Screening and Treatment for Hypercholesterolemia in Children and Adolescents:

Systematic Evidence Review for the U.S. Preventive Services Task Force

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Abstract

OBJECTIVE: This was a systematic evidence review for the U.S. Preventive Services Task Force, intended to synthesize the published evidence regarding the effectiveness of selecting, testing, and managing children and adolescents with dyslipidemia in the course of routine primary care.

METHODS: Literature searches were performed to identify published articles addressing 10 key questions. The review focused on screening relevant to primary care of children without previously identified dyslipidemias, but included treatment trials of children with dyslipidmia because some drugs have only been tested in that population.

RESULTS: Normal values for lipids for children and adolescents are defined according to population levels (percentiles). Age, sex, and racial differences and temporal trends may alter these statistical cut points. Approximately 40-55% of children with elevated total cholesterol and low-density lipoprotein will continue to have elevated lipids on follow-up. Current screening recommendations based on family history will fail to detect substantial numbers (30-60%) of children with elevated lipids.

Drug treatment for dyslipidemia in children has been studied and shown to be effective only for suspected or proven familial monogenic dyslipidemias. Intensive dietary counseling and follow-up can result in improvements in lipids, but these results have not been sustained after the cessation of the intervention. The few trials of exercise are of fair-poor quality and show little or no improvements in lipids for children without monogenic dyslipidemias. Although reported adverse effects were not serious, studies were generally small and not of sufficient duration to determine long-term effects of either short or extended use.

CONCLUSIONS: Several key questions about screening and treatment of dyslipidemia in children and adolescents could not be addressed because of lack of studies, including effectiveness of screening on adult CHD or lipid outcomes, optimal ages and intervals for screening children, or effects of treatment of childhood lipid levels on adult CHD outcomes.

Introduction

Dyslipidemias are disorders of lipoprotein metabolism resulting in abnormal excesses of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglycerides, or deficiency of high-density lipoprotein cholesterol (HDL-C).[1, 2] Dyslipidemia is an established risk factor for coronary heart disease (CHD)—the leading cause of death for adults in the US.[3] Dyslipidemia rarely leads to adverse health outcomes in childhood, but its long-term effects may be considerable. While no long-term studies of the direct relationship between lipid levels measured in children and CHD later in life have been conducted, this relationship can be inferred. Large epidemiologic studies indicate that children's lipid levels correlate with those of adult family members.[4] Children of parents with CHD have a higher prevalence of dyslipidemia in childhood,[5] and identification of dyslipidemia in children can identify families at increased risk for CHD.[4] Studies of children and young adults who died accidentally report correlations between lipid levels and arterial fat deposition,[6, 7] and note early lesions of atherosclerosis (fatty streaks) in the abdominal aorta at age three years, coronary arteries at age 10 years, and further progression with age.[8-12] Increasing prevalence of risk factors for CHD among children, including metabolic syndrome and obesity, as well as continued emphasis on primary prevention of CHD has raised interest in screening children for dyslipidemia.[13-15]

Dyslipidemia is defined by laboratory testing and statistically determined criteria. Elevated LDL-C is the most common clinically significant marker of dyslipidemia in children. The majority of children with dyslipidemia will have idiopathic dyslipidemias (polygenic, risk factor associated, or multi-factorial), while a minority will have

monogenic or secondary dyslipidemias. The more common genetic dyslipidemias include familial hypercholesterolemia (FH), familial combined hyperlipidemia (FCH), familial defective apoprotein-B, and familial hypertriglyceridemia.

Most treatment recommendations advise a low-fat, low-cholesterol diet, such as the American Heart Association (AHA) Step I diet, for children with dyslipidemia beginning at age two years and older.[14] Children younger than two years should not be prescribed a low-fat, low-cholesterol diet because their rapid growth and development require adequate fat and cholesterol intake.[16, 17] Children and adolescents with FH or FCH are the only non-adults for whom trials of drug therapy are available and drugs are approved by the US Food and Drug Administration (FDA). Bile acid-binding resins are the only medications approved for treatment of dyslipidemia for children younger than eight years of age. HMG Co-A reductase inhibitors (statins) are approved for use in older children with heterozygous FH.[18, 19] Other medications used in adults for treatment of hyperlipidemia, such as niacin, are either not recommended for children or have not been adequately evaluated for safety and efficacy in children. Additional interventions for children include dietary supplements (fiber, sterol or stanol margarines, omega-3 fatty acids), exercise, weight loss for overweight children, and identification and treatment of diabetes mellitus or other causes of secondary dyslipidemia.

The relationship between childhood and adult dyslipidemia, increasing prevalence of related CHD risk factors in children (e.g., obesity and diabetes), [13-15] and continued emphasis on a primary prevention approach for CHD has raised interest in screening children for dyslipidemia. Identifying children with dyslipidemia could lead to interventions or treatments that could prevent or delay adult dyslipidemia and CHD. This rationale lends support to consideration of screening for dyslipidemia as part of well-

child care and at other opportunities. Clinic-based screening, neonatal screening, community-based screening, and other prevention strategies have been proposed, but most recommendations support selective strategies testing children who have family members with dyslipidemia or premature CHD and those with unknown family histories.[16, 20]

This evidence review focuses on the strengths and limitations of evidence for identifying and managing children and adolescents with dyslipidemia determined by screening in the course of routine primary care. Its objective is to determine the balance of potential benefits and adverse effects of screening for development of guidelines by the US Preventive Services Task Force (USPSTF). The target population includes children and adolescents age 0 to 21 years without previously-known conditions associated with dyslipidemia. There is potential to identify children and adolescents with dyslipidemia in this population from among three groups: those with undiagnosed monogenic dyslipidemias, such as familial hypercholesterolemia; those with undiagnosed secondary causes of dyslipidemia (diabetes, nephrotic syndrome, hypothyroidism, others); and those with idiopathic dyslipidemia (polygenetic, risk factor associated, or multi-factorial) (Figure 1). Although children and adolescents with idiopathic dyslipidemia generally have less severe lipid abnormalities than children and adolescents with monogenic disorders, such abnormal levels could still potentially improve with intervention.

Methods

Evidence reviews for the USPSTF follow a specific methodology[21] (Figure 2). Key questions examine a chain of evidence about the accuracy and feasibility of

screening children and adolescents for dyslipidemia in primary care or community settings (Key Question 1), abnormal lipid values (Key Question 2a), appropriate tests (Key Question 2b), tracking of lipid levels through childhood to adulthood (Key Question 2c), accuracy of family history (Key Question 2d), role of risk factors in selecting children and adolescents for screening (Key Question 2e), effectiveness of interventions for children and adolescents identified with dyslipidemia (Key Questions 4-8, 10), and adverse effects of screening and interventions (Key Questions 3, 9).

Studies that addressed Key Question 1 (Figure 2) include all components in the continuum of the screening process: the screening evaluation, diagnostic evaluation for those identified by the screening results, interventions for those diagnosed with dyslipidemia, and outcome measures allowing determination of the effectiveness of the overall screening process.

Studies of children with previously diagnosed conditions known to cause dyslipidemia were not included because the scope of this review is screening children without known diagnoses. Specifically, studies of children with diabetes were not included because these children would already be under surveillance for dyslipidemia as a result of their primary disease. This review includes treatment trials of children and adolescents using dietary, exercise, and drug interventions. Trials of drug therapy in children with heterozygous FH or FCH are included because drug treatment trials have been conducted exclusively in this population.

Relevant studies were identified from multiple searches of MEDLINE (1966 through September 2005).[22] We obtained additional articles from recent systematic reviews, reference lists of related studies, reviews, editorials, and websites, and from

consulting experts. Retrieved abstracts were entered into an electronic database (EndNote®).

Investigators reviewed all identified abstracts and determined eligibility by applying inclusion and exclusion criteria specific to each key question. Full-text articles of included abstracts were reviewed for relevance. Eligible studies were English-language, applicable to US clinical practice, and provided primary data relevant to key questions. Studies of risk factors were included only if they provided multivariate adjusted analyses.

For treatment studies**,** full text randomized controlled trials (RCTs), non-controlled clinical trials, and non-controlled prospective studies providing data on the treatment of children and adolescents with diet, drug therapy, exercise, or combinations of these were initially reviewed. Subsequently, only RCTs and meta-analyses of RCTs that reported serum lipid outcomes were included. Crossover trials were included if they reported data prior to crossover. For Key Question 10, outcomes included either adult lipid levels or adult CHD. Information about adverse effects of treatment was obtained from RCTs and additional sources, such as non-randomized controlled treatment trials and non-comparative studies of treatment.

Data were extracted from each study, entered directly into evidence tables, and summarized. Benefits and adverse effects of therapies were considered equally important and both types of outcomes were abstracted. Trials of therapy for children and adolescents with dyslipidemia were categorized by population and intervention. Two reviewers independently rated the RCTs' quality using US Preventive Services Task Force criteria (Appendix 1).[21]

Results

Our literature search identified 2,507 unique citations, including 144 papers about screening and testing for dyslipidemia (Key Question 2); 43 about interventions and tracking of lipid values over time (Key Questions 4-8 and 10); 6 about the adverse effects of screening (Key Question 3) and 84 about adverse effects of treatment (Key Question 9).

Key Question 1. Is screening for dyslipidemia in children/adolescents effective in delaying the onset and reducing the incidence of CHD-related events?

No studies evaluated the effect of screening children and adolescents on adult lipid or disease outcomes.

