.5 percent for 13- to 17-year-olds. Simulated diagnostic yields ranged between 4 and 12 percent for different age and body mass index subgroups. Based on large, recent U.S. studies, the highest diagnostic yield appears to be in obese children (12.3%), children ages 9 to 11 years (7.2%), and adolescents ages 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 among 9- to 11-year-olds was more widely adopted.

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?

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 ages 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.

KQ7. 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.

KQ8. What is the association between intermediate outcomes in childhood and adolescence and future incidence of myocardial infarction (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 ages 12 to 39 years was not associated with death before age 55 years. The study did find that very high TC concentrations (≥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 FH, for whom premature coronary heart disease deaths are expected. The meaning of this finding is unclear because of the small number of deaths in this subgroup.

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 younger than 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 underidentify 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/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 greater than 200 mg/dL or LDL-C concentrations greater than 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 MI 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 body mass index. 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 (MI 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 followup 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.

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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 U.S. 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 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 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 ages 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 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 studies[2] 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's (NCEP's) recommendation for fixed cutoff values to define dyslipidemia in children (TC≥200 mg/dL and LDL-C ≥130 mg/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.

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, type 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 ages 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 dyslipidemia.[12] In the United States, dyslipidemia is experienced disproportionately by adults with Hispanic ethnicity[13] and those of Asian ancestry.[14]

The prevalence of elevated TC in children ages 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, HDL, and very-low-density lipoprotein (VLDL). TC is comprised of 60 to 70 percent LDL-C, 20 to 30 percent HDL-C, and 10 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 CHD. 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] CHD is the leading cause of death in the United States.[19, 20]

Identifying and treating dyslipidemia in adults older than 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 antemortem 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-media thickness (CIMT) at ages 33 to 42 years.[24] A followup of the Bogalusa cohort found that LDL-C concentrations at ages 5 to 17 years predicted CIMT at ages 16 to 19 years.[25] In the Young Finns study, LDL[26, 27] and ApoB/ApoA-1[28] concentrations in adolescence (ages 12 to18 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 postmortem LDL-C plus VLDL-C concentrations and negatively associated with HDL-C concentrations.[29] In that same study, high non–HDL-C and low HDL-C 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 [Coronary Artery Risk Detection in Appalachian Communities] study), 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 nonoptimal lipid concentrations in young adulthood is associated with atherosclerotic changes later in life. One prospective cohort study of 2,824 persons age 18 to 30 years with nonoptimal 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 two 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 (PPV) of only 32.9 percent (NCEP) and 37.3 percent (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 ages 9 to 11 years and again at ages 17 to 21 years) as well as selective screening at other ages.[39]

Laboratory Studies

TC may be measured with fasting or nonfasting serum testing. Concentrations of LDL-C may be calculated with the Friedewald formula:[40] LDL-C = TC – (triglycerides/5) – HDL-C. 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 nonfasting 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.

NCEP, 1992

In 1992, 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 overuse of these drugs in children.[2] The panel recommended selective screening based on a family history of premature CHD, first with TC concentrations and second, if TC concentrations were elevated, obtaining a fasting lipid panel (repeated if abnormal).

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 mg/dL 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 age 10 years 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. 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.

USPSTF, 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 either routine selective or universal screening of infants, children, adolescents, or young adults up to age 20 years, 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 ages 2 to 10 years who had a family history of dyslipidemia or premature CHD or unknown family history with 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 age 8 years and older who had 1) LDL-C concentrations greater than 190 mg/dL, 2) LDL-C concentrations greater than160 mg/dL with family history of CHD and cardiac risk factors, or 3) LDL-C concentrations greater than 130 mg/dL and diabetes.

NHLBI, 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 prepubertal 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 ages 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 greater than 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 age 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 NCEP in 1992. However, normal cholesterol concentrations vary with age and sex throughout childhood. Thus, these cut points (TC ≥200 mg/dL and LDL-C ≥130 mg/dL) may both overidentify and underidentify 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 preschool 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 range.[37]

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 years (I statement).[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 randomized, controlled trials (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 nondrug interventions, such as exercise and dietary interventions.

Chapter 2. Methods

Overview

This systematic review was designed to complement the systematic review supporting the recommendation on screening for FH 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 FH.

KQs and Analytic Framework

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

Screening KQs

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 KQs

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 KQ

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–HDL-C, as well as 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**). Our search included results from: AHRQ, 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 the National Institute for Health and Care 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 KQs 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 KQ 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 1–4), we included studies of asymptomatic persons ages 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 nonfasting lipid measurement, TC or LDL-C alone or in combination with HDL-C) 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 5–7), we included interventions using lipid-lowering drugs or lifestyle interventions, including diet or exercise. We focused on interventions targeting persons ages 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 or greater.[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., 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 the 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-quality 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 quality 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), RCT characteristics (e.g., setting, blinding, methods of measuring outcomes and exposures, duration, and lipid concentrations), outcomes for screening studies (e.g., true positives, diagnostic yield, and PPV), intermediate outcomes (e.g., lipid concentrations and CIMT) and health outcomes (e.g., MI and stroke), and harms.

Data Synthesis and Analysis

The findings are summarized in **Tables 3–14**. We used the 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 KQs 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, KQs, 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, as well as federal partners from the Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, National Institutes of Health, Veteran's Health Administration, and the Military Health Service. We compiled and addressed comments received during this time, as appropriate. Additionally, a draft of the full report was posted on the USPSTF's Web site from December 22, 2015 to January 25, 2016. A few comments were received during this public comment period; there were no changes made to the report based on these comments.

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. 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 report. 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**). The remaining 16 articles are the body of evidence for this review. We included four screening studies (the source for eight articles) (**Table 3**) and two treatment studies (the source for seven articles) (**Table 4**). There was overlap between the two KQs on treatment: two studies (the source for five articles) were included for KQ6 and one study (the source for five articles) was included for KQ7. One of these studies and three 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 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 fair-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 nonfasting 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 PPV from the older Ohio study to compute a simulated diagnostic yield: screening yield × PPV of the initial screen = diagnostic yield.

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

1. *NHANES*. This survey is conducted in consecutive 2-year cycles on a national sample selected with a multistage, stratified sampling design. NHANES is designed to produce results representative of the civilian, noninstitutionalized 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 CARDIAC Program*. Two publications report 2003 to 2008 TC and LDL-C data from this statewide screening program targeting fifth 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 study[49] (**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 persons 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 the sample. The four NHANES publications included here focused on overlapping age ranges, with the lower limit at ages 6 to 8 years and the upper limit at 17 to 19 years. These publications have partially overlapping populations; however, only data from nonoverlapping NHANES samples are shown in **Tables 7–9**. Individuals were not excluded from analyses for a diagnosis of primary or secondary dyslipidemia.

The CARDIAC study recruited fifth-grade students from schools in all 55 West Virginia counties. The racial/ethnic distribution was 93 percent white, 3 percent black, 2 percent biracial, 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 nonfasting blood sample from children and adolescents who presented for well-child care. Those with nonfasting 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 workup or diagnostic evaluation for these children is described.

In CARDIAC, parents of all fifth-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 examination for acanthosis nigricans, and a fasting lipid panel, including TC, LDL-C, HDL-C, and triglyceride 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 CHD, defined as first- or second-degree relatives who had experienced MI, coronary bypass surgery, angioplasty or stent, or coronary death before age 55 years. 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 followup 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 nonfasting 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 publications[55] 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 nongeneralizable populations, inappropriately addressed nonindependence of observations, and the use of nonfasting lipid concentrations. Three articles were excluded for quality, 40 for study design issues, and 24 for screening method (**Appendix C**).

Overall Results and Summary of Findings

The 1989 Ohio study used nonfasting TC concentrations to screen children and adolescents universally. At a cut point of 200 mg/dL, this screening approach had a PPV 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 [SEs] or confidence intervals [CIs]) for the overall population and for relevant subgroups. We applied the PPV of 77 percent and obtained simulated diagnostic yields ranging from 4.8 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 nonfasting 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 greater (i.e., PPV of 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 CIs) 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.

NHANES

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 >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 nonsignificant 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 studies[55] 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, greater than 160 mg/dL with two 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 greater than 190 mg/dL, a concentration consistent with FH.[55]

The CARDIAC Study

The West Virginia CARDIAC study screened 23,263 fifth-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) was 10.7 percent.[7] (Neither of the two publications on this trial reported CIs 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 (>95th percentile). Elevated LDL-C (>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 CHD, 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 for those with a family history and 9.5 percent for those without (**Tables 7** and **8**).[57]

The Health System Study

In this retrospective analysis of automated medical records, children ages 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 (**Tables 7** and **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 the healthy-weight group. The 95% CIs did not overlap. A similar association was found for LDL-C measurements, although the CIs 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 studies[7] 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 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 trials[62] 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 NCEP Step II diet[2] with a multiyear 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 ages 8 to 10 years, whereas the flaxseed trial recruited children ages 8 to 18 years (mean, 13.2 years [standard deviation (SD), 2.3 years]).[60] Girls and boys were well represented in both trials. The dietary trial was conducted in the United States[61] 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 predetermined 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 Clinics study.[65] Children were initially selected on the basis of a nonfasting TC

concentration greater than 175 mg/dL. Children with fasting LDL-C concentrations 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 greater than 200 mg/dL or HDL-C concentrations less than 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 NCEP 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 3 years. During the first 6 months, participants had 11 group visits and two 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 quality[60] 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**).

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 baseline fasting TC concentration for DISC participants was 200 mg/dL (SD, 14.6 mg/dL) for both the intervention and control groups. Mean fasting LDL-C concentrations were 130.6 mg/dL (SD, 12.2 mg/dL) and 130.5 mg/dL (SD, 11.6 mg/dL) for the intervention and control groups, respectively (**Table 10**). Mean baseline HDL-C and triglyceride 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 (87.5%) were assessed at year 7. Mean age at year 7 was 17.0 years (SD, 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 four 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 a 24-hour dietary recall instrument administered by trained certified dietitians on three nonconsecutive 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 total fat intake (as a percentage of energy intake) in the intervention group was 28.5 percent (SD, 5.8%) at year 1 and 28.6 percent (SD, 5.8%) 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 percent (SD, 5.5%) at year 1 and 33.0 percent (SD, 4.7%) 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 $p=0.03$). 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 triglycerides 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**, **Figures 2** and **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 fasting lipid concentrations for participants at baseline were: TC of 208 mg/dL (SD, 30 mg/dL); LDL-C of 138 mg/dL (SD, 25 mg/dL); HDL-C of 49 mg/dL (SD, 12 mg/dL); and triglycerides of 112 mg/dL (SD, 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 of 80 percent (SD, 18%) adherence to the dietary supplement in the placebo group and 85 percent (SD, 12%) 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 triglycerides 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 of 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 NCEP Step II diet and family-based counseling approach are described above under KQ6.

Assessment of Harms

The DISC participants' anthropometric measurements (weight, height, and 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 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, and B12 and calcium, magnesium, phosphorous, thiamine, niacin, riboflavin, folate, iron, and zinc was monitored at these time points to warn of possible deficiencies.

Psychosocial assessments[68] were done at year 3 and included: the Child Behavior Checklist (internalizing, externalizing, social competency, thought problems, anxiety/depression, and 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 quality[69] (**Appendix C**). Other trials were excluded because they were not RCTs.

Overall Results

The DISC trial revealed no harms of a modified NCEP 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 μg/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 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 (≤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 and adjusting for baseline values of age, sex, household income, and number of parents in the household. An interaction term for treatment group × 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 followup (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 followup 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 vs. 110.0 mm Hg; p=0.03; fasting plasma glucose, 87.0 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 nondietary variables did not materially alter these results.

Three random, nonconsecutive, 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 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 good-quality 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 years 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 and 1994 who were ages 12 to 39 years at the time of the survey. Half the participants were female, mean age was 26.1 years (SE, 0.17 years), 77.2 percent were non-Hispanic white, 14.7 percent were non-Hispanic black, and 8.1 percent were Mexican American. Participants whose race/ethnicity was classified as something other than these three categories were excluded from analysis. Baseline mean TC concentration was 182.0 mg/dL (SE, 0.82 mg/dL), and 28.5 percent of participants had TC 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 years from all causes and death before age 55 years 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

Although the included study was of good quality, it was considered to provide fair-quality evidence for KQ8, primarily because its age range was broader than our a priori inclusion criteria and because it is the only included study for KQ8. 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 years 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 an RH 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 age 55 years (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 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%), children ages 9 to 11 years (7.2%), and adolescents ages 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, respectively, provide reasonable estimates of what might be seen for those subgroups if screening among 9- to 11-year-olds was 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 study[7] 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 adulthood[34] is a current limitation of the evidence. Multifactorial dyslipidemia detected in persons younger than age 20 years is likely to resolve in young adulthood;[37] 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 underidentify 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/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 overidentify 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 “nondisease” could result in subtle harms, such as labeling 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 children and adolescents 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 Body of Evidence

The DISC trial enrolled children with milder hyperlipidemia, making it difficult to generalize results to children with TC concentrations greater than 200 mg/dL or LDL-C greater than 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 group[74] 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 (≥240 mg/dL) were 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 greater than 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 ages 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 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/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.

References

1. Cook S, Auinger P, Huang TT. Growth curves for cardio-metabolic risk factors in children and adolescents. J Pediatr. 2009;155(3):S6 e15-26. PMID: 19732566.
2. National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89(3):495-501. PMID: 1741227.
3. Daniels SR. Screening for familial hypercholesterolemia: what is the most effective strategy? Nat Clin Pract Cardiovasc Med. 2008;5(3):130-1. PMID: 18059381.
4. Tamir I, Heiss G, Glueck CJ, et al. Lipid and lipoprotein distributions in white children ages 6-19 yr. The Lipid Research Clinics Program Prevalence Study. J Chronic Dis. 1981;34(1):27-39. PMID: 7451637.
5. Martinez-Gomez D, Eisenmann JC, Gomez-Martinez S, et al. Sedentary behavior, adiposity and cardiovascular risk factors in adolescents. The AFINOS study. Rev Esp Cardiol. 2010;63(3):277-85. PMID: 20196988.
6. Raman A, Sharma S, Fitch MD, et al. Anthropometric correlates of lipoprotein profile and blood pressure in high BMI African American children. Acta Paediatr. 2010;99(6):912-9. PMID: 20064141.
7. Ice CL, Murphy E, Cottrell L, et al. Morbidly obese diagnosis as an indicator of cardiovascular disease risk in children: results from the CARDIAC Project. Int J Pediatr Obes. 2011;6(2):113-9. PMID: 20545480.
8. Kit BK, Kuklina E, Carroll MD, et al. Prevalence of and trends in dyslipidemia and blood pressure among U.S. children and adolescents, 1999-2012. JAMA Pediatr. 2015;169(3):272-9. PMID: 25599372.
9. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311(8):806-14. PMID: 24570244.
10. Gidding SS, Barton BA, Dorgan JA, et al. Higher self-reported physical activity is associated with lower systolic blood pressure: the Dietary Intervention Study in Childhood (DISC). Pediatrics. 2006;118(6):2388-93. PMID: 17142523.
11. Wong ND, Hei TK, Qaqundah PY, et al. Television viewing and pediatric hypercholesterolemia. Pediatrics. 1992;90(1 Pt 1):75-9. PMID: 1614784.
12. Austin MA, Hutter CM, Zimmern RL, et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160(5):407-20. PMID: 15321837.
13. Rodriguez CJ, Daviglus ML, Swett K, et al. Dyslipidemia patterns among Hispanics/Latinos of diverse background in the United States. Am J Med. 2014;127(12):1186-94 e1. PMID: 25195188.
14. Frank AT, Zhao B, Jose PO, et al. Racial/ethnic differences in dyslipidemia patterns. Circulation. 2014;129(5):570-9. PMID: 24192801.
15. Kit BK, Carroll MD, Lacher DA, et al. Trends in serum lipids among U.S. youths aged 6 to 19 years, 1988-2010. JAMA. 2012;308(6):591-600. PMID: 22871871.
16. Gillman MW, Cupples LA, Moore LL, et al. Impact of within-person variability on identifying children with hypercholesterolemia: Framingham Children's Study. J Pediatr. 1992;121(3):342-7. PMID: 1517906.

17. National Institutes of Health. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421. PMID: 12485966.
18. Centers for Disease Control and Prevention. Prevalence of coronary heart disease--United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60(40):1377-81. PMID: 21993341.
19. Hoyert DL. 75 years of mortality in the United States, 1935-2010. NCHS Data Brief. 2012(88):1-8. PMID: 22617094.
20. Minino AM. Death in the United States, 2011. NCHS Data Brief. 2013(115):1-8. PMID: 23742756.
21. Helfand M, Carson S. Screening for Lipid Disorders in Adults: Selective Update of 2001 U.S. Preventive Services Task Force Review. Evidence Synthesis No. 49. AHRQ Publication no. 08-05114-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; April 2008. PMID: 20722146.
22. Newman WP, 3rd, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. N Engl J Med. 1986;314(3):138-44. PMID: 3455748.
23. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998;338(23):1650-6. PMID: 9614255.
24. Davis PH, Dawson JD, Riley WA, et al. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation. 2001;104(23):2815-9. PMID: 11733400.
25. Frontini MG, Srinivasan SR, Xu J, et al. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. Pediatrics. 2008;121(5):924-9. PMID: 18450895.
26. Raitakari OT, Ronnemaa T, Jarvisalo MJ, et al. Endothelial function in healthy 11-year-old children after dietary intervention with onset in infancy: the Special Turku Coronary Risk Factor Intervention Project for children (STRIP). Circulation. 2005;112(24):3786-94. PMID: 16330680.
27. Raitakari OT, Juonala M, Kahonen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA. 2003;290(17):2277-83. PMID: 14600186.
28. Juonala M, Viikari JS, Kahonen M, et al. Childhood levels of serum apolipoproteins B and A-I predict carotid intima-media thickness and brachial endothelial function in adulthood: the cardiovascular risk in young Finns study. J Am Coll Cardiol. 2008;52(4):293-9. PMID: 18634985.
29. McGill HC, McMahan CA, Malcom GT, et al. Effects of Serum Lipoproteins and Smoking on Atherosclerosis in Young Men and Women. Arterioscler Thromb Vasc Biol. 1997;17(1):95-106. PMID: 9012643.
30. McGill HC, Jr., McMahan CA, Zieske AW, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 2000;20(8):1998-2004. PMID: 10938023.

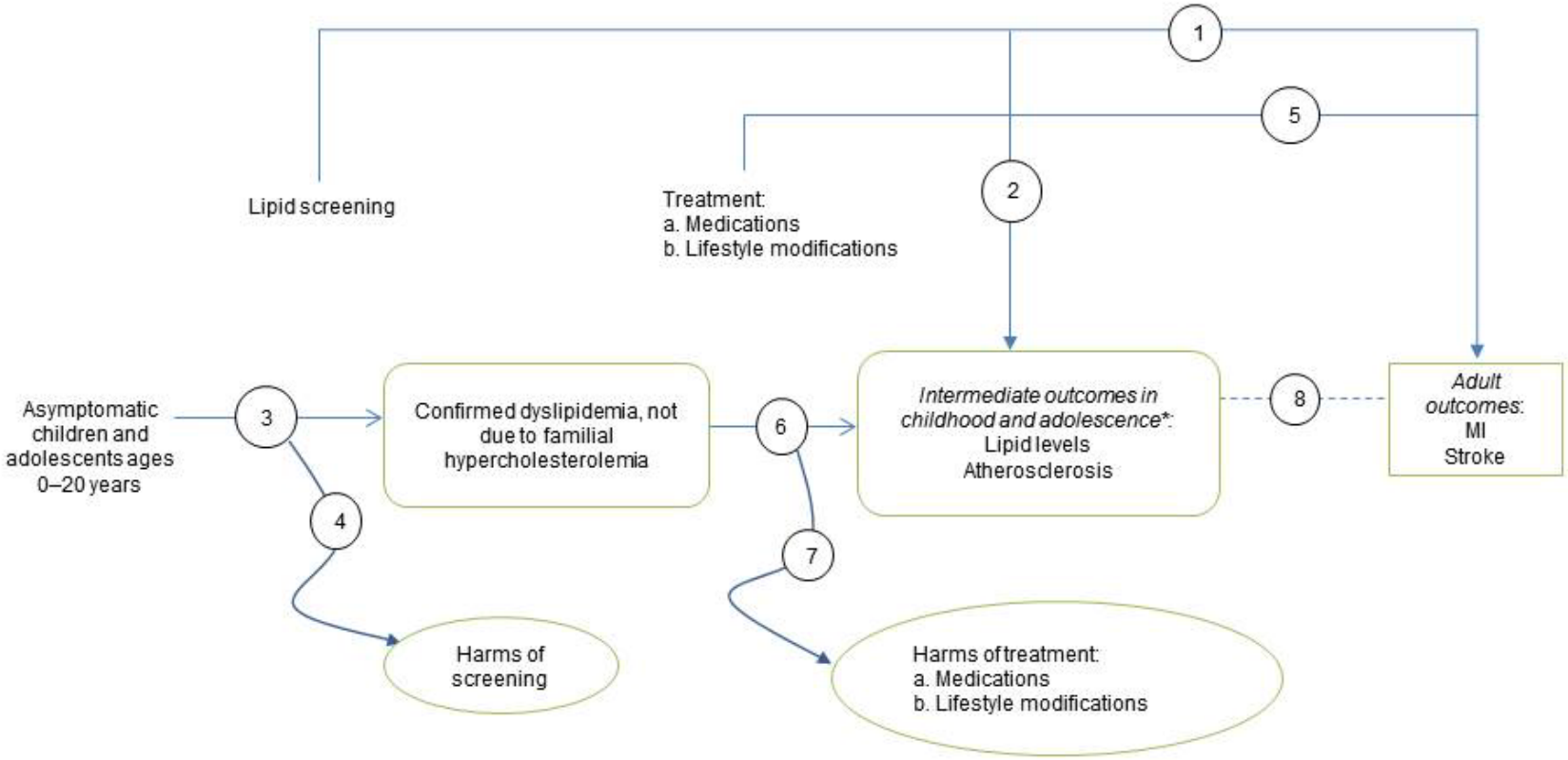
31. Mittelman SD, Gilsanz P, Mo AO, et al. Adiposity predicts carotid intima-media thickness in healthy children and adolescents. J Pediatr. 2010;156(4):592-7 e2. PMID: 20004913.
32. Raynor LA, Schreiner PJ, Loria CM, et al. Associations of retrospective and concurrent lipid levels with subclinical atherosclerosis prediction after 20 years of follow-up: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Ann Epidemiol. 2013;23(8):492-7. PMID: 23889858.
33. Pletcher MJ, Bibbins-Domingo K, Liu K, et al. Nonoptimal lipids commonly present in young adults and coronary calcium later in life: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Ann Intern Med. 2010;153(3):137-46. PMID: 20679558.
34. Haney EM, Huffman LH, Bougatsos C, et al. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the U.S. Preventive Services Task Force. Pediatrics. 2007;120(1):e189-e214. PMID: 17606543.
35. Juhola J, Magnussen CG, Viikari JS, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. J Pediatr. 2011;159(4):584-90. PMID: 21514597.
36. Clarke WR, Schrott HG, Leaverton PE, et al. Tracking of blood lipids and blood pressures in school age children: the Muscatine study. Circulation. 1978;58(4):626-34. PMID: 688572.
37. Magnussen CG, Raitakari OT, Thomson R, et al. Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. Circulation. 2008;117(1):32-42. PMID: 18071074.
38. National Cholesterol Education Program: highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89(3):495-501. PMID: 1538956.
39. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011;128 Suppl 5:S213-56. PMID: 22084329.
40. Harris N, Neufeld EJ, Newburger JW, et al. Analytical performance and clinical utility of a direct LDL-cholesterol assay in a hyperlipidemic pediatric population. Clin Chem. 1996;42(8 Pt 1):1182-8. PMID: 8697574.
41. Skinner AC, Steiner MJ, Chung AE, et al. Cholesterol curves to identify population norms by age and sex in healthy weight children. Clin Pediatr (Phila). 2012;51(3):233-7. PMID: 22157422.
42. Kwiterovich PO. Clinical and laboratory assessment of cardiovascular risk in children: Guidelines for screening, evaluation, and treatment. J Clin Lipidol. 2008;2(4):248-66. PMID: 21291741.
43. U.S. Preventive Services Task Force. Screening for lipid disorders in children: U.S. Preventive Services Task Force recommendation statement. Pediatrics. 2007;120(1):e215-e9. PMID: 17606545.
44. Daniels SR, Greer FR, Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122(1):198-208. PMID: 18596007.

