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Screening for Lipid Disorders in Children and Adolescents: Systematic Evidence Review for the U.S. Preventive Services Task Force

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STRUCTURED ABSTRACT

Context. Dyslipidemias, disorders of lipid metabolism, are important risk factors for coronary heart disease (CHD). Identification of children with dyslipidemias could lead to interventions aimed at decreasing their risk of CHD as adults.

Objective. To determine the strengths and limits of evidence about the effectiveness of selecting, testing, and managing children and adolescents with dyslipidemia in the course of routine primary care. Screening children and adolescents has the potential to identify three groups with dyslipidemia: those with 1) undiagnosed monogenic dyslipidemia, 2) undiagnosed secondary dyslipidemia, and 3) idiopathic dyslipidemia (polygenic, risk factor associated, or multifactorial). Key questions examined a chain of evidence about the accuracy and feasibility of screening children in various settings, tracking of lipid levels through childhood to adulthood, role of risk factors in selecting children for screening, effectiveness of interventions for children identified with dyslipidemia, and adverse effects of screening and interventions.

Data Sources. Relevant studies were identified from multiple searches of MEDLINE, PsychInfo, the Cochrane database of systematic reviews and controlled clinical trials, and EMBASE (1966 to September 2005). Additional articles were obtained from recent systematic reviews, reference lists of pertinent studies, reviews, editorials, and websites, and by consulting experts.

Study Selection. Eligible studies were applicable to U.S. clinical practice, available in English, and provided primary data relevant to key questions. Cohort studies were used for assessment of risk factors. Comparative and non-comparative prospective studies of screening for dyslipidemia in children provided information on the efficacy of these programs and the accuracy of screening with family history information. Randomized, non-randomized and non-comparative studies were used for assessment of risk factors. Only randomized controlled trials were considered for examining the effectiveness of interventions. Studies of children with previously diagnosed monogenic dyslipidemia were considered for the evaluation of treatment because those are the only children in whom some drugs have been tested.

Data Extraction. Data were extracted from each study and entered into evidence tables.

Data Synthesis. Studies were summarized by descriptive methods and rated for quality using criteria developed by the U.S. Preventive Services Task Force (USPSTF). Normal values for lipids for children and adolescents are currently defined according to population levels (percentiles). More recent studies indicate age, sex, and racial differences and temporal trends that shift cut points. Tracking of lipid levels through childhood is strongest for TC and LDL. Approximately 40-55% of children with elevated total cholesterol (TC) and low-density lipoprotein (LDL) defined by percentile will continue to have elevated lipids on follow-up. Current screening recommendations based on family history will fail to detect substantial numbers (30-60%) of children with elevated lipids. Evidence from epidemiologic studies establish a strong statistical association between overweight and elevations in lipids whereas other risk factors (diet, physical inactivity, aerobic capacity/fitness, puberty level and smoking) have not been adequately assessed. 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. Parental non-compliance with screening and follow-up recommendations is reported.

Drug treatment for dyslipidemia in children has been studied only in children with familial monogenic dyslipidemias (familial hypercholesterolemia [FH] or familial combined hyperlipidemia [FCH]). In this population, 9 randomized controlled trials demonstrate the effectiveness of statins for reducing TC and LDL (% mean reduction from meta-analysis of trials: 24.4%[95% CI 19.5, 29.2] for TC, 30.8% [95% CI 24.1, 37.5] for LDL, 8 studies). Two fair quality trials showed benefit from bile acid binding resins. Randomized controlled trials of diet supplements (psyllium, oat, garlic extract, and sterol margarine) and advice showed marginal improvements in lipids in children with monogenic dyslipidemia. For children without monogenic dyslipidemia, a good quality study showed that high intensity counseling is effective in reducing TC and LDL levels while the intervention is sustained, but not after it ceases. Other studies of diet advice showed no or minimal improvement. Dietary fiber supplements had mixed results in two trials in children and adolescents without monogenic dyslipidemia, and one oat bran supplement trial showed no effect. Six trials of exercise demonstrated little or no improvements in lipids for children without monogenic dyslipidemia (% mean reduction from meta-analysis of trials: 0% [-5.6, 5.6] for TC, 3.1% [-7.7, 1.5] for LDL, 4 studies).

Eighty-one controlled and non-controlled studies of treatment reported a variety of adverse effects of drug, diet, exercise, and combination therapy in children and adolescents. There are reports of growth retardation and nutritional dwarfing in children and adolescents for whom formal dietary assessment and advice was delayed. 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. Normal values for lipids for children and adolescents are currently defined according to population levels (percentiles). Tracking of lipid levels in children is variable, although evidence is stronger for TC and LDL than for HDL and TG. Screening using family history misses substantial numbers of children with elevated lipids. Most trials of drug interventions demonstrate improvement, but these trials were performed in selected groups of children. Several key questions could not be addressed because of lack of studies, including the effectiveness of screening on adult CHD or lipid outcomes, optimal ages and intervals for screening children, cost-effectiveness of screening, or the effects of treatment of lipids in childhood on adult CHD outcomes.

Keywords: Dyslipidemia; Children; Screening.

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I. INTRODUCTION

Dyslipidemias are disorders of lipoprotein metabolism, including elevations in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglycerides (TG) or deficiencies of high-density lipoprotein cholesterol (HDL-C) (list of abbreviations in Appendix 1).[1, 2] These disorders can be acquired or familial and are related to genetic conditions such as familial hypercholesterolemia in some individuals. Children and adolescents with dyslipidemia may have dyslipidemia as adults.[3] The relationship between dyslipidemia and coronary heart disease (CHD) in adults is well-established. Young men (mean age 22) with TC above the 75th percentile followed for 30 years on average, had a relative risk of 2.01 (95% CI 1.59, 2.53) for incidence of CHD.[4]

The prevalence of other CHD risk factors, such as overweight, diabetes, and metabolic syndrome, is increasing among children and adolescents.[5, 6] Using criteria of body mass index (BMI) > 95th percentile, 10% of 2-5 year-olds and 16% of children age 6 years and older are overweight, with higher prevalence in minority racial/ethnic groups.[7] Overweight is the primary factor contributing to development of metabolic syndrome in children and adolescents.[8] Metabolic syndrome can be defined by glucose level $\geq$110 mg/dL, systolic or diastolic blood pressure $\geq$90th percentile, TG $\geq$110 mg/dL, HDL-C $\leq$ 40 mg/dL, sex-specific waist circumference $\geq$90th percentile. (Please see Appendix 2 for units of measure conversion formulas.) Children and adolescents with metabolic syndrome are more likely to have evidence of inflammation measured by C-reactive protein (CRP) >3 mg/dL.[9] Metabolic risk factors are common. In a study of 758 U.S. high school students, 17% had three or more of the following metabolic risk factors: Waist circumference, high triglycerides, LDL-C, fibrinogen, HbgA1C, glucose, insulin and cortisol, and low HDL-C.[10]

The relationship between childhood and adult dyslipidemia, increasing prevalence of related CHD risk factors in children,[5, 11, 12] as well as continued emphasis on primary prevention of CHD has raised interest in screening for dyslipidemia in children. Identification of children with dyslipidemia could lead to intervention services or treatment that might prevent or delay adult dyslipidemia and CHD. This rationale lends support to consideration of screening for dyslipidemia as part of routine well-child care and at other opportunities.

This evidence synthesis focuses on the strengths and limitations of evidence about identifying and managing children and adolescents found to have dyslipidemia by screening in the course of routine primary care. Its objective is to determine the balance of potential benefits and adverse effects of screening for the development of guidelines by the U.S. Preventive Services Task Force (USPSTF). The target population includes children and adolescents age 0-21 years without previously known conditions associated with dyslipidemia. Among this population, there is potential to identify children and adolescents with dyslipidemia from among three groups: Those with undiagnosed monogenic dyslipidemias such as familial hypercholesterolemia (FH), those with undiagnosed secondary causes of dyslipidemia, and those with idiopathic dyslipidemia (polygenetic, multi-factorial or risk factor associated) (Figure 1). This evidence synthesis

emphasizes the patient's or parents' perspective in the choice of outcome measures and potential adverse effects, and focuses on tests and interventions that are easily interpreted in the context of primary care. It also considers the generalizability of efficacy studies performed in controlled settings and interprets the use of the tests and interventions in community-based populations.

Other systematic evidence reports that contribute information on this topic include Screening and Interventions for Childhood Overweight[7] and Screening for Dyslipidemia in Adults: Brief Update of 2001 USPSTF Review.[13]

Burden of Condition/Epidemiology

Dyslipidemia rarely leads to frank illness in childhood and health effects are typically delayed many years. Lipid levels are low at birth, increasing to young-adult levels by age 2 or 3.[14, 15] Although no long-term studies of the direct relationship between blood cholesterol levels measured in children and CHD later in life have been conducted, the relationship between childhood cholesterol levels and CHD can be inferred from indirect evidence. The Muscatine Coronary Risk Factor Survey from 1971-73 measured lipid levels of 2,874 school aged children.[16] Children's cholesterol levels correlated with those of family members, and identification of hypercholesterolemia in children also identified families at risk for CHD.[16]

The Bogalusa Heart Study is a long-term epidemiologic study of risk factors for CHD from birth through 31 years.[17] Seven surveys, including more than 3,500 children, have been conducted since 1973.[18] Children of parents with CHD had a higher prevalence of dyslipidemia in childhood.[19] Also, there was a correlation between pre-morbid lipid levels and arterial fat deposition by autopsy of children and young adults who died accidentally.[20-23] Early lesions of atherosclerosis (fatty streaks) began in the abdominal aorta at age three years, the coronary arteries at age 10 years, and progressed over time.[20-24] The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study of adolescent males who had died accidentally found atherosclerotic changes of a magnitude directly related to postmortem LDL-C.[25, 26]

The prevalence of dyslipidemia is determined by the results of laboratory testing and statistically determined criteria. Elevated LDL-C is the most common manifestation of clinically significant dyslipidemia in children. If the cutoff for elevated LDL-C is set at the 95th percentile, then 5% of children in the reference population will have dyslipidemia. Within this group of children with LDL-C levels above the 95th percentile, a minority will have monogenic or secondary dyslipidemias, and the majority will have idiopathic (polygenic, multi-factorial or risk factor associated) dyslipidemias. The more common genetic dyslipidemias are described briefly below. Additional very rare dyslipidemias that can cause adverse effects on health during childhood include homozygous familial hypercholesterolemia, lipoprotein lipase deficiency, Tangier disease, Fish-Eye disease, sitosterolemia, familial hypoalphalipoproteinemia, and abetalipoproteinemia among others.

Familial hypercholesterolemia

Familial hypercholesterolemia (FH) results from a defect in the cell surface receptor that removes LDL-C particles from plasma.[27] The incidence is 1 in 500 in the U.S., Canada, and Europe.[28] and up to 1 in 100 in specific populations (e.g. Transvaal Afrikaners).[29, 30] On average, untreated men with FH have clinically evident CHD by age 40 and women by age 50. Most children with FH require drug treatment. The homozygous form of FH can result in TC levels > 500 mg/dL, LDL-C > 450 mg/dL, xanthomas by age 5, and vascular disease before age 20.[28, 31] Individuals with heterozygous FH display a broad range of lipid levels, with mean TC of 323$\pm$44 mg/dL and mean LDL-C of 262$\pm$45mg/dL.[32]

Familial combined hyperlipidemia

Familial combined hyperlipidemia (FCH) is the most common genetic lipid disorder overall, occurring in 1-2% of the general adult population, and accounts for at least 10% of persons with premature CHD.[32] This group tends to have high triglyceride levels, but LDL may be acceptable, borderline, or high (mean 149$\pm$48 mg/dL),[28] Elevations in LDL, when present, are not generally as extreme as those seen in FH.

Familial defective apoprotein B (apo B)

Familial defective Apo B is characterized by moderate to severe hypercholesterolemia. The mechanism for the effect is a single base substitution in the ApoB gene that diminishes the ability of LDL-C to bind to the LDL-C receptor. Heterozygous familial defective Apo B occurs in 1 in 1,000 Europeans, and approximately 1 in 20 of these have similar phenotypes to those with heterozygous FH.[28]

Familial hypertriglyceridemia

Familial hypertriglyceridemia is autosomal dominant but usually not expressed until adulthood. Obesity can accelerate expression of the phenotype, with moderately elevated (100-200 mg/dL) triglyceride levels in youth and extremely elevated levels in adults.[28]

In a study of diagnoses made systematically for 129 families referred to a single lipid clinic for dyslipidemia and family history of early CHD, 20 had FH, 65 had FCH, 11 had hyper-Apo B and 1 had familial hypertriglyceridemia[33]. Others were unexplained (32), presumed normal (17) or adopted (2).

In addition to detection of monogenic dyslipidemias, screening would also detect secondary causes of dyslipidemia such as diabetes, nephritic syndrome, hypothyroidism and others, and idiopathic dyslipidemia. Included in the idiopathic group are polygenic, environmental and behavioral causes such as overweight and smoking. While children

and adolescents with idiopathic dyslipidemia generally have less severe lipid levels than children and adolescents with familial or rare genetic disorders, levels may be significantly abnormal and could potentially improve with intervention.

Healthcare Interventions

To reduce the burden of dyslipidemia in children, clinic-based screening, community-based screening, and other community-based prevention strategies have been proposed. Most recommendations support selective strategies that test children who have family members with dyslipidemia or premature CHD and those for whom family history is unknown.[34, 35] Alternatively, universal screening for all children has had some proponents, although this approach has not been recommended in recent guidelines.

For children over two years of age with dyslipidemia, most recommendations indicate that the initial intervention is a low-fat, low-cholesterol diet, such as the American Heart Association Step I diet (AHA)[11] (Table 1). Children younger than two years should not be prescribed a low fat diet because the first two years is a period of rapid growth and development that requires an adequate fat and cholesterol intake.[35] If the AHA Step I diet alone does not result in satisfactory improvement in the lipid profile, the AHA Step II diet may be prescribed. This is a more restrictive diet, lower still in fat and cholesterol content than the Step I diet, and should not be prescribed to children without close supervision by a physician and dietitian. If the Step II diet still does not lead to a satisfactory improvement, medications can be considered. In 2000, the AHA modified their dietary recommendations for children,[36] but these changes have not been reflected in American Academy of Pediatrics (AAP) or National Cholesterol Education Program (NCEP) guidelines.

Children and adolescents with FH are the only non-adults for whom trials of drug therapy are available and approved by the U.S. Food and Drug Administration (FDA). The only medications approved by the FDA for treatment of dyslipidemia for children younger than 8 years of age are bile acid-binding resins. However, adherence to a prescribed regimen of bile acid binding resins is difficult due to the character and taste of the compounds. In addition, the lipid lowering effects of bile acid-binding resins in children are limited and do not often result in lipid lowering to the degree desired. Recently, HMG Co-A reductase inhibitors (statins) were approved for use in children with heterozygous familial hypercholesterolemia (FH). Lovastatin, simvastatin, and atorvastatin are FDA approved for adolescent boys and girls at least one year post-menarche ages 10-17, and pravastatin for boys and girls ages 8-18.[37, 38] Other medications used in adults for treatment of hyperlipidemia are either not recommended for children (i.e., niacin) or have not been adequately evaluated for safety and efficacy in children.