Key Question 2. What is the accuracy of screening for dyslipidemia in identifying children/adolescents at increased risk of CHD-related events and other outcomes?

Key Question 2a. What are abnormal lipid values in children/adolescents?

While several studies conducted in the US during the 1970s obtained lipid levels from large samples of normal healthy children,[23-25] current recommendations[14, 16, 20, 26] are based on distributions of lipid and lipoprotein levels obtained from the Lipid Research Clinics (LRC) Prevalence Study.[27] This study included one Canadian and nine US sites and enrolled subjects primarily based on residency within census tracts, school enrollment, and employment in occupational and industrial groups. Fasting (≥ 12 hours) lipoprotein levels were obtained in 15,626 children age 0 to 19 years between 1972 and 1976. The selected populations included a broad range of geographic, socio-economic,

occupational, sex, and ethnic groups, but were not selected to be a representative sample of the North American population.

In the LRC sample, TC levels increased from birth and stabilized at approximately 2 years of age. At puberty, TC levels declined slightly for both boys and girls, and HDL-C levels declined for boys. For all children, the mean serum level for TC was approximately 160 mg/dL and for LDL-C was 100 mg/dL. The 95th percentile level was 200 mg/dL for TC and 130 mg/dL for LDL-C. While results for African American children were similar, they were based on smaller numbers and provided only TC and triglyceride data.[27]

More recent data from the National Health and Nutrition Examination Survey (NHANES) III (1988 to 1994) were derived from 7,499 children and adolescents ages 4 to 19 years. These provided 95th percentile levels of 216 mg/dL for serum TC, and 152 mg/dL for LDL-C.[28] Mean age-specific TC levels peaked at 171 mg/dL at 9 to 11 years and declined at older ages. Girls had significantly higher mean TC and LDL-C levels than boys ($p<0.005$). Non-Hispanic Black children and adolescents had significantly higher mean TC, LDL-C, and HDL-C levels compared to non-Hispanic White and Mexican-American children and adolescents. In linear regression models of these data, age, sex, and race have significant effects on lipid levels questioning the utility of fixed screening cut points.[29]

Key Question 2b. What are the appropriate tests? How well do screening tests (non-fasting total cholesterol, fasting total cholesterol, fasting lipoprotein analysis) identify children and adolescents with dyslipidemia?

In the American Academy of Pediatrics (AAP) and the National Cholesterol Education Program (NCEP) guidelines, TC is used as an initial laboratory measurement for children tested because of a family history of high cholesterol or vascular disease, and a lipoprotein profile is obtained if the patient has a TC over a certain defined target.[16, 20] In children LDL-C is the basis for initiating treatment and determining goals of therapy.

How well TC levels detect elevated LDL-C levels has been examined with LRC data (ages 6 to19, n=1325),[30] and data from the biracial Bogalusa cohort (ages 5 to 17, n=2,857).[31] Elevated levels were defined as >95th percentile. With LRC data, an elevated fasting TC detected children with elevated LDL-C and elevated triglycerides with 69% sensitivity and 98% specificity.[30]

In the Bogalusa cohort, elevated TC detected elevated LDL-C with 44% (white females) to 50% (white males, African American males and females) sensitivity and 90% specificity (African American and white males and females).[31]

In adults, both TC and HDL-C are recommended for screening. While this has not been recommended in guidelines for children and adolescents, it is common in practice.[32] HDL-C may help distinguish false negatives from true negatives when used with TC.[30] In 260 African American adolescents ages 12 to 20 years, fasting TC minus HDL-C above the 95th percentile was 88-96% sensitive and 98% specific for predicting LDL-C $\geq$130 mg/dL.[33] Using a lower threshold of fasting TC $\geq$ the 75th percentile to detect LDL-C $\geq$ the 95th percentile is a sample of Hispanic children ages 4-5, sensitivities were 86% (using an LRC defined 75th percentile) and 96% (using the sample-defined 75th percentile), and specificities were 93% (LRC defined) and 87% (sample defined).[34] A TC > 215 mg/dL is required, however, to accurately identify a child with elevated LDL-C with 95% confidence. No single TC value places a child in the borderline category (170-

200 mg/dL) with 95% confidence.[35] Direct measurement of LDL-C can be done using non-fasting serum samples and may be as precise as calculated LDL-C, but this remains controversial.[36, 37]

Key Question 2c. How well do lipid levels track from childhood to adulthood?

Twenty-three prospective cohort studies contributed information on tracking lipid levels during childhood.[38-60] These studies drew from seven US cohorts and eight non-US cohorts. Approximately 40% to 55% of children with elevated lipids, defined by percentile within a population distribution, will continue to have elevated lipids on follow-up (4-15 years later).[22] None of these studies, however, evaluated the proportion of children and adolescents with lipid levels above the 95th percentile who remained in the top 5% at follow-up.

Key Question 2d. What is the accuracy of family history in determining risk?

Several good-quality studies of diagnostic accuracy evaluated the sensitivity and specificity of family history information in determining risk for dyslipidemia in children and adolescents (Table 1).[33, 34, 61-74] Studies used different definitions of family history such as any parental history of heart attack, other parental risk factors, and varying age definitions of early CHD, and selected different levels of LDL-C or TC as the lipid detection threshold. For example, parental history of early CHD alone was 5% to 17% sensitive for TC >170 mg/dL or LDL-C >130 mg/dL,[34, 63] whereas parent or grandparent history of early CHD was 46% sensitive for LDL >the 95th percentile.[65]

Regardless of the precise definition, using positive family history information to trigger lipid testing misses substantial numbers of children with elevated lipids, ranging

from 17-90% overall and 30-60% in most studies.[33, 64, 65, 68, 70, 72, 75-77] The proportion of children and adolescents qualifying for screening based on family history is generally between 25% to 55%, depending on the sensitivity of the specific family history question.[33, 34, 61-65, 67, 70, 71, 73, 78]

Key Question 2e. What are other important risk factors?

Forty-three cohort and cross-sectional studies of mixed quality with adjusted statistical analyses contributed information on additional risk factors for identifying children at increased risk for elevated lipids and/or CHD-related events.[66, 79-120] Thirty studies examined overweight or body fat composition measures as a risk factor for dyslipidemia.[79-82, 84-86, 89-95, 99, 101-104, 106-112, 114, 115, 117, 119] These measures were the most consistently effective in predicting risk of dyslipidemia, compared to other factors assessed.[22] Childhood overweight, as measured by BMI, was the best independent predictor of adult dyslipidemia after LDL-C, specifically when considering BMI increases from childhood to adulthood.[121] Five of six studies evaluating overweight as a risk found that overweight was associated with abnormal lipid levels.[85, 86, 94, 110, 115, 117]

Key Question 2f. What are effective screening strategies for children/adolescents (including frequency of testing, optimal age for testing)?

Thirty-two studies evaluated screening strategies among children in various settings.[33, 34, 61, 63-66, 68, 70, 72, 76, 77, 122-141] The only RCT compared two regimens for screening college students.[131] All others were non-comparative prospective studies tht described screening interventions and differed considerably in venue (school, pediatric clinic, hospital, or population-based cohort), methods (fasting or non-fasting samples,

method for detecting of positive family history), and outcomes. Most reported low parental compliance with follow-up testing,[76, 136-139] even when follow-up was provided free of charge, as in pre-paid health plans.

Studies demonstrate low compliance among primary care physicians in following current guidelines for screening.[140] In an ancillary study of the Child Adolescent Trial for Cardiovascular Health (CATCH), parents were given recommendations to consult their child's physician if TC exceeded 200 mg/dL on one or more occasions.[141] After physicians examined the children, only 59% were further evaluated for possible elevated cholesterol. Of these, half of the physicians repeated cholesterol tests, 42% asked about family history, 38% made recommendations for dietary management, and only 12% referred children to dietitians.[141]

Neonatal screening for dyslipidemia has been examined in multiple studies of either cord blood testing,[54, 142-155] dried filter paper blood spots from cord blood,[156] or heel sticks of three to seven day old infants. [157-162] No studies screened a general population of infants and followed abnormal results with mutation analysis or LDL-C receptor activity assays making it difficult to determine the value of such screening.

Key Question 3. What are the adverse effects of screening (including false positives, false negatives, labeling)?

Potential adverse effects of screening for dyslipidemia among children were examined in one randomized controlled trial[163] and five non-comparative studies.[76, 136-139] Although one small study showed increased parental reporting of behavior difficulties among children with dyslipidemia, these reports were not objectively confirmed.[139] No

studies reported increased anxiety or depression among screened children or their parents.[137, 138 139]

Key Question 4. In children/adolescents, what is the effectiveness of drug, diet, exercise, and combination therapy in reducing the incidence of adult dyslipidemia, and delaying the onset and reducing the incidence of CHD-related events (including optimal age for initiation of treatment)?

No studies evaluated the effect of a childhood intervention on the incidence of adult dyslipidemia or CHD-related events and outcomes.

Key Questions 5 - 8. What is the effectiveness of drug, diet, exercise, and combination therapy for treating dyslipidemia in children/adolescents?