45. Vinci SR, Rifas-Shiman SL, Cheng JK, et al. Cholesterol testing among children and adolescents during health visits. JAMA. 2014;311(17):1804-7. PMID: 24794376.
46. Joyce N, Wellenius GA, Dore DD, et al. Patterns of Lipid Lowering Therapy among Children Ages 8-20 Years. J Pediatr. 2015;167(1):113-9 e1. PMID: 25953004.
47. Daniels SR, Gidding SS, de Ferranti SD, et al. Pediatric aspects of familial hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):S30-7. PMID: 21600527.
48. United Nations Development Programme. Human Development Index: 2013 Rankings. United Nations Development Programme [2014]. http://hdr.undp.org/en/2013-report.
49. Garcia RE, Moodie DS. Routine cholesterol surveillance in childhood. Pediatrics. 1989;84(5):751-5. PMID: 2640549.
50. Griffin TC, Christoffel KK, Binns HJ, et al. Family history evaluation as a predictive screen for childhood hypercholesterolemia. Pediatric Practice Research Group. Pediatrics. 1989;84(2):365-73. PMID: 2748269.
51. Douglas MB, Birrer RB, Medidi S, et al. Obese children should be screened for hypercholesterolemia. J Health Care Poor Underserved. 1996;7(1):24-35. PMID: 8645782.
52. Manchester RA, McDuffie C, Diamond E. Screening for hypercholesterolemia in college students. J Am Coll Health. 1989;37(4):149-53. PMID: 2926025.
53. Gagliano NJ, Emans SJ, Woods ER. Cholesterol screening in the adolescent. J Adolesc Health. 1993;14(2):104-8. PMID: 8476872.
54. Faigel HC. Screening college students for hypercholesterolemia. J Am Coll Health. 1992;40(6):272-5. PMID: 1602094.
55. Ford ES, Li C, Zhao G, et al. Concentrations of low-density lipoprotein cholesterol and total cholesterol among children and adolescents in the United States. Circulation. 2009;119(8):1108-15. PMID: 19221218.
56. Centers for Disease Control and Prevention. Prevalence of abnormal lipid levels among youths --- United States, 1999-2006. MMWR Morb Mortal Wkly Rep. 2010;59(2):29-33. PMID: 20094024.
57. Ritchie SK, Murphy EC, Ice C, et al. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. Pediatrics. 2010;126(2):260-5. PMID: 20624798.
58. Margolis KL, Greenspan LC, Trower NK, et al. Lipid screening in children and adolescents in community practice: 2007 to 2010. Circ Cardiovasc Qual Outcomes. 2014;7(5):718-26. PMID: 25160839.
59. National Center for Health Statistics. Analytic and Reporting Guidelines: the Third National Health and Nutrition Examination Survey (NHANES III) 1988-1994. Hyattsville, MD: National Center for Health Statistics; Centers for Disease Control and Prevention; 1996.
60. Wong H, Chahal N, Manlhiot C, et al. Flaxseed in pediatric hyperlipidemia: a placebo-controlled, blinded, randomized clinical trial of dietary flaxseed supplementation for children and adolescents with hypercholesterolemia. JAMA Pediatr. 2013;167(8):708-13. PMID: 23733031.

61. Dietary intervention study in children (DISC) with elevated low-density-lipoprotein cholesterol. Design and baseline characteristics. DISC Collaborative Research Group. Ann Epidemiol. 1993;3(4):393-402. PMID: 8275216.
62. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). The Writing Group for the DISC Collaborative Research Group. JAMA. 1995;273(18):1429-35. PMID: 7723156.
63. Obarzanek E, Kimm SY, Barton BA, et al. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC). Pediatrics. 2001;107(2):256-64. PMID: 11158455.
64. Dorgan JF, Liu L, Barton BA, et al. Adolescent diet and metabolic syndrome in young women: Results of the Dietary Intervention Study in Children (DISC) follow-up study. J Clin Endocrinol Metab. 2011;96(12):E1999-2008. PMID: 21994964.
65. Heiss G, Tamir I, Davis CE, et al. Lipoprotein-cholesterol distributions in selected North American populations: the lipid research clinics program prevalence study. Circulation. 1980;61(2):302-15. PMID: 7351055.
66. Lozano P, Henrikson N, Dunn J, et al. Lipid screening in childhood for detection of familial hypercholesterolemia. Rockville, MD: Agency for Healthcare Research and Quality; U.S. Department of Health and Human Services; in process.
67. Obarzanek E, Hunsberger SA, Van Horn L, et al. Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC). Pediatrics. 1997;100(1):51-9. PMID: 9200359.
68. Lavigne JV, Brown KM, Gidding S, et al. A cholesterol-lowering diet does not produce adverse psychological effects in children: three-year results from the dietary intervention study in children. Health Psychol. 1999;18(6):604-13. PMID: 10619534.
69. Guardamagna O, Amaretti A, Puddu PE, et al. Bifidobacteria supplementation: effects on plasma lipid profiles in dyslipidemic children. Nutrition. 2014;30(7-8):831-6. PMID: 24985000.
70. Saydah S, Bullard KM, Imperatore G, et al. Cardiometabolic risk factors among U.S. adolescents and young adults and risk of early mortality. Pediatrics. 2013;131(3):e679-e86. PMID: 23420920.
71. Psaty BM, Rivara FP. Universal screening and drug treatment of dyslipidemia in children and adolescents. JAMA. 2012;307(3):257-8. PMID: 22174386.
72. Van Horn L, Obarzanek E, Friedman LA, et al. Children's adaptations to a fat-reduced diet: the Dietary Intervention Study in Children (DISC). Pediatrics. 2005;115(6):1723-33. PMID: 15930237.
73. Niinikoski H, Lagstrom H, Jokinen E, et al. Impact of repeated dietary counseling between infancy and 14 years of age on dietary intakes and serum lipids and lipoproteins: the STRIP study. Circulation. 2007;116(9):1032-40. PMID: 17698729.
74. Yeste D, Chacon P, Clemente M, et al. Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents. J Pediatr Endocrinol Metab. 2009;22(6):487-92. PMID: 19694195.
75. Expert Panel on Integrated Guidelines for Cardiovascular H, Risk Reduction in C, Adolescents, et al. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5:S213-56. PMID: 22084329.

76. Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35. PMID: 11306229.
77. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. Ottawa: Ottawa Hospital Research Institute [2014]. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
78. Université de Montréal. Intima Media Thickness Regression in Dyslipidemic Teenagers. ClinicalTrials.gov [Internet] Bethesda, MD: National Library of Medicine (U.S.); 2000- [cited 2015 June 3]. https://clinicaltrials.gov/ct2/show/NCT01768481. NLM Identifier: NCT01768481.

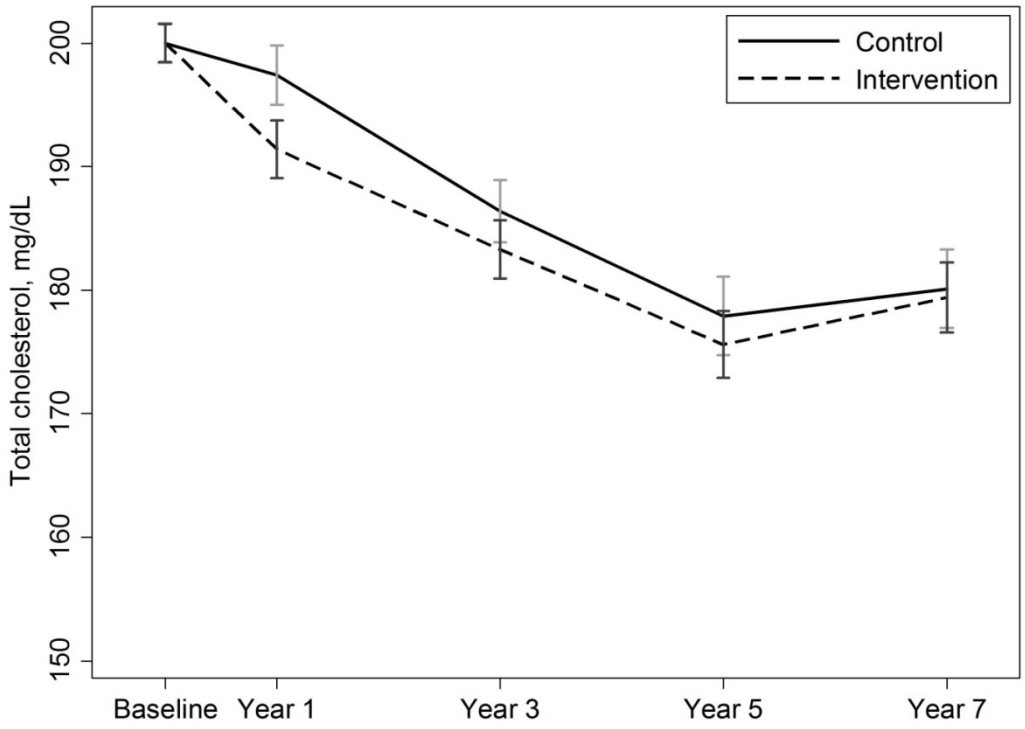
Figure 1. Analytic Framework



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

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

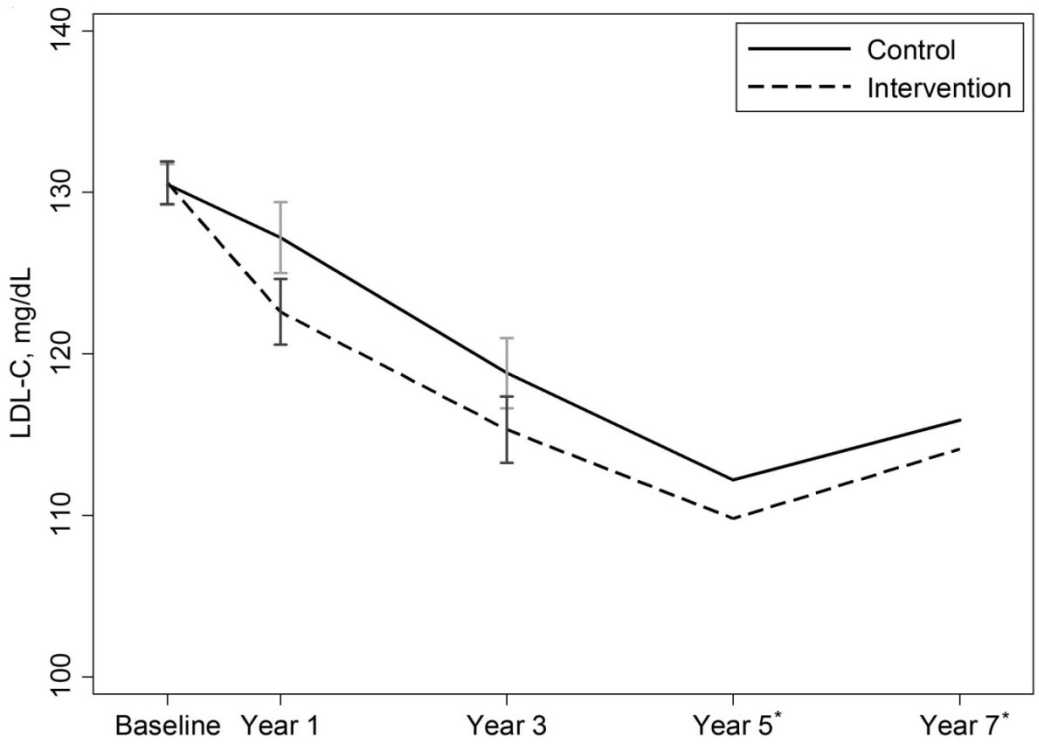
Figure 2. Results From DISC Study: Mean Total Cholesterol



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.

Abbreviation: DISC=Dietary Intervention Study in Children.

Figure 3. Results From DISC Study: Mean 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.

Abbreviation: DISC=Dietary Intervention Study in Children; LDL-C=low-density lipoprotein cholesterol.

Box 1. The National Cholesterol Education Program's Recommended Cut Points to Define Dyslipidemia in Children

Category	Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)
Acceptable	<170	<110
Borderline	170 to 199	110 to 129
High	≥200	≥130

Abbreviation: LDL=low-density lipoprotein.

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[61] 1993	NHLBI[75] CHILD-1 2011	NHLBI[75] CHILD-2-LDL 2011
Target population age	Children and adolescents older than age 2 years	Children and adolescents older than age 2 years	8 to 10 years	2 to 21 years	2 to 21 years
Target population LDL-C	110 to 129 mg/dL	≥130 mg/dL[†]	Moderately elevated LDL-C	Dyslipidemia or other risk factors*	≥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 (% of calories)					
Total fat	≤30%	≤30%	28%	25% to 30%	25% to 30%
Saturated fat	<10%	<7%	<8%	8% to 10%	≤7%
Polyunsaturated fat	<10%	≤10%	9%	Combined poly- and monounsaturated fats ≤20%	-
Monounsaturated fat	Remaining fat calories	Remaining fat calories	11%		~10%
Protein	~15% to 20%	~15% to 20%	14%	-	-
Carbohydrate	~55%	~55%	58%	-	-
Cholesterol (daily intake)	<300 mg/day	<200 mg/day	75 mg/1000 kcal 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

*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 mg/dL start on Step 1 diet and if LDL-C ≥110 mg/dL after 3 months, advance to Step 2 diet.

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.

Table 2. Recommendations for Lipid Assessment From NHLBI Expert Panel Report[39]

Age	Recommendation	Grade*	Recommendation Level†
Birth–12 months	**No lipid screening**	C	*Recommend*
2–8 years	**No routine lipid screening** Measure fasting lipid profile (FLP) x 2;‡ average results§ if:	B	*Recommend*
	• Parent, grandparent, aunt/uncle, or sibling with MI, angina, stroke, or CABG/stent/angioplasty at age <55 years in males or age <65 years in females	B	*Strongly Recommend*
	• Parent with TC ≥240 mg/dL or known dyslipidemia	B	*Strongly Recommend*
	• Child has diabetes, hypertension, BMI ≥95th percentile, or smokes cigarettes	B	*Strongly Recommend*
	• Child has a moderate- or high-risk medical condition§	B	*Strongly Recommend*
9–11 years	**Universal screening** • Non-FLP: Calculate non–HDL-C: Non-HDL-C = TC – HDL-C** Non–HDL-C ≥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 age <10 years; ≥130 mg/dL if age ≥10 years → repeat FLP after 2 weeks but within 3 months → lipid algorithms in NHLBI report§	B	*Strongly Recommend*
12–16 years	**No routine screening**†† Measure FLP x 2;‡ average results, if new knowledge of:	B	*Recommend*
	• Parent, grandparent, aunt/uncle, or sibling with MI, angina, stroke, CABG/stent/angioplasty, or sudden death at age <55 years in males or age <65 years in females	B	*Strongly Recommend*
	• Parent with TC ≥240 mg/dL or known dyslipidemia	B	*Strongly Recommend*
	• Patient has diabetes, hypertension, BMI ≥85th percentile, or smokes cigarettes	B	*Strongly Recommend*
	• Patient has moderate- or high-risk medical condition§	B	*Strongly Recommend*
17–21 years	**Universal screening once in this time period** Non-FLP: Calculate non–HDL-C: non–HDL-C = TC – HDL-C§ **17–19 yrs:** Non–HDL-C ≥145 mg/dL, HDL-C <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 ≥130 mg/dL → repeat FLP after 2 weeks but within 3 months → lipid algorithms in NHLBI report§ **20–21 yrs:** Non–HDL-C ≥190 mg/dL, HDL-C <40 mg/dL** → FLP x 2;‡ average results → ATP III management algorithm§ **OR** FLP: LDL-C ≥160 mg/dL, non–HDL-C ≥190 mg/dL, HDL-C <40 mg/dL, TG ≥150 mg/dL → repeat FLP after 2 weeks but within 3 months, average results → ATP III management algorithm§	B	*Recommend*

*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 Report[39] 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.

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

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
Study with confirmatory testing	Garcia 1989[49] Fair U.S. (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
Study without confirmatory testing – NHANES	Kit 2015[8] Good U.S.	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 noninstitutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1999–2012	3
	Kit 2012[15] Good U.S.	16,116	Cross-sectional	NR	6–19	47.8%–51.3% (range across time periods)	Sample weights were used to obtain prevalence estimates representative of the civilian noninstitutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1988–1994, 1999–2002, 2007–2010	3
	CDC 2010[56] Good U.S.	3,125	Cross-sectional	NR	12–19	48%	Sample weights were used to obtain prevalence estimates representative of the civilian noninstitutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1999–2006	3
	Ford 2009[55] Good U.S.	9,868*	Cross-sectional	NR	6–17*	49.7%*	Sample weights were used to obtain prevalence estimates representative of the civilian noninstitutionalized U.S. population	Nationally representative U.S. sample (NHANES)	1999–2006	3
Studies without confirmatory testing – other large U.S. studies	Margolis 2014[58] Fair U.S.	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

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
	CARDIAC Ice 2011[7] Ritchie 2010[57] Fair U.S. (WV)	23,263	Cross-sectional	10.84 (0.76)	NR	53.2%	93% Caucasian 2% Biracial 3% Black <1% each Asian, Hispanic, and other	Fifth-grade students in all 55 counties of West Virginia, CARDIAC Project	2003– 2008	3

*Represents population for whom TC data were available. The article also includes LDL-C data on 2,724 adolescents ages 12–17 years (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]

Abbreviations: SD=standard deviation, OH=Ohio, NR=not reported, NHANES=National Health and Nutrition Examination Survey; WV=West Virginia, CARDIAC=Coronary Artery Risk Detection in Appalachian Communities.

Table 4. Included Treatment Studies

Study, year Quality Country	N	Study design	Age, years Mean (SD)	Age range	% Female	Race	Population and setting	Dates of data collection	Included for key question(s)
Wong 2013[60] 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 of 135–193 mg/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 1993[61] DISC 1995[62] Obarzanek 1997[67] Lavigne 1999[68] Obarzanek 2001[63] Dorgan 2011[64] Good U.S.	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 ages 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.	1987–2008	6[61-64] 7[62-64, 67, 68]

*Values taken from population described in DISC 1993 article.[61]

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.

Table 5. Included Association Study

Author, Year Quality Country	N	% 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.	9,245	50.4%	26.1 (0.17) 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 Race/ethnicity	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] Fair U.S.	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%

*PPV = positive predictive value computed as true positives divided by number who returned for confirmatory test.
†Diagnostic yield = true positives divided by total screened.

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

Table 7. Weighted Prevalence of Elevated Total Cholesterol Concentration (≥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 (4.4–8.0) 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)

*The included publications used data from overlapping cohorts back to 1999. Shown in this table are data only from the nonoverlapping populations.
†This study did not report age range. The study population was fifth graders with a mean age of 10.84 years (standard deviation, 0.76 years).[7]

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.

Table 8. Weighted Prevalence of Elevated Low-Density Lipoprotein Cholesterol Concentration (≥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 (5.0–13.4) 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)	3–5 y: 6.8 (1.6–12.1) 6–8 y: 7.4 (4.8–9.9) 9–11 y: 8.1 (6.6–9.7) 12–16 y: 7.6 (6.7–8.4) 17–19 y: 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)

*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 years (standard deviation, 0.76 years).[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.

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.

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

*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 years (standard deviation, 0.76 years).[7]

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.

Table 10. Effect of Dietary Intervention on Total and Low-Density Lipoprotein Cholesterol in Children and Adolescents: Results of the Dietary Intervention Study in Children (DISC) 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 (0.74) CG: 9.5 (0.70)	--	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 to 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 to 3.2) p<0.001	IG: 122.6 (18.2) CG: 127.2 (19.4)	-4.8 (-7.4 to -2.2) p<0.001
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 to -0.2) p=0.04	IG: 115.3 (18.7) CG: 118.8 (19.4)	-3.3 (-6.0 to -0.6) p=0.02
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 to 1.2) p=0.18	IG: 109.8 (NR) CG: 112.2 (NR)	-2.7 (NR) p=0.11
Year 7	NR	IG: 283 CG: 265	IG: 17.0 (0.88) CG: 17.0 (0.93)	1.3 mean contacts per year	IG: 179.4 (24.1) CG: 180.1 (26.3)	-1.1 (-5.0 to 2.8) p=0.59	IG: 114.1 (NR) CG: 115.9 (NR)	-2.0 (NR) p=0.25
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**

*Data in this table come from four articles about the DISC trial: DISC 1993,[61] DISC 1995,[62] Obarzanek 2001,[63] and Dorgan 2011.[64]
[†]663 children were randomized. All analyses through year 7 were conducted as intent-to-treat. Numbers of participants assessed at each time point are shown in this column.
[‡]Year 1, 3, and 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).

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.

Table 11. Effect of Dietary Supplement on Lipid Levels in Children and Adolescents (KQ6)

Author, Year Quality Country	N (IG/CG) % 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 supplementation 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% to 2%) 0.20	-5% (-12% to 2%) 0.15	-15% (-24% to -6%) 0.001	26% (4% to 48%) 0.02

Abbreviations: 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 Total and Low-Density Lipoprotein Cholesterol in Children and Adolescents (KQ7)

Author, Year Quality	N IG/CG % Female	Adverse effects assessed systematically	Adverse effects reported	Unexpected benefits
DISC, 1995[62] Obarzanek 1997[67] Lavigne 1999[68] Obarzanek 2001[63] Dorgan 2011[64] Good	663 334/329 45.4%	**All time points (baseline, years 1, 3, 5, and 7*):** Anthropometric measures: height, weight, BMI Dietary assessment: 24-hour recall **Baseline, years 1, 3, and 7* only:** Laboratory studies: ferritin, retinol, zinc, red blood cell folate **Baseline, years 1, 3, and 5 only:** Clinical: Tanner staging **Baseline, years 1 and 3 only:** Laboratory studies: albumin, beta carotene, hemoglobin, vitamin E, copper, tocopherol Clinical: blood pressure Anthropometrics: skinfold thickness, waist circumference **Baseline and year 3 only:** Psychosocial: various instruments†, history of anorexia, bulimia, suicidality **Year 5 and 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‡ (posttrial year 9):** Anthropometric measures: height, weight, BMI, waist circumference Clinical: blood pressure Laboratory studies: fasting glucose, adiposity (DXA scan) Dietary assessment: 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)

*"Year 7" refers to the final followup 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), and Woodcock-Johnson Psycho-Educational Battery.
‡"Year 18" refers to the followup study performed in 2006–2008 (approximately 18 years following original enrollment of study subjects in 1988–1990).

