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# Screening and Treatment for Lipid Disorders in Children and Adolescents: Systematic Evidence Review for the US Preventive Services Task Force

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## ABSTRACT

**OBJECTIVE.** This was a systematic evidence review for the US 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 that addressed 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 dyslipidemia 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, gender, and racial differences and temporal trends may alter these statistical cut points. Approximately 40% to 55% of children with elevated total cholesterol and low-density lipoprotein levels will continue to have elevated lipid levels on follow-up. Current screening recommendations based on family history will fail to detect substantial numbers (30%–60%) of children with elevated lipid levels. 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 lipid levels, but these results have not been sustained after the cessation of the intervention. The few trials of exercise are of fair-to-poor quality and show little or no improvements in lipid levels 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 issues 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 coronary heart disease or lipid outcomes, optimal ages and intervals for screening children, or effects of treatment of childhood lipid levels on adult coronary heart disease outcomes.

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### Key Words

dyslipidemia, children, adolescents, mass screening, cholesterol, interventions

### Abbreviations

TC—total cholesterol  
LDL-C—low-density lipoprotein cholesterol  
HDL-C—high-density lipoprotein cholesterol  
CHD—coronary heart disease  
FH—familial hypercholesterolemia  
FCH—familial combined hyperlipidemia  
AHA—American Heart Association  
USPSTF—US Preventive Services Task Force  
RCT—randomized, controlled trial  
LRC—Lipid Research Clinics  
AAP—American Academy of Pediatrics  
NCEP—National Cholesterol Education Program  
IMT—intima-media thickness

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**D**YSLIPIDEMIAS ARE DISORDERS of lipoprotein metabolism that result in abnormal excesses of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglyceride or deficiency of high-density lipoprotein cholesterol (HDL-C).<sup>1,2</sup> Dyslipidemia is an established risk factor for coronary heart disease (CHD), which is the leading cause of death for adults in the United States.<sup>3</sup> Dyslipidemia rarely leads to adverse health outcomes in childhood, but its long-term effects may be considerable. Although 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.<sup>4</sup> Children of parents with CHD have a higher prevalence of dyslipidemia in childhood,<sup>5</sup> and identification of dyslipidemia in children can identify families at increased risk for CHD.<sup>4</sup> Studies of children and young adults who died accidentally have reported correlations between lipid levels and arterial fat deposition<sup>6,7</sup> and noted early lesions of atherosclerosis (fatty streaks) in the abdominal aorta at 3 years of age, coronary arteries at 10 years of age, and further progression with age.<sup>8–12</sup> 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.<sup>13–15</sup>

Dyslipidemia is defined by laboratory testing and statistically determined criteria. An elevated LDL-C level 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 multifactorial), whereas 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 the age of 2 years or older.<sup>14</sup> Children younger than 2 years should not be prescribed a low-fat, low-cholesterol diet, because their rapid growth and development require adequate fat and cholesterol intake.<sup>16,17</sup> Children and adolescents with FH or FCH are the only nonadults for whom trials of drug therapy are available and drugs are approved by the US Food and Drug Administration. Bile-acid-binding resins are the only medications approved for treatment of dyslipidemia for children younger than 8 years of age. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins) are approved for use in older children with heterozygous FH.<sup>18,19</sup> 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, and 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 (eg, obesity and diabetes),<sup>13–15</sup> 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 to test children who have family members with dyslipidemia or premature CHD and those with unknown family histories.<sup>16,20</sup>

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. Our objective was 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 0 to 21 years old without previously known conditions associated with dyslipidemia. There is potential to identify children and adolescents with dyslipidemia in this population from among 3 groups: those with undiagnosed monogenic dyslipidemias such as FH; those with undiagnosed secondary causes of dyslipidemia (diabetes, nephrotic syndrome, hypothyroidism, others); and those with idiopathic dyslipidemia (polygenetic, risk factor-associated, or multifactorial) (Fig 1). Although children and adolescents with idiopathic dyslipidemia generally have less severe lipid-level 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<sup>21</sup> (Fig 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 his-

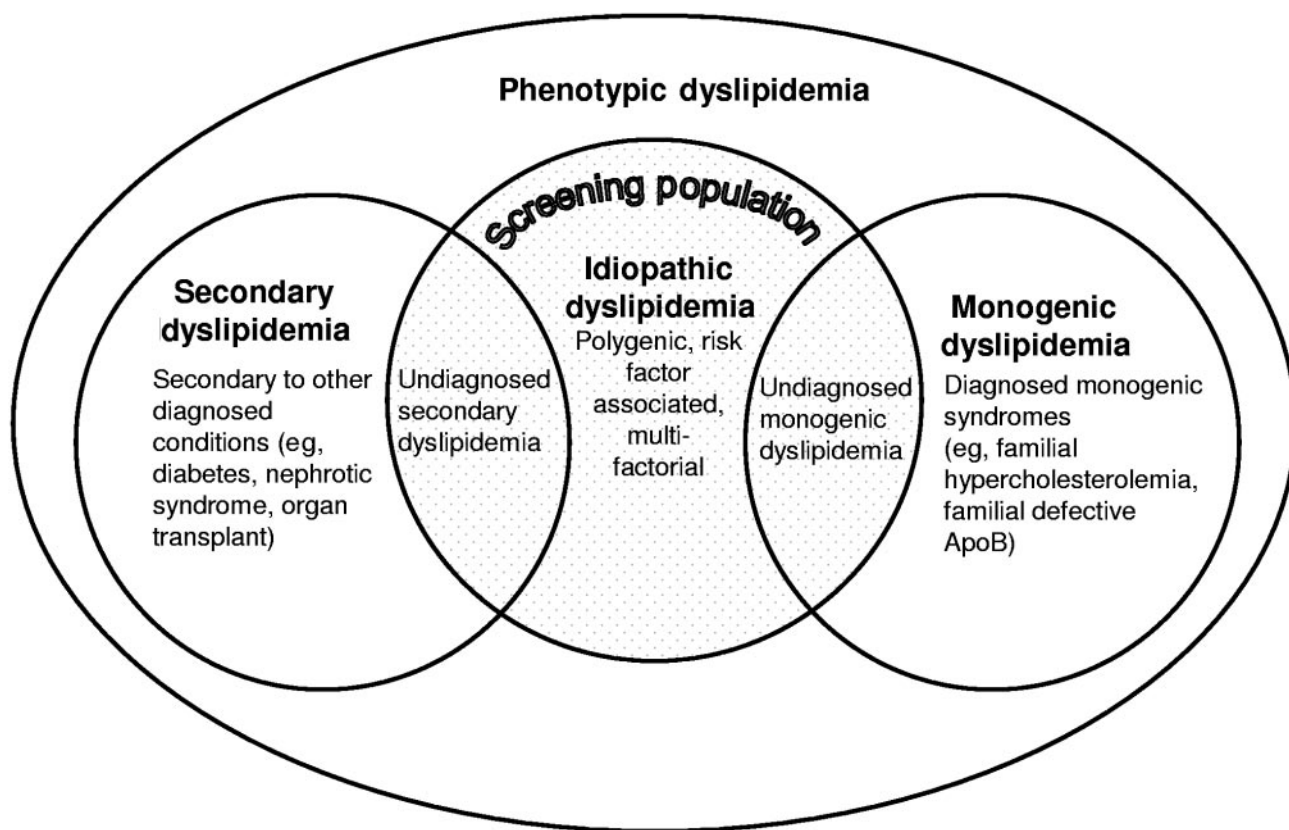


FIGURE 1

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.

tory (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 and 10), and adverse effects of screening and interventions (key questions 3 and 9).

Studies that addressed key question 1 (Fig 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 that allow determination of the effectiveness of the overall screening process.

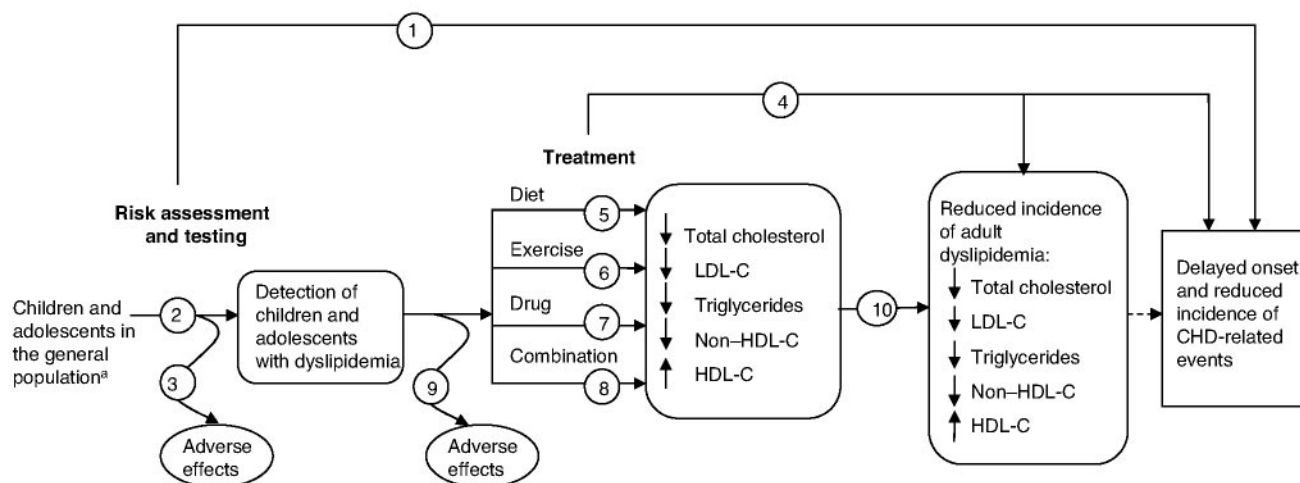
Studies of children with previously diagnosed conditions that are known to cause dyslipidemia were not included, because the scope of this review is screening children without known diagnoses. Specifically, studies of children with diabetes were not included, because these children would already be under surveillance for dyslipidemia as a result of their primary disease. This review includes treatment trials of children and adolescents who used 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).<sup>22</sup> We obtained additional articles from recent systematic reviews, reference lists of related studies, reviews, editorials, and Web sites and from consulting experts. Retrieved abstracts were entered into an electronic database (EndNote; Thomson ResearchSoft, Carlsbad, CA).

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 and applicable to US clinical practice and provided primary data relevant to the key questions. Studies of risk factors were included only if they provided multivariate adjusted analyses.

For treatment studies, full-text randomized, controlled trials (RCTs), noncontrolled clinical trials, and noncontrolled prospective studies that provided data on the treatment of children and adolescents with drug therapy, diet, exercise, or combinations of these interventions were reviewed initially. Subsequently, only RCTs and meta-analyses of RCTs that reported serum



### 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 the appropriate tests? How well do screening tests (nonfasting TC, fasting TC, fasting lipoprotein analysis) identify children/adolescents 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-positive and false-negative results, labeling, etc)?
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 – 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?

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. <sup>a</sup> Includes those without previously known conditions that cause dyslipidemia such as genetic dyslipidemia, diabetes, nephrotic syndrome, organ transplant, and others.

lipid outcomes were included. Crossover trials were included if they reported data before 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 nonrandomized, controlled treatment trials and noncomparative 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 by using USPSTF criteria<sup>21</sup> (Appendix).

## RESULTS

Our literature search identified 2507 unique citations including 144 articles 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-level 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?