Forty RCTs meeting the inclusion criteria addressed the effectiveness of interventions for treatment of dyslipidemia in children and adolescents.[18, 19, 164-201] Statins, bile-acid binding resins, and fibrates have been tested and reported only in children with FH and FCH. Applicability of results from these trials to children without these conditions may be limited. In addition, 18 studies used populations recruited from single lipid clinics.[18, 165-169, 176, 178, 179, 181, 182, 185, 186, 189, 191, 193, 196, 202] Major limitations of trials include fewer than 20 subjects in each study arm,[168, 175, 178, 181, 182, 185, 193, 195] high loss to follow-up,[177, 187, 191] failure of blinding,[174, 191, 192, 196-198] lack of results presented for the period prior to crossover,[166-168, 176, 178, 180-182, 185, 189, 190, 192, 195, 198, 199, 201] lack of intention to treat analyses,[164, 166, 177-180, 182, 184, 187, 189, 191-194, 196-198] and lack of data reported for the placebo group.[179]

Studies in children with probable or definite familial hypercholesterolemia

Drug treatment. Eleven trials evaluated drug therapies for treatment of children with probable or definite heterozygous familial hypercholesterolemia (Table 2).[18, 19, 163, 167, 170, 171, 177, 182, 184, 185, 186] Most of these included children who were already compliant with a recommended low-saturated fat, low-cholesterol diet, and both treatment and control groups were maintained on the diet during the trials.

All the trials of statin drugs,[18, 19, 165, 169, 172, 173, 179, 184, 188] demonstrated improvement in TC and LDL-C among children and adolescents with FH. The decrease in TC compared to baseline ranged from 17-32% for treatment groups vs. changes of +3.6% to –2.3% for placebo groups. The decreases in LDL-C ranged from 19-41% for treatment groups, vs. changes of +0.67% to –3% for placebo groups. Changes in HDL-C and triglycerides were mixed.[165, 169, 172, 173, 179, 184, 188]

Trials of cholestyramine[187] and colestipol[186] demonstrated decreased total cholesterol and LDL-C, but no change in HDL-C or triglycerides. Trials evaluating bezafibrate,[193] vitamins C and E,[182] DHA,[199, 201] p-aminosalicylic acid,[185] combined colestipol and pravastatin vs. colestipol alone[166] and powder vs. pill form of cholestyramine[174] failed to report pre-crossover data.

Diet treatment. Five trials evaluating diet treatments in children with FH or FCH met inclusion criteria. [167, 168, 178, 180, 200] Although trials of sterol margarines and psyllium were crossover trials without pre-crossover results presented, the wash-out periods between treatment phases were four to six weeks, suggesting that results may be valid.[167, 178, 180] TC and LDL-C reductions were significant in these trials (reduction of 7.4-11%

and 10-14% respectively). There was no significant improvement in lipid levels with eight weeks of garlic extract treatment.[200]

Exercise treatment. No studies evaluated exercise treatment for lipid lowering in children with FH.

Studies in children with elevated lipids but not meeting criteria for familial hypercholesterolemia

Drug treatment. No studies evaluated drug interventions in children without monogenic dyslipidemia.

Diet treatment. Dietary interventions in general populations of children and adolescents were addressed in seven studies (Table 3).[170, 171, 174, 190, 191, 194, 196] A trial conducted by the DISC Collaborative Research Group showed that intensive dietary counseling over three years was effective (8% improvement in LDL-C compared to control),[171] but not sustained at five and seven year follow-ups once the intervention ceased.[170] A study of the Parent-Child AutoTutorial (PCAT) program[174] reported 8% improvement in LDL-C compared to the at-risk control group ($p<0.05$). One trial of psyllium did not present pre-crossover data.[81]

Exercise treatment. Six studies [183, 197, 198, 189, 192, 195] evaluated exercise in normal or obese children with elevated lipids (Table 3). Three studies were limited by differential or low completion rates, small numbers of participants, or other deficiencies (lack of blinding, lack of intention to treat analysis).[189, 192, 195] Four trials comparing supervised, scheduled sessions of aerobic and fitness training to control groups showed minimal or

no change in lipids compared to control groups.[189, 192, 197, 198] Two trials showed improvements in HDL-C for the exercise intervention group compared to controls.[183, 195]

Combination diet and exercise treatment. Three trials [175, 177, 164] evaluated combined regimens of diet and exercise (Table 3). While all interventions showed some improvement in lipid levels, a group undertaking exercise, diet, and behavior change had a 23% increase in HDL-C, compared to both the diet plus behavior change group and the control group.[175]

Key Question 9. What are the adverse effects of drug, diet, exercise, and combination therapy in children/adolescents?

Drug treatment

Information about adverse events was reported in 15 studies of statins,[18, 19, 165, 169, 172, 173, 179, 184, 188, 203-208] in 22 studies of bile-acid binding resins [166, 176, 186, 187, 209-227] and in eight studies of various other drugs or drug combinations (Table 4).[26, 185, 193, 228-232] Studies used RCT, open-label trial, and observational designs.

Statins were associated with increased ALT and/or AST levels in some,[169, 188, 204, 207] but not all, studies.[18, 165, 203, 205] Reports of elevated CK levels were similarly conflicting.[172, 173, 184, 188, 204, 205, 207,18, 165, 172, 203]

Bile-acid binding resins were associated with gastrointestinal complaints (8-26%), such as flatulence and constipation, [166, 176, 185-187, 211, 214, 216, 218, 223, 224, 229, 230] and unpalatability (up to 50%).[212, 216-219, 222, 224] One study of cholestyramine reported transient increases in LDH and abnormalities in AST that persisted for six months,[211] but

others showed normal liver function tests.[224, 226, 227] Growth was reported normal in nine studies.[26, 186, 187, 193, 215, 220, 221, 225, 227] One study reported a child whose height for age dropped below –2 S.D. while on colestipol (1 S.D. = 2.4 cm),[213] while growth was normal in all other children in the study. Sexual maturation was followed over 4.3 years of treatment and found to be normal.[225]

Two studies of niacin reported increased liver enzymes (6 of 21 children in one study), and multiple other symptoms such as flushing, abdominal pain, nausea, and headache.[229, 231] There are also case reports of hepatitis[229] and hepatotoxicity[231] with niacin.

Low-fat diet

Nineteen studies of dietary fat restriction reported effects on growth, nutrient intake, laboratory safety parameters, or other adverse effects.[170, 171, 190, 233-248]

Twelve studies reported normal height growth,[170, 190, 234-236, 239, 240, 242, 243, 245-247] although weight loss occurred among three children in two of these studies.[235, 242] Growth failure in one study occurred among 8 of 40 (20%) children with dyslipidemia, three (7.5%) of whom had nutritional dwarfing and no progression of puberty.[241] In this study, families were unsupervised in the implementation of low-fat, low-cholesterol diets for a period up to 4.5 years; those with nutritional dwarfing had longer periods of time between diagnosis and formal dietary assessment and counseling.[241] Failure to thrive has been demonstrated in children under age two years eating fat-restricted diets.[249] although these diets are not recommended for this age group.[16]

Dietary supplements

Fourteen studies provided information about adverse effects of various dietary supplements.[168, 178, 181, 200, 250-259] Two children (4% of the treatment group) reported abdominal discomfort using fiber tablets (containing 50% wheat bran and 50% pectin) administered at 100-150 mg/kg/day.[181, 253, 256] There were no adverse effects with psyllium fiber in two other studies.[181, 253] Other adverse effects of dietary supplements were mild or transient.[22]

Exercise

A school-based program examined the effect of supervised exercise training on the lipid profiles of normal prepubertal children and reported 100% adherence and no adverse effects.[260] In another study, treadmill tests elicited an exaggerated blood pressure response in boys with dyslipidemia.[261]

Key Question 10. Does improving dyslipidemia in childhood reduce the risk of dyslipidemia in adulthood?

No studies were identified that directly evaluated whether treatment of idiopathic dyslipidemia in childhood reduces risk of dyslipidemia in adulthood.

Conclusions

Although many studies have addressed the various aspects of dyslipidemia in children, few key questions about screening have been resolved (Table 5). Studies are not available that address the overarching key question about efficacy of screening children and adolescents for dyslipidemia in delaying the onset and reducing the

incidence of CHD-related events (Key Question 1), effectiveness of treatments (drug, diet, exercise and combination) on reducing incidence of adult dyslipidemia or delaying the onset and reducing the risk of CHD-related events (Key Question 4), or whether improving dyslipidemia in children and adolescents reduces the risk of adult dyslipidemia (Key Question 10).

Studies evaluating risk factors are also limited. Risk factors that might contribute to a risk assessment tool have not been adequately studied. Family history questions are not standardized and have limited diagnostic accuracy. Evidence for risk factors other than family history for predicting dyslipidemia in children is strongest for overweight, but the magnitude of the effect of overweight on lipid levels, and the potential impact of incorporating overweight into a screening strategy for dyslipidemia, have not been addressed. Multiple other risk factors such as diet, physical inactivity, and aerobic capacity/fitness have not been evaluated adequately to assess their contribution to dyslipidemia or their usefulness as screening tools either alone or in combination.

Currently recommended screening strategies have low adherence by providers and limited compliance by parents and children. No trials compared strategies by location, venue, age, or provider. No studies addressed the frequency and optimal age for testing. Adverse effects of screening for dyslipidemia have not been adequately studied.

Drug treatments for dyslipidemia in children have been studied only in children with FH or FCH, the population for whom these drugs are FDA-approved and recommended by the NCEP. Statins are effective for reducing TC and LDL-C in children with FH. It is not clear how this efficacy translates to children with milder and/or non-monogenic dyslipidemia, and it is not known how frequently these medications are used in children without FH in practice. There are no trials with long-term follow-up for adult

lipid outcomes or CHD-related events. Adverse effects of treatment are reported in controlled and non-controlled studies of drug, diet, exercise, and combination therapy in children and adolescents. Studies were generally not of sufficient duration to determine long-term effects of either short or extended use.