Abbreviations: TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, 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.

Table 13. Association* Between Elevated Total and Non–High-Density Lipoprotein Cholesterol and Risk for Death Before Age 55 Years From All and Endogenous Causes Among Participants Ages 12 to 39 Years During NHANES III, With Followup From 1988–2006 (KQ8)[70]

	Males		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 mg/dL	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 mg/dL	1.10 (0.64–1.91)	0.85 (0.42–1.71)	2.00 (1.11–3.62)	1.95 (0.97–3.90)

*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 ng/mL and ≥100 ng/mL). Variables with statistically significant relationships with endogenous causes of death: males: (none); females (blood pressure, hypertension, and cotinine levels 10–99 ng/mL and ≥100 ng/mL).

Abbreviations: TC=total cholesterol, HDL-C=high-density lipoprotein cholesterol, NHANES=National Health and Nutrition Examination Survey, KQ=key question, RH=relative hazard, CI=confidence interval.

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 1 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. 2 were in U.S. primary care settings and are most directly applicable. 1 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 1 study that included confirmatory testing found a diagnostic yield of 5.8%. Data from studies using a single test found simulated diagnostic yields of 4.8% 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 1 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.

Table 14. Summary of Evidence Table

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 – 1 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 (ages 12–39 years) were not reported separately.	N/A – 1 study	NHANES data may not have direct relevance to primary care.	Fair	At followup, 283 people were deceased before age 55 years. Leading causes of death for people ages 12–19 years at baseline were accident, self-inflicted injury, circulatory causes, and cancer. In multivariate models, neither very high cholesterol (TC ≥240 mg/dL) nor moderately increased TC (200–239 mg/dL) was independently associated with death, when both sexes were combined. For females only, very high cholesterol was associated with greater risk of death before age 55 years (RH, 2.58 [95% CI, 1.31 to 5.08]).

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

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, DISC=Dietary Intervention Study in Children, RH=relative hazard, CI=confidence interval.

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

#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*ediatric*:ti,ab,kw)
#11 #9 and #10 from 2007 to 2014, in Trials

MEDLINE

<u>Dyslipidemia screening, screening harms</u>

Database: Ovid MEDLINE(R) without Revisions <1996 to June Week 1 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 2, 2015>, Ovid MEDLINE(R) Daily Update <June 2, 2015>
Search Strategy:
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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 June Week 1 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < June 2, 2015>, Ovid MEDLINE(R) Daily Update < June 2, 2015>
Search Strategy:
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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 June Week 1 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < June 2, 2015>, Ovid MEDLINE(R) Daily Update < June 2, 2015>
Search Strategy:
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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 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < June 2, 2015>, Ovid MEDLINE(R) Daily Update < June 2, 2015>
Search Strategy:
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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]

Search	Query
#11	Search #10 AND publisher[sb] Filters: Publication date from 2007/01/01 to 2015/06/02; 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])

Appendix A. Detailed Methods

Search	Query
#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]	• 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]	• 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?

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

Appendix A Table 2. Inclusion and Exclusion Criteria

	Included	Excluded
Population	**All KQs:** Children and adolescents ages 0 to 20 years **KQs 1–4:** Asymptomatic children and adolescents ages 0 to 20 years **KQs 5–8:** Children and adolescents ages 0 to 20 years with dyslipidemia not due to familial hypercholesterolemia	**KQs 1–4:** Children and adolescents with any of the following: • Known dyslipidemia • Diagnosis associated with secondary dyslipidemia* • Established family history of familial hypercholesterolemia **KQs 5–8:** Children and adolescents with familial hypercholesterolemia
Diseases	**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): • 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) 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	**KQs 5–8:** • Familial hypercholesterolemia • Secondary dyslipidemia*
Screening interventions	**KQs 1–4:** • 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)	**KQs 1–4:** • Genetic screening alone • Cascade screening
Treatments	**KQs 5–7:** • Lipid-lowering medications • Lifestyle modifications, including diet or exercise	**KQs 5–7:** None
Outcomes	**KQs 1, 5, 8:** • MI • Ischemic stroke **KQ3:** • Diagnostic yield (true positives/number screened) • Positive predictive value (true positives/true positives + false positives) **KQ4:** All harms (e.g., false-positive or false-negative results, psychosocial effects, overdiagnosis) **KQs 2, 6:** • Lipid levels (total, LDL, HDL, and non-HDL cholesterol; triglycerides) • Atherosclerosis markers (carotid intima–media thickness, calcium score, pathological findings) **KQ7:** All harms from: • Medications (e.g., adverse events, long-term safety, overtreatment) • Lifestyle modifications (e.g., nutritional, psychosocial)	**KQs 1, 5, 8:** • Diabetes • Metabolic syndrome • Hypothyroidism • Renal failure • Obstructive liver disease • Nephrotic syndrome • Lipodystrophy • Other serum markers (e.g., apolipoprotein A1, C-reactive protein)

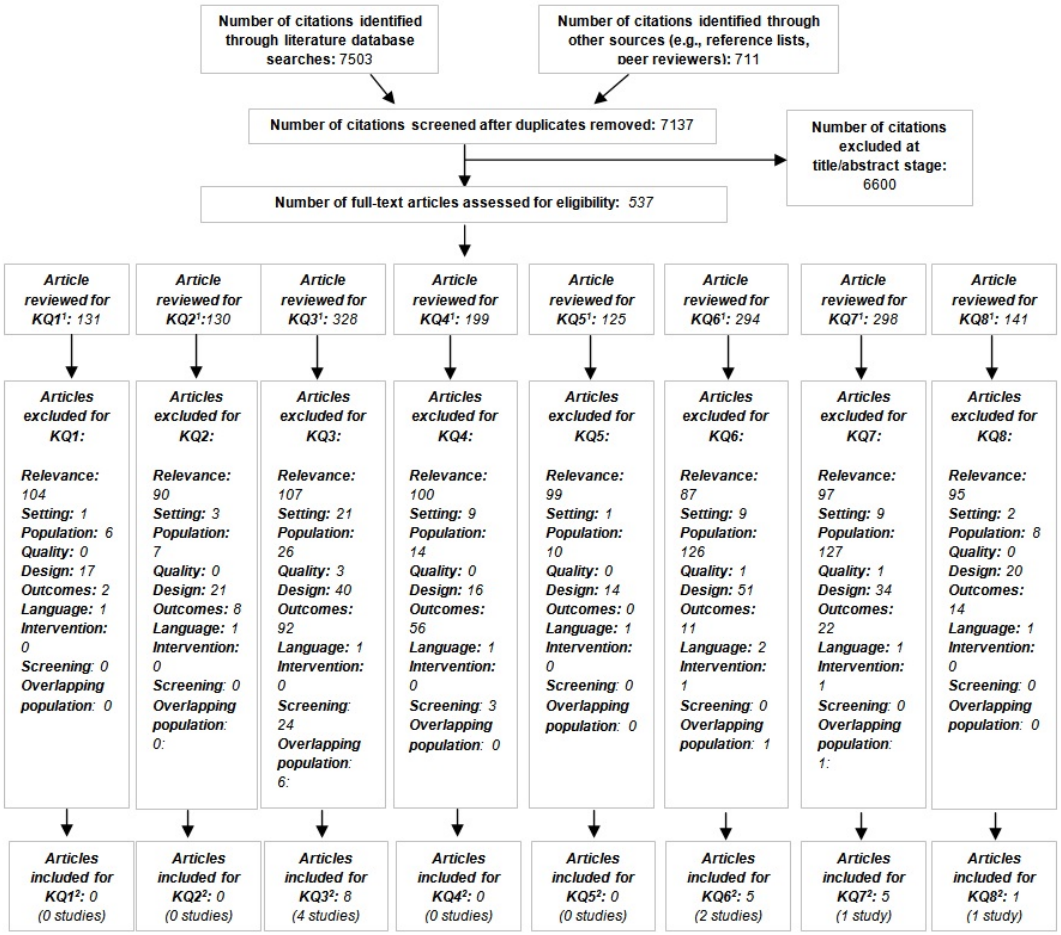
Appendix A Table 2. Inclusion and Exclusion Criteria

	Included	Excluded
Study design	**KQs 1, 2:** RCTs, CCTs, and systematic reviews **KQ3:** RCTs, CCTs, systematic reviews, and cohort 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	**All KQs:** Studies rated as poor quality **KQs 1–3, 5, 6, 8:** Qualitative studies, case reports, cost-effectiveness studies **KQs 1, 2, 5, 6:** Cohort studies **KQs 4, 7:** None
Settings	• 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

*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).

Abbreviations: KQ=key question, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, MI=myocardial infarction, CCT=controlled clinical trial, RCT=randomized, controlled trial, USPSTF=U.S. Preventive Services Task Force, HIV=human immunodeficiency virus.

Appendix A Figure 1. Literature Flow Diagram



[1] Includes 122 articles that were reviewed for all KQs

[2] Number of articles that were not included in the prior review: KQ1=0; KQ2= 0; KQ3=7; KQ4= 0; KQ5=0; KQ6=3; KQ7=3; KQ8=1

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

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

*The exclusion code E3 was not used.
Abbreviations: HDI=Human Development Index, N/A=not applicable.

1. Abe Y, Okada T, Sugiura R, et al. Reference ranges for the non-high-density lipoprotein cholesterol levels in Japanese children and adolescents. J Atheroscler Thromb. 2015;22(7):669-75. PMID: 25739922. **KQ3E6.**
2. Abello F, Cagliero P, Giorgis M, et al. Lycopene supplementation in children affected by primary dyslipidaemia: Effects on lipid profile and oxidative stress. High Blood Press Cardiovasc Prev. 2012;(2):94. **KQ6E13, KQ7E13.**
3. Agirbasli M, Agaoglu NB, Orak N, et al. Sex hormones, insulin resistance and high-density lipoprotein cholesterol levels in children. Horm Res Paediatr. 2010;73(3):166-74. PMID: 20197668. **KQ3E4, KQ4E4.**
4. Akdim F, Tribble DL, Flaim JD, et al. Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidaemia. Eur Heart J. 2011;(21):2650-9. PMID: 21593041. **KQ6E5, KQ7E5.**
5. Akyurek N, Atabek ME, Eklioglu BS, et al. Is there a relationship between cardiovascular risk factors and dehydroepiandrosterone sulfate levels in childhood obesity? J Pediatr Endocrinol Metab. 2014;28(42130):545-50. PMID: 25381943. **KQ1E13, KQ2E13, KQ3E5, KQ4E5, KQ5E13.**
6. Alavian SM, Motlagh ME, Ardalan G, et al. Hypertriglyceridemic waist phenotype and associated lifestyle factors in a national population of youths: CASPIAN Study. J Trop Pediatr. 2008;54(3):169-77. PMID: 18156644. **KQ3E4.**
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. Diabetes Care. 2011;34(9):1998-2004. PMID: 21868776. **KQ3E6.**
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. Am J Clin Nutr. 2002;(2):. PMID: 12145004. **KQ1E5, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
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. Arch Dis Child. 1979;54(9):691-4. PMID: 229774. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
10. Andersen GE, Lous P, Friis-Hansen B. Screening for hyperlipoproteinemia in 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.**
14. Andrade S, Borges N. Effect of fermented milk containing Lactobacillus acidophilus and Bifidobacterium longum on plasma lipids of women with normal or moderately elevated cholesterol. J Dairy Res. 2009;76(4):469-74. PMID: 19825213. **KQ6E5, KQ7E5.**
15. Arca M, Cambuli VM, Montali A, et al. Serum adiponectin is decreased in patients with familial combined hyperlipidemia and normolipaemic relatives and is influenced by lipid-lowering treatment. Nutr Metab Cardiovasc Dis. 2009;19(9):660-6. PMID: 19632099. **KQ6E5, KQ7E5.**
16. Asgary S, Kelishadi R, Rafieian-Kopaei M, et al. Investigation of the lipid-modifying and antiinflammatory effects of Cornus mas L. supplementation on dyslipidemic children and adolescents. Pediatr Cardiol. 2013;34(7):1729-35. PMID: 23625305. **KQ6E4, KQ7E4.**
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.**
18. Bachman RP, Schoen EJ, Stembridge A, et al. Compliance with childhood cholesterol screening among members of a prepaid health plan. Am J Dis Child. 1993;147(4):382-5. PMID: 8456792. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
19. Backes JM, Gibson CA, Ruisinger JF, Moriarty PM. The high-dose rosuvastatin once weekly study (the HD-ROWS). J Clin Lipidol. 2012;6(4):362-7. PMID: 22836073. **KQ6E5, KQ7E5.**
20. Ballantyne CM, Miller M, Niesor EJ, et al. Effect of dalcetrapib plus pravastatin on lipoprotein metabolism and high-density lipoprotein composition and function in dyslipidemic patients: results of a phase IIb dose-ranging study. Am Heart J. 2012;163(3):515-21, 521 e1-3. PMID: 22424025. **KQ6E5, KQ7E5.**
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.**
22. Baloch S, Devrajani B, Baloch M, et al. Lipid profile in children with coronary artery disease in Sindh, Pakistan. World J Cardiol. 2014;6(7):671-4. PMID: 25068027. **KQ8E4.**
23. Bangert SK, Eldridge PH, Peters TJ. Neonatal screening for familial hypercholesterolaemia by immunoturbidimetric assay of apolipoprotein B in dried blood spots. Clin Chim Acta. 1992;213(42007):95-101. PMID: 1477991. **KQ3E13.**
24. Barra S, Cuomo V, Silvestri N, et al. Lipoprotein(a) concentration does not differ between sexes in healthy offspring of patients with premature myocardial 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.**
26. Bastida S, Perea S, Sanchez-Muniz FJ. Do neonates with high serum cholesterol levels have a different high density lipoprotein composition?. Eur J Pediatr. 1998;157(1):66-70. PMID: 9461367. **KQ3E13.**
27. Bastida S, Sanchez-Muniz FJ, Cuena R, et al. High density lipoprotein-cholesterol changes in children with high cholesterol levels at birth. Eur J Pediatr. 2002;161(2):94-8. PMID: 11954759. **KQ3E13.**

28. Bays HE, Chapman RH, Grandy S, et al. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract. 2007;61(5):737-47. PMID: 17493087. **KQ3E7.**
29. Bays HE, Maki KC, Doyle RT, Stein E. The effect of prescription omega-3 fatty acids on body weight after 8 to 16 weeks of treatment for very high triglyceride levels. Postgrad Med. 2009;121(5):145-50. PMID: 19820283. **KQ6E5, KQ7E5.**
30. Bays HE, Maki KC, McKenney J, et al. Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. Curr Med Res Opin. 2010;26(4):907-15. PMID: 20156032. **KQ6E5, KQ7E5.**
31. Bays HE, Shah A, Lin J, et al. Efficacy and tolerability of extended-release niacin/laropiprant in dyslipidemic patients with metabolic syndrome. J Clin Lipidol. 2010;4(6):515-21. PMID: 21122699. **KQ6E5, KQ7E5.**
32. Bays HE, Shah A, Macdonell G, et al. Effects of coadministered ezetimibe plus fenofibrate in mixed dyslipidemic patients with metabolic syndrome. Metab Syndr Relat Disord. 2011;9(2):135-42. PMID: 21117970. **KQ6E5, KQ7E5.**
33. Bazzano LA, Thompson AM, Tees MT, et al. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2011;21(2):94-103. PMID: 19939654. **KQ6E5, KQ7E5.**
34. Becker DJ, French B, Morris PB, et al. Phytosterols, red yeast rice, and lifestyle changes instead of statins: a randomized, double-blinded, placebo-controlled trial. Am Heart J. 2013;166(1):187-96. PMID: 23816039. **KQ6E5, KQ7E5.**
35. Becker DJ, Gordon RY, Morris PB, et al. Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial. Mayo Clin Proc. 2008;83(7):758-64. PMID: 18613992. **KQ6E5, KQ7E5.**
36. Becker M, Staab D, Von Bergmann K. Treatment of severe familial hypercholesterolemia in childhood with sitosterol and sitostanol. J Pediatr. 1993;122(2):292-6. PMID: 8429449. **KQ3E13.**
37. Beeso J, Wong N, Ayling R, et al. Screening for hypercholesterolaemia in 10,000 neonates in a multi-ethnic population. Eur J Pediatr. 1999;158(10):833-7. PMID: 10486088. **KQ3E13.**
38. Bekkers MB, Brunekreef B, Koppelman GH, et al. BMI and waist circumference; cross-sectional and prospective associations with blood pressure and cholesterol in 12-year-olds. PLoS ONE. 2012;7(12):e51801. PMID: 23251628. **KQ3E6.**
39. Belay B, Racine AD, Belamarich PF. For the patient. Disparities in statin trials for children. Ethnicity & Disease. 2009;19(2):218. PMID: 19537236. **KQ6E2, KQ7E2.**
40. Bell DA, Hooper AJ, Bender R, et al. Screening for lipid disorders. Pathology. 2012;44(2):115-21. PMID: 22198257. **KQ1E13.**
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.**
42. Bell L, Hung J, Knuiman M, et al. Body mass index and waist circumference: relationship to cardiometabolic risk factors in children--Busselton Health Study 2005-2007. J Paediatr Child Health. 2013;49(11):955-62. PMID: 23802746. **KQ3E6.**
43. Bell MM, Joseph S. Screening 1140 fifth graders for hypercholesterolemia: family history inadequate to predict results. J Am Board Fam Pract. 1990;3(4):259-63. PMID: 2248092. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**
44. Berenson GS, Srinivasan SR, Frerichs RR, Webber LS. Serum high density lipoprotein and its relationship to cardiovascular disease risk factor variables in children--the Bogalusa heart study. Lipids. 1979;14(1):91-8. PMID: 218070. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
45. Bergmann GG, Gaya A, Halpern R, et al. Waist circumference as screening instrument for cardiovascular disease risk factors in schoolchildren. J Pediatr (Rio J). 2010;86(5):411-6. PMID: 20938592. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**

46. Bergstrom E, Hernell O, Persson LA. Endurance running performance in relation to cardiovascular risk indicators in adolescents. Int J Sports Med. 1997;18(4):300-7. PMID: 9231849. **KQ3E13.**
47. Bibiloni MM, Salas R, Pons A, Tur JA. Prevalence of dyslipidaemia and associated risk factors among Balearic Islands adolescents, a Mediterranean region. Eur J Clin Nutr. 2014;69(6):722-8. PMID: 25351644. **KQ3E7, KQ4E6.**
48. Bielemann RM, Ramires VV, Gigante DP, et al. Longitudinal and cross-sectional associations of physical activity with triglyceride and HDLc levels in young male adults. J Phys Act Health. 2013;11(4):784-9. PMID: 23574796. **KQ1E13, KQ2E13, KQ3E4, KQ4E13, KQ5E13.**
49. Blades BL, Dudman NP, Wilcken DE. Screening for familial hypercholesterolemia in 5000 neonates: a recall study. Pediatr Res. 1988;(5): PMID: 3387172. **KQ3E13.**
50. Bogsrud MP, Ose L, Langslet G, et al. HypoCol (red yeast rice) lowers plasma cholesterol - a randomized placebo controlled study. Scand Cardiovasc J. 2010;44(4):197-200. PMID: 20636227. **KQ6E5, KQ7E5.**
51. Boreham CA, Wallace WF, Nevill A. Training effects of accumulated daily stair-climbing exercise in previously sedentary young women. Prev Med. 2000;(4):. PMID: 10731455. **KQ3E13.**
52. Boulton TJ. The validity of screening for hypercholesterolaemia at different ages from 2 to 17 years. Aust N Z J Med. 1979;9(5):542-6. PMID: 231425. **KQ3E13.**
53. Bradlee ML, Singer MR, Moore LL. Lean red meat consumption and lipid profiles in adolescent girls. J Hum Nutr Diet. 2013;(0):292-300. PMID: 23663235. **KQ3E13.**
54. Braga MF, Grace MG, Lenis J, et al. Efficacy and safety of ursodeoxycholic acid in primary, type IIa or IIb hypercholesterolemia: a multicenter, randomized, double-blind clinical trial. Atherosclerosis. 2009;(2):479-82. PMID: 18801487. **KQ6E5, KQ7E5.**
55. Brewster TG, Waite DJ, Hudson GA. Quantitation of beta-lipoprotein in cord serum by rate nephelometric immunoassay: a potential screening test for familial hypercholesterolemia. Clin Chem. 1982;(5): PMID: 7074903. **KQ3E13.**
56. Brogan K, Danford C, Yeh Y, et al. Cardiovascular disease risk factors are elevated in urban minority children enrolled in head start. Childhood Obes. 2014;10(3):207-13. PMID: 24829071. **KQ3E7, KQ4E6.**
57. Browne B, Vasquez S. Pediatric dyslipidemias: prescription medication efficacy and safety. J Clin Lipidol. 2008;2(3):189-201. PMID: 21291737. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
58. Bundy R, Walker AF, Middleton RW, et al. Artichoke leaf extract (Cynara scolymus) reduces plasma cholesterol in otherwise healthy hypercholesterolemic adults: a randomized, double blind placebo controlled trial. Phytomedicine. 2008;(9):668-75. PMID: 18424099. **KQ6E5, KQ7E5.**
59. Burgos MS, Burgos LT, Camargo MD, et al. Relationship between anthropometric measures and cardiovascular risk factors in children and adolescents. Arq Bras Cardiol. 2013;101(4):288-96. PMID: 23979777. **KQ3E6.**
60. Burke JD, Reilly RA, Morrell JS, et al. The University of New Hampshire's Young Adult Health Risk Screening Initiative. J Am Diet Assoc. 2009;109(10):1751-8. PMID: 19782175. **KQ3E5.**
61. Burns TL, Letuchy EM, Paulos R, et al. Childhood predictors of the metabolic syndrome in middle-aged adults: the Muscatine study. J Pediatr. 2009;155(3):S5 e17-26. PMID: 19732563. **KQ8E6.**
62. Burr JF, Jamnik V, Gledhill N, et al. A cross-sectional examination of the physical fitness and selected health attributes of recreational all-terrain vehicle riders and off-road motorcyclists. J Sports Sci. 2010;28(13):1423-33. PMID: 20845220. **KQ3E6, KQ4E6.**
63. Caballero AE, Bousquet-Santos K, Robles-Osorio L, et al. Overweight Latino children and adolescents have marked endothelial dysfunction and subclinical vascular inflammation in association with excess body fat and insulin resistance. Diabetes Care. 2008;31(3):576-82. PMID: 18083792. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**
64. Cagliero P, Abello F, Guardamagna O. Effects of bifidobacterium supplementation on plasma lipid profile in dyslipidemic children. High Blood Press Cardiovasc Prev. 2013;20(2):93-114. **KQ6E13, KQ7E13.**