Although several studies conducted in the United States during the 1970s obtained lipid levels from large samples of normal healthy children,<sup>23–25</sup> current recommendations<sup>14,16,20,26</sup> are based on distributions of lipid and lipoprotein levels obtained from the Lipid Research Clin-

ics (LRC) Prevalence Study.<sup>27</sup> This study included 1 Canadian and 9 US sites and enrolled subjects primarily on the basis of residency within census tracts, school enrollment, and employment in occupational and industrial groups. Fasting ( $\geq 12$  hours) lipoprotein levels were obtained from 15 626 children 0 to 19 years old between 1972 and 1976. The selected populations included a broad range of geographic, socioeconomic, occupational, gender, 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  $\sim 160$  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. Although the results for black children were similar, they were based on smaller numbers and provided only TC and triglyceride data.<sup>27</sup>

More recent data from the National Health and Nutrition Examination Survey III (1988–1994) were derived from 7499 children and adolescents aged 4 to 19 years. These data provided 95th-percentile levels of 216 mg/dL for serum TC and 152 mg/dL for LDL-C.<sup>28</sup> 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 ( $P[r] < .005$ ). Non-Hispanic black children and adolescents had significantly higher mean TC, LDL-C, and HDL-C levels compared with non-Hispanic white and Mexican-American children and adolescents. In linear regression models of these data, age, gender, and race have significant effects on lipid levels, which raises questions about the utility of fixed screening cut points.<sup>29</sup>

**Key Question 2b: What Are the Appropriate Tests? How Well Do Screening Tests (Nonfasting TC, Fasting TC, Fasting Lipoprotein Analysis) Identify Children and Adolescents With Dyslipidemia?**

In the American Academy of Pediatrics (AAP) and 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.<sup>16,20</sup> In children, the LDL-C level 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 6–19,  $n = 1325$ )<sup>30</sup> and data from the biracial Bogalusa cohort (ages 5–17,  $n = 2857$ ).<sup>31</sup> Elevated levels were defined as  $>95$ th percentile. With LRC data, an elevated fasting TC level identified children with elevated LDL-C and triglyceride levels with 69% sensitivity and 98% specificity.<sup>30</sup>

In the Bogalusa cohort, elevated TC levels detected elevated LDL-C levels with 44% (white females) to 50% (white males, black males and females) sensitivity and 90% specificity (black and white males and females).<sup>31</sup>

In adults, both TC and HDL-C levels are recommended for screening. Although this has not been recommended in guidelines for children and adolescents, it is common in practice (E. Neufeld, MD, PhD [Boston, MA], personal communication regarding screening tests for children, 2005). HDL-C may help distinguish false-negative from true-negative results when used with TC.<sup>30</sup> In 260 black adolescents aged 12 to 20 years, fasting TC minus HDL-C above the 95th percentile was 88% to 96% sensitive and 98% specific for predicting an LDL-C level of  $\geq 130$  mg/dL.<sup>32</sup> Using a lower threshold of fasting TC ( $\geq 75$ th percentile) to detect LDL-C levels  $\geq 95$ th percentile in a sample of Hispanic children aged 4 to 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).<sup>33</sup> A TC level of  $>215$  mg/dL is required, however, to accurately identify a child with elevated LDL-C levels with 95% confidence. No single TC value places a child in the borderline category (170–200 mg/dL) with 95% confidence.<sup>34</sup> Direct measurement of LDL-C levels can be made by using nonfasting serum samples and may be as precise as calculated LDL-C levels, but this remains controversial.<sup>35,36</sup>

**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.<sup>37–59</sup> These studies drew from 7 US cohorts and 8 non-US cohorts. Approximately 40% to 55% of children with elevated lipid levels, defined by percentile within a population distribution, will continue to have elevated lipid levels on follow-up (4–15 years later).<sup>22</sup> None of these studies, however, evaluated the proportion of children and adolescents with lipid levels  $>95$ th 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).<sup>32,33,60–73</sup> 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,<sup>33,62</sup> whereas parental or grandpar-

TABLE 1 Summary of Studies That Evaluated Sensitivity and Specificity of Family History

Author (Year)	Population		Method	Threshold <sup>a</sup>	Sensitivity, %	Specificity, %	No. Eligible for Screening (on the Basis of Population of 1000) <sup>b</sup>	No. Missed (on the Basis of Population of 1000) <sup>b</sup>
	N	Age						
Bell and Joseph <sup>60</sup> (1990)	1140	5th-graders	Family history of high cholesterol or MI at <60 y of age in parent or grandparent	Nonfasting TC >200 mg/dL	64	47	540	46
	1140	5th-graders	As stated above, plus family history of stroke, angina, or hypertension	Nonfasting TC >200 mg/dL	77	24	760	31
	1118	4th-graders	Family history from parents (regarding parents, siblings, grandparents, aunts, uncles); early MI defined as that at <56 y of age for men and women	TC >200 mg/dL	41	68	330	83
Davidson et al <sup>61</sup> (1991)	1118	4th-graders	Parental questionnaire; definition using AAP criteria for early CHD (<50 y for men, <60 y for women)	TC >200 mg/dL	31	66	330	96
	1214	4–10 y	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting TC ≥95th percentile	38 (W); 27 (B)	73 (W); 65 (B)	NA	NA
	2099	11–17 y	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting TC ≥95th percentile	59 (W); 25 (B)	67 (W); 56 (B)	NA	NA
Diller et al <sup>62</sup> (1995), Cincinnati MI Hormone Study	1214	4–10 y	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting LDL ≥95th percentile	41 (W); 20 (B)	73 (W); 63 (B)	NA	NA
	2099	11–17 y	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	Fasting LDL >95th percentile	37 (W); 22 (B)	67 (W); 56 (B)	NA	NA
	232	2–19 y	Parental questionnaire using NCEP definition of family history of premature CVD	LDL ≥130 mg/dL	17	75	246	207
Gagliano et al <sup>63</sup> (1993)	232	2–19 y	Parental questionnaire asking family history of cholesterol level >240 mg/dL	LDL ≥130 mg/dL	61	74	293	99
	232	2–19 y	Both family history of elevated cholesterol level and premature CVD	LDL ≥130 mg/dL	74	55	478	65
	232	2–19 y	Other indicators: obesity, smoking, use of lipid-raising medications, high-fat diet, HTN	LDL ≥130 mg/dL	17.4 (obesity); 9–48 (others)	86 (obesity); 69–95 (others)	547	86
	232	2–19 y	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 ≥130 mg/dL	96	28	746	13
	224	11–20 y	Family history of early MI (<50 y for men, <60 y for women) or elevated lipid levels (TC >200 mg/dL), history obtained from adolescent	TC >85th percentile for gender	36	69	320	94
Gagliano et al <sup>63</sup> (1993)	224	11–20 y	Family history as stated above, history obtained from parent	TC >85th percentile for gender	65	46	589	54
	224	11–20 y	Use of combined family history from adolescent and parent	TC >85th percentile for gender	45	69	361	80

TABLE 1 Continued

Author (Year)	Population		Method	Threshold <sup>a</sup>	Sensitivity, %	Specificity, %	No. Eligible for Screening (on the Basis of Population of 1000) <sup>b</sup>	No. Missed (on the Basis of Population of 1000) <sup>b</sup>
	N	Age						
Griffin et al <sup>64</sup> (1989), 8 office practices	1005	2–13 y	Parental and grandparental history of hypercholesterolemia or CHD at <55 y	Fasting LDL >95th percentile	46	NR	NA	147
	1005	2–13 y	Parental and grandparental history of any risk factor or complication (hypercholesterolemia, diabetes, HTN, gout, obesity, or atherosclerosis before age 55 y)	Fasting LDL >95th percentile	78	NR	NA	59
	1005	2–13 y	Parental and grandparental history of hypercholesterolemia or CHD at <55 y	Fasting LDL >90th percentile	51	63	385	48
	1005	2–13 y	Any history of parent or grandparent with a risk factor or complication (hypercholesterolemia, diabetes, HTN, gout, obesity, or atherosclerosis before age 55 y)	Fasting LDL >90th percentile	80, 38 (high cholesterol alone); 31 (obesity); 18 (sudden death); 17 (gout); 13 (PVD)	37	650	20
	1005	2–13 y	Overweight (weight for height >95th percentile) plus family history of early CHD or hypercholesterolemia	Fasting LDL >90th percentile	57	NR	NA	42
Muhonen et al <sup>65</sup> (1994), Muscatine, IA	1005	2–13 y	Overweight (weight for height >95th percentile) plus family history of any risk factor or complication	Fasting LDL >90th percentile	84	31.0	704	16
	599	14–20 y	Parental history of high cholesterol	Highest decile of fasting TC	34	76	NA	NA
	599	14–20 y	Parental history of high cholesterol	Highest decile of fasting LDL	34	76	NA	NA
	599	14–20 y	Parental history of high cholesterol	Lowest decile of fasting HDL	26	75	NA	NA
O'Loughlin et al <sup>72</sup> (2004), Quebec	2217	9, 13, and 16 y	Parental questionnaire asking personal history of (1) high cholesterol, (2) medications for cholesterol, (3) MI or 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
	2217	9, 13, and 16 y	Parental questionnaire asking personal history of (1) high cholesterol, (2) medications for cholesterol, (3) MI or 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
	2217	9, 13, and 16 y	Parental questionnaire asking personal history of (1) high cholesterol, (2) medications for cholesterol, (3) MI or angina, (4) stroke, CVD, or PVD, or (5) medications for the heart; unknown family history coded as negative	Fasting LDL ≥109 mg/dL ("borderline")	42	70	NA	85
	2217	9, 13, and 16 y	Parental questionnaire asking personal history of (1) high cholesterol, (2) medications for cholesterol, (3) MI or 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")	51	69	NA	19

TABLE 1 Continued

Author (Year)	Population		Method	Threshold <sup>a</sup>	Sensitivity, %	Specificity, %	No. Eligible for Screening (on the Basis of Population of 1000) <sup>b</sup>	No. Missed (on the Basis of Population of 1000) <sup>b</sup>
	N	Age						
Primrose et al <sup>16</sup> (1994), Ireland	1012	12–15 y	History of stroke, angina, or MI in either parent at any age or in first-degree grandparents, uncles, or aunts at <55 y; questionnaires completed by parents	Nonfasting TC >95th percentile according to LRC	33	72	293	125
Resnicow et al <sup>67</sup> (1993)	574	Elementary school age	Parental cholesterol $\geq$ 240 mg/dL in 1 parent only with known and reported value by that parent	Nonfasting TC >200 mg/dL	10	91	90	106
Rifai et al <sup>32</sup> (1996)	260 B	12–20 y	Family history of early CHD or hyperlipidemia	Fasting LDL >110 mg/dL	10	NR	365	184
Sanchez Bayle et al <sup>68</sup> (1992), Spain	2224	2–18 y	Parental history of MI	Fasting TC >200 mg/dL	7	96	49	140
	2224	2–18 y	Parental history of MI	Fasting LDL >135 mg/dL	9	96	49	101
	2224	2–18 y	Parental history of stroke, HTN, diabetes, or hypercholesterolemia (but not MI)	Fasting TC >200 mg/dL	14	90	98	129
	2224	2–18 y	Parental history of stroke, HTN, diabetes, or hypercholesterolemia (but not MI)	Fasting LDL >135 mg/dL	14	91	98	95
Shea et al <sup>33</sup> (1990), Study of Childhood Activity and Nutrition	108 Hispanic	4–5 y	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 Hispanic	4–5 y	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 Hispanic	4–5 y	NCEP guidelines (history of MI or sudden death in the child's parent, aunt, uncle, or grandparent; CHD before age 55 y).	Fasting TC >170 mg/dL	5	92	74	324
Streiner et al <sup>69</sup> (1991), Kaiser population	1001 (38% Hispanic, 33.5% W, 15% B, 11% Asian)	12–21 y	AAP 1998 criteria (known hyperlipidemia in parent or sibling, known MI/angina, current corticosteroid use, juvenile diabetes, hypothyroidism, renal/endocrine/hepatic disease in teenager)	Nonfasting TC $\geq$ 200 mg/dL, repeated fasting TC if initial result was $\geq$ 200 mg/dL, repeated a third time if >30 mg/dL variability between the first 2 measurements	63	60	400	24
Troxler et al <sup>70</sup> (1991)	110, mostly Hispanic	Senior high school students	Questionnaires completed with parental assistance; family history in parents or grandparents of high cholesterol or CHD at <55 y (AAP)	Fasting TC >75th percentile (175 mg/dL)	38	79	218	245
Wadowski et al <sup>73</sup> (1994)	300 B	2–14 y	Family history of CHD in parent or grandparent at <55 y	Fasting TC >215 mg/dL	59	72	327	23

MI indicates myocardial infarction; HTN, hypertension; CVD, cardiovascular disease; PVD, peripheral vascular disease; NA, not applicable; NIH, National Institutes of Health; W, white; B, black.

<sup>a</sup> If not explicitly stated, values are mixed nonfasting/fasting or not reported.

<sup>b</sup> Number eligible for screening and number missed were calculated from available data. In some cases, reported data did not allow for these calculations (indicated with NA).

ental history of early CHD was 46% sensitive for LDL >95th percentile.<sup>64</sup>

Regardless of the precise definition, using positive family-history information to trigger lipid testing misses substantial numbers of children with elevated lipid levels, ranging from 17% to 90% overall and 30% to 60% in most studies.<sup>32,63,64,67,69,71,74–76</sup> The proportion of children and adolescents who qualify for screening on the basis of family history is generally between 25% and 55% depending on the sensitivity of the specific family-history question.\*

#### *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 lipid levels and/or CHD-related events.<sup>65,78–119</sup> Thirty studies examined overweight or body fat composition measures as a risk factor for dyslipidemia.† These measures were the most consistently effective in predicting risk of dyslipidemia compared with other factors assessed.<sup>22</sup> Childhood overweight, as measured by BMI, was the best independent predictor of adult dyslipidemia after LDL-C level, specifically when considering BMI increases from childhood to adulthood.<sup>120</sup> Of 6 studies that evaluated overweight as a risk, 5 found that overweight was associated with abnormal lipid levels.<sup>84,85,93,109,114,116</sup>

#### *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.‡ The only RCT compared 2 regimens for screening college students.<sup>130</sup> All others were noncomparative prospective studies that described screening interventions and differed considerably in venue (school, pediatric clinic, hospital, or population-based cohort), methods (fasting or nonfasting samples, method for detecting positive family history), and outcomes. Most of them reported low parental compliance with follow-up testing<sup>75,135–138</sup> even when follow-up was provided free of charge, as in prepaid health plans.