Directions for future research should include identification of the impact of risk factors other than family history, such as overweight and physical inactivity, on lipids in order to develop risk assessment strategies. Such tools may provide a better indication of actual risk, and could facilitate screening by narrowing the number of children requiring serum lipid testing. New vascular markers such as apolipoprotein B and apolipoprotein A-I may prove to be useful for screening in children.[263, 264] There is a growing literature on non-invasive vascular outcomes such as carotid intima-media thickness (IMT), nitrate dilation, and brachial IMT. Carotid IMT is significantly higher in overweight children, and adult IMT measurements appear to correlate with lipid measurements taken in childhood.[83, 265-268] Further evaluation of arterial IMT as a risk factor identifiable in children and its usefulness as a screening tool may be warranted.

Randomized controlled clinical trials of screening strategies to determine which are more effective than current practice both in terms of parental compliance and provider adherence to guidelines are important. Screening strategies for ensuring adequate assessment of minorities and those with unknown family history deserve attention. Continued follow-up of currently established cohorts to assess the impact of screening for dyslipidemia in childhood on adult CHD outcomes is important.

More rigorous study designs, enrollment of larger population-based samples, and systematic reporting of adverse effects could improve studies of dyslipidemia treatments. Long-term follow-up of children treated with statins to determine the impact of sustained

improvement of lipid levels in childhood on adult lipid levels, adult CHD-outcomes, and long-term safety will help further asses the efficacy and safety of treatment options. Effect of exercise on lipid levels should be evaluated further, particularly in children with lipid levels above the 95th percentile. Standardized methods for collecting and reporting adverse effects in treatment trials would facilitate combining data across trials, and lead to more thorough understanding of the risks of treatment among children and adolescents.

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Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
Bell, 1990[61]	1,140 5th graders	Family history of high cholesterol or MI <age 60 in parent or grandparent	Non-fasting TC > 200 mg/dL	64%	47%	540	46
	1,140 5th graders	As above, plus family history of stroke, angina or hypertension	Non-fasting TC > 200 mg/dL	77%	24%	760	31
Davidson, 1991[62]	1,118 4th graders	Family history from parents (regarding parents, siblings, grandparents, aunts, uncles); early MI defined as < age 56 for men and women	TC > 200 mg/dL	41%	68%	330	83
	1,118 4th graders	Parental questionnaire, definition using AAP criteria for early CHD (< age 50 for men, < age 60 for women)	TC > 200 mg/dL	31%	66%	330	96
Dennison, 1989[72]	1,214, ages 4-10, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting TC $\geq$ 95th percentile	38% for W; 27% for AA	73% for W; 65% for AA	N/A	N/A
	2,099, ages 11-17, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting TC $\geq$ 95th percentile	59% for W; 25% for AA	67% for W; 56% for AA	N/A	N/A
	1,214,ages 4-10, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting LDL $\geq$ 95th percentile	41% for W; 20% for AA	73% for W; 63% for AA	N/A	N/A

Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
Dennison, 1989[72] (continued)	2,099, ages 11-17, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting LDL > 95th percentile	37% for W; 22% for AA	67% for W; 56% for AA	N/A	N/A
Diller, 1995[63]	232, ages 2-19, Cincinnati MI Hormone Study	Parental questionnaire using NCEP definition of family history of premature CVD	LDL $\geq$ 130 mg/dL	17%	75%	246	207
	232, ages 2-19, Cincinnati MI Hormone Study	Parental questionnaire asking family history of cholesterol > 240	LDL $\geq$ 130 mg/dL	61%	74%	293	99
	232, ages 2-19, Cincinnati MI Hormone Study	Both family history of elevated cholesterol and premature CVD	LDL $\geq$ 130 mg/dL	74%	55%	478	65
	232, ages 2-19, Cincinnati MI Hormone Study	Other indicators: obesity, smoking, use of lipid raising medications, high fat diet, HTN	LDL $\geq$ 130 mg/dL	17.4% for obesity, 9-48% for others	86% for obesity, 69-95% for others	547	86
	232, ages 2-19, Cincinnati MI Hormone Study	Family history of premature CHD (NCEP definition), TC>240 mg/dL, or any other risk factor (obesity, smoking, lipid raising medication, high fat diet or HTN).	LDL $\geq$ 130 mg/dL	96%	28%	746	13

Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
Gagliano, 1993[64]	224, ages 11-20	Family history of early MI (< age 50 for men, < age 60 for women) or elevated lipids (TC >200 mg/dL), history obtained from adolescent	TC > 85th percentile for gender	36%	69%	320	94
	224, ages 11-20	Family history as above, history obtained from parent	TC above the 85th percentile for gender	65%	46%	589	54
	224, ages 11-20	Use of combined family history from adolescent and parent	TC above the 85th percentile for gender	45%	69%	361	80
Griffin, 1989[65]	1,005, ages 2-13, 8 office practices	Parent and grandparent history of hypercholesterolemia or CHD < age 55	Fasting LDL > 95th percentile	46%	NR	N/A	147
	1,005, ages 2-13, 8 office practices	Parent and grandparent history of any risk factor or complication (hypercholesterolemia, diabetes, HTN, gout, obesity and atherosclerosis prior to age 55)	Fasting LDL > 95th percentile	78%	NR	N/A	59
	1,005, ages 2-13, 8 office practices	Parent and grandparent history of hypercholesterolemia or CHD < age 55	Fasting LDL > 90th percentile	51%	63%	385	48

Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
Griffin, 1989[65] (continued)	1,005, ages 2-13, 8 office practices	Any history of parent or grandparent with a risk factor or complication (hypercholesterolemia, diabetes, HTN, gout, obesity and atherosclerosis prior to age 55)	Fasting LDL > 90th percentile	80% 38% for high cholesterol alone 31% for obesity 18% for sudden death 17% for gout 13% for PVD	37%	650	20
.	1,005, ages 2-13, 8 office practices	Overweight (weight for height > 95th percentile) plus family history of early CHD or hypercholesterolemia	Fasting LDL > 90th percentile	57%	NR	N/A	42
	1,005, ages 2-13, 8 office practices	Overweight (weight for height > 95th percentile) plus family history any risk factor or complication	Fasting LDL > 90th percentile	84%	31.0%	704	16
Muhonen, 1994[66]	599, ages 14-20, Muscatine, IA	Parental history of high cholesterol	Highest decile of fasting TC	34%	76%	N/A	N/A
	599, ages 14-20, Muscatine, IA	Parental history of high cholesterol	Highest decile of fasting LDL	34%	76%	N/A	N/A

Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
Muhonen, 1994[66] (continued)	599, ages 14-20, Muscatine, IA	Parental history of high cholesterol	Lowest decile of fasting HDL	26%	75%	N/A	N/A
O'Loughlin, 2004[73]	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) medications for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) medications for the heart; unknown family history coded as negative	Fasting LDL≥109 mg/dL ("borderline")	33%	76%	256	44
	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) medications for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) medications for the heart; unknown family history coded as negative	Fasting LDL≥131.5 mg/dL, ("high")	41%	75%	256	12
	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) medications for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) medications for the heart; unknown family history excluded	Fasting LDL≥109 mg/dL, ("borderline")	42%	70%	N/A	85

Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
O'Loughlin, 2004[73] (continued)	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) medications for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) medications for the heart; unknown family history excluded	Fasting LDL≥131.5 mg/dL, ("high")	51%	69%	N/A	19
Primrose, 1994[67]	1,012, ages 12-15, Ireland	History of stroke, angina or heart attack in either parent at any age or in 1st degree grandparents, uncles or aunts < age 55. Questionnaires completed by parents	Non-fasting TC > 95th percentile according to LRC	33%	72%	293	125
Resnicow, 1993[68]	574, elementary school age	Parental cholesterol ≥240 in 1 parent only with known and reported value by that parent	Non-fasting TC > 200 mg/dL	10%	91%	90	106
Rifai, 1996[33]	260, ages 12-20, AA	Family history of early CHD or hyperlipidemia	Fasting LDL > 110 mg/dL	10%	NR	365	184
Sanchez Bayle, 1992[69]	2,224, ages 2-18, Spain	Parental history of MI	Fasting TC>200 mg/dL	7%	96%	49	140

Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
Sanchez Bayle, 1992[69] (continued)	2,224, ages 2-18, Spain	Parental history of MI	Fasting LDL>135 mg/dL	9%	96%	49	101
	2,224, ages 2-18, Spain	Parental history of stroke, HTN, diabetes, or hypercholesterolemia (but not MI)	Fasting TC>200 mg/dL	14%	90%	98	129
	2,224, ages 2-18, Spain	Parental history of stroke, HTN, diabetes, or hypercholesterolemia (but not MI)	Fasting LDL>135 mg/dL	14%	91%	98	95
Shea, 1990[34]	108, ages 4-5, Hispanic, Study of Childhood Activity & Nutrition	AAP definition (maternal hypertension, diabetes, obesity, hyperlipidemia or family history of premature CHD or hyperlipidemia)	Fasting TC > 170 mg/dL	57%	59%	493	148
	108, ages 4-5, Hispanic, Study of Childhood Activity & Nutrition	AHA and NIH Consensus Conference definition (history of hyperlipidemia or premature CHD in the child's parent, aunt, uncle or grandparent)	Fasting TC > 170 mg/dL	46%	70%	352	185
	108, ages 4-5, Hispanic, Study of Childhood Activity & Nutrition	NCEP guidelines (history of MI or sudden death in the child's parent, aunt, uncle, or grandparent; CHD prior to age 55).	Fasting TC > 170 mg/dL	5%	92%	74	324