Additional interventions often recommended in the management of dyslipidemia in children and adolescents include dietary counseling, exercise, weight loss for overweight children, identification and treatment of diabetes mellitus or other secondary cause, and

control of high blood pressure. Dietary supplements such as fiber, omega 3 fatty acids, and sterol or stanol margarines are sometimes considered as interventions for children with dyslipidemia.[39-42]

Prior Recommendations

In 2001, the USPSTF reviewed screening for dyslipidemia in children and adolescents but did not make a recommendation.[43] A 2001 Systematic Evidence Review for the USPSTF found that studies of drug therapy in children were too short (8 weeks to 1 year) and too small to draw definitive conclusions about harms or benefits. Determination of the efficacy, safety, and feasibility of low fat diets in children were also inconclusive.[44]

The NCEP recommendations for adults (Adult Treatment Panel III [ATP III]) recommended that screening begin at age 20 and were updated as recently as 2004.[45] The ATP III and USPSTF guidelines for adults recommend initial testing and risk determination using TC and HDL-C.[13, 34] LDL-C is used as a criterion for initiation of drug therapy.[34]

The NCEP Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents published guidelines in 1992 and have not been updated.[34] This report addressed children up to age 18, and is the basis for the most recent AAP and AHA guidelines. The NCEP report recommended selective screening for children and adolescents with a family history of premature CHD or at least one parent with high TC (TC $\geq$ 240 mg/dL) in the context of regular health care. It recommended that cardiologists make a routine practice of referring the offspring of their adult patients with premature CHD to a source of continuing health care for cholesterol testing and follow-up. Optional cholesterol testing may be appropriate in children and adolescents judged to be at higher risk independent of family history or parental hypercholesterolemia. For example, children and adolescents who are overweight and/or consume excessive amounts of saturated fatty acids, total fat, and/or cholesterol may warrant testing.

The NCEP screening protocol for children and adolescents varies according to the reason for testing (Figure 2). For those being tested because of parental hypercholesterolemia, NCEP guidelines suggest that a non-fasting total cholesterol be the initial test. Further testing with a lipoprotein profile is recommended depending on the level of total cholesterol. For those being tested for family history of premature CHD, a fasting lipoprotein analysis is recommended.[34]

Interventions are determined by results of the fasting lipoprotein analysis (Figure 2). The NCEP panel recommended considering drug therapy in children aged 10 years and older if, after an adequate trial of diet therapy (6-12 months), LDL-C cholesterol remains >190 mg/dL, or LDL-C cholesterol remains >160 mg/dL and there is a family history of premature CHD or at least two or more other risk factors are present. Referral to a specialized lipid center may be appropriate in some cases, especially when high

cholesterol is due to secondary causes or accompanied by multiple risk factors and a family history of premature CHD.[34]

In preparing these recommendations, the NCEP decided not to recommend universal screening for the following reasons: 1) Although high cholesterol levels in childhood generally predict cholesterol elevations in adulthood, many children with high cholesterol levels will not have high enough levels as adults to qualify for individualized treatment; 2) Universal screening could lead to the labeling of many young people as patients with a "disease," causing unjustified anxiety for them and their families; 3) For most children not from high-risk families, there is sufficient opportunity to begin cholesterol-lowering therapies when they reach adulthood; 4) There is insufficient evidence concerning the long-term safety and efficacy of drug therapy in childhood to reduce CHD morbidity and mortality in adulthood and universal screening could lead to overuse of cholesterol-lowering drugs in childhood and adolescence.[34, 46]

The American Academy of Pediatrics Committee on Nutrition published additional guidelines in 1998, slightly modifying the NCEP Report.[35] The committee noted that although the precise fraction of risk for future CHD conveyed by elevated cholesterol levels in childhood is unknown, clear epidemiologic and experimental evidence indicates that the risk is significant. The guidelines stated that diet changes that lower total fat, saturated fat, and cholesterol intake in children > age 2 and adolescents can be applied safely and acceptably, resulting in improved plasma lipid profiles that, if carried into adult life, have the potential to reduce atherosclerotic vascular disease. The guideline also recommended reducing other risk factors. There was no change in the recommended initial screening tests.

The American Heart Association's (AHA) initial "Guide to the Primary Prevention of Cardiovascular Disease," published in 1996 and updated in 2002, does not address prevention in children.[11] In 2003, the AHA published updated guidelines for children that generally follow those set forth by the NCEP Pediatric Panel in 1992.[11] The new AHA guidelines suggest that bile acid-binding resins or statins are usual first-line agents in the treatment of severe dyslipidemia, and that pharmacologic intervention for dyslipidemia should be accomplished in collaboration with a physician experienced in treatment of disorders of cholesterol in pediatric patients. This report also considered hypertriglyceridemia and low HDL-C, with the recommendation of a goal of a fasting triglyceride level <150 mg/dL, and HDL-C >35 mg/dL. No pharmacologic interventions were recommended in children with isolated elevation of fasting triglycerides unless $\geq$400 mg/dL, at which level there is an increased risk of pancreatitis.[11]

Scope of Evidence Synthesis

The patient population, interventions, outcomes, and adverse effects of screening and treatment are summarized in an analytic framework (Figure 3). Corresponding key questions guided the literature review and evidence synthesis. The 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, tracking of lipid levels through childhood to adulthood, role of risk factors in selecting children and adolescents for screening, effectiveness of interventions for children and adolescents identified with dyslipidemia, and adverse effects of screening and interventions. This review includes treatment trials of children and adolescents using dietary, exercise, and drug interventions. Studies of children with previously diagnosed conditions known to cause dyslipidemia (e.g. secondary dyslipidemias and monogenic dyslipidemias) 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 ordinarily already be under surveillance for lipid disorders as a result of their primary disease. Trials of drug therapy in children with heterozygous FH or FCH are included because this population has been exclusively enrolled in treatment trials. Data on cholesterol levels and diagnostic criteria for heterozygous FH are included because identification of previously undiagnosed FH is also a goal of screening (Figure 1).

II. METHODS

Literature Search and Strategy

Relevant studies were identified from multiple searches of MEDLINE (1966 through September 2005) [Appendix 3]. Additional articles were obtained from recent systematic reviews, reference lists of related studies, reviews, editorials, websites and by consulting experts. Retrieved abstracts were entered into an electronic database (EndNote®).

Inclusion/Exclusion Criteria

Investigators reviewed all abstracts identified by the searches and determined eligibility by applying inclusion and exclusion criteria specific to each key question (Appendix 4). Full-text articles of included abstracts were then reviewed for relevance. Eligible studies were English-language, applicable to U.S. clinical practice, and provided primary data relevant to key questions. Studies of children and adolescents with previously diagnosed conditions known to cause dyslipidemia were not included. Animal studies were not included. Studies of risk factors were included only if they provided multivariate adjusted analyses.

For treatment studies**,** full text randomized controlled trials (RCTs), non-controlled clinical trials, and non-controlled prospective studies providing data on the treatment of children and adolescents with diet, drug therapy, exercise, or combinations of these were initially reviewed. Subsequently, only randomized controlled trials and meta-analyses of randomized controlled trials that reported serum lipid outcomes were included. For Key Question 10, outcomes included either adult lipid levels or adult CHD. Studies of other treatment modalities for dyslipidemia (surgery, apheresis) and studies of rare conditions such as homozygous FH were excluded. Information about adverse effects of treatment was obtained from RCTs and additional sources such as non-randomized controlled treatment trials and non-comparative studies of treatment.

Data Extraction and Synthesis

All eligible studies were reviewed and a "best evidence" approach was applied, in which studies with the highest quality and most rigorous design are emphasized.[47] 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 quality of randomized controlled trials using criteria specific to different study designs developed by the U.S. Preventive Services Task Force (Appendix 5).[48] The overall rating is a combination of internal and external validity scores. When reviewers disagreed, a final rating was reached through consensus.

Randomized controlled trials of similar treatments that met additional eligibility criteria were considered for meta-analysis. Meta-analyses were performed to provide estimates of the effectiveness of statins on improving lipid levels in children and adolescents with FH, and of the effectiveness of exercise on improving lipid levels in children and adolescents without FH who were normal or overweight. For each trial, the difference in mean percent change of lipid levels between treatment and control groups and its standard error were obtained and pooled using a random effects model.[49] When the percentage change and its standard error or 95% confidence interval were not reported, they were calculated from the mean and standard error of lipid levels from treatment and control groups at baseline and the endpoint (Appendix 6). A study was excluded when no information on dispersion was reported.

Effects of study level covariates, such as duration, mean age, percentage male/female, and dosage were checked by using random-effects meta regressions.[49] Specifically, drug dose for each statin study was analyzed using an equivalent dose of simvastatin according to published equivalency tables.[50]

Size of Literature Reviewed

A total of 2,507 unique citations were identified by the literature searches (Appendix 4). Included were 160 papers about screening and testing for dyslipidemia (Key Question 2); 68 about interventions and tracking of lipid values over time (Key Questions 4-8 and 10); 8 about the adverse effects of screening (Key Question 3); and 81 about adverse effects of treatment (Key Question 9). Seven papers discussed the costs of screening, but none evaluated cost effectiveness in U.S. population (Key Question 11).

External Review Process

The USPSTF appointed liaisons to advise the Oregon Evidence-based Practice Center in formulating and reporting this systematic evidence review. An additional set of outside experts provided advice in the review formulation stage and commented on a draft version of the evidence synthesis.

III. RESULTS

Key Question 1. Is Screening for Dyslipidemia in Children/adolescents Effective in Delaying the Onset and Reducing the Incidence of CHD-related Events?

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

Key Question 2. What is the Accuracy of Screening for Dyslipidemia in Identifying Children/adolescents at Increased Risk of CHD-related Events and Other Outcomes?

The following sub-questions to Key Question 2 address the accuracy and feasibility of screening children for dyslipidemia.

Key Question 2a. What are Abnormal Lipid Values in Children/adolescents?

Summary

Normal lipid values for children are defined according to percentile cut points within population distributions. In large population-based samples, TC levels increase from birth, stabilize at approximately age two years, peak prior to puberty, then decline slightly. NCEP recommendations are based on results from the Lipid Research Clinics (LRC) Prevalence Study, which determined the 95th percentile cut point for TC as 200 mg/dL and for LDL-C as 130 mg/dL. More recent studies indicate age, sex, and racial differences and temporal trends that shift these cut points.

Evidence

Although several studies conducted in the U.S. during the 1970s obtained lipid levels from large samples of normal healthy children,[51-53] current recommendations[11, 34, 35, 54] are based on distributions of lipid and lipoprotein levels obtained from the Lipid Research Clinics (LRC) Prevalence Study.[14] This study included one Canadian and nine U.S. sites and enrolled subjects primarily based on residency within census tracts, school enrollment, and employment in occupational and industrial groups. Fasting (≥12 hours) lipid and lipoprotein levels were obtained in 15,626 children age 0-19 years between 1972-1976. The selected populations included a broad range of geographic, socio-

economic, occupational, sex, and ethnic groups, but they 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 age two years. At puberty, TC levels declined slightly for both boys and girls, and HDL-C levels declined for boys. For all children, the mean serum level for TC was approximately 160 mg/dL and for LDL-C was 100 mg/dL. The 95th percentile level was 200 mg/dL for TC and 130 mg/dL for LDL-C (Table 2). Results for African American children were similar, however, they were based on smaller numbers and provided TC and triglycerides only.[14]

To determine racial differences, a study of a multi-racial sample of 6,585 U.S. children ages 5-18 years from 22 schools in five states reported non-fasting finger-stick plasma TC levels from 1984-88.[55] The mean TC level for African American children (173 mg/dL) was significantly higher ($p<0.001$) than for Hispanics (168 mg/dL), Asians (165 mg/dL), and Whites (163 mg/dL) (Table 3). The mean TC level for Hispanics was significantly higher than for Whites ($p<0.001$) but not Asians, and higher for girls than boys for Whites only (165 mg/dL vs. 160 mg/dL, $p<0.001$).

More recent data from the National Health and Nutrition Examination Survey (NHANES) III (1988-94) confirm many of these findings. However, in NHANES III mean TC levels among 12-17 year olds decreased by 7 mg/dL from the National Health Examination Survey (NHES) III (1966-1970) and NHANES I (1971-1974) levels shifting percentile cut points upward.[56] NHANES III data from 7,499 children and adolescents ages 4-19 years indicate a 95th percentile cut point for serum TC as 216 mg/dL and for LDL-C as 152 mg/dL.[56] Mean age-specific TC levels peaked at 171 mg/dL at 9-11 years and declined at older ages. Girls had significantly higher mean TC and LDL-C levels than boys ($p<0.005$). Non-Hispanic Black children and adolescents had significantly higher mean TC, LDL-C, and HDL-C levels compared to non-Hispanic White and Mexican American children and adolescents. In linear regression models of these data, age, sex, and race have significant effects on lipid levels questioning the utility of fixed screening cut points.[57]

Key Question 2b. What are the Appropriate Tests? How Well do Screening Tests (Non-fasting Total Cholesterol, Fasting Total Cholesterol, Fasting Lipoprotein Analysis) Identify Individuals with Dyslipidemia?

An appropriate screening test is one that has a strong association with future risk for CHD, or one that can be used to identify people who benefit from treatment.

Summary

TC minus HDL-C above the 95th percentile is 88-96% sensitive and 98% specific for detecting LDL-C ≥130 mg/dL. However, a single TC or HDL-C measurement is insufficient for practitioners to assign children and adolescents to the NCEP risk categories with 95% confidence.

Identification of familial hypercholesterolemia (FH) has traditionally used LDL-C levels alone or combined with family history. In families with known FH, LDL-C levels above the 95th percentile detect FH among first-degree relatives with 95% sensitivity. However, the ability of LDL-C to predict FH decreases when using second and third degree relatives of an FH proband, and decreases further when applying these criteria to the general population. Lipid Research Clinics (LRC) data indicate that TC > the 95th percentile is 69% sensitive and 98% specific for detecting children and adolescents (ages 6-19) with LDL-C > the 95th percentile and TG < the 95th percentile for age and gender. No studies have evaluated lipid levels in the general U.S. population as a diagnostic test for FH using mutation or biochemical analysis as the gold standard.