Studies demonstrated low compliance among primary care physicians in following current guidelines for screening.<sup>139</sup> In an ancillary study of the Child Adolescent Trial for Cardiovascular Health (CATCH), parents were given recommendations to consult their child's physician if his or her TC level exceeded 200 mg/dL on  $\geq 1$  occasion.<sup>140</sup> After physicians examined the children, only 59% were evaluated further for possible elevated cholesterol levels. 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.<sup>140</sup>

Neonatal screening for dyslipidemia has been examined in multiple studies of cord blood testing,<sup>53,141–154</sup> dried filter paper blood spots from cord blood,<sup>155</sup> or heel sticks of 3- to 7-day-old infants.<sup>156–161</sup> No studies screened a general population of infants and followed abnormal results with mutation analysis or LDL-C receptor activity assays, which makes it difficult to determine the value of such screening.

#### **Key Question 3: What Are the Adverse Effects of Screening (Including False-Positive and False-Negative Results, Labeling, etc)?**

Potential adverse effects of screening for dyslipidemia among children were examined in 1 RCT<sup>162</sup> and 5 non-comparative studies.<sup>75,135–138</sup> Although 1 small study showed increased parental reporting of behavior difficulties among children with dyslipidemia, these reports were not confirmed objectively.<sup>138</sup> No studies reported increased anxiety or depression among screened children or their parents.<sup>136–138</sup>

#### **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 that met the inclusion criteria addressed the effectiveness of interventions for treatment of dyslipidemia in children and adolescents.<sup>18,19,163–200</sup> 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.§ Major limitations of trials include <20 subjects in each study arm,|| high loss to follow-up,<sup>176,186,190</sup> failure of blinding,<sup>173,190,191,195–197</sup> lack of results presented for the period before crossover,¶ lack of intention-to-treat analyses,# and lack of data reported for the placebo group.<sup>178</sup>

#### *Studies in Children With Probable or Definite FH*

##### *Drug Treatment*

Eleven trials evaluated drug therapies for treatment of children with probable or definite heterozygous FH (Ta-

\*Refs 32, 33, 60–64, 66, 69, 70, 72, and 77.

†Refs 78–81, 83–85, 88–94, 98, 100–103, 105–111, 113, 114, 116, and 118.

‡Refs 32, 33, 60, 62–65, 67, 69, 71, 75, 76, and 121–140.

§Refs 18, 164–168, 175, 177, 178, 180, 181, 184, 185, 188, 190, 192, 195, and 201.

||Refs 167, 174, 177, 180, 181, 184, 192, and 194.

¶Refs 165–167, 175, 177, 179–181, 184, 188, 189, 191, 194, 197, 198, and 200.

#Refs 163, 165, 176–179, 181, 183, 186, 188, 190–193, and 195–197.

**TABLE 2 RCTs of Drug Treatment for Children With Monogenic Dyslipidemia**

Author (Year)	Drug	Population		Duration of Trial	Significant Changes vs Control				
		N	Age, y		TC	HDL	LDL	TG	Quality Rating
Statins									
Clauss et al <sup>19</sup> (2005)	Lovastatin 20 vs 40 mg/d vs placebo	54 girls	11–18	24 wk	↓	○	↓	○	Good
Couture et al <sup>178</sup> (1998)	Simvastatin 20 mg/d vs placebo	63	8–17	6 wk	↓	↑	↓	↓	Fair
de Jongh et al <sup>164</sup> (2002)	Simvastatin 10 mg/d, doubled every 8 wk up to 40 mg/d vs placebo	50	9–18	28 wk	↓	NR	↓	↓	Poor
de Jongh et al <sup>187</sup> (2002)	Simvastatin 10 mg/d titrating up to 40 mg/d vs placebo	173	10–17	48 wk	↓	NR	↓	NR	Good
Knipscheer et al <sup>172</sup> (1996)	Pravastatin in 3 active drug groups, 5, 10, or 20 mg/d, vs placebo	72	11–17	12 wk	↓	○	↓	○	Good
Lambert et al <sup>183</sup> (1996)	Lovastatin at 10, 20, 30, or 40 mg/d (4 active drug groups, no placebo)	69 boys	≤17	8 wk	↓	↑	↓	NR	Fair
McCrintle et al <sup>168</sup> (2003)	Atorvastatin 10 mg/d vs placebo	187	10–17	26 wk	↓	↑	↓	↓	Good
Stein et al <sup>171</sup> (1999)	Lovastatin starting at 10 mg/d, titrating to 40 mg/d vs placebo	132 boys	10–17	48 wk	↓	○	↓	○	Good
Wiegman et al <sup>18</sup> (2004)	Pravastatin 40 mg/d vs placebo	214	8–18	2 y	↓	○	↓	NR	Good
Bile-acid-binding resins									
Tonstad et al <sup>185</sup> (1996)	Colestipol 10 g/d or 5 g twice daily vs placebo	66 adolescents	NR	8 wk	↓	○	↓	○	Poor
Tonstad et al <sup>186</sup> (1996)	Cholestyramine titrating up from 4 to 8 g/d vs placebo	96 boys	6–11	1 y	↓	○	↓	○	Fair

NR indicates not reported; TG, triglycerides; ↑, significant increase; ↓, significant decrease; ○, no significant change.

ble 2).\*\* Most of these studies 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†† demonstrated improvement in TC and LDL-C levels among children and adolescents with FH. The decrease in TC compared with baseline ranged from 17% to 32% for subjects in the treatment groups versus changes of +3.6% to −2.3% for those in the placebo groups. The decreases in LDL-C level ranged from 19% to 41% for subjects in the treatment groups versus changes of +0.67% to −3% for those in the placebo groups. Changes in HDL-C and triglyceride levels were mixed.‡‡

Trials of cholestyramine<sup>186</sup> and colestipol<sup>185</sup> demonstrated decreased TC and LDL-C levels but no change in HDL-C or triglyceride levels. Trials that evaluated bezafibrate,<sup>192</sup> vitamins C and E,<sup>181</sup> docosahexaenoic acid,<sup>198,200</sup> *p*-aminosalicylic acid,<sup>184</sup> combined colestipol and pravastatin versus colestipol alone,<sup>165</sup> and powder versus pill form of cholestyramine<sup>173</sup> failed to report precross-over data.

#### Diet Treatment

Five trials that evaluated diet treatments in children with FH or FCH met inclusion criteria.<sup>166,167,177,179,199</sup> Although trials of sterol margarines and psyllium were crossover trials without precrossover results presented, the wash-out periods between treatment phases were 4

to 6 weeks, suggesting that results may be valid.<sup>166,177,179</sup> Reductions in TC and LDL-C levels were significant in these trials (reduction of 7.4%–11% and 10%–14%, respectively). There was no significant improvement in lipid levels with 8 weeks of treatment with garlic extract.<sup>199</sup>

#### Exercise Treatment

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

#### Studies in Children With Elevated Lipid Levels but Not Meeting Criteria for FH

##### 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 7 studies (Table 3).§§ A trial conducted by the Dietary Intervention Study in Children (DISC) Collaborative Research Group showed that intensive dietary counseling over 3 years was effective (8% improvement in LDL-C level compared with control)<sup>170</sup> but not sustained at 5- and 7-year follow-ups once the intervention ceased.<sup>169</sup> A study of the Parent-Child AutoTutorial (PCAT) program<sup>173</sup> reported 8% improvement in LDL-C level compared with the at-risk control group ( $P < .05$ ). One trial of psyllium did not present precrossover data.<sup>80</sup>

\*\*Refs 18, 19, 162, 166, 169, 170, 176, 181, and 183–185.

††Refs 18, 19, 164, 168, 171, 172, 178, 183, and 187.

‡‡Refs 164, 168, 171, 172, 178, 183, and 187.

§§Refs 169, 170, 173, 189, 190, 193, and 195.

**TABLE 3 RCTs of Diet and/or Exercise for Children and Adolescents Without Monogenic Dyslipidemia**

Author (Year)	Intervention(s)	Population		Duration of Trial	Significant Changes vs Control					Quality Rating
		N	Age		TC	HDL	LDL	TG		
Diet										
DISC Collaborative Research Group <sup>170</sup> (1995) Gold et al <sup>195</sup> (1991)	Family-oriented behavioral intervention to promote dietary adherence vs usual care	663	8–10 y	3 y	↓	↓ (year 1 only)	↓	○	Good	
	Oat bran-supplemented cereal within AHA Step 1 diet vs cereal within Step 1 diet and no oat bran	49 with TC > 185 mg/dL	10 y (mean)	4 wk	NR	○	○	○	Poor	
	Four 90-min family-oriented nutrition sessions vs one 90-min session	295 with TC > 185	2–15 y	16 wk	○	○	○	○	Poor	
Kuehl et al <sup>189</sup> (1993)	Counseling intervention (same as DISC above) vs usual care	663	8–10 y	4 y (7 y total follow-up)	○	○	○	○	Good	
Obarzanek et al <sup>169</sup> (2001)	PCAT: 10 talking-book lessons and follow-up paper and pencil games for children with a manual for parents vs 45- to 60-min counseling session with parent, child, and registered dietitian and take-home print materials for both child and parents vs usual care	261 with elevated LDL	4–10 y	3-mo follow-up	NR	NR	↓	NR	Good	
Shannon et al <sup>173</sup> (1994)	PCAT: 10 sessions total, 1 per week completed in home by child and parents vs usual care	44 with LDL 90th–99th percentile	4–10 y	6 mo	NR	NR	○	NR	Poor	
Stallings et al <sup>190</sup> (1993)	Fiber cereal with 3.2 g of soluble fiber per serving (dose = 1 box of cereal per d for 3 wk, then 2 boxes per d), with children aged 2–5 y consuming only 1 box per d throughout study, compared to placebo cereal with 0.5 g of fiber	58 with TC > 170 mg/dL and LDL > 110 mg/dL	2–11 y	12 wk	↓	○	↓	○	Poor	
Exercise										
Boreham et al <sup>194</sup> (2000) Ferguson et al <sup>182</sup> (1999)	7-wk stair-climbing program vs no change in activity Exercise program 5 d/wk, 40 min/d (children were paid \$1 per session and given prizes for maintaining a heart rate >150 beats per min) vs no exercise program	25 sedentary females 81 obese children	18–22 y 9.5 y (mean)	7 wk 4 mo	○ ○	↑ <sup>a</sup> ↑	NR ○	NR ↓	Poor Fair	
Kang et al <sup>188</sup> (2002)	Physical activity training with lifestyle intervention 5 d/wk vs lifestyle intervention alone	80 obese children	13–16 y	8 mo	○	○	○	↓	Poor	
Linder et al <sup>196</sup> (1983) Savage et al <sup>197</sup> (1986)	Physical conditioning program vs usual activities Walking/jogging/running 3 d/wk (1.6 km per session) high intensity (heart rate = 75% of V <sub>O<sub>2</sub>max</sub> ) vs low intensity (heart rate = 40% of V <sub>O<sub>2</sub>max</sub> )	50 healthy boys 663 boys	11–17 y 8–9 y (mean)	8 wk 11 wk	○ NR	○ NR	○ ○	○ ○	Fair Fair	
Stergioulas et al <sup>191</sup> (1998) Diet and Exercise	Four 60-min sessions per wk vs no specific training program	58 sedentary boys	10–14 y	2 mo	NR	○	NR	NR	Poor	
Becque et al <sup>174</sup> (1988)	(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 min for 3 d/wk; and (3) no change in activity or diet	36 overweight adolescents	13 y (mean)	20 wk	○	↑	○	○	Fair	
Epstein et al <sup>163</sup> (1989)	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 et al <sup>176</sup> (1985)	"Know Your Body" curriculum yearly, taught 2 h/wk by usual classroom teacher, vs standard curriculum	1115	4th-graders	1 y	○	○	NR	NR	Fair	

↑ indicates significant increase; ↓, significant decrease; ○, no significant change; DISC, Dietary Intervention Study in Children; PCAT, Parent-Child Auto Tutorial Program; NR, not reported; TG, triglycerides.  
<sup>a</sup> This trial reported significant pre-experimental differences between groups in HDL levels ( $P < .05$ ).

### Exercise Treatment

Six studies<sup>182,196,197,188,191,194</sup> evaluated exercise in normal-weight or obese children with elevated lipid levels (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).<sup>188,191,194</sup> Four trials that compared supervised, scheduled sessions of aerobic and fitness training to control groups showed minimal or no change in lipid levels compared with control groups.<sup>188,191,196,197</sup> Two trials showed improvements in HDL-C for the exercise-intervention group compared with controls.<sup>182,194</sup>

### Combination Diet and Exercise Treatment

Three trials<sup>174,176,163</sup> evaluated combined regimens of diet and exercise (Table 3). Although all the interventions showed some improvement in lipid levels, a group that undertook exercise, diet, and behavior changes had a 23% increase in HDL-C levels compared with both the diet-plus-behavior-change group and the control group.<sup>174</sup>

## 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,<sup>||</sup> 22 studies of bile-acid-binding resins,<sup>165,175,185,186,208–226</sup> and 8 studies of various other drugs or drug combinations<sup>26,184,192,227–231</sup> (Table 4). Studies used RCT, open-label-trial, and observational designs.