Table 1. Summary of studies evaluating sensitivity and specificity of family history

Study, year	Population - N, age	Method	Threshold*	Sensitivity	Specificity	Number eligible for screening (based on population of 1,000)†	Number missed (based on population of 1,000)†
Steiner, 1991[70]	1,001, ages 12-21 (38% Hispanic, 33.5% W, 15% AA, 11% Asian), Kaiser population	AAP 1998 criteria (known hyperlipidemia in parent or sibling, known MI/angina, current corticosteroid use, juvenile diabetes, hypothyroidism, renal/endocrine/hepatic disease in teenager)	Non-fasting TC≥200 mg/dL, repeated fasting TC if initial test≥200 mg/dL, repeated a 3rd time if more than 30 mg/dL variability between the 1st two measurements	63%	60%	400	24
Troxler, 1991[71]	110 mostly Hispanic senior high school students	Questionnaires completed with parental assistance; family history in parents or grandparents of high cholesterol or CHD age <55 (AAP)	Fasting TC > 75th percentile (175 mg/dL)	38%	79%	218	245
Wadowski, 1994[74]	300 AA, ages 2-14	Family history of CHD in parent or grandparent at age < 55	Fasting TC > 215 mg/dL	59%	72%	327	23

Key

*If not explicitly stated, values are mixed non-fasting/fasting or not reported.

†Number eligible for screening and number missed were calculated from available data. In some cases, reported data did not allow for these calculations (these indicated with N/A).

Abbreviations

AA = African American, AAP = American Academy of Pediatrics, AHA = American Heart Association, CHD = Coronary heart disease, CVD = Cardiovascular disease, HTN = Hypertension, LDL = Low-density lipoprotein, LRC = Lipid Research Clinic, MI = Myocardial infarction, N/A = Not applicable, NCEP = National Cholesterol Education Program, NIH = National Institutes of Health, PVD = Peripheral vascular disease, TC = Total cholesterol, W = White.

Table 2. Randomized controlled trials of drug treatment for children with monogenic dyslipidemia

Author, year	Drug	Population - N, age	Duration of trial	Significant changes vs. control				Quality rating
				TC	HDL	LDL	TG	
Statins								
Clauss, 2005[19]	Lovastatin 20 mg/d vs. 40 mg/d vs. placebo	54 girls, 11-18 y	24 wk	↓	O	↓	O	Good
Couture, 1998[179]	Simvastatin 20 mg/d vs. placebo	63, 8-17 y	6 wk	↓	↑	↓	↓	Fair
de Jongh, 2002[165]	Simvastatin 10 mg/d, doubled every 8 wk up to 40 mg/d vs. placebo	50, 9-18 y	28 wk	↓	NR	↓	↓	Poor
de Jongh, 2002[188]	Simvastatin 10 mg/d titrating up to 40 mg/d vs. placebo	173, 10-17 y	48 wk	↓	NR	↓	NR	Good
Knipscheer, 1996[173]	Pravastatin in 3 active drug groups: 5, 10, or 20 mg/d vs. placebo	72, 11-17 y	12 wk	↓	O	↓	O	Good
Lambert, 1996[184]	Lovastatin at 10, 20, 30, or 40 mg/d. 4 active drug groups, no placebo)	69 boys, ≤ 17 y	8 wk	↓	↑	↓	NR	Fair
McCrindle, 2003[169]	Atorvastatin 10 mg/d vs. placebo	187, 10-17 y	26 wk	↓	↑	↓	↓	Good

Table 2. Randomized controlled trials of treatment for children with monogenic dyslipidemia

Author, year	Drug	Population - N, age	Duration of Trial	Significant Changes vs. Control				Quality Rating
				TC	HDL	LDL	TG	
Statins, cont.								
Stein, 1999[172]	Lovastatin starting at 10mg/d, titrating to 40 mg/d vs. placebo	132 boys, 10-17 y	48 wk	↓	O	↓	O	Good
Wiegman, 2004[18]	Pravastatin 40 mg/d vs. placebo	214, 8-18 y	2 y	↓	O	↓	NR	Good
Bile-acid Resins								
Tonstad, 1996[186]	Colestipol 10 gm/d or 5 gm twice daily vs. placebo	66 adolescents, NR	8 wk	↓	O	↓	O	Poor
Tonstad, 1996[187]	Cholestyramine titrating up from 4 gm/d to 8 gm/d vs. placebo	96 boys, 6-11 y	1 y	↓	O	↓	O	Fair

Key
↑ = significant increase, ↓= significant decrease, 0= no significant change

Abbreviations
D = Day(s), HDL = High-density lipoprotein, LDL = Low-density lipoprotein, NR = not reported, TC = Total cholesterol, TG = Triglycerides, Wk = Week(s), Y= Year(s).

Table 3. Randomized controlled trials of diet and/or exercise for children and adolescents without monogenic dyslipidemia

Author, year	Intervention(s)	Population - N, age/description	Duration of trial	Significant changes vs. control				Quality rating
				TC	HDL	LDL	TG	
Diet								
DISC Collaborative Research Group, 1995[171]	Family oriented behavioral intervention to promote dietary adherence vs. usual care	663, 8-10 y	3 y	↓	↓ y 1 only	↓	**O**	Good
Gold, 1991[196]	Oat bran supplemented cereal within AHA Step 1 diet vs. cereal within Step 1 diet and no oat bran	49, 10 y (mean) with TC>185 mg/dL	4 wk	**NR**	**O**	**O**	**O**	Poor
Kuehl, 1993[190]	4 90-minute family-oriented nutrition sessions vs. 1 90-minute session	295, 2-15 y with TC≥ 185	16 wk	**O**	**O**	**O**	**O**	Poor
Obarzanek, 2001[170]	Counseling intervention (same as DISC above) vs. usual care	663, 8-10 y	4 y (7 y total follow-up)	**O** 5 & 7 y	**O** 5 & 7 y	**O** 5 & 7 y	**O** 5 & 7 y	Good
Shannon, 1994[174]	Parent-Child Auto Tutorial Program (PCAT): 10 talking book lessons and follow-up paper and pencil games for children with a manual for parents, vs. 45-60 minute counseling session with parent, child and registered dietitian, and take home print materials for both	261, 4-10 y with elevated LDL	3 mo follow-up	**NR**	**NR**	↓	**NR**	Good
Stallings, 1993[191]	Parent-Child Auto Tutorial Program (PCAT): 10 sessions total, 1 per week completed in home by child and parents vs. usual care	44, 4-10 y with LDL 90-99th percentile	6 mo	**NR**	**NR**	**O**	**NR**	Poor

Table 3. Randomized controlled trials of diet and/or exercise for children and adolescents without monogenic dyslipidemia

Author, year	Intervention(s)	Population - N, age/description	Duration of trial	Significant changes vs. control				Quality rating
				TC	HDL	LDL	TG	
Diet, cont.								
Williams, 1995[194]	Fiber cereal with 3.2 grams soluble fiber per serving. Dose=1 box of cereal/d for 3 wk, then 2 boxes/d. Children ages 2-5 consumed only 1 box/d throughout study. Compared to placebo cereal with 0.5 grams fiber	58, 2-11 y with TC>170 mg/dL and LDL> 110mg/dL	12 wk	↓	O	↓	O	Poor
Exercise								
Boreham, 2000[195]	7 wk stair climbing program vs. no change in activity	25 sedentary females, 18-22 y	7 wk	O	↑*	NR	NR	Poor
Ferguson, 1999[183]	Exercise program 5 d/wk, 40 minutes/d; children were paid $1/session and given prizes for maintaining a heart rate > 150 beats per minute vs. no exercise program	81 obese children mean 9.5 y	4 mo	O	↑	O	↓	Fair
Kang, 2002[189]	Physical activity training with lifestyle intervention 5 d/wk vs. lifestyle intervention alone	80 obese children, 13-16 y	8 mo	O	O	O	↓	Poor
Linder, 1983[197]	Physical conditioning program (PA) vs. usual activities	50 healthy boys, 11-17 y	8 wk	O	O	O	O	Fair
Savage, 1986[198]	Walking/jogging/running 3 d/wk (1.6 km/session) high intensity (HR=75% of VO2max) vs. low intensity (HR=40% of VO2max).	663 boys, mean 8-9 y	11 wk	NR	NR	O	O	Fair

Table 3. Randomized controlled trials of diet and/or exercise for children and adolescents without monogenic dyslipidemia

Author, year	Intervention(s)	Population - N, age/description	Duration of trial	Significant changes vs. control				Quality rating
				TC	HDL	LDL	TG	
Exercise, cont.								
Stergioulas, 1998[192]	Four 60 minute sessions/wk vs. no specific training program	58 sedentary boys, 10-14 y	2 mo	**NR**	**O**	**NR**	**NR**	Poor
Diet and Exercise								
Becque, 1988[175]	1. Diet and behavior change: met with dietician and behavior therapist 1 d/wk 2. Exercise plus diet and behavior change: same as above, with exercise program 50 minutes for 3 d/wk 3. No change in activity or diet	36 overweight adolescents, mean 13 y	20 wk	**O**	↑	**O**	**O**	Fair
Epstein, 1989[164]	Diet of 3800-5000 kJ/d monitored by a nutritionist. Information on diet, exercise, stimulus control, reinforcement, modeling and contingency contracting presented to parents and their children in 8 weekly sessions followed by 4 monthly sessions	56 obese (>20% of ideal weight) children, 8-12 y	6 mo	↓	↑	**NR**	↓	Poor
Walter, 1985[177]	"Know Your Body" curriculum yearly, taught 2 hours/wk by usual classroom teacher vs. standard curriculum	1,115 4th graders	1 y	**O**	**O**	**NR**	**NR**	Fair

Key: * This trial reported significant pre-experimental differences between groups in HDL ($p<0.05$). ↑ = significant increase, ↓= significant decrease, 0 = no significant change.