Evidence

In AAP and NCEP guidelines, TC is used as an initial laboratory measurement for children being tested because of a family history of high cholesterol, and a lipoprotein profile is obtained if the patient has a TC over a certain defined target. In children, as in adults, LDL-C is the basis for initiating treatment and determining goals of therapy. How well TC levels detect elevated LDL-C levels has been examined in three different populations, using LRC data (ages 6-19, n=1325),[58] Hispanic children (ages 4-5, n=106)[59] and the biracial Bogalusa cohort (ages 5-17, n=2,857).[60] TC> the 95th percentile detected LDL > the 95th percentile with sensitivities of 44% (White females) to 50% (White males, African American males and females).[60] Specificities were 90% (African American and White males and females).[60] With LRC data, a fasting TC > the 95th percentile had 69% sensitivity and 98% specificity for detecting children with LDL > the 95th percentile and TG <the 95th percentile.[58] Using a lower threshold of fasting TC ≥ 75th percentile to detect LDL ≥ the 95th percentile in a sample of Hispanic children ages 4-5, sensitivities were 86% (using an LRC defined 75th percentile) and 96% (using the sample defined 75th percentile), and specificities were 93% (LRC defined) and 87% (sample defined).[59] Variations in test characteristics are likely due to population differences, or slight differences in definitions of the percentile definition. Use of an absolute cut-off rather than an age and gender adjusted percentile results in higher sensitivity and lower specificity for females.[58]

In adults, the recommended screening tests are TC and HDL-C. While this has not been recommended in guidelines for children and adolescents, it is common in practice.[61] HDL-C may help distinguish false negatives from true negatives among those screened with TC alone.[58] The use of TC and HDL-C in combination as a screening tool has been evaluated[62, 63] In 260 African American adolescents (ages 12-20), fasting TC minus

HDL-C above the 95th percentile was 96% sensitive and 98% specific for predicting LDL-C ≥130 mg/dL. Using data from adolescents who were both non-fasting and fasting, TC minus HDL-C was 88% sensitive and 98% specific.[62]

Using weekly repeated measures of TC and HDL-C, within-person variability and the ability of these tests to reliably classify children and adolescents into NCEP risk categories (TC<170 mg/dL acceptable, TC 170-199 mg/dL borderline, and ≥200 mg/dL high; and for HDL-C <35 mg/dL low, and ≥35 mg/dL acceptable) were assessed. A child needed to have a TC level below 155 mg/dL or above 185 mg/dL to be assigned a category of acceptable or borderline/high (respectively) based on a single measurement. To accurately assign a child to the high category with 95% confidence, a TC > 215 mg/dL was required. No single TC value would place a child in the borderline category (170-200 mg/dL) with 95% confidence. Averaging two TC readings improved the ability to classify children with 95% confidence: a TC <159 mg/dL could reliably assign a child to the acceptable category and a TC of >211 mg/dL could reliably assign a child to the high category. Three TC measurements did not substantially improve the ability to classify children into risk categories.[63]

Likewise, one measurement of HDL-C was required to be <28 mg/dL or > 43 mg/dL to confidently assign (based on the 95% confidence interval) the child to a low HDL (<35 mg/dL) or acceptable (>35 mg/dL) category. With two HDL measurements, the values required were <30 mg/dL and >40 mg/dL respectively.[63]

Direct LDL-C measurement offers the advantage of using nonfasting serum samples. It may be as precise as that calculated LDL-C using the Friedewald formula,[64] but this remains controversial. Immunoseparation and direct determination of plasma LDL-C correctly classified 81% of children according to NCEP cut-offs, compared to 84% of children correctly classified using the Friedewald formula.[64] In another study, however, direct LDL-C correctly classified 83% and 81% of those children with LDL-C >130 mg/dL and ≥190 mg/dL respectively, but only 43-55% of those with LDL-C 130-190 mg/dL. This compared with the Friedwald formula which correctly classified 79-82% of the group between 130-190 (using a gold standard that was β-quantification LDL).[65]

A primary goal of screening in children and adolescents is to identify individuals who are at risk for premature CHD and would benefit from early treatment. The most prevalent condition leading to early CHD is familial hypercholesterolemia (FH). Clinical definitions of FH vary (Table 4A[34-36] and 4B[38, 39, 66-83]). Many studies assume FH is present based on LDL-C levels and clinical data. Studies have used LDL-C levels above the 95th percentile for age and gender with a family history of early CHD as a diagnostic criterion for FH. Others have used LDL-C above a certain level (LDL-C cutoff varies among studies) and a parent with FH, but it is often unclear how the parental diagnosis was made. Still others have used LDL-C levels along with the presence of xanthomas to define FH, though xanthomas are rare in children with FH, especially young children.

The gold standards for diagnosis of FH include either molecular genetic studies identifying a pathogenic mutation in the LDL-C receptor gene, or biochemical studies

showing defective LDL-C receptor activity in cultured fibroblasts. Over 800 LDL-C receptor mutations have been identified in FH,[30, 84, 85] thereby complicating diagnostic confirmation. Some populations (South African Afrikaners, Finnish, French Canadian) have limited numbers of mutations,[30, 85] but this is not true of the U.S. population. LDL-C receptor activity assays are expensive, difficult and not widely available.[30] As a result, clinical trials reporting results in children with FH for the most part included children who likely have FH but who have not had diagnostic confirmation (Table 4B). Although genetic screening has been evaluated in populations where there are few known mutations causing FH,[86, 87] no studies have evaluated LDL-C levels in a general population of U.S. children identified through lipid screening and confirmed suspected cases of FH with mutation analysis. Several descriptive epidemiologic studies have used LDL-C levels for diagnosis within identified FH families[88-90] Even among these studies, only one used families identified by mutation analysis,[89] whereas the others used families identified by either mutation analysis or LDL-C above the 95th percentile along with tendon xanthomata,[88] or by lipid levels alone.[29] LDL-C levels greater than 135 mg/dL,[88] and LDL-C levels above the 95th percentile for age and gender among 1st degree relatives of an FH proband[89] captured 95% of FH cases within families.

The difference in the predictive value of LDL-C levels for diagnosing individuals within families as opposed to in the general population was nicely demonstrated by a study of relatives from 5 large, LDL-C receptor mutation confirmed Utah FH pedigrees. Data from this cohort were used to assess the sensitivity and specificity of mathematically-derived screening criteria in the population of relatives.[91] Differences in predictive values for total cholesterol among 1st, 2nd, and 3rd degree relatives of persons with FH were evaluated and demonstrated graphically (Figure 4). The predictive value of a specific LDL-C level to diagnose FH decreases substantially for 1st, 2nd, and then 3rd degree relatives of FH, and is even lower for the general population. Thus, TC and LDL-C levels that were evaluated for diagnosing FH using FH kindreds do not allow for application of identified LDL-C levels to non-FH families or to general populations. There were no studies identified that evaluated LDL-C levels in a general population of children or adolescents that subsequently confirmed suspected (screen identified) cases of FH with mutation or biochemical analysis.

Key Question 2c. How Well do Lipid Levels Track from Childhood to Adulthood?

Summary

Serial correlations between lipid levels measured in individual children over time are higher for TC (r=0.38-0.78) and LDL-C (r=0.4-0.7), than for HDL-C (r=0-0.8) and TG (r=0.1-0.58). Tracking is generally consistent within a cohort. Age at first measurement and duration of follow-up do not appear to be related to strength of the correlation between measurements. Approximately 40-55% of children with elevated lipids defined

by percentile within a population distribution will continue to have elevated lipids on follow-up. Likewise, the highest quintile of TC at follow-up consists of children and adolescents from the 1st (4-6%), the 2nd (11-13%), the 3rd (19-20%) and the 4th (18-21%) quintiles at baseline. There were no studies of tracking according to other risk factors.

Evidence

Twenty-three prospective cohort studies contributed information on tracking of lipid levels during childhood. Twenty-one studies reported correlation coefficients and are listed on Evidence Table 1,[3, 17, 92-110] whereas 2 studies reported tracking only by percentile and are described in the text.[111, 112] These studies drew from seven U.S. cohorts and eight non-U.S. cohorts.

Correlation coefficients from these studies are displayed both by age at first measurement (Figures 5A-5D) and duration of follow-up (Figures 6A-6D). In both displays, TC and LDL-C track more consistently than do HDL-C and TG. There does not appear to be a clear pattern of improvement in tracking of cholesterol levels with either increasing age or shorter duration of follow-up. Studies noted better tracking for boys and African Americans.[3, 17, 108] The range of correlation coefficients (or tracking coefficients) among the U.S. cohort studies is 0.38 to 0.78 for TC, 0.4 to 0.71 for LDL-C, 0 to 0.79 for HDL-C and 0.1 to 0.58 for TG. HDL-C tracking was worse in one study from the Muscatine cohort (0 to 0.1) than in studies from other cohorts (0.2 to 0.79).
Studies also reported the percentage of children remaining in high-cholesterol classification categories at follow-up (Table 5A).[3, 92, 94, 95, 98, 99, 105, 111] Of children ages 5-18 with two consecutive cholesterol measurements above the 90th percentile in the Muscatine cohort who had lipids measured again at ages 20-30 (n=70), 34% had adult cholesterol levels $\geq$ 240 mg/dL, 37% had adult levels between 200-239 mg/dL, and 29% had adult levels < 200 mg/dL.[113] In the Bogalusa cohort, 196 children were classified in the highest quintile of TC at year one; of those, 55% remained in the highest quintile eight years later.[17] The Child and Adolescent Trial for Cardiovascular Health (CATCH) cohort study is large (n=3,659) and more recent, but has not yet followed the cohort through to adulthood.[3] Between 3rd and 8th grades, 53% remained in the lower quintile and 55% in the highest quintile of TC. Fifty-three percent remained in the lowest quintile and 55% in the highest quintile for HDL-C.[3]

Likewise, some studies have evaluated the derivation of the highest risk group at follow-up (Table 5B).[96, 105, 108, 112] In the Beaver County Lipid Study individuals who were in the top quintile for TC at follow-up (ages 17-30 years), had the following distribution of TC values at baseline (ages 1-14 years): 6% had TC in the 1st (lowest) quintile, 13% in the 2nd, 19% in the 3rd, 21% in the 4th, and 40% in the 5th (highest).[96]

Most tracking studies compared single lipid measurements over time. Repeated lipid measurements in children show variation (see above, Key Question 2a). Therefore, regression to the mean should be considered as one explanation for variability among tracked values.[108, 114] Some adjusted for covariates, or used tracking coefficients.[101]

None of these studies evaluated the proportion of children and adolescents with lipid levels above the 95th percentile who remained in the top 5% at follow-up.

Key Question 2d. What is the Accuracy of Family History in Determining Risk?

Summary

Family histories can be time consuming and difficult to elicit accurately. Screening using family history has been shown to miss substantial numbers (30-60% in general) of children with elevated lipids. Family history definitions vary substantially among studies as do lipid detection thresholds. Those studies that show higher sensitivities (~77%) have low specificities (55% or lower). Population-based estimates of the number of children requiring serum lipid testing based on family history may range from 25-55%, depending on the exact definition of family history and the lipid detection threshold.

Evidence

The AAP and NCEP advocate selective screening for dyslipidemia among children and adolescents who have a family history of early CHD or high cholesterol. Many good quality studies of diagnostic accuracy have evaluated the sensitivity and specificity of family history according to various guidelines for detecting abnormal lipids in children and adolescents (Table 6).[59, 62, 115-128] All of these studies used an appropriately broad spectrum of patients either from pediatricians' offices, schools, or ongoing cohort studies and applied tests of family history and lipid measurement equally. The studies used different definitions of the screening tool (any parental history of heart attack, other parental risk factors, varied age definitions of early CHD), and selected different levels of LDL-C or TC as the lipid detection threshold.

Definitions of a positive family history can vary, including whether grandparents are considered, the age used to define premature CHD (55, 60, or 65, or gender-based), and whether CHD in 1st and 2nd degree relatives is taken into account. Likewise, in these studies, multiple different definitions of family history were evaluated. A family history definition that included a parent or grandparent with CHD prior to age 50-60 and/or cholesterol >240 mg/dL had sensitivities ranging from 46-74% for TC >170 or LDL-C >130 mg/dL.[59, 117] Parental history of early CHD alone was 5-17% sensitive for TC >170 mg/dL or LDL-C >130 mg/dL,[59, 117] whereas parent or grandparent history of early CHD was 46% sensitive for LDL >the 95th percentile.[119]

Regardless of the precise definition, family history has been repeatedly shown to miss substantial numbers of children with elevated lipids, ranging from 17-90% overall and 30-60% in most studies.[62, 118, 119, 122, 124, 126, 129-131] In addition, the proportion of children

and adolescents who qualify for screening based on family history is generally between 25-55% depending on the sensitivity of the specific family history question.[59, 62, 115-119, 121, 124, 125, 127, 132] This compares with the original NCEP estimate based on LRC data that 25% of the child/adolescent population would require screening on the basis of family history.[133] Studies reporting sensitivities above 70% used family history of high cholesterol, early CHD (< age 60), stroke, angina, or hypertension to detect a TC >200 mg/dL;[115] family history of high cholesterol or early CHD to detect LDL $\geq$130 mg/dL[117]; or parent or grandparent history of any risk factor (high cholesterol, diabetes, hypertension, gout, obesity) or atherosclerotic risk factor (MI, angina, sudden death, stroke or PVD) prior to age 55 to detect a fasting LDL >the 95th percentile.[119] Of these studies with the highest sensitivity, most had poor specificity, the highest being 55%.[117]

Obtaining family history can be time consuming and the history is often inaccurate depending on who is giving it. There is concern that African-American Black children and children from single-parent households are more likely to be missed by screening strategies that use family history.[126, 133]

Key Question 2e. What are Other Important Risk Factors?

Summary

Evidence for child and adolescent risk factors for dyslipidemia other than family history is strongest for overweight, but otherwise is lacking for the general population. Epidemiologic cross-sectional and cohort studies report a strong statistical association between overweight and elevations in lipids. The potential impact of incorporating weight measures into a screening tool has not been addressed. Multiple other risk factors (diet, physical inactivity, aerobic capacity/fitness, puberty and smoking) have not been evaluated adequately to assess their contribution to dyslipidemia in children or their usefulness as screening tools.

Evidence

In addition to family history, assessment tools for selective screening could incorporate other risk factors reflecting a child's diet, physical activity level, aerobic capacity/cardiovascular fitness, overweight, and fat distribution. Childhood overweight, as measured by BMI, has been identified in one review as the best independent predictor of adult dyslipidemia after LDL-C. Its predictive power is most notable when considering increase in BMI from childhood to adulthood.[134]

Forty-two cohort and cross-sectional studies of mixed quality with adjusted statistical analyses contributed information on additional risk factors for identifying children at

increased risk for elevated lipids and/or CHD-related events (Evidence Table 2, Tables 7A, 7B, 7C).[18, 120, 135-174]

Thirty studies examined overweight or body fat composition measures as a risk factor[18, 135-141, 144-149, 154, 156-159, 161-167, 169, 170, 172, 174] and it was the most consistently effective in predicting risk of dyslipidemia compared to other factors assessed.

Six studies evaluated overweight as a risk factor along with family history.[140, 141, 148, 165, 170, 172] Italian school girls (n=361) who were overweight, defined as weighing $\geq$ 20% ideal weight, had higher mean LDL-C (126.6 mg/dL for overweight vs 99.5 for those not overweight mg/dL, p<0.001) and mean TC (173.8 mg/dL vs 199.0 mg/dL, p<0.01) with lower mean HDL-C (58.9 mg/dL vs 50.0 mg/dL, p<0.001).[148]

Among 506 inner-city youths aged 5 to 19 who were predominantly African American and Hispanic, those who were overweight had a 1.74 odds ratio for having hypercholesterolemia controlling for age and family history (95% CI=1.34-2.14).[141] Sensitivity of using this overweight measure alone to screen was 42%, with a specificity of 71% for predicting hypercholesterolemia (TC > 170 mg/dL or LDL-C > 110 mg/dL). Combining overweight with family history had a sensitivity of 49% and specificity of 64%.[141]

A Wisconsin study of 2,726 schoolchildren aged 5 to 15 showed BMI was related to adverse levels of all lipids and lipoproteins (TC: r= 0.010 [95% C.I. 0.002, 0.018], LDL-C: r= 0.012 [95% C.I. 0.004, 0.019], HDL-C: r= -0.013 [95% C.I. -0.016, -0.010]).[140] In contrast, a study of 1,081 youths aged 2 to 20 in a pediatric office-based cholesterol screening program showed BMI was not associated with cholesterol level.[172] A study of 458 youths in a suburban Dutch community found that for girls over age 15, TC increased step-wise across quartiles of body weight with the 4th quartile showing a significant difference from the 1st quartile of approximately 7mg/100ml (p<0.05).[170] A multiple regression analysis of 164 highly-selected youths aged 6–16 with heterozygous FH showed that LDL-C was related to FH parent's cholesterol levels, percent body fat, pubertal stage, and non-FH parent's cholesterol level (p<.01), together explaining 40% of variance in LDL-C (CI 25%-55%).[165]

Key Question 2f. What are Effective Screening Strategies for Children/adolescents (Including Frequency of Testing, Optimal Age for Testing)?