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.**
66. Cai L, Wu Y, Cheskin LJ, et al. Effect of childhood obesity prevention programmes on blood lipids: a systematic review and meta-analysis. Obes Rev. 2014;15(12):933-44. PMID: 25263653. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13, KQ6E6.**
67. Camhi SM, Kuo J, Young DR, et al. Identifying adolescent metabolic syndrome using body mass index and waist circumference. Prev Chronic Dis. 2008;5(4):A115. PMID: 18793503. **KQ3E6.**
68. Carson V, Ridgers ND, Howard BJ, et al. Light-intensity physical activity and cardiometabolic biomarkers in US adolescents. PLoS ONE. 2013;8(8):e71417. PMID: 23951157. **KQ6E9, KQ7E9.**
69. Carter SJ, Roberts MB, Salter J, et al. Relationship between Mediterranean Diet Score and atherothrombotic risk: findings from the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. Atherosclerosis. 2010;210(2):630-6. PMID: 20138282. **KQ3E5.**
70. Caserta CA, Pendino GM, Alicante S, et al. Body mass index, cardiovascular risk factors, and carotid intima-media thickness in a pediatric population in southern Italy. J Pediatr Gastroenterol Nutr. 2010;51(2):216-20. PMID: 20512056. **KQ2E13, KQ3E7, KQ4E13.**
71. Castro IA, Monteiro VC, Barroso LP, et al. Effect of eicosapentaenoic/docosahexaenoic fatty acids and soluble fibers on blood lipids of individuals classified into different levels of lipidemia. Nutrition. 2007;(2):127-37. PMID: 17234506. **KQ6E5, KQ7E5.**
72. Castro JJ, Dias T, Chambel P, et al. A randomized double-blind study comparing the efficacy and safety of orlistat versus placebo in obese patients with mild to moderate hypercholesterolemia. Rev Port Cardiol. 2009;(12):1361-74. PMID: 20301983. **KQ6E5, KQ7E5.**
73. Castro PS, Oliveira FL. Prevention of atherosclerosis and drug treatment of high-risk lipid abnormalities in children and adolescents. J Pediatr (Rio J). 2009;85(1):14-Jun. PMID: 19198733. **KQ6E1, KQ7E13.**
74. Cesa CC, Barbiero SM, Petkowicz Rde O, et al. Effectiveness of physical exercise to reduce cardiovascular risk factors in youths: a randomized clinical trial. J Clin Med Res. 2015;7(5):348-55. PMID: 25780484. **KQ6E6, KQ7E6.**
75. Cesar TB, Aptekmann NP, Araujo MP, et al. Orange juice decreases low-density lipoprotein cholesterol in hypercholesterolemic subjects and improves lipid transfer to high-density lipoprotein in normal and hypercholesterolemic subjects. Nutr Res. 2010;30(10):689-94. PMID: 21056284. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
76. Chahal N, Manlhiot C, Wong H, et al. Effectiveness of Omega-3 Polysaturated Fatty Acids (Fish Oil) Supplementation for Treating Hypertriglyceridemia in Children and Adolescents. Clin Pediatr (Phila). 2014;53(7):645-651. PMID: 24647701. **KQ6E5, KQ7E6.**
77. Chahal N, McCrindle B, Manlhiot C, et al. A 4-week randomized clinical trial of flaxseed supplementation in children with hypercholesterolemia. Can J Cardiol. 2011(5):S339. CN-01003383. **KQ6E13, KQ7E13.**
78. Chahal N,Wong H,Manlhiot C, et al. Education for lifestyle-based management of hyperlipidemia in children enhanced by a collaborative approach. J Clin Lipidol. 2014;8(2):187-93. PMID: 24636178. **KQ6E9, KQ7E6.**
79. Chait R, Ramineni R, Fender EA. Precocious virulent coronary atherosclerosis in the very young. Cardiol Young. 2012;22(2):184-7. PMID: 21878143. **KQ8E9.**
80. Chaiton M, O'Loughlin J, Karp I, et al. Depressive symptoms and C-reactive protein are not associated in a population-based sample of adolescents. Int J Behav Med. 2010;17(3):216-22. PMID: 20180088. **KQ3E6, KQ4E6.**
81. Chauhan A, Paunikar P. Update on pediatric hyperlipidemia. Curr Opin Pediatr. 2014;26(2):252-8. PMID: 24553633. **KQ1E2.**
82. Chen YQ, Zhao SP, Chen JZ, et al. The effects of coenzyme A on serum lipids in patients with hyperlipidemia: results of a multicenter clinical trial. J Clin Endocrinol Metab. 2013;98(2):E275-8. PMID: 23293333. **KQ6E5, KQ7E5.**

83. Chikanna S, Upadhyay A, Aneja GK. Lipid profile in high risk children aged 2-10 years. Indian Pediatr. 2010;47(7):630-1. PMID: 20683118. **KQ3E9.**
84. Cho SM, Lee SG, Kim HS, et al. Establishing pediatric reference intervals for 13 biochemical analytes derived from normal subjects in a pediatric endocrinology clinic in Korea. Clin Biochem. 2014;47(18):268-71. PMID: 25241678. **KQ3E6.**
85. Ciftdogan DY, Coskun S, Ulman C, et al. The association of apolipoprotein E polymorphism and lipid levels in children with a family history of premature coronary artery disease. J Clin Lipidol. 2012;6(1):81-7. PMID: 22264578. **KQ3E5, KQ4E5.**
86. Clark J. Does the type intervention method really matter for combating childhood obesity? A systematic review and meta-analysis. J Sports Med Phys Fitness. 2014(0): PMID: 25303076. **KQ6E2.**
87. Clarke JT, Cullen-Dean G, Regelink E, et al. Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. J Pediatr. 1990;116(1):139-41. PMID: 2295954. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
88. Clarke WR, Schrott HG, Leaverton PE, et al. Tracking of blood lipids and blood pressures in school age children: the Muscatine study. Circulation. 1978;58(4):626-34. PMID: 688572. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
89. Clauss SB, Holmes KW, Hopkins P, et al. Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. Pediatrics. 2005(3): PMID: 16140708. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E5.**
90. Cleanthous X, Noakes M, Brinkworth GD, et al. A pilot comprehensive lifestyle intervention program (CLIP)--comparison with qualitative lifestyle advice and simvastatin on cardiovascular risk factors in overweight hypercholesterolaemic individuals. Nutr Metab Cardiovasc Dis. 2011;21(3):165-72. PMID: 20110160. **KQ6E5, KQ7E5.**
91. Clifton PM, Mano M, Duchateau GS, et al. Dose-response effects of different plant sterol sources in fat spreads on serum lipids and C-reactive protein and on the kinetic behavior of serum plant sterols. Eur J Clin Nutr. 2008;62(8):968-77. PMID: 17538539. **KQ6E5, KQ7E5.**
92. Colletti RB, Neufeld EJ, Roff NK, et al. Niacin treatment of hypercholesterolemia in children. Pediatrics. 1993;92(1):78-82. PMID: 8516088. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
93. Comerford KB, Artiss JD, Jen KL, et al. The beneficial effects of alpha-cyclodextrin on blood lipids and weight loss in healthy humans. Obesity (Silver Spring). 2011;19(6):1200-4. PMID: 21127475. **KQ1E5.**
94. Conceicao-Machado ME, Silva LR, Santana ML, et al. Hypertriglyceridemic waist phenotype: association with metabolic abnormalities in adolescents. J Pediatr (Rio J). 2013;89(1):56-63. PMID: 23544811. **KQ3E4.**
95. Cook S, Kavey RE. Dyslipidemia and pediatric obesity. Pediatr Clin North Am. 2011;58(6):1363-73, ix. PMID: 22093856. **KQ1E13, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
96. Corley J,Starr JM, Deary IJ. Serum cholesterol and cognitive functions: the Lothian Birth Cohort 1936. Int Psychogeriatr. 2015;:15-Jan. PMID: 25023928. **KQ7E6.**
97. Cottrell L, John C, Murphy E, et al. Individual-, family-, community-, and policy-level impact of a school-based cardiovascular risk detection screening program for children in underserved, rural areas: the CARDIAC Project. J Obes. 2013;2013(0): PMID: 23840946. **KQ3E13.**
98. Croyle RT, Sun YC, Louie DH. Psychological minimization of cholesterol test results: moderators of appraisal in college students and community residents. Health Psychol. 1993;12(6):503-7. PMID: 8293735. **KQ3E13.**
99. Cunningham TE, Sayers SM, Singh GR, et al. Lipoprotein(a) identifies cardiovascular risk in childhood: the Australian Aboriginal Birth Cohort Study. J Paediatr Child Health. 2011;47(5):257-61. PMID: 21244559. **KQ1E13, KQ2E6, KQ3E6, KQ4E6, KQ5E13.**

Appendix C. Excluded Studies

100. da Luz Giroldo M, Villela Baroncini LA, Champoski AF, et al. Household cardiovascular screening in adolescents from high-risk families. Atherosclerosis. 2013;226(1):286-90. PMID: 23195519. **KQ3E4.**
101. D'Adamo E, Guardamagna O, Chiarelli F, et al. Atherogenic dyslipidemia and cardiovascular risk factors in obese children. Int J Endocrinol. 2015;2015(5):912047. PMID: 25663838. **KQ1E13, KQ2E2, KQ3E13, KQ4E13, KQ5E13.**
102. Dai S, Eissa MA, Steffen LM, et al. Associations of BMI and its fat-free and fat components with blood lipids in children: Project HeartBeat!. Clin Lipidol. 2011;6(2):235-244. PMID: 21818183. **KQ3E6.**
103. Darmady JM, Fosbrooke AS, Lloyd JK. Prospective study of serum cholesterol levels during first year of life. Br Med J. 1972;2(5815):685-8. PMID: 5067674. **KQ1E13, KQ2E13, KQ3E7, KQ4E13, KQ5E13.**
104. Davidson DM, Bradley BJ, Landry SM, et al. School-based blood cholesterol screening. J Pediatr Health Care. 1989;3(1):. PMID: 2492600. **KQ1E13, KQ2E13, KQ3E9, KQ4E13, KQ5E13.**
105. Davidson DM, Van Camp J, Iftner CA, et al. Family history fails to detect the majority of children with high capillary blood total cholesterol. J Sch Health. 1991;61(2):75-80. PMID: 2016863. **KQ3E13.**
106. Davidson MH, Dugan LD, Burns JH, et al. A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. Am J Clin Nutr. 1996;63(1):96-102. PMID: 8604676. **KQ3E13.**
107. Davison N, Fanolua S, Rosaine M, et al. Assessing overweight and obesity in American Samoan adolescents. Pac Health Dialog. 2007;14(2):55-61. PMID: 19588607. **KQ3E4.**
108. de Almeida CA, Pinho AP, Ricco RG, et al. Abdominal circumference as an indicator of clinical and laboratory parameters associated with obesity in children and adolescents: comparison between two reference tables. J Pediatr (Rio J). 2007;83(2):181-5. PMID: 17426873. **KQ3E6.**
109. de Freitas RW, de Araujo MF, Lima AC, et al. Study of lipid profile in a population of university students. Rev Lat Am Enfermagem. 2013;21(5):1151-8. PMID: 24142225. **KQ3E5, KQ4E5.**
110. De Henauw S, Michels N, Vyncke K, et al. Blood lipids among young children in Europe: results from the European IDEFICS study. Int J Obes (Lond). 2014;(0):S67-75. PMID: 25219412. **KQ3E9, KQ4E13, KQ3E6.**
111. de Jongh S, Kerckhoffs MC, Grootenhuis MA, et al. Quality of life. Acta Paediatr. 2003;92(9):1096-101. PMID: 14599077. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
112. de Jongh S, Lilien MR, op't Roodt J, et al. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. J Am Coll Cardiol. 2002;40(12):2117-21. PMID: 12505222. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
113. de Jongh S, Ose L, Szamosi T, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin.. Circulation. 2002;106(17):2231-7. PMID: 12390953. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
114. de Jongh S, Vissers MN, Rol P, et al. Plant sterols lower LDL cholesterol without improving endothelial function in prepubertal children with familial hypercholesterolaemia. J Inherit Metab Dis. 2003;26(4):343-51. PMID: 12971422. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
115. de Kroon ML, Renders CM, van Wouwe JP, et al. The Terneuzen Birth Cohort: BMI change between 2 and 6 years is most predictive of adult cardiometabolic risk. PLoS ONE. 2010;5(11):e13966. PMID: 21103047. **KQ3E6, KQ4E6.**
116. De Rosa G, Bonaventura A, Bianchi L, et al. A randomized, placebo-controlled study on the effects of a nutraceutical combination of red yeast rice, silybum marianum and octasonol on lipid profile, endothelial and inflammatory parameters. J Biol Regul Homeost Agents. 2014;28(2):317-24. PMID: 25001663. **KQ6E5, KQ7E5.**

Appendix C. Excluded Studies

117. de Ferranti S, Shapiro D, Markowitz R, et al. Nonfasting low-density lipoprotein testing: utility for cholesterol screening in pediatric primary care. Clin Pediatr (Phila). 2007;46(5):441-5. PMID: 17556742. **KQ1E6, KQ2E6, KQ3E9, KQ4E13.**
118. Deerochanawong C, Buranakitjaroen P, Nitiyanant W, et al. The Atorvastatin Goal Achievement Across Risk Levels: (ATGOAL) study in Thailand. J Med Assoc Thai. 2007;90(1):72-81. PMID: 17621736. **KQ6E5, KQ7E5.**
119. Demerath E, Muratova V, Spangler E, et al. School-based obesity screening in rural Appalachia. Prev Med. 2003;37(6 Pt 1):553-60. PMID: 14636788. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
120. Dennison BA, Kikuchi DA, Srinivasan SR, et al. Serum total cholesterol screening for the detection of elevated low-density lipoprotein in children and adolescents: the Bogalusa Heart Study. Pediatrics. 1990;85(4):472-9. PMID: 2314959. **KQ1E13, KQ2E13, KQ3E10, KQ4E6, KQ5E13.**
121. Dennison BA, Levine DM. Randomized, double-blind, placebo-controlled, two-period crossover clinical trial of psyllium fiber in children with hypercholesterolemia. J Pediatr. 1993;123(1):24-9. PMID: 8391569. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
122. DeStefano F, Berg RL, Griese GG Jr. Determinants of serum lipid and lipoprotein concentrations in children. Epidemiology. 1995;6(4):446-9. PMID: 7548360. **KQ3E13.**
123. Di Bonito P, Moio N, Sibilio G, et al. Cardiometabolic phenotype in children with obesity. J Pediatr. 2014;165(6):1184-9. PMID: 25241175. **KQ3E5.**
124. Diaz-Rios LK, Chapman-Novakofski K, Malacara JM, et al. Metabolic and nutritional profile differences among Mexican, Mexican-American and Non-Hispanic White children. Rev Invest Clin. 2014;66(1):31-44. PMID: 24762725. **KQ3E5, KQ4E4.**
125. Donin AS, Nightingale CM, Owen CG, et al. Ethnic differences in blood lipids and dietary intake between UK children of black African, black Caribbean, South Asian, and white European origin: the Child Heart and Health Study in England (CHASE). Am J Clin Nutr. 2010;92(4):776-83. PMID: 20739425. **KQ3E6, KQ4E13.**
126. Doshi N, Perrin EM, Lazorick S, et al. Short-term change in body mass index in overweight adolescents following cholesterol screening. Arch Pediatr Adolesc Med. 2009;163(9):812-7. PMID: 19736334. **KQ1E13, KQ2E6, KQ3E6, KQ4E13, KQ5E13.**
127. Douglas MB, Birrer RB, Medidi S, et al. Obese children should be screened for hypercholesterolemia. J Health Care Poor Underserved. 1996;7(1):24-35. PMID: 8645782. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**
128. Duck MM, Hoffman RP. Impaired endothelial function in healthy African-American adolescents compared with Caucasians. J Pediatr. 2007;150(4):400-6. PMID: 17382119. **KQ3E6, KQ4E6.**
129. Dulay D, LaHaye SA, Lahey KA, Day AG. Efficacy of alternate day versus daily dosing of rosuvastatin. Can J Cardiol. 2009;25(2):e28-31. PMID: 19214297. **KQ6E5, KQ7E5.**
130. Eiland LS, Luttrell PK. Use of statins for dyslipidemia in the pediatric population. J Pediatr Pharmacol Ther. 2010;15(3):160-72. PMID: 22477808. **KQ6E2, KQ7E2.**
131. Eisenmann JC, Laurson KR, DuBose KD, et al. Construct validity of a continuous metabolic syndrome score in children. Diabetol Metab Syndr. 2010;2(0):. PMID: 20181030. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**
132. Eisenmann JC, Malina RM. Age-related changes in subcutaneous adipose tissue of adolescent distance runners and association with blood lipoproteins. Ann Hum Biol. 2002;29(4):389-97. PMID: 12160472. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**
133. Eisenmann JC, Welk GJ, Wickel EE, et al. Combined influence of cardiorespiratory fitness and body mass index on cardiovascular disease risk factors among 8-18 year old youth: The Aerobics Center Longitudinal Study. Int J Pediatr Obes. 2007;2(2):66-72. PMID: 17763013. **KQ6E5, KQ7E5.**
134. Eisenmann JC, Welk GJ, Wickel EE, et al. Stability of variables associated with the metabolic syndrome from adolescence to adulthood: the Aerobics Center Longitudinal Study. Am J Hum Biol. 2004;16(6):690-6. PMID: 15495227. **KQ3E13.**

135. Eissa MA, Wen E, Mihalopoulos NL, et al. Evaluation of AAP guidelines for cholesterol screening in youth: Project HeartBeat!. Am J Prev Med. 2009;37(1 Suppl):S71-7. PMID: 19524159. **KQ3E7.**
136. Ekelund U, Luan J, Sherar LB, et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. JAMA. 2012;307(7):704-12. PMID: 22337681. **KQ1E13, KQ2E13, KQ3E9, KQ4E13, KQ5E13.**
137. Enger C, Gately R, Ming EE, et al. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. Am J Cardiol. 2010;(11):1594-601. PMID: 21094360. **KQ7E5.**
138. Escalante Y, Saavedra JM, Garcia-Hermoso A, et al. Improvement of the lipid profile with exercise in obese children: a systematic review. Prev Med. 2012;54(5):293-301. PMID: 22387009. **KQ6E5, KQ7E5.**
139. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769-818. PMID: 21712404. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
140. Faigel HC. Screening college students for hypercholesterolemia. J Am Coll Health. 1992;40(6):272-5. PMID: 1602094. **KQ1E13, KQ2E13, KQ3E10, KQ4E13, KQ5E13.**
141. Fazio S, Guyton JR, Polis AB, et al. Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia. Am J Cardiol. 2010;(4):487-94. PMID: 20152243. **KQ6E5, KQ7E5.**
142. Feeman WE Jr. Screening lipids in children. J Clin Lipidol. 2014;8(2):233-4. PMID: 24636185. **KQ1E2.**
143. Feldman RD, Flack J, Howes L, et al. Impact of age and gender on blood pressure and low-density lipoprotein cholesterol reduction: results of a pooled analysis. Curr Med Res Opin. 2012;28(9):1421-33. PMID: 22809114. **KQ3E5, KQ4E5.**
144. Felszeghy E, Kaposzta R, Juhasz E, et al. Alterations of carbohydrate and lipoprotein metabolism in childhood obesity--impact of insulin resistance and acanthosis nigricans. J Pediatr Endocrinol Metab. 2009;22(12):1117-26. PMID: 20333871. **KQ1E5, KQ2E5, KQ3E6, KQ4E5, KQ5E5.**
145. Feoli-Fonseca JC, Levy E, Godard M, et al. Familial lipoprotein lipase deficiency in infancy: clinical, biochemical, and molecular study. J Pediatr. 1998;133(3):417-23. PMID: 9738727. **KQ3E13.**
146. Ferguson MA, Gutin B, Le NA, et al. Effects of exercise training and its cessation on components of the insulin resistance syndrome in obese children. Int J Obes Relat Metab Disord. 1999;23(8):889-95. PMID: 10490792. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
147. Fernandes J, Lofgren IE. Prevalence of metabolic syndrome and individual criteria in college students. J Am Coll Health. 2011;59(4):313-21. PMID: 21308592. **KQ3E6, KQ4E6.**
148. Ferreira WP, Bertolami MC, Santos SN, et al. One-month therapy with simvastatin restores endothelial function in hypercholesterolemic children and adolescents. Pediatr Cardiol. 2007;28(1):13-Aug. PMID: 17318708. **KQ6E4, KQ7E4.**
149. Finucane FM, Teong L, Pittock S, et al. Adverse metabolic profiles in a cohort of obese Irish children. Ann Clin Biochem. 2008;45(Pt 2):206-9. PMID: 18325187. **KQ3E13, KQ4E13.**
150. Fisher-Hoch SP, Vatcheva KP, Laing ST, et al. Missed opportunities for diagnosis and treatment of diabetes, hypertension, and hypercholesterolemia in a Mexican American population, Cameron County Hispanic Cohort, 2003-2008. Prev Chronic Dis. 2012;9(0):. PMID: 22863308. **KQ3E5, KQ4E13.**
151. Flechtner-Mors M, Wiegand S, Gellhaus I, et al. Screening for co-morbidity in 65,397 obese pediatric patients from Germany, Austria and Switzerland: adherence to guidelines improved from the year 2000 to 2010. Obes Facts. 2013;6(4):360-8. PMID: 23970145. **KQ2E6.**

152. Flouris AD, Bouziotas C, Christodoulos AD, et al. Longitudinal preventive-screening cutoffs for metabolic syndrome in adolescents. Int J Obes (Lond). 2008;32(10):1506-12. PMID: 18698315. **KQ3E6.**
153. Flynn J, Zhang Y, Solar-Yohay S, et al. Clinical and demographic characteristics of children with hypertension. Hypertension. 2012;60(4):1047-54. PMID: 22892814. **KQ3E9.**
154. Flynn SE, Gurm R, DuRussel-Weston J, et al. High-density lipoprotein cholesterol levels in middle-school children: association with cardiovascular risk factors and lifestyle behaviors. Pediatr Cardiol. 2013;35(3):507-13. PMID: 24132620. **KQ3E6, KQ6E5, KQ7E5.**
155. Flynn SE, Gurm R, DuRussel-Weston J, et al. High-density lipoprotein cholesterol levels in middle-school children: association with cardiovascular risk factors and lifestyle behaviors. Pediatr Cardiol. 2014;35(3):507-13. PMID: 24132620. **KQ3E6, KQ4E6.**
156. Foster M, Petocz P, Samman S. Effects of zinc on plasma lipoprotein cholesterol concentrations in humans: a meta-analysis of randomised controlled trials. Atherosclerosis. 2010;210(2):344-52. PMID: 20034629. **KQ6E13, KQ7E13.**
157. Franceschini G, Favari E, Calabresi L, et al. Differential effects of fenofibrate and extended-release niacin on high-density lipoprotein particle size distribution and cholesterol efflux capacity in dyslipidemic patients. J Clin Lipidol. 2013;7(5):414-22. PMID: 24079282. **KQ5E5, KQ6E5, KQ7E13.**
158. Freedman DS, Kahn HS, Mei Z, et al. Relation of body mass index and waist-to-height ratio to cardiovascular disease risk factors in children and adolescents: the Bogalusa Heart Study. Am J Clin Nutr. 2007;86(1):33-40. PMID: 17616760. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**
159. Freedman DS, Mei Z, Srinivasan SR, et al. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. J Pediatr. 2007;150(1):12-17 e2. PMID: 17188605. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**
160. Frontini MG, Srinivasan SR, Xu J, et al. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. Pediatrics. 2008;121(5):924-9. PMID: 18450895. **KQ8E6.**
161. Fuentes MC, Lajo T, Carrion JM, et al. Cholesterol-lowering efficacy of Lactobacillus plantarum CECT 7527, 7528 and 7529 in hypercholesterolaemic adults. Br J Nutr. 2013;(10):1866-72. PMID: 23017585. **KQ6E5, KQ7E5.**
162. Gagliano NJ, Emans SJ, Woods ER. Cholesterol screening in the adolescent. J Adolesc Health. 1993;14(2):104-8. PMID: 8476872. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**
163. Gagne C, Kusters M, Caceres M, et al. Efficacy and safety of ezetimibe monotherapy in 6-10 year old children with heterozygous familial or nonfamilial hypercholesterolemia. J Clin Lipidol. 2013;7(3):257-258. **KQ6E6, KQ7E6.**
164. Garaiova I, Muchova J, Nagyova Z, et al. Effect of a plant sterol, fish oil and B vitamin combination on cardiovascular risk factors in hypercholesterolemic children and adolescents: a pilot study. Nutr J. 2013;12(0):7. PMID: 23297818. **KQ6E9, KQ7E9.**
165. Garcia-Hermoso A, Carmona-Lopez MI, Saavedra JM, et al. Physical exercise, detraining and lipid profile in obese children: a systematic review. Arch Argent Pediatr. 2014;112(6):519-525. PMID: 25362910. **KQ6E13, KQ7E13.**
166. Garoufi A, Vorre S, Soldatou A, et al. Plant sterols-enriched diet decreases small, dense LDL-cholesterol levels in children with hypercholesterolemia: a prospective study. Ital J of Pediatr. 2014;40:42. PMID: 24887013. **KQ6E9, KQ7E6.**
167. Gauer R. Hyperlipidemia treatment in children: the younger, the better. Am Fam Physician. 2010;82(5):. PMID: 20822078. **KQ1E13, KQ2E2, KQ3E13, KQ4E13, KQ5E13.**
168. Gebbers JO. Atherosclerosis, cholesterol, nutrition, and statins--a critical review. Ger Med Sci. 2007;5. PMID: 19675712. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**