Abbreviations: AHA = American Heart Association, D = Day(s), DISC = Dietary Intervention Study in Children, HDL = High-density lipoprotein, LDL = Low-density lipoprotein, Mo = Month(s), NR= not reported, TC = Total cholesterol, TG = Triglycerides, Wk = Week(s), Y = Year(s).

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Statins					
McCrindle, 2003[169]	Atorvastatin	187, 10-17 y	26 wk	None observed; No effect on sexual development.	Increased AST and ALT (1% of patients). None withdrew or stopped medication as a result of increased transaminases.
Clauss, 2005[19]	Lovastatin	54 girls, 10-17 y	24 wk	Abdominal pain (2), diarrhea (1), nausea (1), headache (1), amenorrhea (1). All resolved with patient continuing medication.	Transient decreased HCT.
Lambert, 1996[184]	Lovastatin	69 boys, < 18 y	8 wk	None observed.	Asymptomatic elevations in CK (3).
Stein, 1999[172]	Lovastatin	132, 13 y (mean)	48 wk	No effect on growth or sexual development.	Transient CK elevations in response to exercise. No effect on AST; ALT increased in placebo and treatment groups. DHEAS increased. Tocopheral, CD3, CD4, and CD8 counts decreased.
Wiegman, 2004[18]	Pravastatin	214, 8-18 y	2 y	No effect on growth or sexual development.	No effects on muscle or liver enzyme levels.
Hedman, 2003[203]	Pravastatin	20, 4-15 y	8 wk	Abdominal pain (1), loose stools (1), headache (4), sleep disturbance (2), muscle tenderness or pain at rest (1), muscle tenderness or pain associated with physical training (1).	No effects on serum ALT, CK, or creatinine.

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Statins					
Knipscheer, 1996[173]	Pravastatin	72, 12 y (mean)	12 wk	Rash, nose bleeding, headache, nausea/vomiting, abdominal pain.	CK abnormal in placebo (8), 5 mg/d (6), 10 mg/d (11) and 20 mg/d groups (8). Cortisol abnormal in placebo (2), 5 mg/d (2), 10 mg/d (5), and 20 mg/d (3) groups.
Couture, 1998[179]	Simvastatin	63, 8-17 y	6 wk	None observed.	NR
De Jongh, 2002[165]	Simvastatin	69, 9-18 y	28 wk	None observed.	No significant effects on ALT, AST, and CK.
De Jongh, 2002[188]	Simvastatin	173, 10-17 y	48 wk	Abdominal pain (3), chest pain (1), flatulence (1), myalgia (2), headache (4), sleep disorder (1), weight gain (1), pruritus (1).	Increased ALT (3), AST (3), and CK (1).
Dirisamer, 2003[204]	Simvastatin	20, 10-17 y	18 mo	Transient headache (2). Myalgia (1) for 2 weeks. Transient gastrointestinal complaints (2).	Slightly higher values of CK (2); Transiently elevated ALT and glucose challenge test (1).
Ducobu, 1992[207]	Simvastatin	32, < 17 y	24-36 mo	No effect on growth.	Transient increases in transaminase (1) and CK (2).
Stefanutti, 1999[208]	Simvastatin	16, 7-12 y	12 mo	None observed.	NR
Various or unspecified statins					
Sinzinger, 2004[205]	Various statins	22 professional athletes, 15-27 y	8 y	Muscle pain reported in 84% of periods of statin therapy (mean time of onset was 8.3 d).	Elevated CK in 3 subjects. No increase in liver enzymes.
De Jongh, 2003[206]	Various statins	69, 10-18 y	NR	None observed.	NR

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Bile-acid Binding Resins					
Curtis, 1991[209]	Cholestyramine	1, 7 y	2 y	Loss of dental enamel noted (presumed due to low pH 2.4 of cholestyramine mixed with Kool-Aid® for administration).	Serum calcium, phosphorus, folate, B12 were normal.
Farah, 1977[210] and Farah, 1977[211]	Cholestyramine	20, 4-23 y	16 d	Febrile gastroenteritis (1) after 7 days treatment resulting in discontinuation of therapy.	Serum folate decreased significantly in females. AST increases (2) persisted 6 mo. Transient LDH increases (2). No fat-soluble vitamin malabsorption.
Glueck, 1973[227]	Cholestyramine	36, 7-21	6 mo	None observed. Normal growth.	None observed.
Glueck, 1974[226]	Cholestyramine	30 on diet + BABR, 5-21 y	6 mo average follow-up	NR	Plasma vitamins A and E remained within the normal range.
Glueck, 1977[224]	Cholestyramine	16, 9-17 y	18 mo (16); 24 mo (12); 30-36 mo (7)	Persistent constipation (11). Gritty sensation and poor palatability (5). Chronic fatigue (1). Drop outs after 2 y due to palatability.	No effect on CBC, liver function tests, vitamin A and E, calcium, phosphorus, blood urea nitrogen, fasting blood sugar levels.
Glueck, 1986[225]	Cholestyramine	33, 10.3 y (mean)	4.3 y	No effect on growth or sexual development; 1 competitive cross-country runner had persistently irregular periods.	NR

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Bile-acid Binding Resins					
Koletzko, 1992[215]	Cholestyramine	35 on diet; 14 on diet + BABR, 2-17 y	Diet: mean 17.5 mo Diet + BABR: mean 27.9 mo	None observed. No effect on growth.	NR
Liacouras, 1993[216]	Cholestyramine	87, 10.6 y (mean)	Up to 62 mo	Nausea (12), abdominal bloating (2), severe constipation (1). Poor palatability (73%).	No elevated prothrombin times.
McCrindle, 1997[176]	Cholestyramine	40, 10-18 y	28 wk	Minor gastrointestinal complaints were frequent but did not result in any drop-out.	NR
Tonstad, 1996[187]	Cholestyramine	96, 6-11 y	1 y	No effect on growth. One case of intestinal obstruction caused by adhesions. Unpalatability, headaches, and vomiting were reasons for withdrawals.	Folate deficiency (most subjects taking cholestyramine). Vitamin D levels decreased significantly for those not taking a multi-vitamin.
Tonstad, 1998[219]	Cholestyramine	96, 6-11 y	1 y	Unpalatability in both treatment and placebo groups.	During cholestyramine treatment, plasma total homocysteine increased in subjects with the C677T mutation in 1 or both alleles, but not in subjects with the CC genotype.
West, 1973[220]	Cholestyramine	19, 1-14 y	Up to 20 mo	Some had impaired fat absorption without diarrhea. Growth was normal.	Serum folate decreased in all patients.

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Bile-acid Binding Resins					
West, 1975[221]	Cholestyramine	18, 1-14 y	1 to 2.5 y	No child developed diarrhea. No effect on growth	Decreased red cell folate and mean serum levels of vitamins A, vitamin E and inorganic phosphorus.
West, 1975[222]	Cholestyramine	45, 1-16 y	2-8 y	Adherence was poor due to unpalatability.	Folate deficiency, steatorrhoea, and reduction in serum levels of vitamins A and E and of inorganic phosphorus although not to abnormally low values.
West, 1980[223]	Cholestyramine	35, 1-17 y	1-8 y	Nausea, dizziness and malaise in a female aged 18 y. 1 boy died of intercurrent infection 10 mo after starting meds, not stated whether related to treatment. Transient gastric fullness.	NR
Groot, 1983[212]	Colestipol	33, NR	16 wk	Withdrawals due to unpalatability (5).	NR
Hansen, 1992[213]	Colestipol	30, 1-17 y	8.5 y (diet); 5.5 y (diet followed by diet + BABR)	1 child's height/age decreased below -2 SD. Growth was normal in other children.	NR
Harvengt, 1976[214]	Colestipol	3, 6-18 y	Up to 36 mo	Mild gastrointestinal complaints (flatulence, constipation) during first 3 months, but disappeared despite continued treatment.	Low iron without anemia (1). Serum uric acid level increased during treatment but did not reach abnormal values.