Summary

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, address the frequency and optimal age for testing, or evaluate strategies that might increase provider and parent compliance.

Evidence

Twenty-six studies evaluated screening strategies among children in various settings (Evidence Table 3).[59, 62, 79, 115, 117-120, 122, 124, 126, 130, 131, 133, 175-186] One RCT of college students compared two regimens for screening;[183] all others were non-comparative prospective studies describing screening interventions. Two additional studies addressed parent and physician response to screening results.[187, 188] These and others reported low parental compliance with follow-up testing, even when follow-up was free, as with pre-paid health plans.

Studies demonstrate low compliance among primary care physicians in following current guidelines for screening.[188] In an ancillary study of the Child Adolescent Trial for Cardiovascular Health (CATCH), parents were given recommendations to consult their child's physician if TC exceeded 200 mg/dL on one or more occasion.[187] After physicians saw the children, only 59% were further evaluated for possible elevated cholesterol. Of these, half of the physicians repeated cholesterol tests, 42% asked about family history, 38% made recommendations for dietary management, and only 12% referred children to dietitians.[187]

Neonatal screening

Neonatal screening for dyslipidemia has been examined in multiple studies, mostly using cord blood for analysis of TC[106, 189-202] Other studies have investigated the use of dried filter paper blood spots from cord blood[203] and from heel sticks taken from 3-7 day old infants (the same samples used for routine neonatal screening for conditions such as hypothyroidism and phenylketonuria).[204-209] Five studies had follow-up of cord blood cholesterol levels with serum levels in the children at a later time.[190, 192, 193, 196, 197] One study included serum analysis at birth and 1 year, along with LDL receptor mutation testing of infants with parents who had DNA-documented heterozygous FH, comparing levels in affected newborns to non-affected newborns.[210] Using cord blood, TC and LDL-C levels were elevated in the FH newborns as compared to non-FH newborns, but there were no significant differences between HDL-C or TG. However, differences between FH and non-FH infants in TC and LDL-C were more pronounced when measured at 1 year.[210] No studies were identified that screened a general population of infants and followed up abnormal results with mutation analysis.

Key Question 3. What are the Adverse Effects of Screening (Including False Positives, False Negatives, Labeling)?

Summary

Parental non-compliance with screening and follow-up recommendations is reported to be related to concerns about test accuracy, lack of proof that intervention makes a difference in children, concerns about upsetting the child, refusal by the child, inconvenience, or decisions to institute a diet themselves and have child rechecked subsequently.

Evidence

Potential adverse effects of screening for dyslipidemia among children have been examined in one randomized controlled trial[211] and five studies of various other designs[130, 212-215] Screened college students were randomized to receive desirable results (TC = 174 mg/dL) or borderline-high results (TC = 224 mg/dL). Those who received borderline-high test results rated high cholesterol as a less serious threat to health than did the desirable-feedback subjects, and perceived the test to be less accurate. Higher self-esteem was associated with lower likelihood of requesting information after receiving borderline-high test results.[211]

Parental non-compliance with screening has been demonstrated by two studies of screening. The Child and Adolescent Trial for Cardiovascular Health (CATCH) program measured cholesterol levels in 5,106 children in 3rd grade and in 3,936 of these again in 5th grade. Parents received mailed notification of their children's cholesterol results and a follow-up telephone survey. Parents indicated that a physician had been consulted for only 20% of children. Eighty-four percent of those notified once recalled receiving the notice, yet only 39% of those remembered the results as being high.[187]

Likewise, a pediatric group screened 439 children ages 2-15 as part of well-child exams or non-acute illness including siblings of all those seen. Of the 134 (31%) children who had cholesterol levels above the 75th percentile and were recommended to return for a fasting lipid panel, 51% did so. Parents of children who did not return were contacted 4-6 months later, and 94% remembered their child's screening cholesterol level had been elevated, while 64% remembered that follow-up had been suggested. The most common reason parents provided for lack of timely follow-up were concerns about whether the test was accurate (67%), planning to recheck at next visit (67%), concern that child was upset by initial finger stick (47%, most of whom were parents of children younger than 5 years), lack of proof that intervention for high cholesterol makes a difference in children (40%), inconvenience (40%), and decision to try a low-fat, low-cholesterol diet before having the child's lipids rechecked (40%). Family history of hypercholesterolemia, angina, and stroke were not consistently associated with higher follow-up.[130]

Identification of dyslipidemia in children was associated with increased parental reporting (not confirmed with objective measures) of behavior disturbances in the subsequent 12 months, worse scores on the child behavior checklist, but no differences in depression or anxiety for either the children or the mothers.[213] Children with dyslipidemia (n=36) and matched controls from one large pediatric practice showed no differences measures of well-being, depression and behavior.[215] Older dyslipidemic children (ages 6-10) had more negative health beliefs than younger children (ages 4-6), and younger children's reports of parent's dietary control were negatively related to the children's feelings of acceptance.[212] Parents of children diagnosed with FH reported perceptions of burdensome follow-up causing conflicts between themselves and their children, and difficulty changing diet. Although the older children interviewed as part of this study tended to remember feeling sad, angry, or worried about heart problems, none reported that these worries interfered with their usual activities.[214] Children with greater problem solving skills have demonstrated better compliance with recommended diet and greater reductions in LDL-C following traditional diet counseling.[216]

Limitations of the literature around adverse effects of screening include small sample sizes, mostly observational studies, and the hypothetical nature of risks in the screened populations.

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 meeting inclusion criteria evaluated the effect of a childhood intervention on the incidence of adult dyslipidemia, or the onset or incidence of 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?

Summary

Statins and bile acid binding resins are effective for reducing TC and LDL-C in children with FH, the only population for whom they have been studied. These trials might not generalize to children without FH. Trials of other agents are methodologically limited. Diet supplements (psyllium, oat, sterol margarine) and counseling are marginally effective in lowering lipid levels in children with FH or FCH, as well as in children with idiopathic (risk factor associated) dyslipidemia. Trials show minimal if any improvement

in lipids with exercise among children from the general population (overweight or normal weight). No trials evaluate exercise treatments in children with FH.

Evidence

Forty randomized controlled trials met inclusion criteria and are included in this report (Evidence Table 4).[37-41, 66-69, 71-78, 80-82, 217-236] Of these, ten are rated good quality,[37, 38, 40, 69, 71, 76, 78, 218-220] 12 fair,[41, 66, 67, 72, 74, 81, 221, 222, 225, 232, 233, 235] and 18 poor.[39, 68, 73, 75, 77, 80, 82, 217, 223, 224, 226-231, 234, 236] Drug therapy interventions included bile acid binding resins, anti-oxidants (vitamin C and E), docosahexaenoic acid (DHA), HMG-CoA Reductase Inhibitors (statins), and combination therapy. Studies of other types of interventions included exercise therapy and advice, dietary products (margarine, flour, cereal, garlic extract), dietary advice, and combinations of these. Major limitations include 20 or fewer subjects in each arm,[39, 67, 73, 82, 221, 223, 224, 230, 234-236] high loss to follow-up,[77, 81, 222] lipid measures that are non-standardized or not reported as such, varied inclusion criteria (Table 4B), failure of blinding,[77, 220, 228, 231-233] lack of results presented for the period prior to crossover,[39, 41, 73-75, 223, 224, 227, 234, 236] and lack of intention to treat analyses.[41, 66, 67, 72, 75, 77, 81, 82, 217, 222, 224, 226, 228, 229, 231-233] In addition, one trial did not report data for the placebo group.[66]

Statins, bile-acid binding resins, and fibrates have been tested only in children with FH and FCH. Applicability of results from these trials to children without these conditions may be difficult. We assessed external validity for each study using the following criteria: population-based (vs recruited from a lipid clinic), presence of a run-in period, number of participants, and reimbursement for participants. Eleven studies were population-based,[67, 69, 72, 78, 219-222, 225, 230, 233] while others used populations recruited from single lipid clinics.[37, 39-41, 66, 68, 73-77, 80, 82, 223, 224, 226, 231, 237] Fourteen reported the presence of a run-in period,[37, 39-41, 66, 67, 69, 71-76, 78, 80, 82, 223, 224, 228, 234-236] one of which did not exclude any participant after the run-in period.[66] Five trials failed to report or were unclear about the presence of a run-in period.[227, 229-231, 238] Three studies reported reimbursement or free medication for participants;[75, 225, 226] others did not mention this. Only 24 studies had 50 or more participants.[37, 38l, 40, 66, 68, 69, 71, 72, 76, 78, 80, 81, 217-220, 222, 225-229, 232, 233] Pharmaceutical or cereal company funding was reported in 14 studies; 16 other studies did not report funding source.

Studies in children with probable or definite familial hypercholesterolemia

Drug treatment. Eighteen trials meeting inclusion criteria evaluated drug therapies for treatment of children with probable or definite heterozygous familial hypercholesterolemia (Table 8).[37, 38, 66, 68, 69, 71-76, 78, 80-82, 224, 234, 236] Most of these studies included children who were already compliant with a recommended low-fat, low-cholesterol diet. These diets are presented in Table 1. Both treatment and control groups were maintained on the diet during these trials.

All the trials of statin drugs, including one trial of atorvastatin,[76] three of lovastatin,[38, 72, 78] two of pravastatin[37, 71] and three of simvastatin,[66, 68, 69] demonstrated improvement in TC and LDL-C among children and adolescents with FH. The decrease in TC ranged from -17% to -32% compared to baseline for treatment groups vs. changes of +3.6% to –2.3% for placebo. The decreases in LDL-C ranged from –19% to –41% for treatment groups, vs. changes of +0.67% to –3% for placebo. HDL-C decreased in the one trial of atorvastatin,[76] increased in one[72] but not the other trial of lovastatin,[78] did not change in the one trial of pravastatin that reported HDL-C,[71] and increased in two trials of simvastatin[66, 68] but not the third.[69] Overall, HDL-C increased between +1% and +11% for treatment groups, vs. –1% to +4.8% for placebo groups. Triglyceride changes varied, with only simvastatin demonstrating lower triglycerides in all three trials that evaluated it.[66, 68, 69] Overall, the range of triglyceride change with treatment was +9% to –24%, vs. placebo +4% to –12%.
Results from eight trials of statins, six good,[37, 38, 69, 71, 76, 78] one fair,[66] and one poor[68] quality, were included in a meta-analysis (Figures 7-9). Data from studies reporting triglyceride outcomes were not sufficient for meta-analysis. Pooled estimates for all doses combined included 24.4% (95% C.I. 19.5, 29.2) mean reduction in TC, 30.8% (95% C.I. 24.1, 37.5) mean reduction in LDL-C, and 3.3% (95% C.I. 1.0, 5.7) mean increase in HDL-C. Using drug-adjusted equivalent doses showed linear relationships between dose and drug effect as well as between dose and mean age of the study participants (lower doses associated with younger age, p=0.90, p=0.0029). Other study level covariates, such as duration and percent male or female, were not associated with drug effects. Exclusion of the poor quality study did not affect the results.

One fair quality trial of cholestyramine[81] and one poor quality trial of colestipol[80] demonstrated decreased total cholesterol and LDL-C but no change in HDL-C or triglycerides. One fair quality study without pre-crossover results demonstrated that patients ages 10-18 preferred and were more compliant with a pill form vs. powder form of cholestyramine.[74]

Poor quality trials evaluating bezafibrate,[82] vitamins C and E,[224] DHA,[234, 236] p-aminosalicylic acid,[73] and a head-to-head comparison of combined colestipol and pravastatin vs. colestipol alone,[75] failed to report pre-crossover data. Trials of vitamin C and E and DHA included children and adolescents with FH as well as FCH.

Non-invasive measures of vascular outcomes were evaluated in one good quality study that showed regression of mean carotid intima-media thickness (IMT) over two years with treatment with pravastatin,[37] and in two poor quality trials without pre-crossover data that showed improvement in brachial artery flow-mediated dilation with vitamins C and E treatment, and DHA.[224, 234]

Diet treatment. Of the five trials meeting inclusion criteria that evaluated diet treatments in children with FH (Table 9), one was rated good quality,[40] three fair,[41, 67, 235] and one poor.[39] These trials evaluated plant sterol margarines vs. placebo margarine,[39-41], psyllium-enriched cereal,[67] and garlic extract.[235] Although all three trials of sterol

margarines were crossover trials without pre-crossover results presented, the wash-out periods between treatment periods were 4-6 weeks in two of these trials, making it more likely that the results of these trials are valid.[40, 41] For these two studies, the mean decreases in TC were -7.4% to –11%, the decreases in LDL-C were –10% to –14%. The differences in HDL-C and triglyceride levels were not significant. The third trial of sterol margarine had no washout period between the treatment arms, but showed similar results (-11% change in TC, -15% for LDL-C, non-significant changes for HDL-C and TG).[39] The trial of psyllium-enriched cereal found a 8% decrease in TC in the treatment group vs. –3% in the placebo group, and a decrease in LDL-C of –10% in the treatment group vs. –0.5% in the placebo group, with non-significant post-crossover results for both HDL-C and TG.[67] There was no significant improvement in lipid levels with 8 weeks of garlic extract treatment.[235]

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

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

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

Diet treatment. Dietary interventions in general populations of children and adolescents were addressed in eight studies, three of good quality,[218-220] and five of poor quality (Table 10).[77, 223, 227, 229, 231] Two of the good quality studies were from the multi-center Dietary Intervention Study in Children trial. [218, 219] These and other trials[77, 227] tested the effect of dietary advice for families and children on dietary outcomes and lipid levels. A good quality trial by the DISC Collaborative Research Group showed that intensive counseling and follow-up over three years reduced TC and LDL-C and improved dietary intake.[219] Lipid lowering results were not sustained at five and seven year follow-up, after the intervention ceased, but improvements in diet remained significant.[218] One good quality study of the Parent-Child AutoTutorial (PCAT) program[220] reported 8% improvement in LDL-C ($p<0.05$) compared to the at-risk control group. Another poor quality study of PCAT found decreases in both treatment and control groups, but no between-group differences.[77] A poor quality study of single vs. multiple nutritional advice sessions found 7-8% decreases in TC and LDL-C for the multiple session group, vs. 3% decrease in TC in the single session group.[227]

Dietary supplements trials included two poor quality studies of psyllium [223, 229], and one poor quality study of oat bran.[231] Psyllium supplements decreased TC and LDL-C (5% and 9% greater decreases in fiber group over control using Step I diet) in the one trial,[229] but had no effect in the other,[223] The trial of oat bran showed no significant changes in lipids.[231]

Exercise treatment. Six studies, three fair quality[225, 232, 233] and the three poor quality[226, 228, 230] meeting inclusion criteria evaluated exercise in normal or obese children with elevated lipids (Table 11). The poor studies were rated poor because of differential or low completion rates (51-52%), small numbers of participants (≤20) resulting in low generalizability, among other problems (lack of blinding, lack of intention to treat).