Statins were associated with increased alanine aminotransferase and/or aspartate aminotransferase levels in some,<sup>168,187,203,206</sup> but not all,<sup>18,164,202,204</sup> of these studies. Reports of elevated creatine kinase levels were similarly conflicting.<sup>¶¶</sup>

Bile-acid-binding resins were associated with gastrointestinal complaints (8%–26%), such as flatulence and constipation,<sup>##</sup> and unpalatability (up to 50%).<sup>211,215–218,221,223</sup> One study of cholestyramine reported transient increases in lactate dehydrogenase and abnormalities in aspartate aminotransferase levels that persisted for 6 months,<sup>210</sup> but others showed normal liver-function test results.<sup>223,225,226</sup> Growth was reported to be normal in 9 studies.<sup>\*\*\*</sup> One study reported a child whose height for age dropped below –2 SD while on colestipol (1 SD = 2.4 cm),<sup>212</sup> whereas 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.<sup>224</sup>

Two studies of niacin reported increased liver enzyme levels (6 of 21 children in 1 study) and multiple other symptoms such as flushing, abdominal pain, nausea, and headache.<sup>228,230</sup> There are also case reports of hepatitis<sup>228</sup> and hepatotoxicity<sup>230</sup> with the use of niacin.

|| |||Refs 18, 19, 164, 168, 171, 172, 178, 183, 187, and 202–207.

¶¶¶Refs 18, 164, 171, 172, 183, 187, 202–204, and 206.

##Refs 165, 175, 184–186, 210, 213, 215, 217, 222, 223, 228, and 229.

\*\*\*Refs 26, 185, 186, 192, 214, 219, 220, 224, and 226.

### Low-Fat Diet

Nineteen studies of dietary fat restriction reported effects on growth, nutrient intake, laboratory safety parameters, or other adverse effects.<sup>169,170,189,232–247</sup>

Twelve studies reported normal height growth,<sup>+++</sup> although weight loss occurred among 3 children in 2 of these studies.<sup>234,241</sup> In 1 study, growth failure occurred in 8 (20%) of 40 children with dyslipidemia, 3 (7.5%) of whom had nutritional dwarfing and no progression of puberty.<sup>240</sup> 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.<sup>240</sup> Failure to thrive has been demonstrated in children under 2 years of age who eat fat-restricted diets<sup>248</sup>; these diets are not recommended for children in this age group.<sup>16</sup>

### Dietary Supplements

Fourteen studies provided information about adverse effects of various dietary supplements.<sup>167,177,180,199,249–258</sup> Two children (4% of the treatment group) reported abdominal discomfort using fiber tablets (containing 50% wheat bran and 50% pectin) administered at 100 to 150 mg/kg per day.<sup>180,252,255</sup> There were no adverse effects with psyllium fiber in 2 other studies.<sup>180,252</sup> Other adverse effects of dietary supplements were mild or transient.<sup>22</sup>

### 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.<sup>259</sup> In another study, treadmill tests elicited an exaggerated blood-pressure response in boys with dyslipidemia.<sup>260</sup>

## 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 resolved the various aspects of dyslipidemia in children, few key questions about screening have been addressed (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 dyslipi-

+++Refs 169, 189, 233–235, 238, 239, 241, 242, and 244–246.

**TABLE 4 Adverse Effects Reported in Studies of Statins, Bile-Acid–Binding Resins, and Other Drugs and Combinations**

Author, year, title	Drug	Population		Duration of Trial	Adverse Effects of Treatment	
		N	Age		Clinical Effects	Laboratory Effects
Statins						
McCrindle et al <sup>168</sup> (2003)	Atorvastatin	187	10–17 y	26 wk	None observed; no effect on sexual development	Increased AST and ALT levels (1% of patients); none withdrew or stopped medication as a result of increased transaminase levels
Clauss et al <sup>119</sup> (2005)	Lovastatin	54 girls	10–17 y	24 wk	Abdominal pain (2), diarrhea (1), nausea (1), headache (1), and amenorrhea (1), all resolved with patient continuing medication	Transient decreased HCT
Lambert et al <sup>183</sup> (1996)	Lovastatin	69 boys	<18 y	8 wk	None observed	Asymptomatic elevations in CK level (3)
Stein et al <sup>171</sup> (1999)	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 level; ALT level increased in placebo and treatment groups; DHEAS increased; tocopherol, CD3, CD4, and CD8 counts decreased
Wiegman et al <sup>118</sup> (2004)	Pravastatin	214	8–18 y	2 y	No effect on growth or sexual development	No effects on muscle or liver enzyme levels.
Hedman et al <sup>202</sup> (2003)	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), and muscle tenderness or pain associated with physical training (1)	No effects on serum ALT, CK, or creatinine levels
Knipscheer et al <sup>172</sup> (1996)	Pravastatin	72	12 y (mean)	12 wk	Rash, nose-bleeding, headache, nausea/vomiting, and abdominal pain	CK level abnormal in placebo (8), 5 mg/d (6), 10 mg/d (11), and 20 mg/d groups (8); cortisol level abnormal in placebo (2), 5 mg/d (2), 10 mg/d (5), and 20 mg/d (3) groups
Couture et al <sup>178</sup> (1998)	Simvastatin	63	8–17 y	6 wk	None observed	NR
de Jongh et al <sup>164</sup> (2002)	Simvastatin	69	9–18 y	28 wk	None observed	No significant effects on ALT, AST, and CK levels
de Jongh et al <sup>187</sup> (2002)	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), and pruritus (1)	Increased ALT (3), AST (3), and CK (1) levels
Dirisamer et al <sup>203</sup> (2003)	Simvastatin	20	10–17 y	18 mo	Transient headache (2), myalgia (1) for 2 wk, and transient gastrointestinal complaints (2)	Slightly higher values of CK (2); transiently elevated ALT level and glucose challenge test (1)
Ducobu et al <sup>206</sup> (1992)	Simvastatin	32	<17 y	24–36 mo	No effect on growth	Transient increases in transaminase (1) and CK (2) levels
Srefanutti et al <sup>207</sup> (1999)	Simvastatin	16	7–12 y	12 mo	None observed	NR
Various or unspecified statins	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 level in 3 subjects; no increase in liver enzyme levels
Sinzinger and O'Grady <sup>204</sup> (2004)	Various statins	69	10–18 y	NR	None observed	NR
De Jongh et al <sup>205</sup> (2003)	Cholestyramine	1	7 y	2 y	Loss of dental enamel noted (presumed caused by low pH 2.4 of cholestyramine mixed with Kool-Aid for administration)	Serum calcium, phosphorus, folate, and B <sub>12</sub> levels were within the reference ranges
Bile-acid-binding resins	Cholestyramine	20	4–23 y	16 d	Febrile gastroenteritis (1) after 7-d treatment resulting in discontinuation of therapy	Serum folate level decreased significantly in females; AST-level increases (2) persisted 6 mo; transient LDH increases (2); no fat-soluble vitamin malabsorption
Curtis et al <sup>208</sup> (1991)						
Farah et al <sup>209</sup> (1977) and Farah et al <sup>210</sup> (1977)						

TABLE 4 Continued

Author, year, title	Drug	Population		Duration of Trial	Adverse Effects of Treatment	
		N	Age		Clinical Effects	Laboratory Effects
Glueck et al <sup>226</sup> (1973)	Cholestyramine	36	7–21	6 mo	None observed; normal growth	None observed
Glueck et al <sup>225</sup> (1974)	Cholestyramine	30 on diet + BBR	5–21 y	6-mo average follow-up	NR	Plasma vitamins A and E levels remained within the reference ranges
Glueck et al <sup>223</sup> (1977)	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); dropouts after 2 y resulting from palatability	No effect on CBC, liver-function test results, or vitamin A and E; calcium, phosphorus, serum urea nitrogen, or fasting blood sugar levels
Glueck et al <sup>224</sup> (1986)	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
Koletzko et al <sup>214</sup> (1992)	Cholestyramine	35 on diet; 14 on diet + BBR	2–17 y	Mean: 17.5 mo (diet) and 27.9 mo (diet + BBR)	None observed; no effect on growth	NR
Liacouras et al <sup>215</sup> (1993)	Cholestyramine	87	10.6 y (mean)	Up to 62 mo	Nausea (12), abdominal bloating (2), and severe constipation (1); poor palatability (73%)	No elevated prothrombin times
McCrindle et al <sup>175</sup> (1997)	Cholestyramine	40	10–18 y	28 wk	Minor gastrointestinal complaints were frequent but did not result in any dropout	NR
Tonstad et al <sup>186</sup> (1996)	Cholestyramine	96	6–11 y	1 y	No effect on growth; 1 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 multivitamin
Tonstad et al <sup>218</sup> (1998)	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 and Lloyd <sup>219</sup> (1973)	Cholestyramine	19	1–14 y	Up to 20 mo	Some had impaired fat absorption without diarrhea; growth was normal	Serum folate level decreased in all patients
West and Lloyd <sup>220</sup> (1975)	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 et al <sup>221</sup> (1975)	Cholestyramine	45	1–16 y	2–8 y	Adherence was poor because of unpalatability	Folate deficiency, steatorrhea, and reduction in serum levels of vitamins A and E and of inorganic phosphorus, although not to abnormally low values
West et al <sup>222</sup> (1980)	Cholestyramine	35	1–17 y	1–8 y	Nausea, dizziness, and malaise in an 18-y-old female; 1 boy died of intercurrent infection 10 mo after starting treatment (not stated whether death was related to treatment); transient gastric fullness	NR
Groot et al <sup>211</sup> (1983)	Colestipol	33	NR	16 wk	Withdrawals because of unpalatability (5)	NR
Hansen et al <sup>213</sup> (1992)	Colestipol	30	1–17 y	8.5 y (diet); 5.5 y (diet followed by diet + BBR)	1 child's height/age decreased below –2 SD; growth was normal in other children	NR
Harvengt and Desager <sup>213</sup> (1976)	Colestipol	3	6–18 y	Up to 36 mo	Mild gastrointestinal complaints (flatulence, constipation) during first 3 mo but disappeared despite continued treatment	Low iron level without anemia (1); serum uric-acid level increased during treatment but did not reach abnormal values

TABLE 4 Continued

Author, year, title	Drug	Population		Duration of Trial	Adverse Effects of Treatment		
		N	Age		Clinical Effects	Laboratory Effects	
McCindle et al <sup>165</sup> (2002)	Colestipol	40	9–18 y	36 wk	Constipation (18%), stomachache (21%), headache (11%), and muscle aches (6%)	NR	
Schwarz et al <sup>166</sup> (1980)	Colestipol	23	5–17 y	Up to 24 mo	Poor palatability (6); Raynaud disease phenomenon occurred during therapy (1), but treatment continued without recurrence	Serum vitamins A and E levels decreased significantly after 18–24 mo of colestipol	
Tonstad et al <sup>165</sup> (1996)	Colestipol	66	13.2 y (mean)	52 wk	Gastrointestinal adverse effects (8) including constipation, dyspepsia, flatulence, nausea, decreased appetite, and abdominal pain; growth was normal	Reduced serum folate level after 8 wk; decreased serum vitamin E and carotenoid levels; decreased vitamin D levels (not significant) in subjects who were more compliant after 1 y	
Tonstad and Ose <sup>217</sup> (1996)	Colestipol	27	10–16 y	6 mo (colestipol); 6 y (mean; for diet)	No effect on growth; difficulty swallowing the tablets (2), flatulence (1), and abdominal discomfort (1)	NR	
Other drugs and combinations							
Baker et al <sup>166</sup> (1982)	Probuco	7	6–21 y	15–21 mo	Nausea in 1 patient; no effect on growth and development	None observed	
Becker et al <sup>227</sup> (1992)	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%) levels; bezafibrate: ALP level remained lower, and iron increased by 26%; combination: transferrin increased 20% and reached abnormal levels in 2, and all other laboratory values were within reference ranges	
Colletti et al <sup>228</sup> (1993)	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%), and hepatitis (1)	Dose-related, reversible serum aminotransferase level elevations [6 [4 with crystalline and 2 with sustained-release form of niacin]]	
Malloy et al <sup>164</sup> (1978)	<i>p</i> -aminosalicylic 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; thyrotropin and thyroxine levels within the reference ranges	
McDuffie et al <sup>229</sup> (2002)	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 <sup>230</sup> (1989)	Diet + drug or combined drugs: BARR; BARR + niacin; lovastatin or simvastatin	30	1–20 y	1–9 y	None observed	Resin + niacin together produced elevated AST and ALT levels, decreased albumin levels, and clinical symptoms of hepatotoxicity (1)	
Steinmetz et al <sup>231</sup> (1981)	Fenofibrate	17	4–19 y	18 mo	NR	Increased ALT and AST (4) levels; decreased uric acid, bilirubin, inorganic phosphates, ALP, and GGT levels	
Wheeler et al <sup>192</sup> (1985)	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 level (1) and transient rise in ALT level (1)	

(No.) indicates the number of participants who experienced the effect; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BARR, bile-acid-binding resin; CBC, complete blood count; CK, creatine kinase; DHEAS, dehydroepiandrosterones; GGT,  $\gamma$ -glutamyl transpeptidase; HCT, hematocrit; LDH, lactate dehydrogenase; NR, not reported.