169. Gelissen IC, Nguyen HL, Tiao DK, et al. Statin use in Australian children: a retrospective audit of four pediatric hospitals. Paediatr Drugs. 2014;16(5):417-23. PMID: 25164329. **KQ6E9, KQ7E6.**

170. Giannini C, Diesse L, D'Adamo E, et al. Influence of the Mediterranean diet on carotid intima-media thickness in hypercholesterolaemic children: a 12-month intervention study. Nutr Metab Cardiovasc Dis. 2013;24(1):75-82. PMID: 23809150. **KQ6E9, KQ7E6.**

171. Gidding SS, Prospero C, Hossain J, et al. A double-blind randomized trial of fish oil to lower triglycerides and improve cardiometabolic risk in adolescents. J Pediatr. 2014;165(3):497-503 e2. PMID: 25008950. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

172. Gilardini L, Pasqualinotto L, Di Matteo S, et al. Factors associated with early atherosclerosis and arterial calcifications in young subjects with a benign phenotype of obesity. Obesity (Silver Spring). 2011;19(8):1684-9. PMID: 21273999. **KQ1E13, KQ2E5, KQ3E13, KQ4E13, KQ5E13.**

173. Gillman MW, Cupples LA, Moore LL, et al. Impact of within-person variability on identifying children with hypercholesterolemia: Framingham Children's Study. J Pediatr. 1992;121(3):342-7. PMID: 1517906. **KQ3E13.**

174. Giordano P, Del Vecchio GC, Cecinati V, et al. Metabolic, inflammatory, endothelial and haemostatic markers in a group of Italian obese children and adolescents. Eur J Pediatr. 2011;170(7):845-50. PMID: 21210148. **KQ3E6.**

175. Giugliano RP, Desai NR, Kohli P, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet. 2012;(9858):2007-17. PMID: 23141813. **KQ6E5, KQ7E5.**

176. Glueck CJ, Fallat R, Tsang R. Pediatric familial type II hyperlipoproteinemia: therapy with diet and cholestyramine resin. Pediatrics. 1973;52(5):669-79. PMID: 4355362. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

177. Glueck CJ, Mellies MJ, Dine M, et al. Safety and efficacy of long-term diet and diet plus bile acid-binding resin cholesterol-lowering therapy in 73 children heterozygous for familial hypercholesterolemia. Pediatrics. 1986;78(2):338-48. PMID: 3526270. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

178. Glueck CJ, Tsang RC, Fallat RW, et al. Plasma vitamin A and E levels in children with familial type II hyperlipoproteinemia during therapy with diet and cholestyramine resin. Pediatrics. 1974;54(1):51-5. PMID: 4365953. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

179. Goff DC Jr, Donker GA, Ragan JD Jr, et al. Cholesterol screening in pediatric practice. Pediatrics. 1991;88(2):250-8. PMID: 1861922. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

180. Goldstein JL, Albers JJ, Schrott HG, et al. Plasma lipid levels and coronary heart disease in adult relatives of newborns with normal and elevated cord blood lipids. Am J Hum Genet. 1974;26(6):727-35. PMID: 4440681. **KQ1E5, KQ2E5, KQ3E7, KQ4E5, KQ5E5.**

181. Graves L, Garnett SP, Cowell CT, et al. Waist-to-height ratio and cardiometabolic risk factors in adolescence: findings from a prospective birth cohort. Pediatr Obes. 2014;9(5):327-38. PMID: 23894119. **KQ1E13, KQ2E13, KQ3E5, KQ4E6, KQ5E13.**

182. Griffin TC, Christoffel KK, Binns HJ, et al. Family history evaluation as a predictive screen for childhood hypercholesterolemia. Pediatric Practice Research Group. Pediatrics. 1989;84(2):365-73. PMID: 2748269. **KQ1E13, KQ2E13, KQ3E7, KQ4E13, KQ5E13.**

183. Grontved A, Ried-Larsen M, Moller NC, et al. Muscle strength in youth and cardiovascular risk in young adulthood (the European Youth Heart Study). Br J Sports Med. 2013;49(2):90-4. PMID: 23525553. **KQ3E6.**

184. Groot PH, Dijkhuis-Stoffelsma R, Grose WF, et al. The effects of colestipol hydrochloride on serum lipoprotein lipid and apolipoprotein B and A-I concentrations in children heterozygous for familial hypercholesterolemia. Acta Paediatr Scand. 1983;72(1):81-5. PMID: 6407278. **KQ3E13.**

185. Guardamagna O, Abello F, Baracco V, et al. Primary hyperlipidemias in children: effect of plant sterol supplementation on plasma lipids and markers of cholesterol synthesis and absorption. Acta Diabetol. 2011;48(2):127-33. PMID: 21057823. **KQ6E9, KQ7E9.**
186. Guardamagna O, Abello F, Baracco V, et al. The treatment of hypercholesterolemic children: efficacy and safety of a combination of red yeast rice extract and policosanols. Nutr Metab Cardiovasc Dis. 2011;21(6):424-9. PMID: 20153154. **KQ6E5, KQ7E5.**
187. Guardamagna O, Abello F, Cagliero P, et al. Could dyslipidemic children benefit from glucomannan intake? Nutrition. 2013;(42193):1060-1065. PMID: 23759268. **KQ6E5, KQ7E5.**
188. Guardamagna O, Abello F, Saracco P, et al. Endothelial activation, inflammation and premature atherosclerosis in children with familial dyslipidemia. Atherosclerosis. 2009;207(2):471-5. PMID: 19560772. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
189. Guardamagna O, Amaretti A, Puddu PE, et al. Bifidobacteria supplementation: effects on plasma lipid profiles in dyslipidemic children. Nutrition. 2014;30(42193):831-6. PMID: 24985000. **KQ6E10, KQ7E10.**
190. Gultom LC, Sjarif DR, Sudoyo HA, et al. The role of apolipoprotein E polymorphism in improving dyslipidemia in obese adolescents following physical exercise and National Cholesterol Education Program Step II intervention. J Pediatr Endocrinol Metab. 2015;28(42130):597-603. PMID: 25870958. **KQ6E9.**
191. Guo S, Beckett L, Chumlea WC, et al. Serial analysis of plasma lipids and lipoproteins from individuals 9-21 y of age. Am J Clin Nutr. 1993;58(1):61-7. PMID: 8317391. **KQ3E13.**
192. Guven A, Sanisoglu SY. Pubertal progression and serum lipid profile in obese children. J Pediatr Endocrinol Metab. 2008;21(2):135-46. PMID: 18422026. **KQ3E5, KQ4E5.**
193. Guyton JR, Brown BG, Fazio S, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in patients with type IIa or type IIb hyperlipidemia. J Am Coll Cardiol. 2008;(16):1564-72. PMID: 18420099. **KQ6E5, KQ7E5.**
194. Gylling H, Hallikainen M, Nissinen MJ, et al. The effect of a very high daily plant stanol ester intake on serum lipids, carotenoids, and fat-soluble vitamins. Clin Nutr. 2010;(1):112-8. PMID: 19709787. **KQ6E5, KQ7E5.**
195. Gylling H, Plat J, Turley S, et al. Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. Atherosclerosis. 2014;232(2):346-60. PMID: 24468148. **KQ6E9, KQ7E9.**
196. Haas GM, Bertsch T, Schwandt P. Prehypertension and cardiovascular risk factors in children and adolescents participating in the community-based prevention education program family heart study. Int J Prev Med. 2014;5(Suppl 1):S50-6. PMID: 24791192. **KQ3E7, KQ4E6.**
197. Hammond J, Chinn S, Richardson H, et al. Response to venepuncture for monitoring in primary schools. Arch Dis Child. 1994;(5): PMID: 8017955. **KQ1E13, KQ2E13, KQ3E13, KQ4E6, KQ5E13.**
198. Hanlin ER, Hendricks B, Jenkins K, et al. Cardiovascular risk profile: comparison between white and Southeast Asian youth in Wausau SCHOOL Project. WMJ. 2009;108(4):189-93. PMID: 19753824. **KQ3E7.**
199. Hardy OT, Wiecha J, Kim A, et al. Effects of a multicomponent wellness intervention on dyslipidemia among overweight adolescents. J Pediatr Endocrinol Metab. 2012;25(42006):79-82. PMID: 22570954. **KQ6E5, KQ7E5.**
200. Harel Z, Riggs S, Vaz R, et al. Isolated low HDL cholesterol emerges as the most common lipid abnormality among obese adolescents. Clin Pediatr (Phila). 2010;49(1):29-34. PMID: 19628760. **KQ3E7, KQ4E7.**
201. Hauenschild A, Ewald N, Schnell-Kretschmer H, et al. Successful long-term treatment of severe hypertriglyceridemia by feedback control with lipid self-monitoring. Ann Nutr Metab. 2008;52(3):215-20. PMID: 18544976. **KQ5E13, KQ6E5, KQ7E5.**
202. Haymond S, Mohanty N. Pediatric lipid screening rates in the us are low: what can labs do to help? Clin Chem. 2015;61(8):1019-21. PMID: 25724661. **KQ3E6.**

203. Heintjes EM, Penning-van Beest FJ, Johansson S, et al. Comparison of incidences of cardiovascular events among new users of different statins: a retrospective observational cohort study. Curr Med Res Opin. 2009;25(11):2621-9. PMID: 19743959. **KQ7E5.**
204. Hernandez-Mijares A, Banuls C, Rocha M, et al. Effects of phytosterol ester-enriched low-fat milk on serum lipoprotein profile in mildly hypercholesterolaemic patients are not related to dietary cholesterol or saturated fat intake. Br J Nutr. 2010;(7):1018-25. PMID: 20456813. **KQ6E5, KQ7E5.**
205. Higashikawa F, Noda M, Awaya T, et al. Reduction of serum lipids by the intake of the extract of garlic fermented with Monascus pilosus: a randomized, double-blind, placebo-controlled clinical trial. Clin Nutr. 2012;31(2):261-6. PMID: 22041543. **KQ6E5, KQ7E5.**
206. Hirschler V, Maccallini G, Calcagno M, et al. Waist circumference identifies primary school children with metabolic syndrome abnormalities. Diabetes Technol Ther. 2007;9(2):149-57. PMID: 17425440. **KQ3E6, KQ4E6.**
207. Hirschler V, Maccallini G, Sanchez M, et al. Association between triglyceride to HDL-C ratio and insulin resistance in indigenous Argentinean children. Pediatr Diabetes. 2014;(0): PMID: 25303644. **KQ3E4, KQ4E6.**
208. Hirschler V, Molinari C, Maccallini G, et al. Comparison of different anthropometric indices for identifying dyslipidemia in school children. Clin Biochem. 2011;44(42225):659-64. PMID: 21349259. **KQ3E4, KQ4E4.**
209. Ho M, Garnett SP, Baur LA, et al. Impact of dietary and exercise interventions on weight change and metabolic outcomes in obese children and adolescents: a systematic review and meta-analysis of randomized trials. JAMA Pediatrics. 2013;167(8):759-68. PMID: 23778747. **KQ6E2, KQ7E13.**
210. Ho M, Garnett SP, Baur L, et al. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. Pediatrics. 2012;130(6):e1647-71. PMID: 23166346. **KQ6E5, KQ7E5.**
211. Holl RW, Hoffmeister U, Thamm M, et al. Does obesity lead to a specific lipid disorder? Analysis from the German/Austrian/Swiss APV registry. Int J Pediatr Obes. 2011;(0):53-8. PMID: 21905817. **KQ1E13, KQ2E13, KQ3E11, KQ4E6, KQ5E13.**
212. Homma S, Troxclair DA, Zieske AW, et al. Histological changes and risk factor associations in type 2 atherosclerotic lesions (fatty streaks) in young adults. Atherosclerosis. 2011;219(1):184-90. PMID: 21831377. **KQ8E9.**
213. House BT, Shearrer GE, Miller SJ, et al. Increased eating frequency linked to decreased obesity and improved metabolic outcomes. Int J Obes (Lond). 2014;(0): PMID: 24840081. **KQ6E5, KQ7E5.**
214. Howard JK, Bindler RM, Dimico GS, et al. Cardiovascular risk factors in children: a Bloomsday research report. J Pediatr Nurs. 1991;6(4):222-9. PMID: 1865311. **KQ3E13.**
215. Hrafnkelsson H, Magnusson KT, Thorsdottir I, et al. Result of school-based intervention on cardiovascular risk factors. Scand J Prim Health Care. 2014;32(4):149-155. PMID: 25424464. **KQ6E5, KQ7E5.**
216. Hsia DS, Gwilliam NR, Ferrell LB, et al. Morbidly obese paediatric patients are not adequately screened for comorbidities. Clin Obes. 2013;3(42006):11-Jul. PMID: 25586387. **KQ4E6.**
217. Hu T, Mills KT, Yao L, et al. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am J Epidemiol. 2012;176(0):S44-54. PMID: 23035144. **KQ6E5, KQ7E5.**
218. Huang CJ, Kwok CF, Chou CH, et al. The effect of exercise on lipid profiles and inflammatory markers in lean male adolescents: a prospective interventional study. J Investig Med. 2014;63(1):29-34. PMID: 25415059. **KQ6E5, KQ7E5.**
219. Huang RC, de Klerk N, Mori TA, et al. Differential relationships between anthropometry measures and cardiovascular risk factors in boys and girls. Int J Pediatr Obes. 2011;6(42037):e271-82. PMID: 20815762. **KQ3E6, KQ4E13.**

220. Huijgen R, Vissers MN, Kindt I, et al. Assessment of carotid atherosclerosis in normocholesterolemic individuals with proven mutations in the low-density lipoprotein receptor or apolipoprotein B genes. Circ Cardiovasc Genet. 2011;4(4):413-7. PMID: 21642693. **KQ6E5, KQ7E5.**

221. Hussein O, Minasian L, Itzkovich Y, et al. Ezetimibe's effect on platelet aggregation and LDL tendency to peroxidation in hypercholesterolaemia as monotherapy or in addition to simvastatin. Br J Clin Pharmacol. 2008;65(5):637-45. PMID: 18241285. **KQ6E5, KQ7E5.**

222. I'Allemand D, Wiegand S, Reinehr T, et al. Cardiovascular risk in 26,008 European overweight children as established by a multicenter database. Obesity (Silver Spring). 2008;16(7):1672-9. PMID: 18451769. **KQ3E11.**

223. Iannuzzi A, Licenziati MR, Acampora C, et al. Increased carotid intima-media thickness and stiffness in obese children. Diabetes Care. 2004;27(10):2506-8. PMID: 15451928. **KQ1E13, KQ2E6, KQ3E13, KQ4E13, KQ5E13.**

224. Imamura H, Nagata A, Oshikata R, et al. High-density lipoprotein cholesterol subfractions and lecithin: cholesterol acyltransferase activity in collegiate soccer players. Int J Sports Med. 2013;34(5):398-401. PMID: 23152129. **KQ6E5, KQ7E5.**

225. Inoue DS, De Mello MT, Foschini D, et al. Linear and undulating periodized strength plus aerobic training promote similar benefits and lead to improvement of insulin resistance on obese adolescents. J Diabetes Complications. 2015;29(2):258-64 PMID: 25441178. **KQ6E5, KQ7E5.**

226. Iughetti L. Drugs for children with hypercholesterolemia: be cautious. J Pediatr Endocrinol Metab. 2009;22(6):483-5. PMID: 19694194. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

227. Izzo R, Simone G, Giudice R, et al. Effects of nutraceuticals on prevalence of metabolic syndrome and on calculated Framingham Risk Score in individuals with dyslipidemia. J Hypertens. 2010;28(7):1482-7. PMID: 20498621. **KQ6E5, KQ7E5.**

228. Jago R, Drews KL, McMurray RG, et al. Fatness, fitness, and cardiometabolic risk factors among sixth-grade youth. Med Sci Sports Exerc. 2010;42(8):1502-10. PMID: 20139783. **KQ3E6, KQ4E13.**

229. Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012;18 Suppl 1:1-78. PMID: 22522068. **KQ6E9, KQ7E9.**

230. Jenssen BP, Jacobson MS. Screening adolescents for lipid disorders: what is the best approach?. Adolesc Med State Art Rev. 2008;19(3):507-20. PMID: 19227389. **KQ1E13.**

231. Jiang X, Srinivasan SR, Webber LS, et al. Association of fasting insulin level with serum lipid and lipoprotein levels in children. Arch Intern Med. 1995;155(2):190-6. PMID: 7811129. **KQ3E13.**

232. Jones PH, Goldberg AC, Knapp HR, et al. Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia. Am Heart J. 2010;160(4):759-66. PMID: 20934572. **KQ6E5, KQ7E5.**

233. Joseph SV, Jacques H, Plourde M, et al. Conjugated linoleic acid supplementation for 8 weeks does not affect body composition, lipid profile, or safety biomarkers in overweight, hyperlipidemic men. J Nutr. 2011;(7):1286-91. PMID: 21593349. **KQ6E5, KQ7E5.**

234. Juhola J, Magnussen CG, Viikari JS, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. J Pediatr. 2011;159(4):584-90. PMID: 21514597. **KQ8E6.**

235. Juonala M, Viikari JS, Kahonen M, et al. Childhood levels of serum apolipoproteins B and A-I predict carotid intima-media thickness and brachial endothelial function in adulthood: the cardiovascular risk in young Finns study. J Am Coll Cardiol. 2008;52(4):293-9. PMID: 18634985. **KQ1E13, KQ2E9, KQ3E13, KQ4E13, KQ5E13.**

236. Kaistha A, Deckelbaum RJ, Starc TJ, et al. Overrestriction of dietary fat intake before formal nutritional counseling in children with hyperlipidemia. Arch Pediatr Adolesc Med. 2001;155(11):1225-30. PMID: 11695931. **KQ3E13.**

Appendix C. Excluded Studies

237. Kallio MJ, Salmenpera L, Siimes MA, et al. Tracking of serum cholesterol and lipoprotein levels from the first year of life. Pediatrics. 1993;91(5):949-54. PMID: 8474815. **KQ3E13.**

238. Kapur NK. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. Expert Rev Cardiovasc Ther. 2007;5(2):161-75. PMID: 17338662. **KQ6E2, KQ7E2.**

239. Kastelein JJP, Kusters M, Caceres M, et al. Efficacy and safety of ezetimibe monotherapy in children six to ten years of age with heterozygous familial or non-familial hypercholesterolemia. J Am Coll Cardiol. 2013;(10):E1466. **KQ6E6, KQ7E6.**

240. Katzmarzyk PT, Perusse L, Malina RM, et al. Stability of indicators of the metabolic syndrome from childhood and adolescence to young adulthood: the Quebec Family Study. J Clin Epidemiol. 2001;54(2):190-5. PMID: 11166535. **KQ3E13.**

241. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. J Cardiovasc Nurs. 2007;22(3):218-53. PMID: 17545824. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**

242. Kelder SH, Osganian SK, Feldman HA, et al. Tracking of physical and physiological risk variables among ethnic subgroups from third to eighth grade: the Child and Adolescent Trial for Cardiovascular Health cohort study. Prev Med. 2002;(3): PMID: 11902849. **KQ3E13.**

243. Kelishadi R, Hashemipour M, Sheikh-Heidar A, et al. Changes in serum lipid profile of obese or overweight children and adolescents following a lifestyle modification course. Arya Atherosclerosis. 2012;8(3):143-8. PMID: 23359278. **KQ6E9.**

244. Kelishadi R, Razaghi EM, Gouya MM, et al. Association of physical activity and the metabolic syndrome in children and adolescents: CASPIAN Study. Horm Res. 2007;67(1):46-52. PMID: 17035710. **KQ1E4, KQ2E4, KQ3E4, KQ4E4, KQ5E4.**

245. Kelley GA, Kelley KS. Aerobic exercise and lipids and lipoproteins in children and adolescents: a meta-analysis of randomized controlled trials. Atherosclerosis. 2007;191(2):447-53. PMID: 16806228. **KQ6E5, KQ7E5.**

246. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. Prev Med. 2009;48(1): PMID: 19013187. **KQ6E5, KQ7E5.**

247. Kelley GA, Kelley KS. Effects of aerobic exercise on non-high-density lipoprotein cholesterol in children and adolescents: a meta-analysis of randomized controlled trials. Prog Cardiovasc Nurs. 2008;23(3):128-32. PMID: 19039893. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**

248. Kelly AS, Steinberger J, Jacobs DR, et al. Predicting cardiovascular risk in young adulthood from the metabolic syndrome, its component risk factors, and a cluster score in childhood. Int J Pediatr Obes. 2011;6(42037):e283-9. PMID: 21070100. **KQ8E6.**

249. Kenny D, Ward OC, Mulhern B, et al. Failure of cord serum cholesterol and betalipoprotein as screening tests for familial hyperlipoproteinaemia. Ir J Med Sci. 1984;(3): PMID: 6724853. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

250. Keska A, Lutoslawska G, Czajkowska A, et al. Variability in HOMA-IR, lipoprotein profile and selected hormones in young active men. ScientificWorldJournal. 2013;2013: PMID: 24348155. **KQ3E4.**

251. Khalil A, Aggarwal A, Arora S, et al. Lipoprotein (a)--lipid profile and apolipoprotein B in children of young parents with coronary artery disease. Indian Heart J. 2011;63(5):450-3. PMID: 23550425. **KQ3E4.**