In these studies, lipid levels were lower than those typically used to define FH (LDL-C<160mg/dL and TC<240 mg/dL). Two trials comparing supervised, scheduled sessions of aerobic and fitness training to control groups who received no specific regimen showed improvements in HDL-C for the intervention group.[230, 233] The others showed minimal or no change in lipids compared to control groups.[225, 226, 228, 232]

A meta-analysis of these six exercise trials in healthy and/or overweight children and adolescents without identified FH or monogenic dyslipidemia showed non-significant increases in TC, LDL-C and HDL-C (Figures 10-12). This result did not change with exclusion of the poor quality studies, or with exclusion of the study of college-age women (an outlier because of age). However, trials were problematic because baseline lipid levels were different between the treatment and control groups,[225, 230, 233] suggesting that randomization may have been flawed. In these studies, the magnitude of difference in the baseline difference between the two groups could be larger or as large as the difference between baseline and endpoint.[225, 230, 233] These trials generally had small sample sizes and may not have had enough power to detect a significant effect. Also, most trials only reported the mean lipid level and its associated variance (or S.D.) at baseline and endpoint for both treatment and control groups, and our method to calculate standard error of percent change may have yielded a conservative estimate because the correlation between baseline and endpoints is ignored in the calculation (see Appendix 6).

Combination Diet and Exercise Treatment. Three trials meeting inclusion criteria, two fair[221, 222] and one poor,[217] evaluated combined regimens of diet and exercise in this population (Table 12). One study showed a 23% increase in HDL-C for the exercise, diet plus behavior change group compared with no significant changes for either the diet plus behavior change or the control groups.[221] One "Know Your Body" curriculum study encouraged adoption of regular exercise programs and an AHA prudent diet,[239] and found a small decrease in TC that became significant after adjustment for age, gender and race.[222] The third trial combined the diet alone and diet plus exercise groups for analysis and found a 4% decrease in TC in the intervention groups compared to a 2.2% increase in the waiting list control group (p=0.03), a 20% increase in HDL-C compared to 6.5% increase in the control group (p=0.007), and a 41% decrease in TG for the intervention group vs. an 8% decrease for the control group (p=0.01).[217]

Key Question 9. What are the Adverse Effects of Drug, Diet, Exercise, and Combination Therapy in Children/adolescents?

Summary

Statin drugs are associated with elevations in liver enzymes and creatinine kinase (CK), and bile-acid binding resins are associated with non-serious gastrointestinal side effects and subclinical decreases in serum vitamins and minerals. There are reports of growth failure in children and adolescents on low-fat diets, particularly those who were placed on low-fat diets without formal nutritional assessment and advice. Most studies of children over two years old on low-fat diets reported normal growth and development. Studies were variable in the quality of adverse effect assessment and reporting, and too short to determine long-term effects.

Evidence

Tables 13-17 and Evidence Table 5 provide details about adverse effects reported in studies of drug, diet, exercise, and combination therapies in children with elevated lipid levels. Data on safety of longer-term and more widespread use of statin drugs in adults are available in the recent Drug Class Review on HMG-Co Reductase Inhibitors, a systematic review of adverse effects of statins conducted by the Oregon EPC and updated in June 2005.[50]

Drug treatment

Information about adverse events was reported in 15 studies of statins (Table 13),[37, 38, 66, 68-72, 76, 78, 240-244] in 22 studies of bile-acid binding resins (Table 14) reported in 23 publications,[74, 75, 80, 81, 245-263] and in 9 studies of various other drugs or drug combinations (Table 15).[54, 73, 82, 264-269] Studies used randomized controlled trial, open-label trial, non-comparative, retrospective, and other descriptive designs. Where possible, prevalence rates are reported for studies with more than 20 participants.

Statins were associated with increased ALT and AST in three studies (0-3% of participants in RCTs),[69, 76, 241] while six other studies found no changes in liver enzymes overall.[37, 68, 78, 240, 242, 243] CK levels were elevated in five studies (range 0.5-4% reporting a significant change in CK, with one study reporting 45% having any abnormal CK test, but none statistically significant),[69, 71, 72, 241-243] were normal in four studies,[37, 68, 78, 240] and subjects reported myalgia in four studies.[69, 240-242] Normal sexual development was reported in four studies.[37, 38, 76, 78] No studies observed an adverse effect of statins on sexual development or endocrine function, although one study observed an 18% increase in dehydroepiandrosterone sulfate (DHEA) levels with lovastatin compared with a 5% increase with placebo.[78] Other adverse effects of statins include gastrointestinal complaints in four studies,[69, 71, 240, 241] rash/pruritus in two studies,[69, 71] and headache in

three studies.[69, 71, 241] A study of psychological effects found no adverse effects associated with statin therapy.[70] Statins have known drug interactions with erythromycin which can precipitate rhabdomyolosis.[50, 76]

Bile-acid binding resins were associated with gastrointestinal complaints (8-26%), such as flatulence and constipation, in 11 studies,[74, 75, 80, 81, 247, 250, 252, 254, 256, 259, 260] and their unpalatability (up to 50%) was noted in seven studies.[248, 252, 253, 255, 258-260] Reduced serum folate occurred with colestipol in one study [80] and with cholestyramine in five studies,[81, 247, 256-258] one of which reported reduced folate occurring only in the females.[247] Other studies reported no reduction of serum folate after 2 to 3 years of treatment with colestipol.[250, 253] One study of cholestyramine[257] and one study of colestipol[253] reported a significant decrease in serum levels of vitamins A and E and inorganic phosphorus, but others demonstrated normal vitamin A and E levels over time.[260, 262] One study of cholestyramine reported transient increases in LDH, and abnormalities in SGOT that persisted for 6 month,[247] but others showed normal liver function tests.[260, 262] One study reported a child whose height for age dropped below –2 S.D. while on colestipol (1 S.D. = 2.4 cm).[249] Growth was reported normal in seven studies,[80, 81, 250, 251, 256, 257, 261] including sexual maturation over 4.3 years of treatment.[261] There was one case report of extensive loss of dental enamel in a 7-year-old boy after two years of cholestyramine use. This is thought to have resulted from mixing cholestyramine in Kool-Aid and the child holding the mixture in the mouth for 10 to 15 minutes before swallowing.[245] Serum calcium, phosphorus folate, and vitamin B12 values, and results of a radioactive bone mineral analysis were normal.

Other drugs studied were fenofibrate, bezafibrate, niacin, dextrothyroxine (D-T4), orlistat, P-aminosalicylic acid, and probucol. These studies enrolled small numbers (7-30, mean 15.8) of subjects. A study of fenofibrate reported significant decreases in total alkaline phosphatase, uric acid, inorganic phosphates, and bilirubin, and increases in ALT and AST levels.[269] A study of bezafibrate observed high alkaline phosphatase in one child.[82] The combination of bezafibrate and sitosterol resulted in decreased alkaline phosphatase and increased transferrin levels (by 20%) in two subjects.[264]

Two of two studies of niacin reported increased liver enzymes (6 of 21 children in one study), and multiple other symptoms (flushing, abdominal pain, nausea, headache).[266, 268] One seven year-old girl developed an influenza-like febrile illness with serum aminotransferase levels >400 IU/L two days after starting niacin. Niacin was considered a possible cause and was discontinued.[266] In another study of niacin combined with a bile-acid binding resin, one participant developed clinical symptoms of hepatotoxicity.[268]

P-aminosalicylic acid was associated with mild gastric irritation.[73] A study of probucol reported nausea in one of seven patients, but probucol was otherwise well-tolerated, and growth and development were normal after 15 to 21 months of treatment.[54] Orlistat was associated with a significant drop in 25-hydroxy-vitamin D levels after one month.[267] Three of 20 subjects enrolled in this study required additional vitamin D supplementation despite the prescription of a daily multivitamin containing vitamin D. In a study of the effects of D T4 on the pituitary-thyroid axis of hypercholesterolemic children, an increase

in the basal level of T3 was observed after treatment with D-T4, and the expected stimulation of TSH and T3 secretion in response to TRH was absent.[265]

Low-fat diet

Nineteen studies of dietary fat restriction reported effects on growth, nutrient intake, laboratory safety parameters, or other adverse effects (Table 16).[218, 219, 227, 270-285]

Twelve studies reported normal height growth,[218, 227, 271-273, 276, 277, 279, 280, 282-284] although weight loss occurred among three children in two of these studies.[272, 279] Weight loss in one subject was caused by anorexia nervosa, and in another by a parent-instituted vegetarian diet that was more restrictive than recommended.[279]

Growth failure in one study occurred among 8 of 40 (20%) children with dyslipidemia, 3 (7.5%) of whom had nutritional dwarfing and no progression of puberty.[278] Those with growth failure were ages 7-13 at diagnosis. In this study, families received general advice to reduce dietary fat and cholesterol at the time of diagnosis, but the specific recommendations varied in each case and implementation by the families was unsupervised. The period of unmonitored dietary restriction ranged from 2 weeks to 4.5 years and those with nutritional dwarfing had longer periods of time between diagnosis and formal dietary assessment and counseling.[278] Total energy and zinc consumption were lower in those with growth failure. All three children with nutritional dwarfing had inadequate intake of multiple different vitamins and minerals. Other studies reported inadequate intake of vitamin D,[274] vitamin E,[219, 285], and zinc.[219] Failure to thrive has been demonstrated in children under age two eating fat-restricted diets.[286] Fat-restricted diets are not recommended for children under age two because fat and cholesterol are necessary for normal growth and development in children under age two.[35]

A study of lymphocyte T subset counts found significant decreases in CD3, CD4, and CD8 after six months of dietary therapy.[275] The changes in CD3 and CD8 counts were significantly correlated with changes in triglyceride serum levels. In all cases, lymphocyte T subset counts remained within normal ranges. The other immune indexes (immunoglobulins G, A, M, and complements C3, C4, and Factor B) did not change significantly.

Two studies of the psychological effects of diet therapy reported no adverse effects in academic function, psychological symptoms, and family function,[281] or in behavioral and emotional assessment scores.[271]

A retrospective study of familial chylomicronemia observed patients in whom dietary intervention since infancy had provided at most 10% of energy as long-chain triglycerides.[282] The study observed abnormal values for serum iron, alkaline phosphatase, and total calcium. Two children experienced severe abdominal pain, and an adolescent female developed acute pancreatitis after using an oral contraceptive agent.

Dietary supplements

Fourteen studies provided information about the adverse effects of various dietary supplements, including fiber, rapeseed oil, plant sterol or stanol esters, fish oil, soy-protein beverage, garlic extract, locust bean gum, and antioxidant vitamins (Table 17).[39, 41, 223, 235, 287-296]

Two children (4% of the treatment group) reported abdominal discomfort using fiber tablets that contained 50% wheat bran and 50% pectin, administered at 100-150 mg/kg/day.[223, 290, 293] There were no adverse effects with psyllium fiber in two other studies.[223, 290]

Studies of rapeseed oil alone,[291] or in combination with sitostanol[39] did not report adverse effects, and both studies reported that the diets were well-tolerated with good compliance. A plant sterol ester spread that provided 1.6 g/day of sterol ester reported an increase in ALT of 16.8% of participants.[41] A longer study of plant sterol ester spread reported increased retinol levels, but no increase in transaminases.[287] Sitosterol and sitostanol given in succession decreased alkaline phosphatase.[288] In a study of fish oil (5 g/day), epistaxis occurred in eight of 11 subjects, thought to be secondary to decreased platelets that can occur with omega-3 fatty acids. Prothrombin and partial thromboplastin times and platelet counts were normal, and there was no evidence of liver dysfunction.[289] After adjustment for lipid changes, lycopene was 8.1% lower ($p=0.015$), and serum levels of retinol were 15.6% higher ($p<0.001$), compared with controls. Studies of antioxidant vitamin therapy,[292] substitution of a soy-protein beverage for cow's milk,[294] and garlic extract[235] showed no significant adverse effects. A study of locust bean gum food products reported increased rectal gas that resolved after 1 to 2 weeks, with no other adverse effects or abnormal lab values.[296]

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.[297] In another study, treadmill tests elicited an exaggerated blood pressure response in boys with dyslipidemia.[298] These subjects had significantly higher blood pressures after exercise compared with normal controls (systolic 182 vs. 160 mmHg, $p<0.0003$; diastolic 77 vs. 9 mmHg, $p<0.03$), and their systolic blood pressures remained significantly higher at the end of recovery (120 vs. 112 mmHg, $p<0.005$).

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 the risk of dyslipidemia in adulthood. Indirect

evidence includes: Tracking of lipid during childhood and adolescence (40-55% remain in the highest quintile); and data from young adults whose CHD risk 22-42 years later was associated with their baseline lipid levels.[4] Identification and treatment of previously undiagnosed secondary dyslipidemia (e.g. hypothyroidism) can improve lipids. Children with FH continue to fully express the phenotype in adulthood and the natural history of this disease is early CHD. Thus, in FH populations, long-term placebo controlled trials of drug therapy may be unethical.

Key Question 11. What are the Cost Issues Involved in Screening for Dyslipidemia in Children/adolescents?

Seven studies addressed the cost of screening children and adolescents. These studies reported overall costs of screening but did not relate it to effectiveness of the screening test, or take a societal perspective on the analysis of cost.[130, 177, 178, 182, 183, 299, 300] The only cost-effectiveness study identified was based in England and used a simulated population ages 16-54.[301] This study determined that population screening of 16 year olds only was as cost-effective as family tracing. However, these results may not be applicable to the U.S. No cost-effectiveness studies addressed screening in children younger than 16.

IV. DISCUSSION

Conclusions

A summary of the evidence included in this review is presented in Table 18. Overall, there was inadequate evidence to address key questions about efficacy of screening children and adolescents for dyslipidemia for delaying the onset and reducing the incidence of CHD-related events, 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, whether improving dyslipidemia in children and adolescents reduces the risk of adult dyslipidemia, and cost-effectiveness of screening for dyslipidemia in children and adolescents.

Normal values for lipids in children are currently defined according to population levels (percentiles). The NCEP has defined levels of LDL-C for which drug treatment (LDL-C >190 mg/dL or LDL-C >160 mg/dL with family history of early CHD), further evaluation, diet therapy and testing (LDL-C >130 mg/dL), and diet therapy with increased surveillance (LDL-C 110-129 mg/dL) are recommended. There is concern that the LRC values that have defined normal lipid levels in children were performed with such rigor (assured fasting, research coordinators to facilitate follow-up) that they may not be applicable to a general screening population where assessments are less controlled. Also, demographic shifts toward a more overweight population of children may make the LRC values less representative of the current population.

The most appropriate screening test is one that accurately predicts future risk and benefit from treatment. Screening recommendations for children with a family history of parental high cholesterol include an initial TC followed by a repeat TC and/or lipoprotein profile depending on the degree of elevation in TC. In practice, screening is often performed using TC and HDL-C, rather than TC alone follow-up by lipoprotein analysis if indicated by guidelines. Using LRC data, fasting TC > the 95th percentile detected an LDL-C above the 95th percentile for age and gender with 69% sensitivity and 98% specificity. However, recent data suggest that no single value of TC is sufficient to place a child confidently in the NCEP risk categories. Assessments of the diagnostic accuracy with which LDL-C levels predict familial hypercholesterolemia (FH) have been performed in known FH families, but not tested in the general population of children. The gold standard for diagnosis of FH is mutation analysis or fibroblast LDL-C receptor activity level testing. These confirmatory tests have not been applied to population screening trials.

Studies of lipid level tracking within childhood and from childhood to adulthood demonstrate large ranges of correlation. Serial correlations measured in individual children over time are more consistently higher for TC (r=0.38-0.78) and LDL-C (r=0.4-0.7), than for HDL-C (r=0-0.8) and TG (r=0.1-0.58). Approximately 40-55% of children with elevated lipids (by percentile) will continue to have elevated lipids on follow-up. Of

those in the highest quintile of TC at follow-up, 15-19% had TC levels in the 1st or 2nd (lowest) quintiles at baseline.