**TABLE 5** Summary of Evidence

Arrow	Key Question	Quality of Evidence	Conclusions
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/adolescents at increased risk of CHD-related events?	See subquestions below	See subquestions below
2a	What are abnormal lipid values in children?	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 $\geq$ 190 mg/dL or LDL $\geq$ 160 mg/dL with family history of early CHD), additional evaluation, diet therapy and testing (LDL $>$ 130 mg/dL), and diet therapy with increased surveillance (LDL = 110–129 mg/dL) are recommended.
2b	What are the appropriate tests? How well do screening tests (nonfasting TC, fasting TC, fasting lipid analysis) identify children/adolescents 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 $>$ 95th percentile predicts LDL $>$ 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 lipid levels (by percentile) will continue to have elevated lipid levels on follow-up.
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 lipid levels and family history and overweight. There is inadequate evidence to show the magnitude of the effect of overweight on lipid levels 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-positive and false-negative results, labeling, etc?	Fair	Studies demonstrate lack of parental compliance with screening and follow-up recommendations. Reasons for noncompliance 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.

TABLE 5 Continued

Arrow	Key Question	Quality of Evidence	Conclusions
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
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 levels in children with FH. It is not clear how this efficacy translates to children with milder and/or nonfamilial forms of dyslipidemia. Diet supplements (psyllium, oat, sterol margarine) and counseling were marginally effective both in children and adolescents with FH/FCH 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 noncontrolled 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 liver enzymes (aspartate aminotransferase, alanine aminotransferase) and CK levels. Bile-acid-binding resins were associated with adverse gastrointestinal effects and decreased levels of serum vitamins and minerals. Low-fat diets have 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 >2 y old on monitored low-fat diets. Few adverse effects other than elevated blood pressure were noted with exercise. The duration of follow-up in these studies ranged from 10 d to 8 y. 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

CK indicates creatine kinase; LFT, liver-function test; TG, triglycerides.

demia in children and adolescents reduces the risk of adult dyslipidemia (key question 10).

Studies that evaluated risk factors are also limited. Risk factors that might contribute to a risk-assessment tool have not been studied adequately. 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, has 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 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 studied adequately.

Drug treatments for dyslipidemia in children have been studied only in children with FH or FCH, the population for whom these drugs are Food and Drug Administration–approved and recommended by the NCEP. Statins are effective for reducing TC and LDL-C levels in children with FH; it is not clear how this efficacy translates to children with milder and/or nonmonogenic 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 noncontrolled 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 lipid levels 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 who require serum lipid testing. New vascular markers such as apolipoprotein B and apolipoprotein A-I may prove to be useful for screening in children.<sup>261,262</sup> There is a growing literature on noninvasive 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 seem to correlate with lipid measurements taken in childhood.<sup>263–266</sup> Additional 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 in terms of both 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 assess the efficacy and safety of treatment options. The effect of exercise on lipid levels should be evaluated further, particularly in children with lipid levels >95th percentile. Standardized methods for collecting and reporting adverse effects in treatment trials would facilitate combining data across trials and lead to a more thorough understanding of the risks of treatment among children and adolescents.

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#### REFERENCES

1. Ahmed SM, Clasen ME, Donnelly JE. Management of dyslipidemia in adults. *Am Fam Physician*. 1998;57:2192–2204
2. Newman Dorland WA, ed. *Dorland's Illustrated Medical Dictionary*. 29th ed. Philadelphia, PA: WB Saunders; 2000
3. Centers for Disease Control and Prevention. Mortality from coronary heart disease and acute myocardial infarction: United States, 1998. *MMWR Morb Mortal Wkly Rep*. 2001;50:90–93
4. Schrott HG, Bucher KA, Clarke WR, Lauer RM. The Muscatine Hyperlipidemia Family Study program. *Prog Clin Biol Res*. 1979;32:619–646
5. Bao W, Srinivasan SR, Valdez R, Greenlund KJ, Wattigney WA, Berenson GS. Longitudinal changes in cardiovascular risk from childhood to young adulthood in offspring of parents with coronary artery disease: the Bogalusa Heart Study. *JAMA*. 1997;278:1749–1754

6. Kwiterovich PO Jr. Prevention of coronary disease starting in childhood: what risk factors should be identified and treated? *Coron Artery Dis.* 1993;4:611–630
7. Pathological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. *JAMA.* 1990;264:3018–3024
8. 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;314:138–144
9. Freedman DS, Newman WP 3rd, Tracy RE, et al. Black-white differences in aortic fatty streaks in adolescence and early adulthood: the Bogalusa Heart Study. *Circulation.* 1988;77:856–864
10. Berenson GS, Wattigney WA, Tracy RE, et al. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (the Bogalusa Heart Study). *Am J Cardiol.* 1992;70:851–858
11. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med.* 1998;338:1650–1656
12. Strong JP, Zieske AW, Malcom GT. Lipoproteins and atherosclerosis in children: an early marriage? *Nutr Metab Cardiovasc Dis.* 2001;11(suppl 5):16–22
13. Eyre H, Kahn R, Robertson RM, et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation.* 2004;109:3244–3255
14. Kavey REW, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K. American heart association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *J Pediatr.* 2003;142:368–372
15. Williams CL, Hayman LL, Daniels SR, et al. Cardiovascular health in childhood: a statement for health professionals from the Committee on Atherosclerosis, Hypertension, and Obesity in the Young (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association [published correction appears in *Circulation.* 2002;106:1178]. *Circulation.* 2002;106:143–160
16. American Academy of Pediatrics, Committee on Nutrition. Cholesterol in childhood. *Pediatrics.* 1998;101:141–147
17. American Heart Association. Step I, Step II and TLC diets. Available at: [www.americanheart.org/presenter.jhtml?identifier=4764](http://www.americanheart.org/presenter.jhtml?identifier=4764). Accessed April 29, 2005
18. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA.* 2004;292:331–337
19. Clauss SB, Holmes KW, Hopkins P, et al. Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics.* 2005;116:682–688
20. National Cholesterol Education Program. Report of the expert panel on blood cholesterol levels in children and adolescents. *Pediatrics.* 1992;89(3 pt 2):525–584
21. Harris RP, Helfand M, Woolf SH, 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.
22. Haney EM, Huffman LH, Bougatsos CM, et al. *Screening for Dyslipidemia in Children and Adolescents: Systematic Evidence Synthesis.* Rockville, MD: Agency for Healthcare Research and Quality; 2006. Available at: [www.ahrq.gov/clinic/uspstf/uspstf.htm](http://www.ahrq.gov/clinic/uspstf/uspstf.htm). Accessed April 27, 2007
23. National Heart Lung and Blood Institute. *Cardiovascular Profile of 15,000 Children of School Age in Three Communities 1971–1975.* Bethesda, MD: US Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health; 1978
24. Berenson GS. *Cardiovascular Risk Factors in Children.* New York, NY: Oxford University Press; 1980
25. National Center for Health Statistics. *Serum Cholesterol Levels of Persons 4–74 Years of Age by Socioeconomic Characteristics: United States, 1971–74.* Hyattsville, MD: US Department of Health Education and Welfare, Public Health Service, National Center for Health Statistics; 1980
26. Baker SG, Joffe BI, Mendelsohn D, Seftel HC. Treatment of homozygous familial hypercholesterolaemia with probucol. *S Afr Med J.* 1982;62:7–11
27. Lipid Research Clinics Program. *The Lipid Research Clinics Population Studies Data Book.* Vol 1. Bethesda, MD: National Institutes of Health, Lipid Metabolism Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute; 1980
28. Hickman TB, Briefel RR, Carrol MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4–19 years: data from the third National Health and Nutrition Examination Survey. *Prev Med.* 1998;27:879–890
29. Labarthe DR, Dai S, Fulton JE. Cholesterol screening in children: insights from Project HeartBeat! and NHANES III. *Prog Pediatr Cardiol.* 2003;17:169–178
30. Kwiterovich PO Jr, Heiss G, Johnson N, Chase GA, Tamir I, Rifkind B. 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.* 1982;115:192–204
31. Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Serum total cholesterol screening for the detection of elevated low-density lipoprotein in children and adolescents: the Bogalusa Heart Study. *Pediatrics.* 1990;85:472–479
32. Rifai N, Neufeld E, Ahlstrom P, Rimm E, D'Angelo L, Hicks JM. Failure of current guidelines for cholesterol screening in urban African-American adolescents. *Pediatrics.* 1996;98:383–388.
33. Shea S, Basch CE, Irigoyen M, et al. Failure of family history to predict high blood cholesterol among Hispanic preschool children. *Prev Med.* 1990;19:443–455
34. Gillman MW, Cupples LA, Moore LL, Ellison RC. Impact of within-person variability on identifying children with hypercholesterolemia: Framingham Children's Study. *J Pediatr.* 1992;121:342–347
35. 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;42:1182–1188.
36. Ticho BS, Neufeld EJ, Newburger JW, Harris N, Baker A, Rifai N. Utility of direct measurement of low-density lipoprotein cholesterol in dyslipidemic pediatric patients. *Arch Pediatr Adolesc Med.* 1998;152:787–791
37. Bao W, Srinivasan SR, Wattigney WA, Berenson GS. Usefulness of childhood low-density lipoprotein cholesterol level in predicting adult dyslipidemia and other cardiovascular risks. The Bogalusa Heart Study. *Arch Intern Med.* 1996;156:1315–1320
38. Freedman DS, Shear CL, Srinivasan SR, Webber LS, Berenson GS. Tracking of serum lipids and lipoproteins in children over an 8-year period: the Bogalusa Heart Study. *Prev Med.* 1985;14:203–216
39. 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;14:91–98
40. 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; 34:324–333
  41. Clarke WR, Schrott HG, Leaverton PE, Connor WE, Lauer RM. Tracking of blood lipids and blood pressures in school age children: the Muscatine study. *Circulation*. 1978;58:626–634
  42. Lauer RM, Lee J, Clarke WR. Predicting adult cholesterol levels from measurements in childhood and adolescence: the Muscatine Study. *Bull N Y Acad Med*. 1989;65:1127–1142
  43. Stuhldreher WL, Orchard TJ, Donahue RP, Kuller LH, Gloninger MF, Drash AL. Cholesterol screening in childhood: sixteen-year Beaver County Lipid Study experience. *J Pediatr*. 1991;119:551–556
  44. Namboodiri KK, Green PP, Walden C, et al. The Collaborative Lipid Research Clinics Program Family Study. II. Response rates, representativeness of the sample, and stability of lipid and lipoprotein levels. *Am J Epidemiol*. 1984;119:944–958
  45. Laskarzewski P, Morrison JA, de Groot I, et al. Lipid and lipoprotein tracking in 108 children over a four-year period. *Pediatrics*. 1979;64:584–591
  46. Guo S, Beckett L, Chumlea WC, Roche AF, Siervogel RM. Serial analysis of plasma lipids and lipoproteins from individuals 9–21 y of age. *Am J Clin Nutr*. 1993;58:61–67
  47. Baumgartner RN, Guo S, Roche AF. Tracking of lipids and lipoproteins in adolescents from 12–22 years of age. The Fels longitudinal study. *Ann N Y Acad Sci*. 1991;623:406–409
  48. Twisk JW, Kemper HC, van Mechelen W, Post GB. 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;145:888–898
  49. Mohler B, Ackermann-Lieblich 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 Präventivmed*. 1996;41:333–340
  50. 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;32:312–323.
  51. Katzmarzyk PT, Perusse L, Malina RM, Bergeron J, Despres JP, Bouchard C. Stability of indicators of the metabolic syndrome from childhood and adolescence to young adulthood: the Quebec Family Study. *J Clin Epidemiol*. 2001;54:190–195
  52. Kallio MJ, Salmenpera L, Siimes MA, Perheentupa J, Miettinen TA. Tracking of serum cholesterol and lipoprotein levels from the first year of life. *Pediatrics*. 1993;91:949–954
  53. Bastida S, Sanchez-Muniz FJ, Cuena R, Perea S, Aragones A. High density lipoprotein-cholesterol changes in children with high cholesterol levels at birth. *Eur J Pediatr*. 2002;161:94–98
  54. 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: 713–724
  55. Porkka KV, Viikari JS, Taimela S, Dahl M, Akerblom HK. 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; 140:1096–1110
  56. Fuentes RM, Notkola IL, Shemeikka S, Tuomilehto J, Nissinen A. Tracking of serum total cholesterol during childhood: an 8-year follow-up population-based family study in eastern Finland. *Acta Paediatr*. 2003;92:420–424
  57. Eisenmann JC, Welk GJ, Wickel EE, Blair SN; Aerobics Center Longitudinal Study. Stability of variables associated with the metabolic syndrome from adolescence to adulthood: the Aerobics Center Longitudinal Study. *Am J Hum Biol*. 2004;16: 690–696
  58. Nicklas TA, von Duvillard SP, Berenson GS. Tracking of serum lipids and lipoproteins from childhood to dyslipidemia in adults: the Bogalusa Heart Study. *Int J Sports Med*. 2002; 23(suppl 1):S39–S43
  59. Orchard TJ, Donahue RP, Kuller LH, Hodge PN, Drash AL. Cholesterol screening in childhood: does it predict adult hypercholesterolemia? The Beaver County experience. *J Pediatr*. 1983;103:687–691
  60. Bell MM, Joseph S. Screening 1140 fifth graders for hypercholesterolemia: family history inadequate to predict results. *J Am Board Fam Pract*. 1990;3:259–263
  61. Davidson DM, Van Camp J, Iftner CA, Landry SM, Bradley BJ, Wong ND. Family history fails to detect the majority of children with high capillary blood total cholesterol. *J Sch Health*. 1991;61:75–80
  62. Diller PM, Huster GA, Leach AD, Laskarzewski PM, Sprecher DL. Definition and application of the discretionary screening indicators according to the National Cholesterol Education Program for Children and Adolescents. *J Pediatr*. 1995;126: 345–352
  63. Gagliano NJ, Emans SJ, Woods ER. Cholesterol screening in the adolescent. *J Adolesc Health*. 1993;14:104–108
  64. Griffin TC, Christoffel KK, Binns HJ, McGuire PA. Family history evaluation as a predictive screen for childhood hypercholesterolemia. Pediatric Practice Research Group. *Pediatrics*. 1989;84:365–373
  65. Muhonen LE, Burns TL, Nelson RP, Lauer RM. Coronary risk factors in adolescents related to their knowledge of familial coronary heart disease and hypercholesterolemia: the Muscatine Study. *Pediatrics*. 1994;93:444–451
  66. Primrose ED, Savage JM, Boreham CA, Cran GW, Strain JJ. Cholesterol screening and family history of vascular disease. *Arch Dis Child*. 1994;71:239–242
  67. Resnicow K, Cross D, Lacosse J, Nichols P. Evaluation of a school-site cardiovascular risk factor screening intervention. *Prev Med*. 1993;22:838–856
  68. Sanchez Bayle M, Gonzalez Vergaz A, Garcia Cuartero B, Santos Tapia M, Gonzalez Requejo A. Is a parental history of coronary arterial disease in children as discriminating as their lipoprotein profile? Nino Jesus Group. *Int J Cardiol*. 1992;36: 267–271
  69. Steiner NJ, Neinstein LS, Pennbridge J. Hypercholesterolemia in adolescents: effectiveness of screening strategies based on selected risk factors. *Pediatrics*. 1991;88:269–275
  70. Troxler RG, Park MK, Miller MA, Karnavas BA, Lee DH. Predictive value of family history in detecting hypercholesterolemia in predominantly Hispanic adolescents. *Tex Med*. 1991; 87:75–79
  71. Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Parental history of cardiovascular disease as an indication for screening for lipoprotein abnormalities in children. *J Pediatr*. 1989;115:186–194
  72. O'Loughlin J, Lauzon B, Paradis G, et al. Usefulness of the American Academy of Pediatrics recommendations for identifying youths with hypercholesterolemia. *Pediatrics*. 2004; 113:1723–1727
  73. Wadowski SJ, Karp RJ, Murray-Bachmann R, Senft C. Family history of coronary artery disease and cholesterol: screening children in a disadvantaged inner-city population. *Pediatrics*. 1994;93:109–113
  74. Washington RL, Harrigan L, Day M. Early experience in treating hyperlipidemia in children. *Ann N Y Acad Sci*. 1991;623: 434
  75. Lannon CM, Earp J. Parents' behavior and attitudes toward