252. Kianbakht S, Abasi B, Perham M, et al. Antihyperlipidemic effects of Salvia officinalis L. leaf extract in patients with hyperlipidemia: a randomized double-blind placebo-controlled clinical trial. Phytother Res. 2011;25(12):1849-53. PMID: 21506190. **KQ6E13, KQ7E13.**
253. Kim IK, Lee HJ, Kang JH, et al. Relationship of serum retinol-binding protein 4 with weight status and lipid profile among Korean children and adults. Eur J Clin Nutr. 2011;65(2):226-33. PMID: 21102613. **KQ3E6, KQ4E6.**
254. Kim J, Bhattacharjee R, Kheirandish-Gozal L, et al. Insulin sensitivity, serum lipids, and systemic inflammatory markers in school-aged obese and nonobese children. Int J Pediatr. 2010. PMID: 21274450. **KQ3E6, KQ4E6.**
255. Klakk H, Andersen LB, Heidemann M, et al. Six physical education lessons a week can reduce cardiovascular risk in school children aged 6-13 years: A longitudinal study. Scand J Public Health. 2013. PMID: 24055828. **KQ5E5, KQ6E6, KQ7E13.**
256. Kleiser C, Schienkiewitz A, Schaffrath Rosario A, et al. Indicators of overweight and cardiovascular disease risk factors among 11- to 17-year-old boys and girls in Germany. Obes Facts. 2011;4(5):379-85. PMID: 22166758. **KQ3E11, KQ4E6.**
257. Koren MJ, Scott R, Kim JB, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2012;(9858):1995-2006. PMID: 23141812. **KQ6E5, KQ7E5.**
258. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2531-40. PMID: 24691094. **KQ6E5, KQ7E5.**
259. Koskinen J, Kahonen M, Viikari JS, et al. Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in young Finns study. Circulation. 2009;120(3):229-36. PMID: 19581494. **KQ1E13, KQ2E5, KQ3E13, KQ4E13, KQ5E13.**
260. Kostapanos MS, Milionis HJ, Agouridis AD, et al. Rosuvastatin treatment is associated with an increase in insulin resistance in hyperlipidaemic patients with impaired fasting glucose. Int J Clin Pract. 2009;63(9):1308-13. PMID: 19691613. **KQ6E5, KQ7E5.**
261. Kouda K, Nakamura H, Nishio N, et al. Trends in body mass index, blood pressure, and serum lipids in Japanese children: Iwata population-based annual screening (1993-2008). J Epidemiol. 2010;20(3):212-8. PMID: 20208399. **KQ3E6, KQ4E13.**
262. Koulouridis E, Georgalidis K, Kostimpa I, et al. Metabolic syndrome risk factors and estimated glomerular filtration rate among children and adolescents. Pediatr Nephrol. 2010;25(3):491-8. PMID: 20012104. **KQ3E6, KQ4E13.**
263. Krishna R, Anderson MS, Bergman AJ, et al. Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in healthy individuals: two double-blind, randomised placebo-controlled phase I studies. Lancet. 2007;(9603):1907-14. PMID: 18068514. **KQ6E5, KQ7E5.**
264. Krysiak R, Zmuda W, Okopien B. The effect of ezetimibe and simvastatin on hemostasis in patients with isolated hypercholesterolemia. Fundam Clin Pharmacol. 2012;26(3):424-31. PMID: 21392096. **KQ6E5, KQ7E5.**
265. Kuehl KS, Cockerham JT, Hitchings M, et al. Effective control of hypercholesterolemia in children with dietary interventions based in pediatric practice. Prev Med. 1993;22(2):154-66. PMID: 8483855. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
266. Kumar SS, Lahey KA, Day A, et al. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate versus atorvastatin monotherapy in the treatment of dyslipidemia. Lipids Health Dis. 2009:56. PMID: 20017910. **KQ6E5, KQ7E5.**
267. Kunz F, Pechlaner C, Hortnagl H, et al. The smoker's paradox and the real risk of smoking. Eur J Epidemiol. 2005;20(2):161-7. PMID: 15792283. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**

268. Kuo P, Syu JT, Tzou IL, et al. Prevalence and trend of dyslipidaemia from 1996 to 2006 among normal and overweight adolescents in Taiwan. BMJ Open. 2014;4(2):e003800. PMID: 24578534. **KQ3E4, KQ4E4.**

269. Kurabayashi M, Sakuma I, Kawamori R, et al. Can intensive lipid-lowering therapy with statins ameliorate atherosclerosis in Japanese patients? Rationale and design of the JART study. J Atheroscler Thromb. 2010;17(4):416-22. PMID: 20215710. **KQ6E2, KQ7E2.**

270. Kusunoki T, Morimoto T, Sakuma M, et al. Total and low-density lipoprotein cholesterol levels are associated with atopy in schoolchildren. J Pediatr. 2011;158(2):334-6. PMID: 21146186. **KQ3E7, KQ4E6.**

271. Kwiterovich PO Jr, Barton BA, McMahon RP, et al. Effects of diet and sexual maturation on low-density lipoprotein cholesterol during puberty: the Dietary Intervention Study in Children (DISC). Circulation. ;96(8):2526-33. PMID: 9355889. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

272. Kwiterovich PO Jr, Heiss G, Johnson N, et al. Assessment of plasma total cholesterol as a test to detect elevated low density (beta) lipoprotein cholesterol levels (type IIa hyperlipoproteinemia) in young subjects from a population-based sample. Am J Epidemiol. ;115(2):192-204. PMID: 7058778. **KQ1E13, KQ2E13, KQ3E9, KQ4E13, KQ5E13.**

273. Kwiterovich PO Jr. Recognition and management of dyslipidemia in children and adolescents. J Clin Endocrinol Metab. 2008;93(11):4200-9. PMID: 18697860. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**

274. Kwiterovich PO. Cut points for lipids and lipoproteins in children and adolescents: should they be reassessed? Clin Chem. 2008;54(7):1113-5. PMID: 18593961. **KQ3E2.**

275. Lamaida N, Capuano E, Pinto L, et al. The safety of statins in children. Acta Paediatr. 2013;102(9):857-62. PMID: 23631461. **KQ7E5.**

276. Lamb MM, Ogden CL, Carroll MD, et al. Association of body fat percentage with lipid concentrations in children and adolescents: United States, 1999-2004. Am J Clin Nutr. 2011;94(3):877-83. PMID: 21775565. **KQ3E6.**

277. Lambert M, Lupien PJ, Gagne C, et al. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. Canadian Lovastatin in Children Study Group. Pediatrics. 1996;97(5):619-28. PMID: 8628597. **KQ3E13.**

278. Lansing AM, Barbie RN, Shaheen KA. Regional cholesterol screening: problems and potentials. J Ky Med Assoc. 1990;88(4):170-4. PMID: 2110237. **KQ3E13.**

279. Lapinleimu J, Lapinleimu H, Nuotio IO, et al. Expression of common familial dyslipidemias in early childhood. Atherosclerosis. 2009;204(2):573-9. PMID: 19026413. **KQ1E13, KQ2E13, KQ3E7, KQ4E13, KQ5E13.**

280. Larsson B, Vaara I. Cholesterol screening of seven-year-old children. How to identify children at risk. Acta Paediatr. 1992;(4):. PMID: 1606391. **KQ3E13.**

281. Lazarou C, Matalas AL. Breakfast intake is associated with nutritional status, Mediterranean diet adherence, serum iron and fasting glucose: the CYFamilies study. Public Health Nutr. 2014;18(7):1308-16. PMID: 25287356. **KQ3E4, KQ4E4.**

282. Lee CW, Baek SH, Hong TJ, et al. A multicenter, eight-week treatment, single-step titration, open-label study assessing the percentage of Korean dyslipidemic patients achieving LDL cholesterol target with atorvastatin starting doses of 10 mg, 20 mg and 40 mg. Cardiovasc Drugs Ther. 2010;24(2):181-8. PMID: 20383571. **KQ6E5, KQ7E5.**

283. Lee JM, Gebremariam A, Card-Higginson P, et al. Poor performance of body mass index as a marker for hypercholesterolemia in children and adolescents. Arch Pediatr Adolesc Med. 2009;163(8):716-23. PMID: 19652103. **KQ3E11.**

284. Lee SH, Park S, Kang SM, et al. Effect of atorvastatin monotherapy and low-dose atorvastatin/ezetimibe combination on fasting and postprandial triglycerides in combined hyperlipedemia. J Cardiovasc Pharmacol Ther. 2012;17(1):65-71. PMID: 21386036. **KQ6E5, KQ7E5.**

285. Lee S, Bacha F, Gungor N, et al. Comparison of different definitions of pediatric metabolic syndrome: relation to abdominal adiposity, insulin resistance, adiponectin, and inflammatory biomarkers. J Pediatr. 2008;152(2):177-84. PMID: 18206686. **KQ3E6, KQ4E6.**
286. Lee S, Burns SF, White D, et al. Effects of acute exercise on postprandial triglyceride response after a high-fat meal in overweight black and white adolescents. Int J Obes (Lond). 2013;37(7):966-71. PMID: 23507997. **KQ6E5, KQ7E5.**
287. LeFevre M. Screening for hyperlipidemia in children: primum non nocere. Am Fam Physician. 2010;82(5):. PMID: 20822079. **KQ1E13, KQ2E2, KQ3E13, KQ4E13, KQ5E13.**
288. Lenicek Krleza J, Ethuranovic V, Bronic A, et al. Multiple presence of prothrombotic risk factors in Croatian children with arterial ischemic stroke and transient ischemic attack. Croat Med J. 2013;54(4):346-54. PMID: 23986275. **KQ8E9.**
289. Li C, Ford ES, McBride PE, et al. Non-high-density lipoprotein cholesterol concentration is associated with the metabolic syndrome among US youth aged 12-19 years. J Pediatr. 2011;158(2):201-7. PMID: 20828715. **KQ3E6, KQ4E6.**
290. Li J, Motsko SP, Goehring EL, et al. Longitudinal study on pediatric dyslipidemia in population-based claims database. Pharmacoepidemiol Drug Saf. 2010;19(1):90-8. PMID: 20035528. **KQ3E9, KQ4E6, KQ6E9, KQ7E6.**
291. Liacouras CA, Coates PM, Gallagher PR, et al. Use of cholestyramine in the treatment of children with familial combined hyperlipidemia. The Journal of pediatrics. 1993;122(3):477-82. PMID: 8441109. **KQ3E13.**
292. Lilly CL, Gebremariam YD, Cottrell L, et al. Trends in serum lipids among 5th grade CARDIAC participants, 2002-2012. J Epidemiol Community Health. 2014;68(3):218-23. PMID: 24218074. **KQ3E11, KQ4E13.**
293. Lim J. The current state of dyslipidemia in Korean children and adolescents and its management in clinical practice. Ann Pediatr Endocrinol Metab. 2013;18(1):8-Jan. PMID: 24904843. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
294. Lin X, Racette SB, Lefevre M, et al. Combined effects of ezetimibe and phytosterols on cholesterol metabolism: a randomized, controlled feeding study in humans. Circulation. 2011;124(5):596-601. PMID: 21768544. **KQ6E5, KQ7E5.**
295. Liu J, Wade TJ, Tan H, et al. Cardiovascular risk factors and anthropometric measurements of adolescent body composition: a cross-sectional analysis of the Third National Health and Nutrition Examination Survey. Int J Obes (Lond). 2007;31(1):59-64. PMID: 16652133. **KQ3E6.**
296. Liu Y, Wang J, Zhang R, et al. A good response to oil with medium- and long-chain fatty acids in body fat and blood lipid profiles of male hypertriglyceridemic subjects. Asia Pac J Clin Nutr. 2009;18(3):351-8. PMID: 19786383. **KQ6E5, KQ7E5.**
297. Llorente-Cantarero FJ, Perez-Navero JL, Benitez-Sillero Jde D, et al. Evaluation of metabolic risk in prepubertal girls versus boys in relation to fitness and physical activity. Gend Med. 2012;9(6):436-44. PMID: 23102933. **KQ3E6.**
298. Loprinzi PD, Lee IM, Andersen RE, et al. Association of concurrent healthy eating and regular physical activity with cardiovascular disease risk factors in U.S. youth. Am J Health Promot. 2014;30(1):. PMID: 25372232. **KQ3E6, KQ4E6.**
299. Love-Osborne KA, Nadeau KJ, Sheeder J, et al. Presence of the metabolic syndrome in obese adolescents predicts impaired glucose tolerance and nonalcoholic fatty liver disease. J Adolesc Health. 2008;42(6):543-8. PMID: 18486862. **KQ3E5.**
300. Luke JN, Brown AD, Brazionis L, et al. Exploring clinical predictors of cardiovascular disease in a central Australian Aboriginal cohort. Eur J Prev Cardiol. 2013;20(2):246-53. PMID: 22345691. **KQ3E5.**
301. Luong DQ, Oster R, Ashraf AP. Metformin treatment improves weight and dyslipidemia in children with metabolic syndrome. J Pediatr Endocrinol Metab. 2014;(0):. PMID: 25210757. **KQ6E9, KQ7E6.**

302. Maccubbin D, Bays HE, Olsson AG, et al. Lipid-modifying efficacy and tolerability of extended-release niacin/laropiprant in patients with primary hypercholesterolaemia or mixed dyslipidaemia. Int J Clin Pract. 2008;(12):1959-70. PMID: 19166443. **KQ6E5, KQ7E5.**
303. Machado RB, Bernardes CR, de Souza IM, et al. Is lipid profile determination necessary in women wishing to use oral contraceptives?. Contraception. 2013;87(6):801-5. PMID: 23312931. **KQ3E5.**
304. Macias Saint-Gerons D, de la Fuente Honrubia C, Montero Corominas D, et al. Standard and intensive lipid-lowering therapy with statins for the primary prevention of vascular diseases: a population-based study. Eur J Clin Pharmacol. 2014;70(1):99-108. PMID: 24062166. **KQ8E6.**
305. Macknin M, Kong T, Weier A, et al. Plant-based, no-added-fat or American Heart Association diets: impact on cardiovascular risk in obese children with hypercholesterolemia and their parents. J Pediatr. 2015;166(4):953-9 e1-3. PMID: 25684089. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E5.**
306. Maggio AB, Martin XE, Saunders Gasser C, et al. Medical and non-medical complications among children and adolescents with excessive body weight. BMC Pediatr. 2014;14: PMID: 25220473. **KQ3E5, KQ4E5.**
307. Magnussen CG, Raitakari OT, Thomson R, et al. Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. Circulation. 2008;117(1):32-42. PMID: 18071074. **KQ1E9, KQ2E6, KQ3E9, KQ4E13, KQ5E13.**
308. Magnussen CG, Venn A, Thomson R, et al. The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the cardiovascular risk in Young Finns study, the Bogalusa Heart study, and the CDAH (Childhood Determinants of Adult Health) study. J Am Coll Cardiol. 2009;53(10):860-9. PMID: 19264243. **KQ1E6, KQ2E9, KQ3E9, KQ4E9, KQ5E13.**
309. Maki KC, Bays HE, Dicklin MR, et al. Effects of prescription omega-3-acid ethyl esters, coadministered with atorvastatin, on circulating levels of lipoprotein particles, apolipoprotein CIII, and lipoprotein-associated phospholipase A2 mass in men and women with mixed dyslipidemia. J Clin Lipidol. 2011;(6):483-92. PMID: 22108152. **KQ6E5, KQ7E5.**
310. Maki KC, Butteiger DN, Rains TM, et al. Effects of soy protein on lipoprotein lipids and fecal bile acid excretion in men and women with moderate hypercholesterolemia. J Clin Lipidol. 2010;(6):531-42. PMID: 21122701. **KQ6E5, KQ7E5.**
311. Malinowski JM, Gehret MM. Phytosterols for dyslipidemia. Am J Health Syst Pharm. 2010;67(14):1165-73. PMID: 20592321. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
312. Malve H, Kerkar P, Mishra N, et al. LDL-cholesterol lowering activity of a blend of rice bran oil and safflower oil (8:2) in patients with hyperlipidaemia: a proof of concept, double blind, controlled, randomised parallel group study. J Indian Med Assoc. 2010;108(11):785-8. PMID: 21510583. **KQ6E4, KQ7E4.**
313. Manchester RA, McDuffie C, Diamond E. Screening for hypercholesterolemia in college students. J Am Coll Health. 1989;37(4):149-53. PMID: 2926025. **KQ3E9.**
314. Marti B, Vartiainen E. Relation between leisure time exercise and cardiovascular risk factors among 15-year-olds in eastern Finland. J Epidemiol Community Health. 1989;43(3):228-33. PMID: 2607300. **KQ3E13.**
315. Martin L, Oepen J, Reinehr T, et al. Ethnicity and cardiovascular risk factors: evaluation of 40,921 normal-weight, overweight or obese children and adolescents living in Central Europe. Int J Obes (Lond). 2014;39(1):45-51. PMID: 25214149. **KQ3E7, KQ4E6.**
316. Martin SS, Blaha MJ, Toth PP, et al. Very large database of lipids: rationale and design. Clin Cardiol. 2013;36(11):641-8. PMID: 24122913. **KQ3E9.**

317. Martinez-Gomez D, Eisenmann JC, Gomez-Martinez S, et al. Sedentary behavior, adiposity and cardiovascular risk factors in adolescents. The AFINOS study. Rev Esp Cardiol. 2010;63(3):277-85. PMID: 20196988. **KQ3E6, KQ4E6.**
318. Martinez-Lopez S, Sarria B, Sierra-Cinos JL, et al. Realistic intake of a flavanol-rich soluble cocoa product increases HDL-cholesterol without inducing anthropometric changes in healthy and moderately hypercholesterolemic subjects. Food Funct. 2014;5(2):364-74. PMID: 24394704. **KQ6E5, KQ7E5.**
319. Martinez-Vizcaino V, Martinez MS, Aguilar FS, et al. Validity of a single-factor model underlying the metabolic syndrome in children: a confirmatory factor analysis. Diabetes Care. 2010;33(6):1370-2. PMID: 20299487. **KQ3E6.**
320. Martino F, Puddu PE, Pannarale G, et al. Low dose chromium-polynicotinate or policosanol is effective in hypercholesterolemic children only in combination with glucomannan. Atherosclerosis. 2013;(1):198-202. PMID: 23453352. **KQ6E13, KQ7E13.**
321. Matsuyama T, Shoji K, Takase H, et al. Effects of phytosterols in diacylglycerol as part of diet therapy on hyperlipidemia in children. Asia Pac J Clin Nutr. 2007;16(1):40-8. PMID: 17215179. **KQ6E9, KQ7E9.**
322. McCourt HJ, Hunter SJ, Cardwell CR, et al. Adiponectin multimers, body weight and markers of cardiovascular risk in adolescence: Northern Ireland Young Hearts Project. Int J Obes (Lond). 2013;37(9):1247-53. PMID: 23318722. **KQ3E6.**
323. McCrindle BW, American Heart Association Writing Group, Urbina EM, et al. Summary of the American Heart Association's scientific statement on drug therapy of high-risk lipid abnormalities in children and adolescents. Arterioscler Thromb Vasc Biol. 2007;27(5):982-5. PMID: 17442893. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
324. McCrindle BW, Helden E, Cullen-Dean G, et al. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. Pediatr Res. 2002;51(6):715-21. PMID: 12032266. **KQ3E13.**
325. McCrindle BW, Manlhiot C, Millar K, et al. Population trends toward increasing cardiovascular risk factors in Canadian adolescents. J Pediatr. 2010;157(5):837-43. PMID: 20955854. **KQ3E7, KQ4E13.**
326. McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007;115(14):1948-67. PMID: 17377073. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
327. Mendelson M, Michallet AS, Monneret D, et al. Impact of exercise training without caloric restriction on inflammation, insulin resistance and visceral fat mass in obese adolescents. Pediatr Obes. 2014; PMID: 25088157. **KQ6E5, KQ7E5.**
328. Menees S, Zhang D, Le J, et al. Variations in carotid artery intima-media thickness during the cardiac cycle in children. J Am Soc Echocardiogr. 2010;23(1):58-63. PMID: 19962856. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
329. Messiah SE, Arheart KL, Lipshultz SE, et al. Body mass index, waist circumference, and cardiovascular risk factors in adolescents. J Pediatr. 2008;153(6):845-50. PMID: 18675434. **KQ1E13, KQ2E13, KQ3E7, KQ4E13, KQ5E13.**
330. Messiah SE, Vidot DC, Gurnurkar S, et al. Obesity is significantly associated with cardiovascular disease risk factors in 2- to 9-year-olds. J Clin Hypertens (Greenwich). 2014;16(12):889-94. PMID: 25307314. **KQ3E6, KQ4E6.**
331. Miazgowski T, Safranow K, Krzyzanowska-Swiniarska B, et al. Adiponectin, visfatin and regional fat depots in normal weight obese premenopausal women. Eur J Clin Invest. 2013;43(8):783-90. PMID: 23650969. **KQ3E5.**
332. Michels N, De Henauw S, Breidenassel C, et al. European adolescent ready-to-eat-cereal (RTEC) consumers have a healthier dietary intake and body composition compared with non-RTEC consumers. Eur J Nutr. 2014;54(4):653-64. PMID: 25403942. **KQ3E5, KQ4E13.**

333. Miettinen TA, Gylling H, Viikari J, et al. Synthesis and absorption of cholesterol in Finnish boys by serum non-cholesterol sterols: the cardiovascular risk in Young Finns Study. Atherosclerosis. 2008;200(1):177-83. PMID: 18178213. **KQ3E6, KQ4E6.**
334. Mietus-Snyder M, Drews KL, Otvos JD, et al. Low-density lipoprotein cholesterol versus particle number in middle school children. J Pediatr. 2013;163(2):355-62. PMID: 23415622. **KQ3E6.**
335. Mietus-Snyder M, Krauss RM. Lipid metabolism in children and adolescents: Impact on vascular biology. J Clin Lipidol. 2008;2(3):127-37. PMID: 21291731. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
336. Mitka M. Screening misses high LDL in many youths. JAMA. 2010;304(9):952-3. PMID: 20810367. **KQ3E2, KQ4E2.**
337. Mittelman SD, Gilsanz P, Mo AO, et al. Adiposity predicts carotid intima-media thickness in healthy children and adolescents. J Pediatr. 2010;156(4):592-7 e2. PMID: 20004913. **KQ1E13, KQ2E13, KQ3E7, KQ4E13, KQ5E13.**
338. Mizuno K, Nakaya N, Teramoto T, et al. Usefulness of LDL-C-related parameters to predict cardiovascular risk and effect of pravastatin in mild-to-moderate hypercholesterolemia. J Atheroscler Thromb. 2012;19(2):176-85. PMID: 22129522. **KQ6E5, KQ7E5.**
339. Mohammadi A, Sahebkar A, Iranshahi M, et al. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. Phytother Res. 2013;(3):374-9. PMID: 22610853. **KQ6E6, KQ7E6.**
340. Mohiuddin SM, Pepine CJ, Kelly MT, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J. 2009;157(1):195-203. PMID: 19081418. **KQ6E5, KQ7E5.**
341. Mohler B, Ackermann-Liebrich U, Steffen T, Staehelin HB. Cholesterol screening in childhood: results of a 9-year follow-up study in Swiss and Italian children in Switzerland. Soz Praventivmed. 1996;41(6):333-40. PMID: 9008838. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**
342. Moller NC, Grontved A, Wedderkopp N, et al. Cardiovascular disease risk factors and blood pressure response during exercise in healthy children and adolescents: the European Youth Heart Study. J Appl Physiol (1985). 2010;109(4):1125-32. PMID: 20634358. **KQ3E6, KQ4E6.**
343. Moodie D. Cholesterol screening in children. Congenit Heart Dis. 2012;7(1):. PMID: 22276662. **KQ1E13.**
344. Moran A, Jacobs DR Jr, et al. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. Circulation. 2008;117(18):2361-8. PMID: 18427135. **KQ3E6.**
345. Moreno LA, Sarria A, Lazaro A, et al. Lymphocyte T subset counts in children with hypercholesterolemia receiving dietary therapy. Ann Nutr Metab. 1998;42(5):261-5. PMID: 9812016. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
346. Morrison JA, Friedman LA, Gray-McGuire C, et al. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics. 2007;120(2):340-5. PMID: 17671060. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**
347. Morrison JA, Glueck CJ, Daniels SR, et al. High-sensitivity C reactive protein: associations with cardiovascular risk factors and tracking in female adolescents and young adults. ISRN Pediatr. 2011;2011. PMID: 22482065. **KQ3E6, KQ4E6.**
348. Morrison JA, Glueck CJ, Daniels S, et al. Paradoxically high adiponectin in obese 16-year-old girls protects against appearance of the metabolic syndrome and its components seven years later. J Pediatr. 2011;158(2):208-14 e1. PMID: 20869727. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**
349. Morrison JA, Glueck CJ, Horn PS, et al. Childhood predictors of adult type 2 diabetes at 9- and 26-year follow-ups. Arch Pediatr Adolesc Med. 2010;164(1):53-60. PMID: 20048242. **KQ2E6.**
350. Morrison KM, Dyal L, Conner W, et al. Cardiovascular risk factors and non-invasive assessment of subclinical atherosclerosis in youth. Atherosclerosis. 2010;208(2):501-5. PMID: 19699477. **KQ1E13, KQ2E9, KQ3E13, KQ4E13, KQ5E13.**