Evidence for risk factors other than family history for predicting dyslipidemia in children is strongest for overweight, but otherwise lacking. Epidemiologic cross-sectional and cohort studies establish a strong statistical association between overweight and dyslipidemia. A BMI $\geq$ 95th percentile, has been shown to be a stronger correlate of cumulative CHD risk (OR=19.2; 95% CI 7.6-48.5) than hyperinsulinemia. However, the magnitude of the effect of overweight on lipids, and the potential impact of incorporating overweight into a screening tool for dyslipidemia have not been addressed. Some risk factors may be useful for identifying groups of children and/or adolescents with idiopathic dyslipidemia. Multiple other risk factors (diet, physical inactivity, and aerobic capacity/fitness) have not been evaluated adequately to assess their contribution to dyslipidemia in children or their usefulness as screening tools either alone or in combination.

Currently recommended screening strategies have low adherence by providers, and limited compliance by parents and children. No trials compare strategies (location, venue, age, provider) for screening in children and adolescents. No studies address the frequency and optimal age for testing. Family history questions have limited diagnostic accuracy and have not been universally agreed upon. Studies of screening in children and adolescent and NCEP evaluate measures of TC, while adult guidelines focus on TC and HDL-C. Some experts suggest applying TC and HDL-C screening tests to children and adolescents.

There is a growing literature on the association between lipid levels in children and non-invasive vascular outcomes. Carotid intima-media thickness (IMT) is significantly higher among overweight children compared to non-overweight children,[302] and among children with FH compared with non-affected siblings.[83] Impaired nitrate dilation is lower and brachial IMT higher in children with diabetes and FH compared with healthy children.[303] Data from the Muscatine cohort demonstrate that measurement of adult carotid IMT correlates with lipid measurements taken in childhood, and those with TC in the upper quartile as measured at age 8-18 had an OR of 1.53 (men) and 1.43 (women) for a 1 standard deviation increase in carotid IMT.[304] Further exploration into arterial IMT as a risk factor identifiable in children may be warranted to evaluate its usefulness in screening and/or decisions about treatment.[305]

Adverse effects of screening include parental non-compliance with screening and follow-up recommendations. This is reported to be related to concerns about test accuracy, lack of proof that intervention makes a difference in children, concerns about upsetting the child, refusal by the child, inconvenience, or decisions to institute a diet themselves and have the child rechecked subsequently.

Drug treatment for dyslipidemia in children has been studied only in children with FH, the population for whom these drugs are FDA-approved and recommended by the NCEP. Statins are effective for reducing TC and LDL-C in children with FH. It is not clear how

this efficacy translates to children with milder and/or non-monogenic dyslipidemia (i.e. idiopathic dyslipidemia), and it is not known how frequently these medications are used in children without FH in practice. Studies of bile acid binding resins demonstrate improved TC and LDL-C, but were few and fair/poor quality. Niacin has been used, but is not FDA approved for children.[266, 306] Target lipid levels for children who warrant treatment for dyslipidemia are outlined in the NCEP and AAP guidelines (Fig 1); the recently updated adult (ATP III) guidelines suggest more aggressive targets for adults that are not applicable to children.

Diet supplements (psyllium, oat, sterol or stanol margarines) and advice were minimally effective in both children and adolescents with FH or FCH and those without. Exercise treatments provided little to no improvement in children and adolescents without identified monogenic dyslipidemia. There were no RCTs of exercise in FH populations.

Adverse effects of treatment are reported in controlled and non-controlled studies of drug, diet, exercise, and combination therapy in children and adolescents. Statin drugs were associated primarily with elevations in LFTs and CK. Bile-acid binding resins were associated with GI side effects and decreased levels of serum vitamins and minerals. Niacin has not been systematically studied in children. Low-fat diets have been associated with growth retardation, nutritional dwarfing, and inadequate calorie and nutrient intake in children placed on a low-fat diet prior to formal nutrition counseling.[278, 285] Other studies report normal growth and development in children over 2 years of age on monitored low-fat diets. Few side effects other than elevated blood pressure in children with FH were noted with exercise. The duration of follow-up in these studies ranged from 10 days to eight years. Studies were generally not of sufficient duration to determine long-term effects of either short or extended use.

Limitations of the Literature

In assessing the evidence for screening and treatment of children with dyslipidemia, there remain several areas of uncertainty. Current screening guidelines are based on population norms obtained 30 years ago and do not take into account age, sex, race differences and temporal trends. They are based on family history assessments that have been shown to miss large numbers of children with dyslipidemia and that might lead to bias against detecting elevated lipids in African American children and adolescents, or children and adolescents from single-parent families. Tracking studies follow large percentiles (quartiles, quintiles) rather than focusing on those children and adolescents above the 95th percentile who are likely to have the highest risk. Risk factors that might contribute to a risk assessment tool have not been adequately studied. Screening strategies including methods for assuring adequate assessment of minorities and those with unknown family history, and improving provider and parental compliance with guidelines deserve attention. Studies of statins include only children with FH, are relatively small and of short duration. There are no trials with long-term follow-up for adult lipid outcomes or CHD-related events. Studies of treatments (drug, diet and exercise) for dyslipidemia

could be improved by use of more rigorous study designs, enrollment of larger population-based samples and systematic reporting of adverse effects.

In summary, although many studies about various aspects of dyslipidemia in children have been published, there are conclusive answers for few of the questions addressing primary care providers when faced with screening the general population of children and adolescents. Good evidence exists for the efficacy of statin treatments in children and adolescents with FH and the unreliable diagnostic accuracy of family history for detecting high lipid levels in children. Although current literature demonstrates imperfect tracking of TC and LDL-C through childhood and from childhood to adulthood, there are no studies evaluating tracking for those with lipids above the 95th percentile. Guidelines remain based on LRC data rather than updated population norms.

Future Research

Directions for future research should include identification of the impact that risk factors other than family history (such as overweight, physical inactivity) have on lipids, in order to develop risk assessment tools. Such tools may provide a better indication of a child's actual risk, and could serve to facilitate screening by narrowing the number of children requiring serum lipid testing. Further research into non-invasive screening strategies for screening, such as arterial IMT may be useful.[304] Randomized controlled clinical trials of screening strategies to determine those that may be more effective than those currently in practice, both in terms of parental compliance and provider adherence to guidelines are important. There should be continued follow-up of currently established cohorts to assess the impact of screening for dyslipidemia in childhood on adult CHD outcomes.

To further assess the efficacy and safety of treatment options in children and adolescents with dyslipidemia, long-term follow-up of children treated with statins for impact of sustained improvement of lipid in childhood on adult lipid levels, adult CHD-outcomes and long-term safety will be useful. The impact of exercise on lipid levels should be evaluated further, particularly in children with lipid levels above the 95th percentile. There is a need for improved reporting of adverse effects in trials and use of standardized methods for reporting so that data can be combined across trials. Cost-effectiveness of universal screening vs. screening via family history as currently recommended should be evaluated.

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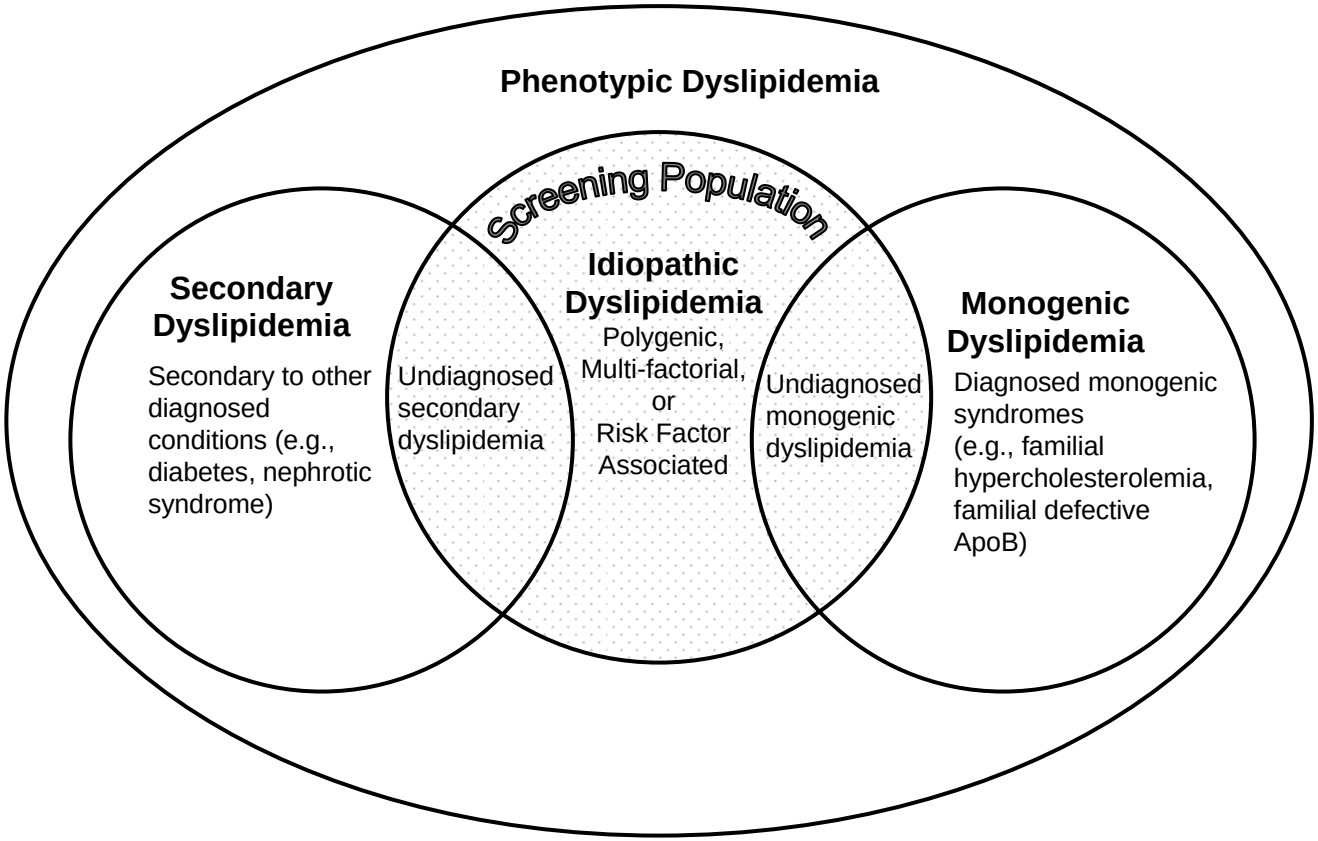
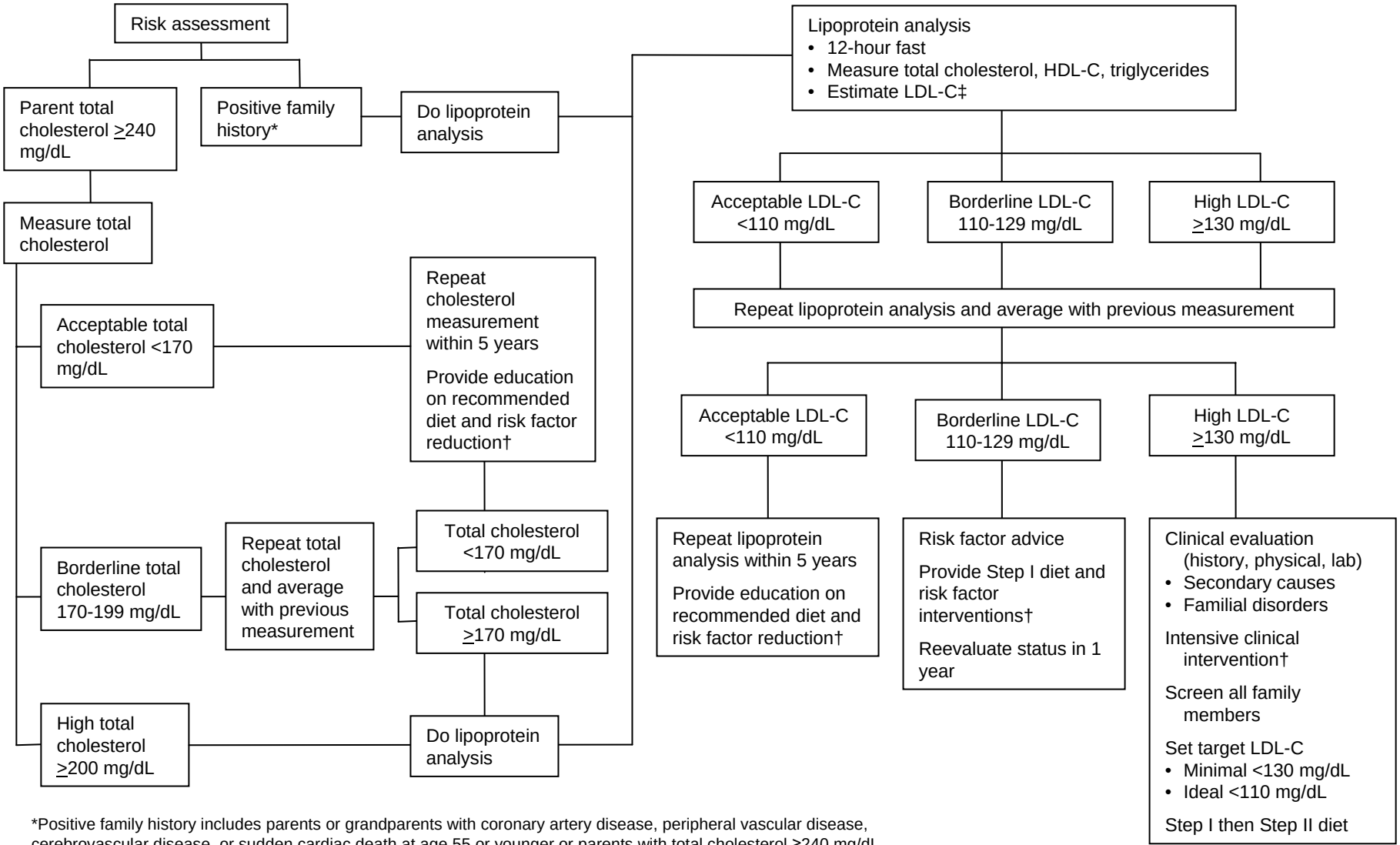
Figure 1. Defining the Screening Population