- screening children for high serum cholesterol levels. *Pediatrics*. 1992;89(6 pt 2):1159–1163
76. Boulton TJ. The validity of screening for hypercholesterolemia at different ages from 2 to 17 years. *Aust N Z J Med*. 1979;9:542–546
77. Williams RR, Hunt SC, Barlow GK, et al. Prevention of familial cardiovascular disease by screening for family history and lipids in youths. *Clin Chem*. 1992;38(8B pt 2):1555–1560.
78. Andersen LB, Wedderkopp N, Hansen HS, Cooper AR, Froberg K. Biological cardiovascular risk factors cluster in Danish children and adolescents: the European Youth Heart Study. *Prev Med*. 2003;37:363–367
79. Bergström E, Hernell O, Persson LA. Endurance running performance in relation to cardiovascular risk indicators in adolescents. *Int J Sports Med*. 1997;18:300–307
80. Bonora E, Zenere M, Branzi P, et al. Influence of body fat and its regional localization on risk factors for atherosclerosis in young men. *Am J Epidemiol*. 1992;135:1271–1278
81. Bonora E, Targher G, Branzi P, et al. Cardiovascular risk profile in 38-year and 18-year-old men. Contribution of body fat content and regional fat distribution. *Int J Obes Relat Metab Disord*. 1996;20:28–36
82. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: the Muscatine Study. *Circulation*. 2001;104:2815–2819
83. Demerath E, Muratova V, Spangler E, Li J, Minor VE, Neal WA. School-based obesity screening in rural Appalachia. *Prev Med*. 2003;37:553–560
84. DeStefano F, Berg RL, Griese GG Jr. Determinants of serum lipid and lipoprotein concentrations in children. *Epidemiology*. 1995;6:446–449
85. Douglas MB, Birrer RB, Medidi S, Schluskel YR. Obese children should be screened for hypercholesterolemia. *J Health Care Poor Underserved*. 1996;7:24–35
86. Durant RH, Linder CW, Jay S, Harkness JW, Gray RG. The influence of a family history of CHD risk factors on serum lipoprotein levels in black children and adolescents. *J Adolesc Health Care*. 1982;3:75–81
87. Durant RH, Linder CW, Mahoney OM. Relationship between habitual physical activity and serum lipoprotein levels in white male adolescents. *J Adolesc Health Care*. 1983;4:235–240
88. Durant RH, Baranowski T, Rhodes T, et al. Association among serum lipid and lipoprotein concentrations and physical activity, physical fitness, and body composition in young children. *J Pediatr*. 1993;123:185–192
89. Dwyer T, Gibbons LE. The Australian Schools Health and Fitness Survey: physical fitness related to blood pressure but not lipoproteins. *Circulation*. 1994;89:1539–1544
90. Eisenmann JC, Malina RM. Age-related changes in subcutaneous adipose tissue of adolescent distance runners and association with blood lipoproteins. *Ann Hum Biol*. 2002;29:389–397
91. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics*. 1999;103:1175–1182.
92. Fripp RR, Hodgson JL, Kwiterovich PO, Werner JC, Schuler HG, Whitman V. Aerobic capacity, obesity, and atherosclerotic risk factors in male adolescents. *Pediatrics*. 1985;75:813–818
93. Giovannini M, Bellu R, Ortisi MT, Incerti P, Riva E. Cholesterol and lipoprotein levels in Milanese children: relation to nutritional and familial factors. *J Am Coll Nutr*. 1992;11(suppl):285–315
94. Glassman MS, Schwarz SM. Cholesterol screening in children: should obesity be a risk factor? *J Am Coll Nutr*. 1993;12:270–273
95. Howard JK, Bindler RM, Dimico GS, et al. Cardiovascular risk factors in children: a Blookmsday research report. *J Pediatr Nurs*. 1991;6:222–229
96. Järvisalo MJ, Jartti L, Nanto-Salonen K, et al. Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children. *Circulation*. 2001;104:2943–2947
97. Larsson B, Vaara I. Cholesterol screening of seven-year-old children: how to identify children at risk. *Acta Paediatr*. 1992;81:315–318
98. 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*. 1997;96:2526–2533
99. Mácek M, Bell D, Rutenfranz J, et al. A comparison of coronary risk factors in groups of trained and untrained adolescents. *Eur J Appl Physiol Occup Physiol*. 1989;58:577–582
100. 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;43:228–233
101. Raitakari OT, Taimela S, Porkka KV, Viikari JS. Effect of leisure-time physical activity change on high-density lipoprotein cholesterol in adolescents and young adults. *Ann Med*. 1996;28:259–263
102. Resnicow K, Futterman R, Vaughan RD. Body mass index as a predictor of systolic blood pressure in a multiracial sample of US schoolchildren. *Ethn Dis*. 1993;3:351–361
103. Ribeiro JC, Guerra S, Oliveira J, et al. Physical activity and biological risk factors clustering in pediatric population. *Prev Med*. 2004;39:596–601
104. Shear CL. The relationship between parental history of vascular disease and cardiovascular disease risk factors in children: the Bogalusa Heart Study. *Am J Epidemiol*. 1985;122:762–771
105. Simon JA, Morrison JA, Similo SL, McMahon RP, Schreiber GB. Correlates of high-density lipoprotein cholesterol in black girls and white girls: the NHLBI Growth and Health Study. *Am J Public Health*. 1995;85:1698–1702
106. Suter E, Hawes MR. Relationship of physical activity, body fat, diet, and blood lipid profile in youths 10–15 yr. *Med Sci Sports Exerc*. 1993;25:748–754
107. Thorland WG, Gilliam TB. Comparison of serum lipids between habitually high and low active pre-adolescent males. *Med Sci Sports Exerc*. 1981;13:316–321
108. Tolfrey K, Campbell IG, Jones AM. Selected predictor variables and the lipid-lipoprotein profile of prepubertal girls and boys. *Med Sci Sports Exerc*. 1999;31:1550–1557
109. Tonstad S, Leren TP, Sivertsen M, Ose L. Determinants of lipid levels among children with heterozygous familial hypercholesterolemia in Norway. *Arterioscler Thromb Vasc Biol*. 1995;15:1009–1014
110. Twisk JW, Kemper HC, Van Mechelen W, Post GB. Clustering of risk factors for coronary heart disease: the longitudinal relationship with lifestyle. *Ann Epidemiol*. 2001;11:157–165
111. Twisk JW, Kemper HC, van Mechelen W, Post GB, van Lenthe FJ. Body fatness: longitudinal relationship of body mass index and the sum of skinfolds with other risk factors for coronary heart disease. *Int J Obes Relat Metab Disord*. 1998;22:915–922
112. Twisk JW, Kemper HC, Mellenbergh GJ, van Mechelen W, Post GB. Relation between the longitudinal development of lipoprotein levels and lifestyle parameters during adolescence and young adulthood. *Ann Epidemiol*. 1996;6:246–256
113. van Lenthe FJ, van Mechelen W, Kemper HC, Twisk JW. Association of a central pattern of body fat with blood pressure and lipoproteins from adolescence into adulthood. The Amsterdam Growth and Health Study. *Am J Epidemiol*. 1998;147:686–693