351. Morrison KM, Xu L, Tarnopolsky M, et al. Screening for dysglycemia in overweight youth presenting for weight management. Diabetes Care. 2012;35(4):711-6. PMID: 22271926. **KQ3E6.**
352. Moschonis G, Mavrogianni C, Karatzi K, et al. Increased physical activity combined with more eating occasions is beneficial against dyslipidemias in children. The Healthy Growth Study. Eur J Nutr. 2013;52(3):1135-44. PMID: 22868822. **KQ3E6, KQ6E9, KQ7E9.**
353. Muhonen LE, Burns TL, Nelson RP, et al. Coronary risk factors in adolescents related to their knowledge of familial coronary heart disease and hypercholesterolemia: the Muscatine Study. Pediatrics. 1994;93(3):444-51. PMID: 8115204. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**
354. Muros JJ, Zabala M, Oliveras-Lopez MJ, et al. Effect of physical activity, nutritional education, and consumption of evoo on lipid, physiological, and anthropometric profiles in a pediatric population. J Phys Act Health. 2014. PMID: 25409189. **KQ6E5, KQ7E5.**
355. Muros JJ, Zabala M, Oliveras-Lopez MJ, et al. Results of a 7-week school-based physical activity and nutrition pilot program on health-related parameters in primary school children in southern Spain. Pediatr Exerc Sci. 2013;25(2):248-61. PMID: 23504925. **KQ6E5, KQ7E5.**
356. Musso C, Graffigna M, Soutelo J, et al. Cardiometabolic risk factors as apolipoprotein B, triglyceride/HDL-cholesterol ratio and C-reactive protein, in adolescents with and without obesity: cross-sectional study in middle class suburban children. Pediatr Diabetes. 2011;12(3 Pt 2):229-34. PMID: 21518411. **KQ1E13, KQ2E4, KQ3E4, KQ4E4, KQ5E13.**
357. Nambiar S, Hughes I, Davies PS. Developing waist-to-height ratio cut-offs to define overweight and obesity in children and adolescents. Public Health Nutr. 2010;13(10):1566-74. PMID: 20100388. **KQ3E6.**
358. Nenseter MS, Bogsrud MP, Graesdal A, et al. LDL-apheresis affects markers of endothelial function in patients with homozygous familial hypercholesterolemia. Thromb Res. 2012;130(5):823-5. PMID: 22728023. **KQ1E13, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
359. Neovius M, Rossner SM, Vagstrand K, et al. Adiposity measures as indicators of metabolic risk factors in adolescents. Obes Facts. 2009;2(5):294-301. PMID: 20057196. **KQ3E6.**
360. Newman WP 3rd,Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. N Engl J Med. 1986;314(3):138-44. PMID: 3455748. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
361. Nielsen TR, Gamborg M, Fonvig CE, et al. Changes in lipidemia during chronic care treatment of childhood obesity. Child Obes. 2012;8(6):533-41. PMID: 23181919. **KQ6E5, KQ7E13.**
362. Niinikoski H, Pahkala K, Ala-Korpela M, et al. Effect of repeated dietary counseling on serum lipoproteins from infancy to adulthood. Pediatrics. 2012;(3):e704-13. PMID: 22331346. **KQ6E5, KQ7E5.**
363. Noto D, Cefalu AB, Barraco G, et al. Plasma non-cholesterol sterols: a useful diagnostic tool in pediatric hypercholesterolemia. Pediatr Res. 2010;67(2):200-4. PMID: 20091938. **KQ1E13.**
364. Oda E, Kawai R, Aizawa Y. Lymphocyte count was significantly associated with hyper-LDL cholesterolemia independently of high-sensitivity C-reactive protein in apparently healthy Japanese. Heart Vessels. 2012;27(4):377-83. PMID: 21655904. **KQ3E6, KQ4E6.**
365. O'Grady MJ, Brown AM, O'Neill MB. Cholesterol screening in an at-risk pediatric population. Pediatr Cardiol. 2008;29(3):609-13. PMID: 18094916. **KQ3E9, KQ4E6.**
366. Oh ES, Lee SH, Park MS, et al. Modeling of the LDL cholesterol-lowering effect of atorvastatin in Korean dyslipidemic patients and non-patient volunteers. Int J Clin Pharmacol Ther. 2012;50(9):647-56. PMID: 22981146. **KQ6E5, KQ7E5.**
367. Okosun IS, Lyn R, Davis-Smith M, et al. Validity of a continuous metabolic risk score as an index for modeling metabolic syndrome in adolescents. Ann Epidemiol. 2010;20(11):843-51. PMID: 20933191. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**

368. Okuda M, Sugiyama S, Kunitsugu I, et al. Use of body mass index and percentage overweight cutoffs to screen Japanese children and adolescents for obesity-related risk factors. J Epidemiol. 2010;20(1):46-53. PMID: 19855138. **KQ3E7, KQ4E6.**

369. O'Loughlin J, Lauzon B, Paradis G, et al. Usefulness of the American Academy of Pediatrics recommendations for identifying youths with hypercholesterolemia. Pediatrics. 2004;113(6):1723-7. PMID: 15173497. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

370. Olson K, Hendricks B, Murdock DK, et al. The triglyceride to HDL ratio and its relationship to insulin resistance in pre- and postpubertal children: observation from the Wausau School Project. Cholesterol. 2012;2012. PMID: 22811895. **KQ3E6, KQ4E6.**

371. Ondrak KS, McMurray RG, Bangdiwala SI, et al. Influence of aerobic power and percent body fat on cardiovascular disease risk in youth. J Adolesc Health. 2007;41(2):146-52. PMID: 17659218. **KQ6E5, KQ7E5.**

372. Orchard TJ, Donahue RP, Kuller LH, et al. Cholesterol screening in childhood: does it predict adult hypercholesterolemia? The Beaver County experience. J Pediatr. 1983;103(5):687-91. PMID: 6631595. **KQ1E13, KQ2E13, KQ3E9, KQ4E6, KQ5E13.**

373. Pacifico L, Bonci E, Andreoli G, et al. Association of serum triglyceride-to-HDL cholesterol ratio with carotid artery intima-media thickness, insulin resistance and nonalcoholic fatty liver disease in children and adolescents. Nutr Metab Cardiovasc Dis. 2014;24(7):737-43. PMID: 24656140. **KQ2E9.**

374. Parker BA, Gregory SM, Lorson L, et al. A randomized trial of coenzyme Q10 in patients with statin myopathy: rationale and study design. J Clin Lipidol. 2013;7(3):187-93. PMID: 23725917. **KQ7E5.**

375. Pasiakos SM, Karl JP, Lutz LJ, et al. Cardiometabolic risk in US Army recruits and the effects of basic combat training. PLoS ONE. 2012;7(2):e31222. PMID: 22384004. **KQ6E5, KQ7E5.**

376. Patel DA, Srinivasan SR, Chen W, et al. Serum alanine aminotransferase and its association with metabolic syndrome in children: the Bogalusa Heart Study. Metab Syndr Relat Disord. 2011;9(3):211-6. PMID: 21476865. **KQ1E13, KQ2E13, KQ3E6, KQ4E6, KQ5E13.**

377. Pedrosa C, Oliveira BM, Albuquerque I, et al. Obesity and metabolic syndrome in 7-9 years-old Portuguese schoolchildren. Diabetol Metab Syndr. 2010;2(1) PMID: 20537155. **KQ3E6, KQ4E6.**

378. Perez CM, Ortiz AP, Fuentes-Mattei E, et al. High prevalence of cardiometabolic risk factors in Hispanic adolescents: correlations with adipocytokines and markers of inflammation. J Immigr Minor Health. 2014;16(5):865-73. PMID: 23828626. **KQ3E9, KQ4E6.**

379. Petkeviciene J, Klumbiene J, Kriaucioniene V, et al. Anthropometric measurements in childhood and prediction of cardiovascular risk factors in adulthood: Kaunas cardiovascular risk cohort study. BMC Public Health. 2015;15(9):218. PMID: 25880559. **KQ6E6.**

380. Pinto Pereira SM, Power C. Life course body mass index, birthweight and lipid levels in mid-adulthood: a nationwide birth cohort study. Eur Heart J. 2013;34(16):1215-24. PMID: 23234645. **KQ8E6.**

381. Plachta-Danielzik S, Landsberg B, Johannsen M, et al. Association of different obesity indices with blood pressure and blood lipids in children and adolescents. Br J Nutr. 2008;100(1):208-18. PMID: 18346303. **KQ3E6.**

382. Plana N, Nicolle C, Ferre R, et al. Plant sterol-enriched fermented milk enhances the attainment of LDL-cholesterol goal in hypercholesterolemic subjects. Eur J Nutr. 2008;(1):32-9. PMID: 18193377. **KQ6E5, KQ7E5.**

383. Pletcher MJ, Bibbins-Domingo K, Liu K, et al. Nonoptimal lipids commonly present in young adults and coronary calcium later in life: the CARDIA (Coronary Artery Risk Development in Young Adults) study. Ann Intern Med. 2010;153(3):137-46. PMID: 20679558. **KQ2E13, KQ3E13, KQ4E13.**

384. Poisson SN, Schardt TQ, Dingman A, et al. Etiology and treatment of arterial ischemic stroke in children and young adults. Curr Treat Options Neurol. 2014;16(10):315. PMID: 25227455. **KQ8E2.**

385. Polonsky SM, Bellet PS, Sprecher DL. Primary hyperlipidemia in a pediatric population: classification and effect of dietary treatment. Pediatrics. 1993;91(1):92-6. PMID: 8416512. **KQ1E13, KQ2E13, KQ3E9, KQ4E13, KQ5E13.**

386. Porkka KV, Viikari JS, Akerblom HK. Tracking of serum HDL-cholesterol and other lipids in children and adolescents: the Cardiovascular Risk in Young Finns Study. Prev Med. 1991;20(6):713-24. PMID: 1766943. **KQ3E13.**

387. Porkka KV, Viikari JS, Taimela S, et al. Tracking and predictiveness of serum lipid and lipoprotein measurements in childhood: a 12-year follow-up. The Cardiovascular Risk in Young Finns study. Am J Epidemiol. 1994;140(12):1096-110. PMID: 7998592. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

388. Pratt RE, Kavey RE, Quinzi D. Combined dyslipidemia in obese children: response to a focused lifestyle approach. J Clin Lipidol. 2014;8(2):181-6. PMID: 24636177. **KQ6E9, KQ7E9.**

389. Prentice D, Kilty HL, Stearne K, et al. Prevalence of cardiovascular risk factors in grade nine students. Can J Cardiovasc Nurs. 2008;18(3)12-6. PMID: 18727282. **KQ3E11.**

390. Primrose ED, Savage JM, Boreham CA, et al. Cholesterol screening and family history of vascular disease. Arch Dis Child. 1994;71(3):239-42. PMID: 7979498. **KQ1E13, KQ2E13, KQ3E9, KQ4E13, KQ5E13.**

391. Puccetti L, Scarpini F, Auteri A, et al. Genetics of the coenzyme Q10 pathway and rosuvastatin-induced muscle effects. J Pediatr. 2011;158(3):520-1. PMID: 21276592. **KQ7E2.**

392. Putaala J, Haapaniemi E, Kaste M, et al. Statins after ischemic stroke of undetermined etiology in young adults. Neurology. 2011;77(5):426-30. PMID: 21810695. **KQ8E6.**

393. Qorbani M, Kelishadi R, Farrokhi-Khajeh-Pasha Y, et al. Association of anthropometric measures with cardiovascular risk factors and metabolic syndrome in normal-weight children and adolescents: the CASPIAN III study. Obes Facts. 2013;6(5):483-92. PMID: 24157679. **KQ3E4.**

394. Quijada Z, Paoli M, Zerpa Y, et al. The triglyceride/HDL-cholesterol ratio as a marker of cardiovascular risk in obese children; association with traditional and emergent risk factors. Pediatr Diabetes. 2008;9(5):464-71. PMID: 18507788. **KQ3E5.**

395. Racil G, Ben Ounis O, Hammouda O, et al. Effects of high vs. moderate exercise intensity during interval training on lipids and adiponectin levels in obese young females. Eur J Appl Physiol. 2013;113(10):2531-40. PMID: 23824463. **KQ6E5, KQ7E13.**

396. Rajaram S, Haddad EH, Mejia A, et al. Walnuts and fatty fish influence different serum lipid fractions in normal to mildly hyperlipidemic individuals: a randomized controlled study. Am J Clin Nutr. 2009;89(5):1657S-1663S. PMID: 19339404. **KQ6E5, KQ7E5.**

397. Ramachandran S, Abbas A, Saraf S, et al. Significant increase in high-density lipoprotein cholesterol with fibrates is associated with low pretreatment high-density lipoprotein cholesterol: findings from an outpatient clinic setting. Metab Syndr Relat Disord. 2012;10(3):189-94. PMID: 22283634. **KQ6E5, KQ7E5.**

398. Raman A, Sharma S, Fitch MD, et al. Anthropometric correlates of lipoprotein profile and blood pressure in high BMI African American children. Acta Paediatr. 2010;99(6):912-9. PMID: 20064141. **KQ3E6, KQ4E13.**

399. Raynor LA, Schreiner PJ, Loria CM, et al. Associations of retrospective and concurrent lipid levels with subclinical atherosclerosis prediction after 20 years of follow-up: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Ann Epidemiol. 2013;23(8):492-7. PMID: 23889858. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**

400. Redondo O, Villamor E, Valdes J, et al. Validation of a BMI cut-off point to predict an adverse cardiometabolic profile with adiposity measurements by dual-energy X-ray absorptiometry in Guatemalan children. Public Health Nutr. 2014;(0):8-Jan. PMID: 24955816. **KQ3E13.**

Appendix C. Excluded Studies

401. Reeves MJ, Gargano JW, Luo Z, et al. Effect of pretreatment with statins on ischemic stroke outcomes. Stroke. 2008;39(6):1779-85. PMID: 18369173. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
402. Ribas SA, Cunha DB, Sichieri R, et al. Effects of psyllium on LDL-cholesterol concentrations in Brazilian children and adolescents: a randomised, placebo-controlled, parallel clinical trial. Br J Nutr. 2014;(0):8-Jan. PMID: 25391814. **KQ6E4, KQ7E4.**
403. Richard Hobbs FD, Gensini G, John Mancini GB, et al. International open-label studies to assess the efficacy and safety of single-pill amlodipine/atorvastatin in attaining blood pressure and lipid targets recommended by country-specific guidelines: the JEWEL programme. Eur J Cardiovasc Prev Rehabil. 2009;16(4):472-80. PMID: 19407658. **KQ6E5, KQ7E5.**
404. Ried-Larsen M, Grontved A, Moller NC, et al. Associations between objectively measured physical activity intensity in childhood and measures of subclinical cardiovascular disease in adolescence: prospective observations from the European Youth Heart Study. Br J Sports Med. 2013;(0):. PMID: 23584828. **KQ6E8, KQ7E8.**
405. Rifai N, Neufeld E, Ahlstrom P, et al. Failure of current guidelines for cholesterol screening in urban African-American adolescents. Pediatrics. 1996;98(3 Pt 1):383-8. PMID: 8784361. **KQ3E7.**
406. Riggio S, Mandraffino G, Sardo MA, et al. Pulse wave velocity and augmentation index, but not intima-media thickness, are early indicators of vascular damage in hypercholesterolemic children. Eur J Clin Invest. 2010;40(3):250-7. PMID: 20415700. **KQ6E13.**
407. Robinson JG, Ballantyne CM, Hsueh WA, et al. Age, abdominal obesity, and baseline high-sensitivity C-reactive protein are associated with low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B responses to ezetimibe/simvastatin and atorvastatin in patients with metabolic syndrome. J Clin Lipidol. 2013;(4):292-303. PMID: 23890516. **KQ6E5, KQ7E5.**
408. Robinson JG, Ballantyne CM, Hsueh W, et al. Achievement of specified low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol apolipoprotein B, and high-sensitivity C-reactive protein levels with ezetimibe/simvastatin or atorvastatin in metabolic syndrome patients with and without atherosclerotic vascular disease (from the VYMET study). J Clin Lipidol. 2011;(6):474-82. PMID: 22108151. **KQ6E5, KQ7E5.**
409. Rodriguez-Rodriguez E, Ortega RM, Gonzalez-Rodriguez LG, et al. Vitamin D deficiency is an independent predictor of elevated triglycerides in Spanish school children. Eur J Nutr. 2011;50(5):373-8. PMID: 21103884. **KQ3E6.**
410. Rohatgi A. Cholesterol screening in children: makes sense but what is the impact? Future Cardiol. 2010;6(3):275-80. PMID: 20462333. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
411. Romero JB, Briones E, Palacios GC, et al. Subclinical metabolic abnormalities associated with obesity in prepubertal Mexican schoolchildren. J Pediatr Endocrinol Metab. 2010;23(6):589-96. PMID: 20662332. **KQ3E9, KQ4E6.**
412. Rosenberg E, Lamping DL, Joseph L, et al. Cholesterol screening of children at high risk: behavioural and psychological effects. CMAJ. 1997;(4):. PMID: 9054818. **KQ1E13, KQ2E13, KQ3E13, KQ4E5, KQ5E13.**
413. Roseneu M, Van Biervliet JP. Screening and follow-up of infants with dyslipoproteinemia. Prog Clin Biol Res. 1985. PMID: 3933016. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
414. Rowan C, Brinker AD, Nourjah P, et al. Rhabdomyolysis reports show interaction between simvastatin and CYP3A4 inhibitors. Pharmacoepidemiol Drug Saf. 2009;18(4):301-9. PMID: 19206087. **KQ7E5.**
415. Ruano G, Windemuth A, Wu AH, et al. Mechanisms of statin-induced myalgia assessed by physiogenomic associations. Atherosclerosis. 2011;218(2):451-6. PMID: 21868014. **KQ7E5.**

416. Rubba F, Gentile M, Iannuzzi A, et al. Vascular preventive measures: the progression from asymptomatic to symptomatic atherosclerosis management. Evidence on usefulness of early diagnosis in women and children. Future Cardiol. 2010;6(2):211-20. PMID: 20230262. **KQ8E2.**

417. Ruiz N, Rangel A, Rodriguez C, et al. Relationship among nocturnal sleep deficit, excess weight and metabolic alterations in adolescents. Arch Argent Pediatr. 2014;112(6):511-8. PMID: 25362909. **KQ3E13, KQ4E13.**

418. Rytter D, Bech BH, Halldorsson T, et al. No association between the intake of marine n-3 PUFA during the second trimester of pregnancy and factors associated with cardiometabolic risk in the 20-year-old offspring. Br J Nutr. 2013;110(11):2037-46. PMID: 23680230. **KQ3E9.**

419. Sabin MA, Magnussen CG, Juonala M, et al. The role of pharmacotherapy in the prevention and treatment of paediatric metabolic syndrome--Implications for long-term health: part of a series on Pediatric Pharmacology, guest edited by Gianvincenzo Zuccotti, Emilio Clementi, and Massimo Molteni. Pharmacol Res. 2012;65(4):397-401. PMID: 22037094. **KQ6E2, KQ7E2.**

420. Sabzghabaee AM, Ataei E, Kelishadi R, et al. Effect of hibiscus sabdariffa calices on dyslipidemia in obese adolescents: a triple-masked randomized controlled trial. Mater Sociomed. 2013;25(2):76-9. PMID: 24082826. **KQ6E13.**

421. Sabzghabaee AM, Khayam I, Kelishadi R, et al. Effect of Zizyphus jujuba fruits on dyslipidemia in obese adolescents: a triple-masked randomized controlled clinical trial. Med Arch. 2013;67(3):156-9. PMID: 23848030. **KQ6E4, KQ7E4.**

422. Sabzghabaee A, Kelishadi R, Jelokhanian H, et al. Clinical effects of Portulaca oleracea seeds on dyslipidemia in obese adolescents: a triple-blinded randomized controlled trial. Med Arch. 2014;68(3):195-9. PMID: 25195352. **KQ6E13, KQ7E13.**

423. Safavi M, Farajian S, Kelishadi R, et al. The effects of synbiotic supplementation on some cardio-metabolic risk factors in overweight and obese children: a randomized triple-masked controlled trial. Int J Food Sci Nutr. 2013;64(6):687-93. PMID: 23477506. **KQ6E4, KQ7E4.**

424. Salawi HA, Ambler KA, Padwal RS, et al. Characterizing severe obesity in children and youth referred for weight management. BMC Pediatr. 2014;14(0):. PMID: 24947311. **KQ3E9, KQ4E6.**

425. Salazar MR, Carbajal HA, Espeche WG, et al. Relation among the plasma triglyceride/high-density lipoprotein cholesterol concentration ratio, insulin resistance, and associated cardio-metabolic risk factors in men and women. Am J Cardiol. 2012;109(12):1749-53. PMID: 22449634. **KQ3E4.**

426. Sanchez Bayle M, Gonzalez Vergaz A, Garcia Cuatero B, et al. Is a parental history of coronary arterial disease in children as discriminating as their lipoprotein profile? Nino Jesus Group. Int J Cardiol. 1992;36(3):267-71. PMID: 1428260. **KQ3E6.**

427. Sanchez-Bayle M, Gonzalez-Requejo A, Pelaez MJ, et al. A cross-sectional study of dietary habits and lipid profiles. The Rivas-Vaciamadrid study. Eur J Pediatr. 2008;167(2):149-54. PMID: 17333272. **KQ3E6, KQ6E5, KQ7E5.**

428. Savitha M, Sandeep B. The study of lipid profile, diet and other cardiovascular risk factors in children born to parents having premature ischemic heart disease. Indian J Community Med. 2011;36(4):291-5. PMID: 22279260. **KQ3E4, KQ4E4.**

429. Schwandt P, Bertsch T, Haas GM. Anthropometric screening for silent cardiovascular risk factors in adolescents: The PEP Family Heart Study. Atherosclerosis. 2010;211(2):667-71. PMID: 20417933. **KQ3E7, KQ4E13.**

430. Seo H, Jeon BD, Ryu S. Persimmon vinegar ripening with the mountain-cultivated ginseng ingestion reduces blood lipids and lowers inflammatory cytokines in obese adolescents. J Exerc Nutrition Biochem. 2015;19(1):10-Jan. PMID: 25960949. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E5.**