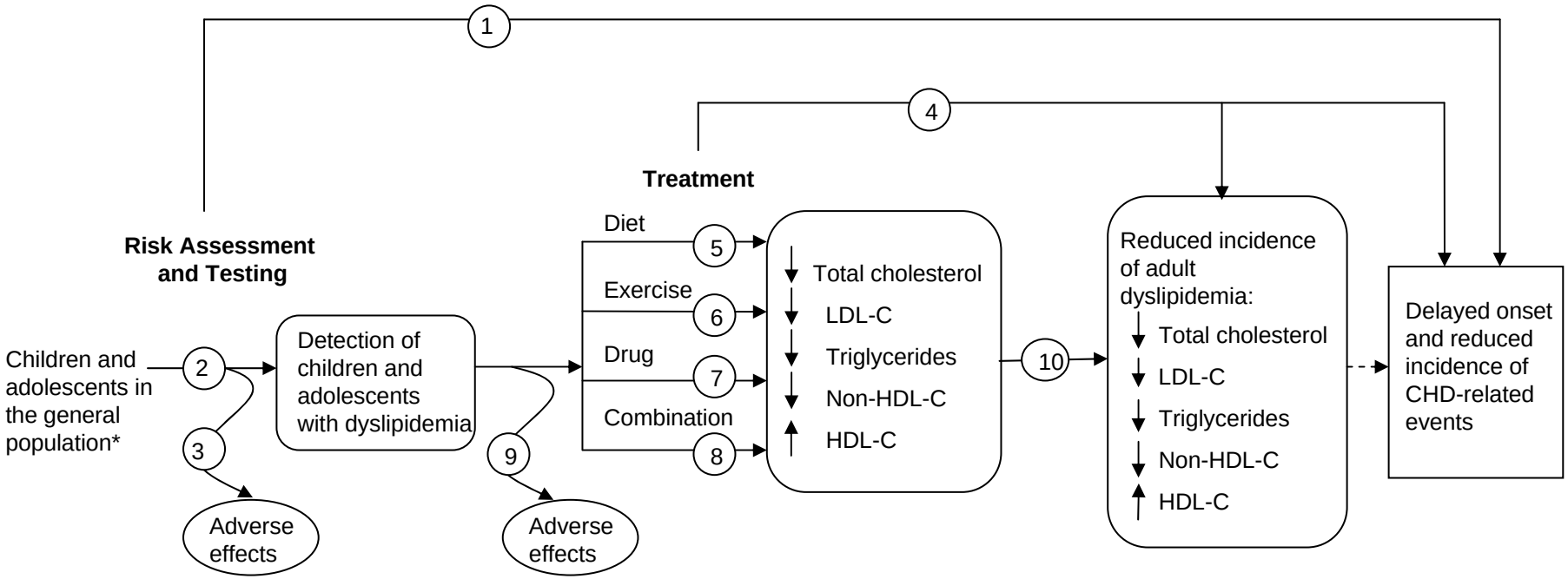
Children and adolescents identified by screening include those with undiagnosed monogenic dyslipidemia, undiagnosed secondary dyslipidemia, and idiopathic (polygenic, multi-factorial or risk factor associated) dyslipidemia. Children and adolescents with previously known monogenic or secondary dyslipidemia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

Figure 2. National Cholesterol Education Program Guidelines for Risk Assessment and Classification of Children



*Positive family history includes parents or grandparents with coronary artery disease, peripheral vascular disease, cerebrovascular disease, or sudden cardiac death at age 55 or younger or parents with total cholesterol ≥240 mg/dL.
†Includes smoking cessation, weight loss, exercise, blood pressure control as appropriate.
‡Estimated LDL-C=Total cholesterol – HDL-C – (Triglycerides/5)
Figure adapted from Pediatrics, 101(1), American Academy of Pediatrics Committee on Nutrition, *Cholesterol in Childhood*, 141-147, (1998).

Figure 3. Analytic Framework and Key Questions



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

Continued

Figure 3. Analytic Framework and Key Questions

Key Questions

1.	Is screening for dyslipidemia in children/adolescents effective in delaying the onset and reducing the incidence of CHD-related events?
2.	What is the accuracy of screening for dyslipidemia in identifying children/adolescents at increased risk of CHD-related events?
2a.	What are abnormal lipid values in children/adolescents?
2b.	What are appropriate tests? How well do screening tests (non-fasting total cholesterol, fasting total cholesterol, fasting lipoprotein analysis) identify individuals with dyslipidemia?
2c.	How well do lipid levels track from childhood to adulthood?
2d.	What is the accuracy of family history in determining risk?
2e.	What are other important risk factors?
2f.	What are effective screening strategies for children/adolescents (including frequency of testing, optimal age for testing)?
3.	What are the adverse effects of screening (including false positives, false negatives, labeling)?
4.	In children/adolescents, what is the effectiveness of drug, diet, exercise, and combination therapy in reducing the incidence of adult dyslipidemia, and delaying the onset and reducing the incidence of CHD-related events (including optimal age for initiation of treatment)?
5, 6, 7, 8.	What is the effectiveness of drug, diet, exercise or 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?
11.	What are the cost issues involved in screening for dyslipidemia in children/adolescents?

Figure 4. Probability Distribution for Heterozygous Familial Hypercholesterolemia, Relative, and the General Population

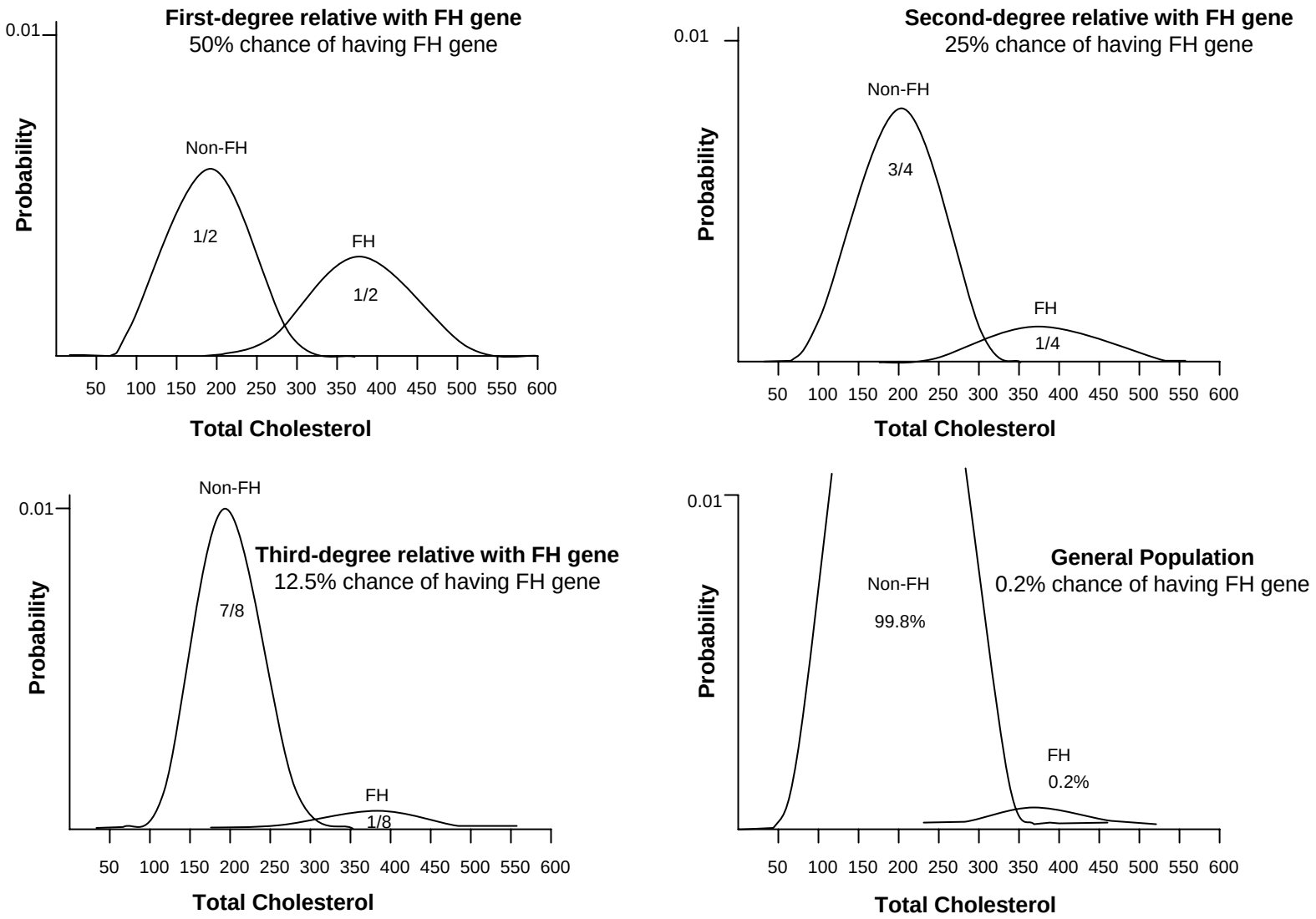


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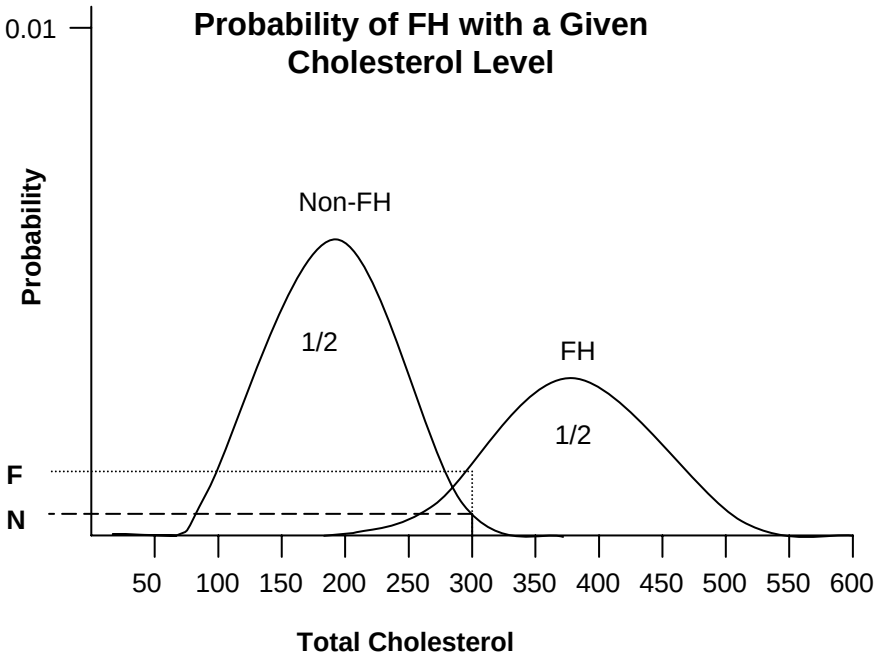
Figure 4. Probability Distribution for Heterozygous Familial Hypercholesterolemia, Relative, and the General Population



For a given cholesterol level of 300 mg/dL, a point probability for FH is indicated by the vertical height below that point on the curve for non-FH (N) and FH (F) distributions. The ratio of point probabilities (F/N) estimates the odds that a person with that cholesterol level comes from the FH distribution or the non-FH distribution.

Figure 5a. Studies of Tracking: Total Cholesterol Levels Based on Age at Start of Study

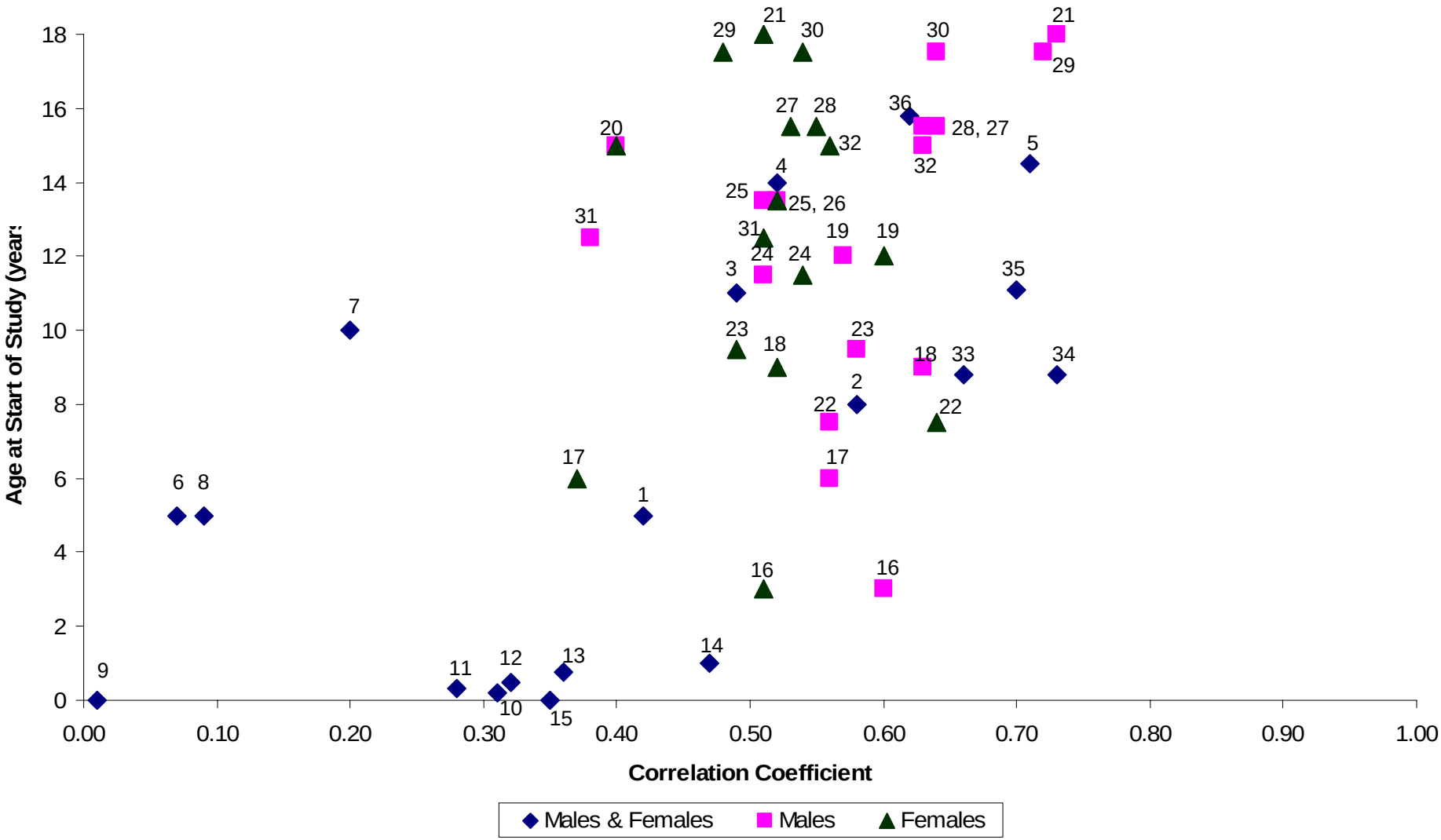


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Figure 5a. Studies of Tracking: Total Cholesterol Levels Based on Age at Start of Study

KEY

	Study, year	Age at follow-up (years)		Study, year	Age at follow-up (years)
1.	Berenson, 1979	7	22.	Lauer, 1989	20-25
2.	Berenson, 1979	10	23.	Lauer, 1989	20-25
3.	Berenson, 1979	13	24.	Lauer, 1989	20-25
4.	Berenson, 1979	16	25.	Lauer, 1989	20-25
5.	Twisk, 1997	27-30	26.	Lauer, 1989	26-30
6.	Mohler, 1996	10	27.	Lauer, 1989	20-25
7.	Mohler, 1996	14	28.	Lauer, 1989	26-30
8.	Mohler, 1996	14	29.	Lauer, 1989	20-25
9.	Kallio, 1993	5	30.	Lauer, 1989	26-30
10.	Kallio, 1993	5	31.	Stuhldreher, 1991	27-30 (mean age 28)
11.	Kallio, 1993	5	32.	Baumgartner, 1991	< 21
12.	Kallio, 1993	5	33.	Kelder, 2002	14.1
13.	Kallio, 1993	5	34.	Kelder, 2002	11.1
14.	Kallio, 1993	5	35.	Kelder, 2002	14.1
15.	Bastida, 2002	4	36.	Eisenmann, 2004	15.8
16.	Porkka, 1994	15			
17.	Porkka, 1994	18			
18.	Porkka, 1994	21			
19.	Porkka, 1994	24			
20.	Porkka, 1994	27			
21.	Porkka, 1994	30			