114. van Stiphout WA, Hofman A, de Bruijn AM, Valkenburg HA. Distributions and determinants of total and high-density lipoprotein cholesterol in Dutch children and young adults. *Prev Med.* 1985;14:169–180
115. Ward SD, Melin JR, Lloyd FP, Norton JA Jr, Christian JC. Determinants of plasma cholesterol in children: a family study. *Am J Clin Nutr.* 1980;33:63–70
116. Wong ND, Hei TK, Qaqundah PY, Davidson DM, Bassin SL, Gold KV. Television viewing and pediatric hypercholesterolemia. *Pediatrics.* 1992;90:75–79
117. Jiang X, Srinivasan SR, Webber LS, Wattigney WA, Berenson GS. Association of fasting insulin level with serum lipid and lipoprotein levels in children, adolescents, and young adults: the Bogalusa Heart Study. *Arch Intern Med.* 1995;155:190–196
118. Gliksman MD, Lazarus R, Wilson A. Differences in serum lipids in Australian children: is diet responsible? *Int J Epidemiol.* 1993;22:247–254
119. Kunz F, Pechlaner C, Hortnagl H, Pfister R. The smoker's paradox and the real risk of smoking. *Eur J Epidemiol.* 2005;20:161–167
120. Berenson GS, Srinivasan S. Cholesterol as a risk factor for early atherosclerosis: the Bogalusa Heart Study. *Prog Pediatr Cardiol.* 2003;17:113–122
121. Bachman RP, Schoen EJ, Stembridge A, Jurecki ER, Imagire RS. Compliance with childhood cholesterol screening among members of a prepaid health plan. *Am J Dis Child.* 1993;147:382–385
122. Bistrizter T, Rosenzweig L, Barr J, et al. Lipid profile with paternal history of coronary heart disease before age 40. *Arch Dis Child.* 1995;73:62–65
123. Davidson DM, Bradley BJ, Landry SM, Iftner CA, Bramblett SN. School-based blood cholesterol screening. *J Pediatr Health Care.* 1989;3:3–8
124. Dennison BA, Jenkins PL, Pearson TA. Challenges to implementing the current pediatric cholesterol screening guidelines into practice. *Pediatrics.* 1994;94:296–302
125. Faigel HC. Screening college students for hypercholesterolemia. *J Am Coll Health.* 1992;40:272–275
126. Garcia RE, Moodie DS. Routine cholesterol surveillance in childhood. *Pediatrics.* 1989;84:751–755
127. Hammond J, Chinn S, Richardson H, Rona R. Response to venepuncture for monitoring in primary schools. *Arch Dis Child.* 1994;70:367–369
128. Heyden S, Schneider KA, Roberts KF. Effectiveness of education-screening on cholesterol levels of students. *Ann Nutr Metab.* 1991;35:71–76
129. Lansing AM, Barbie RN, Shaheen KA. Regional cholesterol screening: problems and potentials. *J Ky Med Assoc.* 1990;88:170–174
130. Manchester RA, McDuffie C, Diamond E. Screening for hypercholesterolemia in college students. *J Am Coll Health.* 1989;37:149–153
131. Polonsky SM, Bellet PS, Sprecher DL. Primary hyperlipidemia in a pediatric population: classification and effect of dietary treatment. *Pediatrics.* 1993;91:92–96
132. Skovby F, Micic S, Jepsen B, et al. Screening for familial hypercholesterolaemia by measurement of apolipoproteins in capillary blood. *Arch Dis Child.* 1991;66:844–847
133. Sveger T, Flodmark CE, Nordborg K, Nilsson-Ehle P, Borgfors N. Hereditary dyslipidemias and combined risk factors in children with a family history of premature coronary artery disease. *Arch Dis Child.* 2000;82:292–296
134. Goff DC Jr, Donker GA, Ragan JD Jr, et al. Cholesterol screening in pediatric practice. *Pediatrics.* 1991;88:250–258
135. McHale SM, Tershakovec AM, Corneal DA, Tournier BA, Shannon BM. Psychosocial factors in nutrition education for hypercholesterolemic children. *Ann Behav Med.* 1998;20:233–240
136. Rosenberg E, Lamping DL, Joseph L, Pless IB, Franco ED. Cholesterol screening of children at high risk: behavioural and psychological effects. *CMAJ.* 1997;156:489–496
137. Tonstad S. Familial hypercholesterolaemia: a pilot study of parents' and children's concerns. *Acta Paediatr.* 1996;85:1307–1313
138. Rosenthal SL, Knauer-Black S, Stahl MP, Catalanotto TJ, Sprecher DL. The psychological functioning of children with hypercholesterolemia and their families: a preliminary investigation. *Clin Pediatr (Phila).* 1993;32:135–141
139. Sinaiko AR, Prineas RJ. Reduction of cardiovascular disease: what is the role of the pediatrician? *Pediatrics.* 1998;102(5). Available at: [www.pediatrics.org/cgi/content/full/102/5/e61](http://www.pediatrics.org/cgi/content/full/102/5/e61)
140. Nader PR, Yang M, Luepker RV, et al. Parent and physician response to children's cholesterol values of 200 mg/dL or greater: the Child and Adolescent Trial for Cardiovascular Health Experiment. *Pediatrics.* 1997;99(5). Available at: [www.pediatrics.org/cgi/content/full/99/5/e5](http://www.pediatrics.org/cgi/content/full/99/5/e5)
141. 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;157:66–70
142. 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;68:541–545
143. Kenny D, Ward OC, Mulhern B, Rashied AA. Failure of cord serum cholesterol and beta-lipoprotein as screening tests for familial hyperlipoproteinaemia. *Ir J Med Sci.* 1984;153:100–105
144. Cress HR, Shaher RM, Greenberg MH, Laffin R. Lipoproteins in neonates. *J Pediatr.* 1974;84:585–587
145. Barnes K, Nestel PJ, Pryke ES, Whyte HM. Neonatal plasma lipids. *Med J Aust.* 1972;2(18):1002–1005
146. 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;54:691–694
147. Goldstein JL, Albers JJ, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Plasma lipid levels and coronary heart disease in adult relatives of newborns with normal and elevated cord blood lipids. *Am J Hum Genet.* 1974;26:727–735
148. Darmady JM, Fosbrooke AS, Lloyd JK. Prospective study of serum cholesterol levels during first year of life. *Br Med J.* 1972;2(5815):685–688
149. Tsang RC, Fallat RW, Glueck CJ. Cholesterol at birth and age 1: comparison of normal and hypercholesterolemic neonates. *Pediatrics.* 1974;53:458–470
150. Kwitterovich PO Jr, Levy RI, Fredrickson DS. Neonatal diagnosis of familial type-II hyperlipoproteinaemia. *Lancet.* 1973;1(7795):118–121
151. Andersen GE, Nielsen HG. Neonatal screening for hyperlipoproteinemia: methods for direct estimation of cord serum VLDL + LDL. *Clin Chim Acta.* 1976;66:29–41
152. Van Biervliet JP, Vercaemst R, De Keersgieter W, Vinaimont N, Caster H, Rosseneu M. Evolution of lipoprotein patterns in newborns. *Acta Paediatr Scand.* 1980;69:593–596
153. 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;28:1192–1196
154. Wood WG, Schumacher M, Weigert S. (Apo)lipoprotein(a) concentrations at birth and in the first days and months of life: studies on the distribution of serum levels and the predictive value of measurements made at this time. *Eur J Clin Chem Clin Biochem.* 1995;33:139–145

155. Vladutiu GD, Glueck CJ, Schultz MT, McNeely S, Guthrie R. beta-Lipoprotein quantitation in cord blood spotted on filter paper: a screening test. *Clin Chem*. 1980;26:1285-1290
156. 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;11(suppl 1):87-90
157. Blades BL, Dudman NP, Wilcken DE. Screening for familial hypercholesterolemia in 5000 neonates: a recall study. *Pediatr Res*. 1988;23:500-504
158. 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(1-3):95-101
159. Van Biervliet JP, Vinaimont N, Caster H, Rosseneu M, Belpaire F. A screening procedure for dyslipoproteinemia in the newborn: apoprotein quantitation on dried blood spots. *Clin Chim Acta*. 1982;120:191-200
160. Roseneu M, Van Biervliet JP. Screening and follow-up of infants with dyslipoproteinemia. *Prog Clin Biol Res*. 1985;188:79-86
161. Beeso J, Wong N, Ayling R, et al. Screening for hypercholesterolaemia in 10,000 neonates in a multi-ethnic population. *Eur J Pediatr*. 1999;158:833-837
162. Croyle RT, Sun YC, Louie DH. Psychological minimization of cholesterol test results: moderators of appraisal in college students and community residents. *Health Psychol*. 1993;12:503-507
163. Epstein LH, Kuller LH, Wing RR, Valoski A, McCurley J. The effect of weight control on lipid changes in obese children. *Am J Dis Child*. 1989;143:454-457
164. de Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol*. 2002;40:2117-2121
165. McCrindle BW, Helden E, Cullen-Dean G, Conner WT. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. *Pediatr Res*. 2002;51:715-721
166. de Jongh S, Vissers MN, Rol P, Bakker HD, Kastelein JJ, Stroes ES. Plant sterols lower LDL cholesterol without improving endothelial function in prepubertal children with familial hypercholesterolaemia. *J Inherit Metab Dis*. 2003;26:343-351
167. Gylling H, Siimes MA, Miettinen TA. Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia. *J Lipid Res*. 1995;36:1807-1812
168. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr*. 2003;143:74-80
169. 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;107:256-264
170. DISC Collaborative Research Group. 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;273:1429-1435
171. Stein EA, Illingworth DR, Kwiterovich PO Jr, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 1999;281:137-144
172. Knipscheer HC, Boelen CC, Kastelein JJ, et al. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res*. 1996;39:867-871
173. Shannon BM, Tershakovec AM, Martel JK, Achterberg CL, Cortner JA. Reduction of elevated LDL-cholesterol levels of 4- to 10-year-old children through home-based dietary education. *Pediatrics*. 1994;94:923-927
174. Becque MD, Katch VL, Rocchini AP, Marks CR, Moorehead C. Coronary risk incidence of obese adolescents: reduction by exercise plus diet intervention. *Pediatrics*. 1988;81:605-612
175. McCrindle BW, O'Neill MB, Cullen-Dean G, Helden E. Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: a randomized, crossover trial. *J Pediatr*. 1997;130:266-273
176. Walter HJ, Hofman A, Connelly PA, Barrett LT, Kost KL. Primary prevention of chronic disease in childhood: changes in risk factors after one year of intervention. *Am J Epidemiol*. 1985;122:772-781
177. Amundsen AL, Ose L, Nenseter MS, Ntanios FY. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia. *Am J Clin Nutr*. 2002;76:338-344
178. Couture P, Brun LD, Szots F, et al. Association of specific LDL receptor gene mutations with differential plasma lipoprotein response to simvastatin in young French Canadians with heterozygous familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 1998;18:1007-1012
179. Davidson MH, Dugan LD, Burns JH, Sugimoto D, Story K, Drennan K. A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. *Am J Clin Nutr*. 1996;63:96-102
180. Dennison BA, Levine DM. Randomized, double-blind, placebo-controlled, two-period crossover clinical trial of psyllium fiber in children with hypercholesterolemia. *J Pediatr*. 1993;123:24-29
181. Engler MM, Engler MB, Malloy MJ, et al. Antioxidant vitamins C and E improve endothelial function in children with hyperlipidemia: Endothelial Assessment of Risk From Lipids in Youth (EARLY) Trial. *Circulation*. 2003;108:1059-1063
182. 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;23:889-895
183. 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;97:619-628
184. Malloy MJ, Kane JP, Rowe JS. Familial hypercholesterolemia in children: treatment with *p*-aminosalicylic acid. *Pediatrics*. 1978;61:365-372
185. Tonstad S, Sivertsen M, Aksnes L, Ose L. Low dose colestipol in adolescents with familial hypercholesterolaemia. *Arch Dis Child*. 1996;74:157-160
186. Tonstad S, Knudtson J, Sivertsen M, Refsum H, Ose L. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr*. 1996;129:42-49
187. 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;106:2231-2237
188. Kang HS, Gutin B, Barbeau P, et al. Physical training improves insulin resistance syndrome markers in obese adolescents. *Med Sci Sports Exerc*. 2002;34:1920-1927
189. Kuehl KS, Cockerham JT, Hitchings M, Slater D, Nixon G, Rifai N. Effective control of hypercholesterolemia in children with dietary interventions based in pediatric practice. *Prev Med*. 1993;22:154-166