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Bile-acid Binding Resins					
McCrindle, 2002[166]	Colestipol	40, 9-18 y	36 wk	Constipation (18%), stomachache (21%), headache (11%), muscle aches (6%).	NR
Schwarz, 1980[217]	Colestipol	23, 5-17 y	Up to 24 mo	Poor palatability (6). Reynauld's phenomenon occurred during therapy (1) but treatment continued without recurrence.	Serum vitamins A and E decreased significantly after 18-24 mo of colestipol.
Tonstad, 1996[186]	Colestipol	66, 13.2 y (mean)	52 wk	Gastrointestinal side effects (8), including constipation, dyspepsia, flatulence, nausea, decreased appetite, abdominal pain. Growth was normal.	Reduced serum folate after 8 wk. Decreased serum vitamin E and carotenoids. Decreased vitamin D levels (not significant) in subjects who were more compliant after 1 y.
Tonstad, 1996 [218]	Colestipol	27, 10-16 y	6 mo for colestipol; 6 y (mean) for diet	No effect on growth. Difficulty swallowing the tablets (2); flatulence (1); abdominal discomfort (1).	NR
Other drugs and combinations					
Baker, 1982[26]	Probucol	7, 6-21 y	15-21 mo	Nausea in 1 patient; No effect on growth and development.	None observed.
Becker, 1992[228]	Sitosterol and bezafibrate, in sequence and in combination	7, 8.4 y (mean)	3 mo sitosterol; 3 mo bezafibrate; 24 mo sitosterol + bezafibrate	Decreased appetite for the first 2 wk on sitosterol (2).	Sitosterol: slight, significant decrease in hemoglobin (-5%) and ALP (-19%). Bezafibrate: ALP remained lower; iron increased by 26%. Combination: transferrin increased 20% and reached abnormal levels in 2; all other lab values normal.

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Other drugs and combinations					
Colletti, 1993[229]	Niacin	21, 4-14 y	1-19 mo, average 8.1 mo	18 of 21 patients reported some adverse effect. Flushing (71%), itching (19%), abdominal pain (14%), nausea (14%), headache (14%), constipation (5%), hepatitis (1).	Dose related, reversible serum aminotransferase elevations (6: 4 with crystalline and 2 with sustained release form of niacin).
Malloy, 1978[185]	P-amnosali-cylic acid	20, 5-21 y	6 mo	Mild gastric irritation that remitted with oral antacid treatment.	Normal AST, ALT, ALP, bilirubin, and glucose levels in fasting serum; normal TSH and thyroxine.
McDuffie, 2002[230]	Orlistat	20, 14.6 y (mean)	3 mo	Gastrointestinal effects related to increased fat excretion that resolved within the first 6 wk of treatment. 1 subject withdrew because of intolerance of adverse effects.	Decreased 25-hydroxy vitamin D levels at 1 mo; 3 subjects required additional vitamin D supplementation despite the prescription of a daily multivitamin containing vitamin D.
Stein, 1989[231]	Diet + drug or combined drugs: BABR; BABR + niacin; lovastatin or simvastatin	30, 1-20 y	1-9 y	None observed.	Resin + niacin together produced elevated AST and ALT, decreased albumin and clinical symptoms of hepatotoxicity (1).
Steinmetz, 1981[232]	Fenofibrate	17, 4-19 y	18 mo	NR	Increased ALT and AST (4); Decreased uric acid, bilirubin, inorganic phosphates, ALP, and GGT.

Table 4. Adverse effects reported in studies of statins, bile-acid binding resins, and other drugs and combinations

				Adverse effects of treatment	
Author, year, title	**Drug**	**Population - N, age**	**Duration of trial**	**Clinical effects**	**Laboratory effects**
Other drugs and combinations					
Wheeler, 1985[193]	Bezafibrate	14, 4-15 y	3 mo	None observed. No effect on growth. All subjects declared preference for this drug over cholestyramine.	Increased alkaline phosphatase (1), transient rise in ALT (1).

Key: (#) = Number of participants experiencing effect.

Abbreviations: ALP = Alkaline phosphate, ALT = Alanine aminotransaminase, AST = Aspartate aminotransferase, BABR = Bile acid binding resin, CBC = Complete blood count, CK = Creatine kinase, D = Day(s), DHEAS = Dehydroepiandrosterones, GGT = Gamma-Glutamyl Transpeptidase, HCT = Hematocrit, LDH = Lactate dehydrogenase, Mo = Month(s), NR = Not reported, RCT = Randomized controlled trial, TSH = Thyroid stimulating hormone, Wk = Week(s), Y = Year(s).

Table 5. Summary of evidence

Arrow	Key question	Quality of evidence	
1	Is screening for dyslipidemia in children effective in delaying the onset and reducing the incidence of CHD-related events?	No evidence.	No evidence.
2	What is the accuracy of screening for dyslipidemia in identifying children at increased risk of CHD-related events?	See below (subquestions).	See below (subquestions).
2a	What are abnormal lipid values in children/adolescents?	Fair to Poor	Normal values for lipids in children are currently defined according to population levels (percentiles). NCEP recommendations are based on LRC data, which defines the 95th percentile for TC as 200 mg/dL and for LDL as 130 mg/dL. There are more recent studies suggesting that age, gender, racial differences and temporal trends shift these cut points. The NCEP has defined levels of LDL for which drug treatment (LDL≥190mg/dL or LDL≥160mg/dL with family history of early CHD), further evaluation, diet therapy and testing (LDL>130mg/dL) and diet therapy with increased surveillance (LDL110-129mg/dL) are recommended.
2b	What are appropriate tests? How well do screening tests (non-fasting total cholesterol, fasting total cholesterol, fasting lipoprotein analysis) identify individuals with dyslipidemia?	Poor	The most appropriate test is one that accurately predicts future risk and benefit from treatment. In the general population of children there have not been adequate studies to determine these characteristics. Data from few studies suggest that TC above the 95th percentile predicts LDL above the 95th percentile with 44-69% sensitivity. TC minus HDL might be a more sensitive test, but has not been extensively evaluated. A single TC measurement is inadequate to classify children and adolescents into NCEP risk categories with 95% confidence.
2c	How well do lipid levels track from childhood to adulthood?	Good	Serial correlations measured in individual children over time are higher for TC (r=0.38-0.78) and LDL (r=0.4-0.7) than for HDL and TG. Approximately 40-55% of children with elevated lipids (by percentile) will continue to have elevated lipids on follow-up.

Table 5. Summary of evidence

Arrow	Key question	Quality of evidence	Conclusions
2d	What is the accuracy of family history in determining risk?	Good	Multiple good quality studies evaluating the use of family history as a diagnostic test for dyslipidemia in children using varied and large populations demonstrate that family history is an imperfect screening tool for detecting dyslipidemia among children.
2e	What are other important risk factors?	Good for family history; Good for obesity; Poor for all other risk factors.	Evidence from epidemiologic cross-sectional and cohort studies establishes statistical associations between elevations in lipids and family history and overweight. There is inadequate evidence to show the magnitude of the effect of overweight on lipids, or the impact that incorporating weight measures into a screening tool could have. Multiple other risk factors (diet, physical inactivity, aerobic capacity/fitness, puberty level and smoking) have not been evaluated adequately to assess their contribution to dyslipidemia in children or their usefulness as screening tools.
2f	What are effective screening strategies for children/adolescents (including frequency of testing, optimal age for testing)?	Poor	Currently recommended screening strategies have limited diagnostic accuracy, low adherence to guidelines by providers, and limited compliance by parents and children. No trials compare strategies of screening in children. No studies address the frequency and optimal age for testing.
3	What are the adverse effects of screening including false positives, false negatives, labeling, etc?	Fair	Studies demonstrate lack of parental compliance with screening and follow-up recommendations. Reasons for non-compliance include concern about test accuracy, lack of proof that intervention makes a difference in children, concern about upsetting the child, refusal by the child, inconvenience, or parental decision to institute a diet themselves and have child rechecked subsequently.
4	In children and adolescents, what is the effectiveness of drug, diet, exercise, and combination therapy in reducing the incidence of adult dyslipidemia, and delaying the onset and reducing the incidence of CHD-related events and other outcomes (including optimal age for initiation of treatment)?	No evidence.	No evidence.

Table 5. Summary of evidence

Arrow	Key question	Quality of evidence	Conclusions
5-8	What is the effectiveness of drug, diet, exercise, and combination therapy for treating dyslipidemia in children/adolescents (including the incremental benefit of treating dyslipidemia in childhood)?	Good quality studies with fair external validity for drug therapy. Fair to poor for diet and exercise treatments.	Statins are effective for reducing TC and LDL in children with familial hypercholesterolemia. It is not clear how this efficacy translates to children with milder and/or non-familial forms of dyslipidemia. Diet supplements (psyllium, oat, sterol margarine) and counseling were marginally effective in both FH/FCH children and adolescents and those without identified monogenic dyslipidemia. Exercise treatments showed minimal to no improvements in children without monogenic dyslipidemia.
9	What are the adverse effects of drug, diet, exercise, and combination therapy in children/adolescents?	Fair	Controlled and non-controlled studies of treatment reported adverse effects of drug, diet, exercise, and combination therapy in children and adolescents. Statin drugs were associated primarily with elevations in LFTs and CK. Bile-acid binding resins were associated with GI side effects and decreased levels of serum vitamins and minerals. Low fat diet has been associated with growth retardation and nutritional dwarfing in 3 children who were placed on low-fat diets without formal advice and monitoring. Most studies show normal growth and development in children over 2 years old on monitored low-fat diets. Few side effects other than elevated blood pressure were noted with exercise. The duration of follow-up in these studies ranged from 10 days to 8 years. Studies were generally not of sufficient duration to determine long-term effects of either short or extended use.
10	Does improving dyslipidemia in childhood reduce the risk of dyslipidemia in adulthood?	No evidence.	No evidence.

Abbreviations

CHD = Coronary heart disease, CK = Creatine kinase, FH = Familial hyperlipidemia, FCH = Familial Combined Hyperlipidemia, HDL = High-density Lipoprotein, LDL = Low-density Lipoprotein, LFT = Liver function test, NCEP = National Cholesterol Education Program, RCT = Randomized controlled trial, TC = Total cholesterol, TG = Triglycerides.