431. Shah S, Ceska R, Gil-Extremera B, et al. Efficacy and safety of extended-release niacin/laropiprant plus statin vs. doubling the dose of statin in patients with primary hypercholesterolaemia or mixed dyslipidaemia. Int J Clin Pract. 2010;64(6):727-38. PMID: 20518948. **KQ6E5, KQ7E5.**

432. Shannon BM, Tershakovec AM, Martel JK, et al. Reduction of elevated LDL-cholesterol levels of 4- to 10-year-old children through home-based dietary education. Pediatrics. 1994;94(6 Pt 1):923-7. PMID: 7971012. **KQ3E13.**

433. Shashaj B, Bedogni G, Graziani MP, et al. Origin of cardiovascular risk in overweight preschool children: a cohort study of cardiometabolic risk factors at the onset of obesity. JAMA Pediatrics. 2014;168(10):917-24. PMID: 25111132. **KQ2E13, KQ3E5, KQ4E13.**

434. Shea S, Basch CE, Irigoyen M, et al. Failure of family history to predict high blood cholesterol among hispanic preschool children. Prev Med. 1990;19(4):443-55. PMID: 2204914. **KQ3E13.**

435. Shepherd J, Vidt DG, Miller E, et al. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. Cardiology. 2007;107(4):433-43. PMID: 17363845. **KQ6E5, KQ7E5.**

436. Shirasawa T, Ochiai H, Ohtsu T, et al. LDL-cholesterol and body mass index among Japanese schoolchildren: a population-based cross-sectional study. Lipids Health Dis. 2013;12. PMID: 23705977. **KQ3E6.**

437. Silva IT, Mello AP, Sanches LB, et al. Is plasma alpha-tocopherol associated with electronegative LDL in obese adolescents? J Nutr Sci Vitaminol (Tokyo). 2013;59(2):100-7. PMID: 23727639. **KQ3E4.**

438. Skinner AC, Steiner MJ, Chung AE, et al. Cholesterol curves to identify population norms by age and sex in healthy weight children. Clin Pediatr (Phila). 2012;51(3):233-7. PMID: 22157422. **KQ3E9.**

439. Skovby F, Micic S, Jepsen B, et al. Screening for familial hypercholesterolaemia by measurement of apolipoproteins in capillary blood. Arch Dis Child. 1991;66(7):844-7. PMID: 1863097. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**

440. Smith MEB, Lee NJ, Haney E, et al. Drug Class Review: HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin: Final Report Update 5. 2009. PMID: 21089253. **KQ6E6, KQ7E6.**

441. Sniderman AD, Hogue JC, Bergeron J, et al. Non-HDL cholesterol and apoB in dyslipidaemia. Clin Sci (Lond). 2008;114(2):149-55. PMID: 17868037. **KQ1E13, KQ2E13, KQ3E5, KQ4E13, KQ5E13.**

442. Soerensen KV, Thorning TK, Astrup A, et al. Effect of dairy calcium from cheese and milk on fecal fat excretion, blood lipids, and appetite in young men. Am J Clin Nutr. 2014;99(5):984-91. PMID: 24622806. **KQ6E5, KQ7E5.**

443. Spinneker A, Egert S, Gonzalez-Gross M, et al. Lipid, lipoprotein and apolipoprotein profiles in European adolescents and its associations with gender, biological maturity and body fat--the HELENA Study. Eur J Clin Nutr. 2012;66(6):727-35. PMID: 22252104. **KQ3E6.**

444. Stakos DA, Papaioannou HI, Angelidou I, et al. Plasma leptin and adiponectin concentrations correlate with cardiometabolic risk and systemic inflammation in healthy, non-obese children. J Pediatr Endocrinol Metab. 2014;27(42067):221-8. PMID: 24150199. **KQ3E6, KQ4E6.**

445. Stefanutti C, Vivenzio A, Di Giacomo S, et al. Aorta and coronary angiographic follow-up of children with severe hypercholesterolemia treated with low-density lipoprotein apheresis. Transfusion. 2009;49(7):1461-70. PMID: 19389031. **KQ6E5, KQ7E5.**

446. Stein EA. Statins and children: whom do we treat and when?. Circulation. 2007;116(6):594-5. PMID: 17679628. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**

447. Steiner NJ, Neinstein LS, Pennbridge J. Hypercholesterolemia in adolescents: effectiveness of screening strategies based on selected risk factors. Pediatrics. 1991;88(2):269-75. PMID: 1861925. **KQ1E13, KQ2E13, KQ3E10, KQ4E13, KQ5E13.**

448. Stephens MB, Reamy BV, Primary Care Education Research Learning Network, et al. A novel approach using an electronic medical record to identify children and adolescents at risk for dyslipidemia: a study from the Primary Care Education and Research Learning (PEARL) network. J Am Board Fam Med. 2008;21(4):356-7. PMID: 18612063. **KQ3E6.**

449. Stock J. Controversies in dyslipidaemia management. Atherosclerosis. 2012;221(2):321-4. PMID: 22305261. **KQ6E2, KQ7E2.**
450. Stoedefalke K. Effects of exercise training on blood lipids and lipoproteins in children and adolescents. J Sports Sci Med. 2007;6(3):313-318. PMID: 24149417. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E5, KQ6E2, KQ7E2**
451. Stuhldreher WL, Orchard TJ, Donahue RP, et al. Cholesterol screening in childhood: sixteen-year Beaver County Lipid Study experience. J Pediatr. 1991;119(4):551-6. PMID: 1919885. **KQ3E13.**
452. Sudhop T, Reber M, Tribble D, et al. Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men. J Lipid Res. 2009;50(10):2117-23. PMID: 19380898. **KQ6E5, KQ7E5.**
453. Sultan SM, Schupf N, Dowling MM, et al. Review of lipid and lipoprotein(a) abnormalities in childhood arterial ischemic stroke. Int J Stroke. 2014;9(1):79-87. PMID: 24148253. **KQ8E2.**
454. Sun C, Pezic A, Tikellis G, et al. Effects of school-based interventions for direct delivery of physical activity on fitness and cardiometabolic markers in children and adolescents: a systematic review of randomized controlled trials. Obesity Rev. 2013;14(10):818-38. PMID: 23734662. **KQ6E5, KQ7E5.**
455. Sundaram ME, Berg RL, Economos C, et al. The relationship between childhood BMI and adult serum cholesterol, LDL, and ankle brachial index. Clin Med Res. 2014;12(42006):33-9. PMID: 24415747. **KQ8E5.**
456. Superko HR, Garrett BC, King SB, et al. Effect of combination nicotinic acid and gemfibrozil treatment on intermediate density lipoprotein, and subclasses of low density lipoprotein and high density lipoprotein in patients with combined hyperlipidemia. Am J Cardiol. 2009;(3):387-92. PMID: 19166694. **KQ6E5, KQ7E5.**
457. Sveger T, Flodmark CE, Nordborg K, et al. Hereditary dyslipidemias and combined risk factors in children with a family history of premature coronary artery disease. Arch Dis Child. 2000;82(4):292-6. PMID: 10735834. **KQ3E13.**
458. Tan AT, Low LP, Lim CH, et al. Effects of rosuvastatin on low-density lipoprotein cholesterol and plasma lipids in Asian patients with hypercholesterolemia. J Atheroscler Thromb. 2009;16(4):509-16. PMID: 19729865. **KQ6E5, KQ7E5.**
459. Tapola NS, Lyyra ML, Kolehmainen RM, et al. Safety aspects and cholesterol-lowering efficacy of chitosan tablets. J Am Coll Nutr. 2008;27(1):22-30. PMID: 18460478. **KQ6E5, KQ7E5.**
460. Task Force for the management of dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society, Catapano AL, Reiner Z, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis. 2011;(1):S1-44. PMID: 21723445. **KQ6E2, KQ7E2.**
461. Teber S, Deda G, Akar N, et al. Lipoprotein (a) levels in childhood arterial ischemic stroke. Clin Appl Thromb Hemost. 2010;16(2):214-7. PMID: 19752039. **KQ8E13.**
462. Tekin N, Ersoy B, Coskun S, et al. Ambulatory blood pressure parameters in office normotensive obese and non-obese children: relationship with insulin resistance and atherosclerotic markers. Med Princ Pract. 2014;23(2):154-9. PMID: 24247272. **KQ3E6, KQ4E6.**
463. Telford RD, Cunningham RB, Waring P, et al. Physical education and blood lipid concentrations in children: the LOOK randomized cluster trial. PLoS ONE. 2013;(10):. PMID: 24204594. **KQ6E5, KQ7E5.**
464. Terai N, Spoerl E, Fischer S, et al. Statins affect ocular microcirculation in patients with hypercholesterolaemia. Acta Ophthalmol. 2011;89(6):e500-4. PMID: 21457486. **KQ7E5.**
465. Teramoto T, Shirakawa M, Kikuchi M, et al. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib in Japanese patients with dyslipidemia. Atherosclerosis. 2013;230(1):52-60. PMID: 23958252. **KQ6E5, KQ7E5.**

466. Tershakovec AM, Jawad AF, Stallings VA, et al. Growth of hypercholesterolemic children completing physician-initiated low-fat dietary intervention. J Pediatr. 1998;133(1):28-34. PMID: 9672506. **KQ3E13.**
467. Theuwissen E, Mensink RP. Simultaneous intake of beta-glucan and plant stanol esters affects lipid metabolism in slightly hypercholesterolemic subjects. J Nutr. 2007;(3):583-8. PMID: 17311944. **KQ6E5, KQ7E5.**
468. Thomas NE, Davies B, Baker JS, et al. Lipoprotein(a) in healthy Welsh schoolchildren aged 12-13 years. Arch Dis Child. 2009;94(12):998-9. PMID: 19933615. **KQ1E13, KQ2E13, KQ3E7, KQ4E13, KQ5E13.**
469. Thomas NE, Jasper M, Williams DR, et al. Secular trends in established and novel cardiovascular risk factors in Welsh 12-13 year olds: a comparison between 2002 and 2007. Ann Hum Biol. 2011;38(1):22-7. PMID: 20450386. **KQ3E9, KQ4E13.**
470. Thompson GR, Catapano A, Saheb S, et al. Severe hypercholesterolaemia: therapeutic goals and eligibility criteria for LDL apheresis in Europe. Curr Opin Lipidol. 2010;21(6):492-8. PMID: 20935563. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
471. Thorp AA, Howe PR, Mori TA, et al. Soy food consumption does not lower LDL cholesterol in either equol or nonequol producers. Am J Clin Nutr. 2008;(2):298-304. PMID: 18689364. **KQ6E5, KQ7E5.**
472. Tobisch B, Blatniczky L, Barkai L. Cardiometabolic risk factors and insulin resistance in obese children and adolescents: relation to puberty. Pediatr Obes. 2013;10(1):37-44. PMID: 24227418. **KQ3E4.**
473. Todd DM, Walsh R, Tran M, et al. Cardiovascular risk factors in suburban American late-adolescents: a cross-sectional, community-based study. Ann Clin Lab Sci. 2012;42(4):375-83. PMID: 23090733. **KQ3E6.**
474. Togashi K, Masuda H, Iguchi K. Effect of diet and exercise treatment for obese Japanese children on abdominal fat distribution. Res Sports Med. 2010;18(1):62-70. PMID: 20391247. **KQ6E5, KQ7E5.**
475. Tokarev SA, Buganov AA. Evaluation and prognosis of non-infectious risk in children in dependence on age and period of living in the Far North. Alaska Med. 2007;49(2 Suppl):142-4. PMID: 17929624. **KQ3E4, KQ4E6.**
476. Torres MD, Tormo MA, Campillo C, et al. Etiologic and cardiovascular risk factors in obese children from Extremadura in Spain. Their relationship with insulin resistance and plasma adipocytokine levels. Rev Esp Cardiol. 2008;61(9):923-9. PMID: 18775233. **KQ3E6.**
477. Toth PP, Ballantyne CM, Davidson MH, et al. Changes in prescription patterns before and after reporting of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial (ENHANCE) results and expected effects on low-density lipoprotein-cholesterol reduction. J Clin Lipidol. 2012;6(2):180-91. PMID: 22385552. **KQ6E5, KQ7E5.**
478. Tresaco B, Moreno LA, Ruiz JR, et al. Truncal and abdominal fat as determinants of high triglycerides and low HDL-cholesterol in adolescents. Obesity (Silver Spring). 2009;17(5):1086-91. PMID: 19180070. **KQ3E6.**
479. Tribble DL, Farnier M, Macdonell G, et al. Effects of fenofibrate and ezetimibe, both as monotherapy and in coadministration, on cholesterol mass within lipoprotein subfractions and low-density lipoprotein peak particle size in patients with mixed hyperlipidemia. Metabolism. 2008;(6):796-801. PMID: 18502262. **KQ6E5, KQ7E5.**
480. Tseng ML, Ho CC, Chen SC, et al. A simple method for increasing levels of high-density lipoprotein cholesterol: a pilot study of combination aerobic- and resistance-exercise training. Int J Sport Nutr Exerc Metab. 2013;23(3):271-81. PMID: 23166203. **KQ6E5, KQ7E5.**
481. Twisk JW, Kemper HC, Mellenbergh GJ, et al. Relation between the longitudinal development of lipoprotein levels and lifestyle parameters during adolescence and young adulthood. Ann Epidemiol. 1996;6(3):246-56. PMID: 8827160. **KQ3E13.**

482. Twisk JW, Kemper HC, van Mechelen W, et al. Tracking of risk factors for coronary heart disease over a 14-year period: a comparison between lifestyle and biologic risk factors with data from the Amsterdam Growth and Health Study. Am J Epidemiol. 1997;145(10):888-98. PMID: 9149660. **KQ3E13.**

483. Twisk JW, Kemper HC, Van Mechelen W, et al. Clustering of risk factors for coronary heart disease. The longitudinal relationship with lifestyle. Ann Epidemiol. 2001;11(3):157-65. PMID: 11248580. **KQ3E13.**

484. Tzeng TB, Schneck DW, Birmingham BK, et al. Population pharmacokinetics of rosuvastatin: implications of renal impairment, race, and dyslipidaemia. Curr Med Res Opin. 2008;24(9):2575-85. PMID: 18674408. **KQ6E5, KQ7E5.**

485. Upadhyay UD, Waddell EN, Young S, et al. Prevalence, awareness, treatment, and control of high LDL cholesterol in New York City, 2004. Prev Chronic Dis. 2010;7(3):A61. PMID: 20394700. **KQ3E5, KQ4E5.**

486. Urbina EM, Khoury PR, McCoy CE, et al. Triglyceride to HDL-C ratio and increased arterial stiffness in children, adolescents, and young adults. Pediatrics. 2013;131(4):e1082-90. PMID: 23460684. **KQ3E9.**

487. Van Biervliet JP, Vercaemst R, De Keersgieter W, et al. Evolution of lipoprotein patterns in newborns. Acta Paediatr Scand. 1980;69(5):593-6. PMID: 7234379. **KQ3E13.**

488. Van Biervliet JP, Vinaimont N, Caster H, et al. A screening procedure for dyslipoproteinemia in the newborn. Apoprotein quantitation on dried blood spots. Clin Chim Acta. 1982;120(2):191-200. PMID: 7067144. **KQ3E13.**

489. van Stiphout WA, Hofman A, de Bruijn AM, et al. Distributions and determinants of total and high-density lipoprotein cholesterol in Dutch children and young adults. Prev Med. 1985;14(2):169-80. PMID: 4048079. **KQ1E13, KQ2E13, KQ3E7, KQ4E7, KQ5E13.**

490. Verduci E, Agostoni C, Radaelli G, et al. Blood lipids profile in hyperlipidemic children undergoing different dietary long chain polyunsaturated supplementations: a preliminary clinical trial. Int J Food Sci Nutr. 2013;(0):. PMID: 24228803. **KQ6E5, KQ7E5.**

491. Vieira Cunha Lima SC, Oliveira Lyra C, Galvao Bacurau Pinheiro L, et al. Association between dyslipidemia and anthropometric indicators in adolescents. Nutr Hosp. 2011;26(2):304-10. PMID: 21666967. **KQ1E13, KQ2E4, KQ3E4, KQ4E4, KQ5E13.**

492. Viggiano D, De Filippo G, Rendina D, et al. Screening of metabolic syndrome in obese children: a primary care concern. J Pediatr Gastroenterol Nutr. 2009;49(3):329-34. PMID: 19590449. **KQ3E6.**

493. Vinci SR, Rifas-Shiman SL, Cheng JK, et al. Cholesterol testing among children and adolescents during health visits. JAMA. 2014;311(17):1804-7. PMID: 24794376. **KQ3E6.**

494. Vizcaino VM, Aguilar FS, Martinez MS, et al. Association of adiposity measures with blood lipids and blood pressure in children aged 8-11 years. Acta Paediatr. 2007;96(9):1338-42. PMID: 17718788. **KQ3E6.**

495. Vobecky JS, David P, Vobecky J. Dietary habits in relation to tracking of cholesterol level in young adolescents: a nine-year follow-up. Ann Nutr Metab. 1988;32(42130):312-23. PMID: 3254688. **KQ3E13.**

496. Volek JS, Phinney SD, Forsythe CE, et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids. 2009;(4):297-309. PMID: 19082851. **KQ6E5, KQ7E5.**

497. Vrablik M, Dobiasova M, Zlatohlavek L, et al. Biomarkers of cardiometabolic risk in obese/overweight children: effect of lifestyle intervention. Physiol Res. 2014. PMID: 25157663. **KQ6E5, KQ7E5.**

498. Wadowski SJ, Karp RJ, Murray-Bachmann R, et al. Family history of coronary artery disease and cholesterol: screening children in a disadvantaged inner-city population. Pediatrics. 1994;93(1):109-13. PMID: 8265303. **KQ3E7.**

499. Wallner A, Hirz A, Schober E, et al. Evolution of cardiovascular risk factors among 18-year-old males in Austria between 1986 and 2005. Wien Klin Wochenschr. 2010;122(42130):152-8. PMID: 20361378. **KQ3E6, KQ4E6.**
500. Ward SD, Melin JR, Lloyd FP, et al. Determinants of plasma cholesterol in children--a family study. Am J Clin Nutr. 33(1):63-70. PMID: 7355782. **KQ3E13.**
501. Wasay M, Saadatnia M, Venketasubramanian N, et al. Predictors of cerebral venous thrombosis and arterial ischemic stroke in young Asian women. J Stroke Cerebrovasc Dis. 2012;21(8):689-94. PMID: 21511496. **KQ8E5.**
502. Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. Br J Nutr. 2008;99(2):281-6. PMID: 17697400. **KQ6E5, KQ7E5.**
503. Wei M, Xiong P, Zhang L, et al. Perilla oil and exercise decrease expressions of tumor necrosis factor-alpha, plasminogen activator inhibitor-1 and highly sensitive C-reactive protein in patients with hyperlipidemia. J Tradit Chin Med. 2013;(2):170-5. PMID: 23789212. **KQ6E4, KQ7E4.**
504. Weiss R, Otvos JD, Sinnreich R, et al. The triglyceride to high-density lipoprotein-cholesterol ratio in adolescence and subsequent weight gain predict nuclear magnetic resonance-measured lipoprotein subclasses in adulthood. J Pediatr. 2011;158(1):44-50. PMID: 20801459. **KQ1E13, KQ2E6, KQ3E13, KQ4E13, KQ5E13.**
505. White J, Jago R. Fat distribution, physical activity and cardiovascular risk among adolescent girls. Nutr Metab Cardiovasc Dis. 2013;23(3):189-95. PMID: 22397881. **KQ3E6.**
506. Wierzbicki AS, Viljoen A. Hyperlipidaemia in paediatric patients: the role of lipid-lowering therapy in clinical practice. Drug Safety. 2010;33(2):115-25. PMID: 20082538. **KQ6E2, KQ7E2.**
507. Wiesen J, Adkins M, Fortune S, et al. Evaluation of pediatric patients with mild-to-moderate hypertension: yield of diagnostic testing. Pediatrics. 2008;122(5):e988-93. PMID: 18977966. **KQ3E5.**
508. Wijnstok NJ, Twisk JW, Young IS, et al. Inflammation markers are associated with cardiovascular diseases risk in adolescents: the Young Hearts project 2000. J Adolesc Health. 2010;47(4):346-51. PMID: 20864003. **KQ1E13, KQ2E13, KQ3E6, KQ4E13, KQ5E13.**
509. Wilcken DE, Blades BL, Dudman NP. A neonatal screening approach to the detection of familial hypercholesterolaemia and family-based coronary prevention. J Inherit Metab Dis. 1988;87-90. PMID: 3141689. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
510. Willi SM, Hirst K, Jago R, et al. Cardiovascular risk factors in multi-ethnic middle school students: the HEALTHY primary prevention trial. Pediatr Obes. 2012;7(3):230-9. PMID: 22461375. **KQ3E9, KQ4E6.**
511. Williams CL, Bollella M, Spark A, et al. Soluble fiber enhances the hypocholesterolemic effect of the step I diet in childhood. J Am Coll Nutr. 1995;14(3):251-7. PMID: 8586774. **KQ1E13, KQ2E13, KQ3E13, KQ4E13, KQ5E13.**
512. Williams DM, Fraser A, Sayers A, et al. Associations of childhood 25-hydroxyvitamin D2 and D3 and cardiovascular risk factors in adolescence: prospective findings from the Avon Longitudinal Study of Parents and Children. Eur J Prev Cardiol. 2014;21(3):281-90. PMID: 23185083. **KQ3E6.**
513. Williams RR, Hunt SC, Barlow GK, et al. Prevention of familial cardiovascular disease by screening for family history and lipids in youths. Clinical chemistry. 1992;38(8B Pt 2):1555-60. PMID: 1643739. **KQ3E13.**
514. Wilson DP, Gidding SS. Learning more about dyslipidemia in childhood. J Pediatr. 2013;164(3):442-4. PMID: 24373576. **KQ1E2.**
515. Wong ND, Hei TK, Qaqundah PY, et al. Television viewing and pediatric hypercholesterolemia. Pediatrics. 1992;90(1 Pt 1):75-9. PMID: 1614784. **KQ3E13.**
516. Yeste D, Chacon P, Clemente M, et al. Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents. J Pediatr Endocrinol Metab. 2009;22(6):487-492. PMID: 19694195. **KQ6E9, KQ7E9.**

517. Yokokawa H, Yasumura S, Tanno K, et al. Serum low-density lipoprotein to high-density lipoprotein ratio as a predictor of future acute myocardial infarction among men in a 2.7-year cohort study of a Japanese northern rural population. J Atheroscler Thromb. 2011;18(2):89-98. PMID: 20972352. **KQ3E6, KQ4E6, KQ8E6.**

518. Yoshinaga M, Sameshima K, Tanaka Y, et al. Association between the number of cardiovascular risk factors and each risk factor level in elementary school children. Circ J. 2008;72(10):1594-7. PMID: 18756035. **KQ3E6.**

519. Yu CC, Li AM, Chan KO, et al. Orlistat improves endothelial function in obese adolescents: a randomised trial. J Paediatr Child Health. 2013;49(11):969-75. PMID: 23735004. **KQ6E5, KQ7E5.**

520. Zachariah JP, Johnson PK. Pediatric lipid management: an earlier approach. Endocrinol Metab Clin North Am. 2014;43(4):981-92. PMID: 25432392. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**

521. Zung A, Shachar S, Zadik Z, et al. Soy-derived isoflavones treatment in children with hypercholesterolemia: a pilot study. J Pediatr Endocrinol Metab. 2010;(42006):133-41. PMID: 20432816. **KQ6E9, KQ7E6.**

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)