190. Stallings VA, Cortner JA, Shannon BM, et al. Preliminary report of a home-based education program for dietary treatment of hypercholesterolemia in children. *Am J Health Promot.* 1993;8:106–108
191. Stergioulas A, Tripolitsioti A, Messinis D, Bouloukos A, Nounopoulos C. The effects of endurance training on selected coronary risk factors in children. *Acta Paediatr.* 1998;87:401–404
192. Wheeler KA, West RJ, Lloyd JK, Barley J. Double blind trial of bezafibrate in familial hypercholesterolaemia. *Arch Dis Child.* 1985;60:34–37
193. Williams CL, Bollella M, Spark A, Puder D. Soluble fiber enhances the hypocholesterolemic effect of the step I diet in childhood. *J Am Coll Nutr.* 1995;14:251–257
194. Boreham CA, Wallace WF, Nevill A. Training effects of accumulated daily stair-climbing exercise in previously sedentary young women. *Prev Med.* 2000;30:277–281
195. Gold K, Wong N, Tong A, et al. Serum apolipoprotein and lipid profile effects of an oat-bran-supplemented, low-fat diet in children with elevated serum cholesterol. *Ann N Y Acad Sci.* 1991;623:429–431
196. Linder CW, DuRant RH, Mahoney OM. The effect of physical conditioning on serum lipids and lipoproteins in white male adolescents. *Med Sci Sports Exerc.* 1983;15:232–236
197. Savage MP, Petratis MM, Thomson WH, Berg K, Smith JL, Sady SP. Exercise training effects on serum lipids of prepubescent boys and adult men. *Med Sci Sports Exerc.* 1986;18:197–204
198. Engler MM, Engler MB, Malloy M, et al. Docosahexaenoic acid restores endothelial function in children with hyperlipidemia: results from the EARLY study. *Int J Clin Pharmacol Ther.* 2004;42:672–679
199. McCrindle BW, Helden E, Conner WT. Garlic extract therapy in children with hypercholesterolemia. *Arch Pediatr Adolesc Med.* 1998;152:1089–1094
200. Engler MM, Engler MB, Malloy MJ, Paul SM, Kulkarni KR, Mietus-Snyder ML. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). *Am J Cardiol.* 2005;95:869–871
201. Fernandes J, Dijkhuis-Stoffelsma R, Groot PH, Grose WF, Ambagtsheer JJ. The effect of a virtually cholesterol-free, high-linoleic-acid vegetarian diet on serum lipoproteins of children with familial hypercholesterolemia (type II-A). *Acta Paediatr Scand.* 1981;70:677–682
202. Hedman M, Neuvonen PJ, Neuvonen M, Antikainen M. Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia. *Clin Pharmacol Ther.* 2003;74:178–185
203. Dirisamer A, Hachemian N, Bucek RA, Wolf F, Reiter M, Widhalm K. The effect of low-dose simvastatin in children with familial hypercholesterolaemia: a 1-year observation. *Eur J Pediatr.* 2003;162:421–425
204. Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. *Br J Clin Pharmacol.* 2004;57:525–528
205. de Jongh S, Kerckhoffs MC, Grootenhuys MA, Bakker HD, Heymans HS, Last BF. Quality of life, anxiety and concerns among statin-treated children with familial hypercholesterolaemia and their parents. *Acta Paediatr.* 2003;92:1096–1101
206. Ducobu J, Brasseur D, Chaudron JM, et al. Simvastatin use in children. *Lancet.* 1992;339:1488
207. Stefanutti C, Lucani G, Vivenzio A, Di Giacomo S. Diet only and diet plus simvastatin in the treatment of heterozygous familial hypercholesterolemia in childhood. *Drugs Exp Clin Res.* 1999;25:23–28
208. Curtis DM, Driscoll DJ, Goldman DH, Weidman WH. Loss of dental enamel in a patient taking cholestyramine. *Mayo Clin Proc.* 1991;66:1131
209. Farah JR, Kwiterovich PO, Neill CA. A study of the dose-effect relationship of cholestyramine in children with familial hypercholesterolemia. *Adv Exp Med Biol.* 1977;82:212–215
210. Farah JR, Kwiterovich PO Jr, Neill CA. Dose-effect relation of cholestyramine in children and young adults with familial hypercholesterolaemia. *Lancet.* 1977;1(8002):59–63
211. Groot PH, Dijkhuis-Stoffelsma R, Grose WF, Ambagtsheer JJ, Fernandes J. 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;72:81–85
212. Hansen D, Michaelsen KF, Skovby F. Growth during treatment of familial hypercholesterolemia. *Acta Paediatr.* 1992;81:1023–1025
213. Harvengt C, Desager JP. Colestipol in familial type II hyperlipoproteinemia: a three-year trial. *Clin Pharmacol Ther.* 1976;20:310–314
214. Koletzko B, Kupke I, Wendel U. Treatment of hypercholesterolemia in children and adolescents. *Acta Paediatr.* 1992;81:682–685
215. Liacouras CA, Coates PM, Gallagher PR, Cortner JA. Use of cholestyramine in the treatment of children with familial combined hyperlipidemia. *J Pediatr.* 1993;122:477–482
216. Schwarz KB, Goldstein PD, Witztum JL, Schonfeld G. Fat-soluble vitamin concentrations in hypercholesterolemic children treated with colestipol. *Pediatrics.* 1980;65:243–250
217. Tonstad S, Ose L. Colestipol tablets in adolescents with familial hypercholesterolaemia. *Acta Paediatr.* 1996;85:1080–1082
218. Tonstad S, Refsum H, Ose L, Ueland PM. The C677T mutation in the methylenetetrahydrofolate reductase gene predisposes to hyperhomocysteinemia in children with familial hypercholesterolemia treated with cholestyramine. *J Pediatr.* 1998;132:365–368
219. West RJ, Lloyd JK. Use of cholestyramine in treatment of children with familial hypercholesterolaemia. *Arch Dis Child.* 1973;48:370–374
220. West RJ, Lloyd JK. The effect of cholestyramine on intestinal absorption. *Gut.* 1975;16:93–98
221. West RJ, Fosbrooke AS, Lloyd JK. Treatment of children with familial hypercholesterolaemia. *Postgrad Med J.* 1975;51(8 suppl):82–87
222. West RJ, Lloyd JK, Leonard JV. Long-term follow-up of children with familial hypercholesterolaemia treated with cholestyramine. *Lancet.* 1980;2(8200):873–875
223. Glueck CJ, Tsang RC, Fallat RW, Mellies M. Therapy of familial hypercholesterolemia in childhood: diet and cholestyramine resin for 24 to 36 months. *Pediatrics.* 1977;59:433–441
224. Glueck CJ, Mellies MJ, Dine M, Perry T, Laskarzewski P. Safety and efficacy of long-term diet and diet plus bile acid-binding resin cholesterol-lowering therapy in 73 children heterozygous for familial hypercholesterolemia [published retraction appears in Glueck CJ, Laskarzewski P, Mellies MJ, Perry T. *Pediatrics.* 1987;80:766]. *Pediatrics.* 1986;78:338–348
225. Glueck CJ, Tsang RC, Fallat RW, Scheel D. Plasma vitamin A and E levels in children with familial type II hyperlipoproteinemia during therapy with diet and cholestyramine resin. *Pediatrics.* 1974;54:51–55
226. Glueck CJ, Fallat RW, Tsang R. Pediatric familial type II hyperlipoproteinemia: therapy with diet and cholestyramine resin. *Pediatrics.* 1973;52:669–679
227. Becker M, Staab D, Von Bergman K. Long-term treatment of severe familial hypercholesterolemia in children: effect of sitosterol and bezafibrate. *Pediatrics.* 1992;89:138–142
228. Colletti RB, Neufeld EJ, Roff NK, McAuliffe TL, Baker AL,

- Newburger JW. Niacin treatment of hypercholesterolemia in children. *Pediatrics*. 1993;92:78–82
229. McDuffie JR, Calis KA, Uwaifo GI, et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res*. 2002;10:642–650
  230. Stein EA. Treatment of familial hypercholesterolemia with drugs in children. *Arteriosclerosis*. 1989;9(1 suppl):1145–1151
  231. Steinmetz J, Morin C, Panek E, Siest G, Drouin P. Biological variations in hyperlipidemic children and adolescents treated with fenofibrate. *Clin Chim Acta*. 1981;112:43–53
  232. Copperman N, Schebendach J, Arden MR, Jacobson MS. Nutrient quality of fat- and cholesterol-modified diets of children with hyperlipidemia. *Arch Pediatr Adolesc Med*. 1995;149:333–336
  233. Tonstad S, Novik TS, Vandvik IH. Psychosocial function during treatment for familial hypercholesterolemia. *Pediatrics*. 1996;98:249–255
  234. Segall MM, Tamir I, Fosbrooke AS, Lloyd JK, Wolff OH. Effects of short-term high-carbohydrate feeding on serum triglyceride of children with familial hypercholesterolaemia. *Arch Dis Child*. 1970;45:393–398
  235. Witschi JC, Singer M, Wu-Lee M, Stare FJ. Family cooperation and effectiveness in a cholesterol-lowering diet. *J Am Diet Assoc*. 1978;72:384–389
  236. McKenzie J, Dixon LB, Smiciklas-Wright H, Mitchell D, Shannon B, Tershakovec A. Change in nutrient intakes, number of servings, and contributions of total fat from food groups in 4- to 10-year-old children enrolled in a nutrition education study. *J Am Diet Assoc*. 1996;96:865–873
  237. Moreno LA, Sarria A, Lazaro A, Lasiera MP, Larrad L, Bueno M. Lymphocyte T subset counts in children with hypercholesterolemia receiving dietary therapy. *Ann Nutr Metab*. 1998;42:261–265
  238. Sánchez-Bayle M, Gonzalez-Requejo A, Baeza J, et al. Diet therapy for hypercholesterolemia in children and adolescents: a follow-up. *Arch Pediatr Adolesc Med*. 1994;148:28–32
  239. Rose V, Allen DM, Pearse RG, Chapell J. Primary hyperlipoproteinemia in childhood and adolescence: identification and treatment of persons at risk for premature atherosclerosis. *Can Med Assoc J*. 1976;115:753–756, 779
  240. Lifshitz F, Moses N. Growth failure: a complication of dietary treatment of hypercholesterolemia. *Am J Dis Child*. 1989;143:537–542
  241. Cetta F, Driscoll DJ, Lucas AR, et al. Growth patterns of hyperlipidemic children enrolled in a preventive cardiovascular health clinic. *Clin Pediatr (Phila)*. 1994;33:588–592
  242. Jacobson MS, Tomopoulos S, Williams CL, Arden MR, Deckelbaum RJ, Stare TJ. Normal growth in high-risk hyperlipidemic children and adolescents with dietary intervention. *Prev Med*. 1998;27:775–780
  243. 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;18:604–613
  244. Feoli-Fonseca JC, Levy E, Godard M, Lambert M. Familial lipoprotein lipase deficiency in infancy: clinical, biochemical, and molecular study. *J Pediatr*. 1998;133:417–423
  245. Sánchez-Bayle M, Soriano-Guillen L. Influence of dietary intervention on growth in children with hypercholesterolaemia. *Acta Paediatr*. 2003;92:1043–1046
  246. Tershakovec AM, Jawad AF, Stallings VA, et al. Growth of hypercholesterolemic children completing physician-initiated low-fat dietary intervention. *J Pediatr*. 1998;133:28–34
  247. Kaistha A, Deckelbaum RJ, Stare TJ, Couch SC. Overrestriction of dietary fat intake before formal nutritional counseling in children with hyperlipidemia. *Arch Pediatr Adolesc Med*. 2001;155:1225–1230
  248. Pugliese MT, Weyman-Daum M, Moses N, Lifshitz F. Parental health beliefs: a cause of non-organic failure to thrive. *Pediatrics*. 1987;80:175–181
  249. Amundsen AL, Ntanios F, Put N, Ose L. Long-term compliance and changes in plasma lipids, plant sterols and carotenoids in children and parents with FH consuming plant sterol ester-enriched spread. *Eur J Clin Nutr*. 2004;58:1612–1620
  250. Becker M, Staab D, Von Bergmann K. Treatment of severe familial hypercholesterolemia in childhood with sitosterol and sitostanol. *J Pediatr*. 1993;122:292–296
  251. Clarke JT, Cullen-Dean G, Regelink E, Chan L, Rose V. Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. *J Pediatr*. 1990;116:139–141
  252. Glassman M, Spark A, Berezin S, Schwartz S, Medow M, Newman LJ. Treatment of type IIa hyperlipidemia in childhood by a simplified American Heart Association diet and fiber supplementation. *Am J Dis Child*. 1990;144:973–976
  253. Gulesserian T, Widhalm K. Effect of a rapeseed oil substituting diet on serum lipids and lipoproteins in children and adolescents with familial hypercholesterolemia. *J Am Coll Nutr*. 2002;21:103–108
  254. Mietus-Snyder M, Malloy MJ. Endothelial dysfunction occurs in children with two genetic hyperlipidemias: improvement with antioxidant vitamin therapy. *J Pediatr*. 1998;133:35–40
  255. Sánchez-Bayle M, Gonzalez-Requejo A, Asensio-Anton J, Ruiz-Jarabo C, Fernandez-Ruiz ML, Baeza J. The effect of fiber supplementation on lipid profile in children with hypercholesterolemia. *Clin Pediatr (Phila)*. 2001;40:291–294
  256. Laurin D, Jacques H, Moorjani S, et al. Effects of a soy-protein beverage on plasma lipoproteins in children with familial hypercholesterolemia. *Am J Clin Nutr*. 1991;54:98–103
  257. Schlierf G, Oster P, Heuck CC, Raetzer H, Schellenberg B. Sitosterol in juvenile type II hyperlipoproteinemia. *Atherosclerosis*. 1978;30:245–248
  258. Zavoral JH, Hannan P, Fields DJ, et al. The hypolipidemic effect of locust bean gum food products in familial hypercholesterolemic adults and children. *Am J Clin Nutr*. 1983;38:285–294
  259. Tolfrey K, Campbell IG, Batterham AM. Exercise training induced alterations in prepubertal children's lipid-lipoprotein profile. *Med Sci Sports Exerc*. 1998;30:1684–1692
  260. Kavey RE, Kveselis DA, Gaum WE. Valvular and pediatric congenital heart disease: exaggerated blood pressure response to exercise in children with increased low-density lipoprotein cholesterol. *Am Heart J*. 1997;133:162–168
  261. Barter PF, Ballantyne C, Carmena R, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259:247–258
  262. Chan DC, Watts GF. Apolipoproteins as markers and managers of coronary risk [published correction appears in *QJM*. 2006;99:807]. *QJM*. 2006;99:277–287
  263. Iannuzzi A, Licenziati MR, Acampora C, et al. Increased carotid intima-media thickness and stiffness in obese children. *Diabetes Care*. 2004;27:2506–2508
  264. Wiegman A, de Groot E, Hutten BA. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. *Lancet*. 2004;363:369–370
  265. Järvisalo MJ, Lehtimäki T, Raitakari O. Determinants of arterial nitrate-mediated dilation in children: role of oxidized low-density lipoprotein, endothelial function, and carotid intima-media thickness. *Circulation*. 2004;109:2885–2889
  266. Rodenburg J, Vissers MN, Wiegman A, Trip MD, Bakker HD, Kastelein JJ. Familial hypercholesterolemia in children. *Curr Opin Lipidol*. 2004;15:405–411

## APPENDIX USPSTF Quality Rating Criteria

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### 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 on basis of above-listed 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 ( $>100$ ) of 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 (50–100 subjects) and a “medium” spectrum of patients
- Poor: has important limitations such as uses inappropriate reference standard, screening test improperly administered, biased ascertainment of reference standard, and/or very small sample size of very narrow selected spectrum of patients

### RCTs and cohort studies

#### Criteria

- Initial assembly of comparable group
  - 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, crossovers, 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
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs

#### Definition of ratings on basis of above-listed criteria

- Good, meets all criteria: comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%); 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
  - 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 the outcome assessment)
  - 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 on basis of above-listed criteria

- Good: appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate  $\geq 80\%$ ; 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 workup bias but with response rate  $<80\%$  or attention to some, but not all, important confounding variables
- Poor: major selection or diagnostic workup biases, response rates  $<50\%$ , or inattention to confounding variables

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Source: Harris RP, Helfand M, Woolf SH, et al. *Am J Prev Med.* 2001;20(3 suppl):21–35.

**Screening and Treatment for Lipid Disorders in Children and Adolescents:  
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