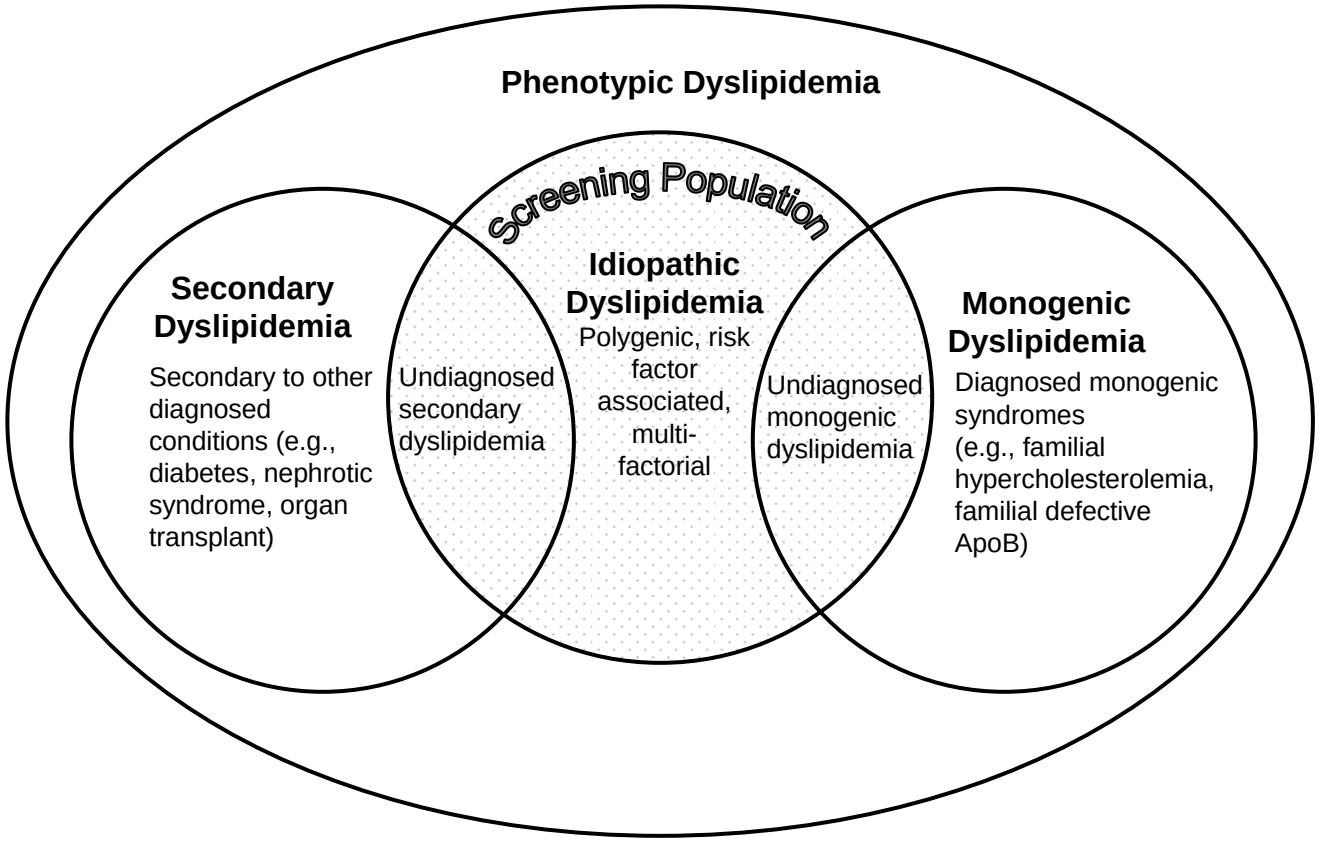
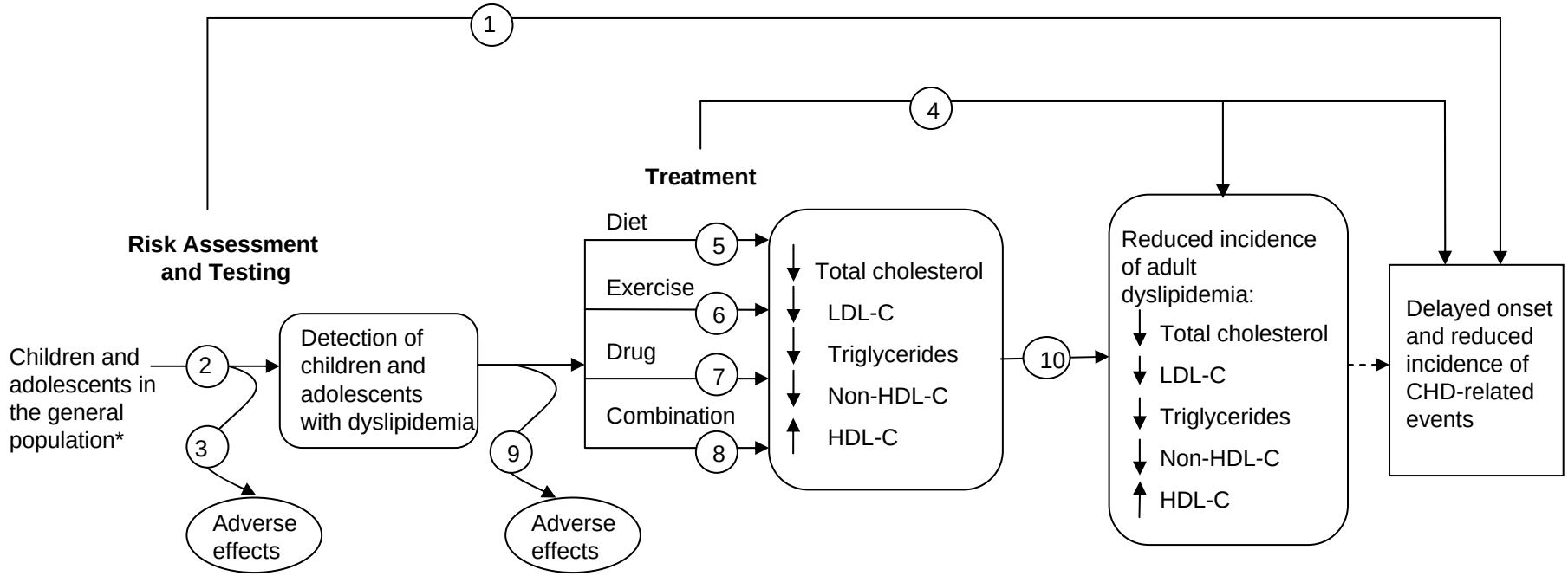


Figure 1. Defining the screening population.
Children and adolescents identified by screening include those with undiagnosed monogenic dyslipidemia, undiagnosed secondary dyslipidemia, and idiopathic (polygenic or risk factor driven) dyslipidemia. Children and adolescents with previously known monogenic or secondary dyslipidemia would be specifically evaluated for these indications and are not included in the screening pool for the general population.

Figure 2. Analytic framework and key questions.
The analytic framework represents an outline of the systematic evidence review and includes patient populations, risk assessment and testing, treatment, and outcomes. The key questions examine a chain of evidence about the accuracy, effectiveness, feasibility of screening asymptomatic children for dyslipidemia in primary care settings, adverse effects of screening, risk factors, effectiveness of interventions, and adverse effects of interventions.



Key Questions

1. Is screening for dyslipidemia in children/adolescents effective in delaying the onset and reducing the incidence of CHD-related events?
2. What is the accuracy of screening for dyslipidemia in identifying children/adolescents at increased risk of CHD-related events?
   - 2a. What are abnormal lipid values in children/adolescents?
   - 2b. What are appropriate tests? How well do screening tests (non-fasting total cholesterol, fasting total cholesterol, fasting lipoprotein analysis) identify individuals with dyslipidemia?
   - 2c. How well do lipid levels track from childhood to adulthood?
   - 2d. What is the accuracy of family history in determining risk?
   - 2e. What are other important risk factors?
   - 2f. What are effective screening strategies for children/adolescents (including frequency of testing, optimal age for testing)?
3. What are the adverse effects of screening (including false positives, false negatives, labeling)?
4. In children/adolescents, what is the effectiveness of drug, diet, exercise, and combination therapy in reducing the incidence of adult dyslipidemia, and delaying the onset and reducing the incidence of CHD-related events (including optimal age for initiation of treatment)?

5, 6, 7, 8. What is the effectiveness of drug, diet, exercise, and combination therapy for treating dyslipidemia in children/adolescents?

9. What are the adverse effects of drug, diet, exercise, and combination therapy in children/adolescents?
10. Does improving dyslipidemia in childhood reduce the risk of dyslipidemia in adulthood?

*Includes those without previously known conditions that cause dyslipidemia such as genetic dyslipidemia, diabetes, nephrotic syndrome, organ transplant, and others.

Appendix 1. U. S. Preventive Services Task Force quality rating criteria[1]

Diagnostic accuracy studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized controlled trials (RCTs) and cohort studies

Criteria:

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered

Appendix 1. U. S. Preventive Services Task Force quality rating criteria[1]

- Analysis: adjustment for potential confounders for cohort studies, or intension-to-treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case control studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Appendix 1. U. S. Preventive Services Task Force quality rating criteria[1]

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

Reference

1. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001; 20(3 Suppl):21-35.