Figure 5b. Studies of Tracking: LDL-C Levels Based on Age at Start of Study

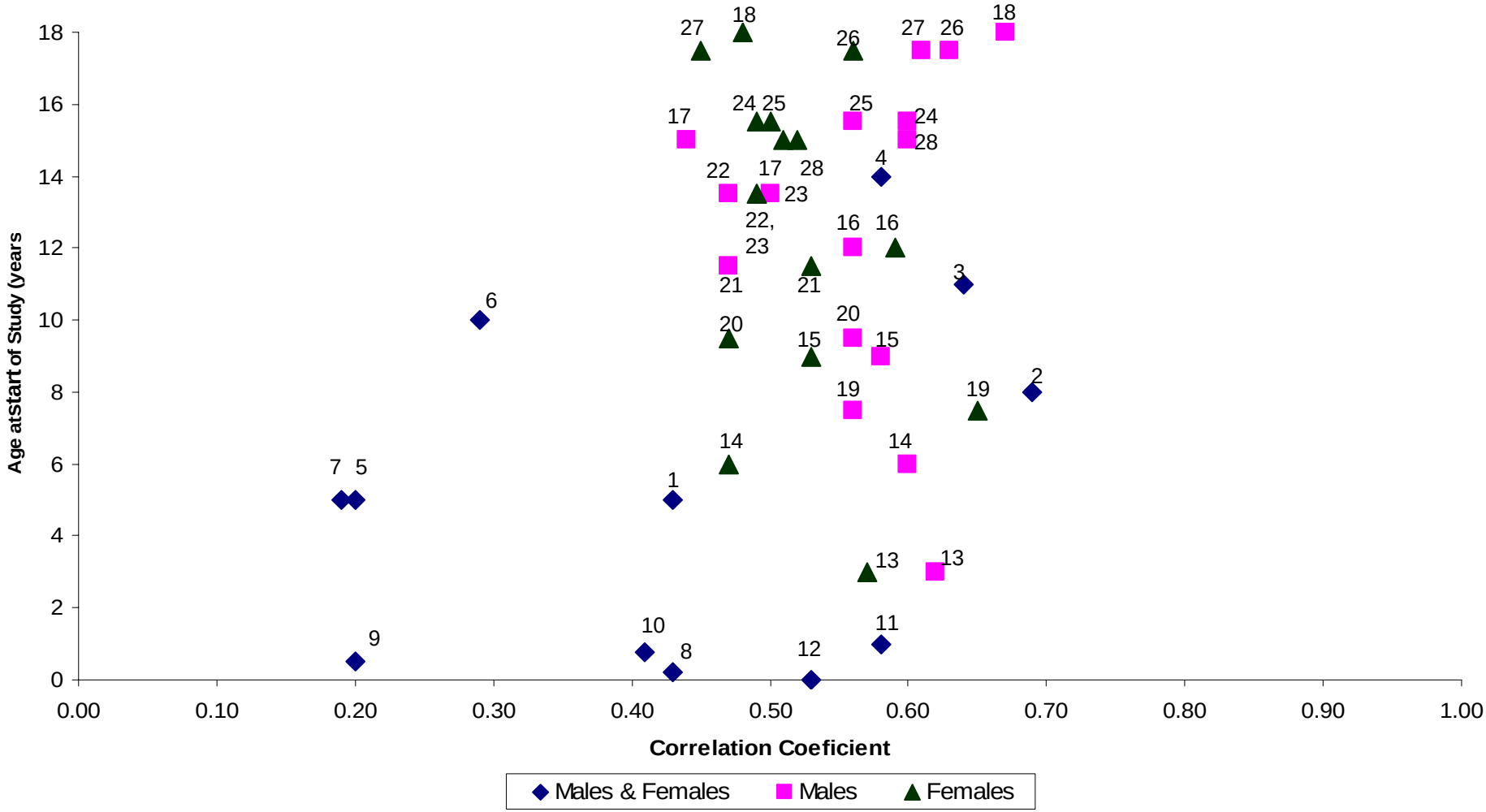

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Figure 5b. Studies of Tracking: LDL-C Levels Based on Age at Start of Study

Key

	Study, year	Age at follow-up (years)
1.	Berenson, 1979	7
2.	Berenson, 1979	10
3.	Berenson, 1979	13
4.	Berenson, 1979	16
5.	Mohler, 1996	10
6.	Mohler, 1996	14
7.	Mohler, 1996	14
8.	Kallio, 1993	5
9.	Kallio, 1993	5
10.	Kallio, 1993	5
11.	Kallio, 1993	5
12.	Bastida, 2002	4
13.	Porkka, 1994	15
14.	Porkka, 1994	18
15.	Porkka, 1994	21
16.	Porkka, 1994	24
17.	Porkka, 1994	27
18.	Porkka, 1994	30
19.	Lauer, 1989	20-25
20.	Lauer, 1989	20-25
21.	Lauer, 1989	20-25
22.	Lauer, 1989	20-25
23.	Lauer, 1989	26-30
24.	Lauer, 1989	20-25
25.	Lauer, 1989	26-30
26.	Lauer, 1989	20-25
27.	Lauer, 1989	26-30
28.	Baumgartner, 1991	< 21

Figure 5c. Studies of Tracking: HDL-C Levels Based on Age at Start of Study

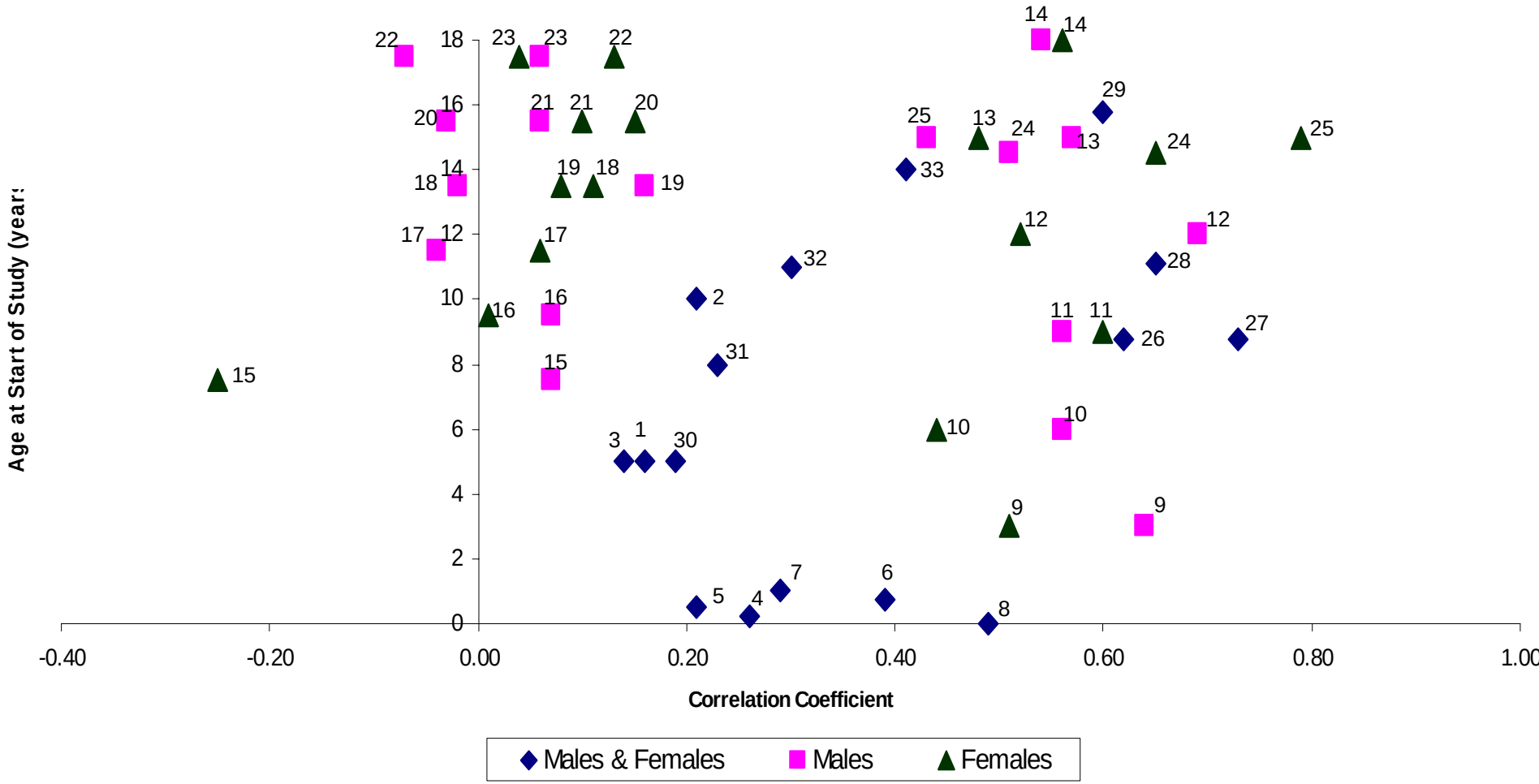

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Figure 5c. Studies of Tracking: HDL-C Levels Based on Age at Start of Study

Key

	Study, year	Age at follow-up (years)		Study, year	Age at follow-up (years)
1.	Mohler, 1996	10	20.	Lauer, 1989	20-25
2.	Mohler, 1996	14	21.	Lauer, 1989	26-30
3.	Mohler, 1996	14	22.	Lauer, 1989	20-25
4.	Kallio, 1993	5	23.	Lauer, 1989	26-30
5.	Kallio, 1993	5	24.	Twisk, 1997	27-30
6.	Kallio, 1993	5	25.	Baumgartner, 1991	< 21
7.	Kallio, 1993	5	26.	Kelder, 2002	14.1
8.	Bastida, 2002	4	27.	Kelder, 2002	11.1
9.	Porkka, 1994	15	28.	Kelder, 2002	14.1
10.	Porkka, 1994	18	29.	Eisenmann, 2004	15.8
11.	Porkka, 1994	21	30.	Berenson, 1979	7
12.	Porkka, 1994	24	31.	Berenson, 1979	10
13.	Porkka, 1994	27	32.	Berenson, 1979	13
14.	Porkka, 1994	30	33.	Berenson, 1979	16
15.	Lauer, 1989	20-25			
16.	Lauer, 1989	20-25			
17.	Lauer, 1989	20-25			
18.	Lauer, 1989	20-25			
19.	Lauer, 1989	26-30			

Figure 5d. Studies of Tracking: Triglyceride Levels Based on Age at Start of Study

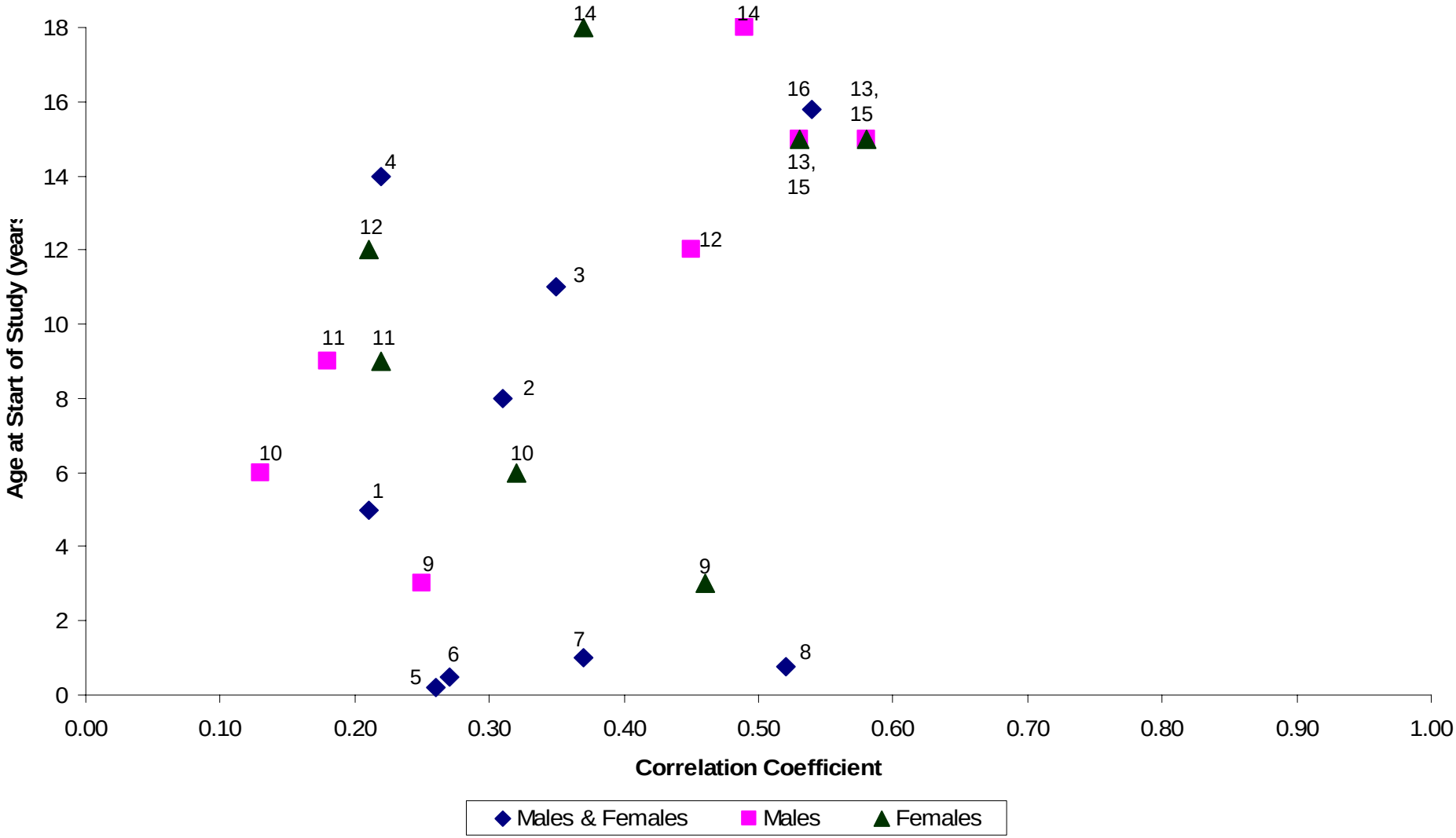

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Figure 5d. Studies of Tracking: Triglyceride Levels Based on Age at Start of Study

Key

	Study, year	Age at follow-up (years)
1.	Berenson, 1979	7
2.	Berenson, 1979	10
3.	Berenson, 1979	13
4.	Berenson, 1979	16
5.	Kallio, 1993	5
6.	Kallio, 1993	5
7.	Kallio, 1993	5
8.	Kallio, 1993	5
9.	Porkka, 1994	15
10.	Porkka, 1994	18
11.	Porkka, 1994	21
12.	Porkka, 1994	24
13.	Porkka, 1994	27
14.	Porkka, 1994	30
15.	Baumgartner, 1991	< 21
16.	Eisenmann, 2004	15.8

Figure 6a. Studies of Tracking: Total Cholesterol Levels Based on Duration of Study

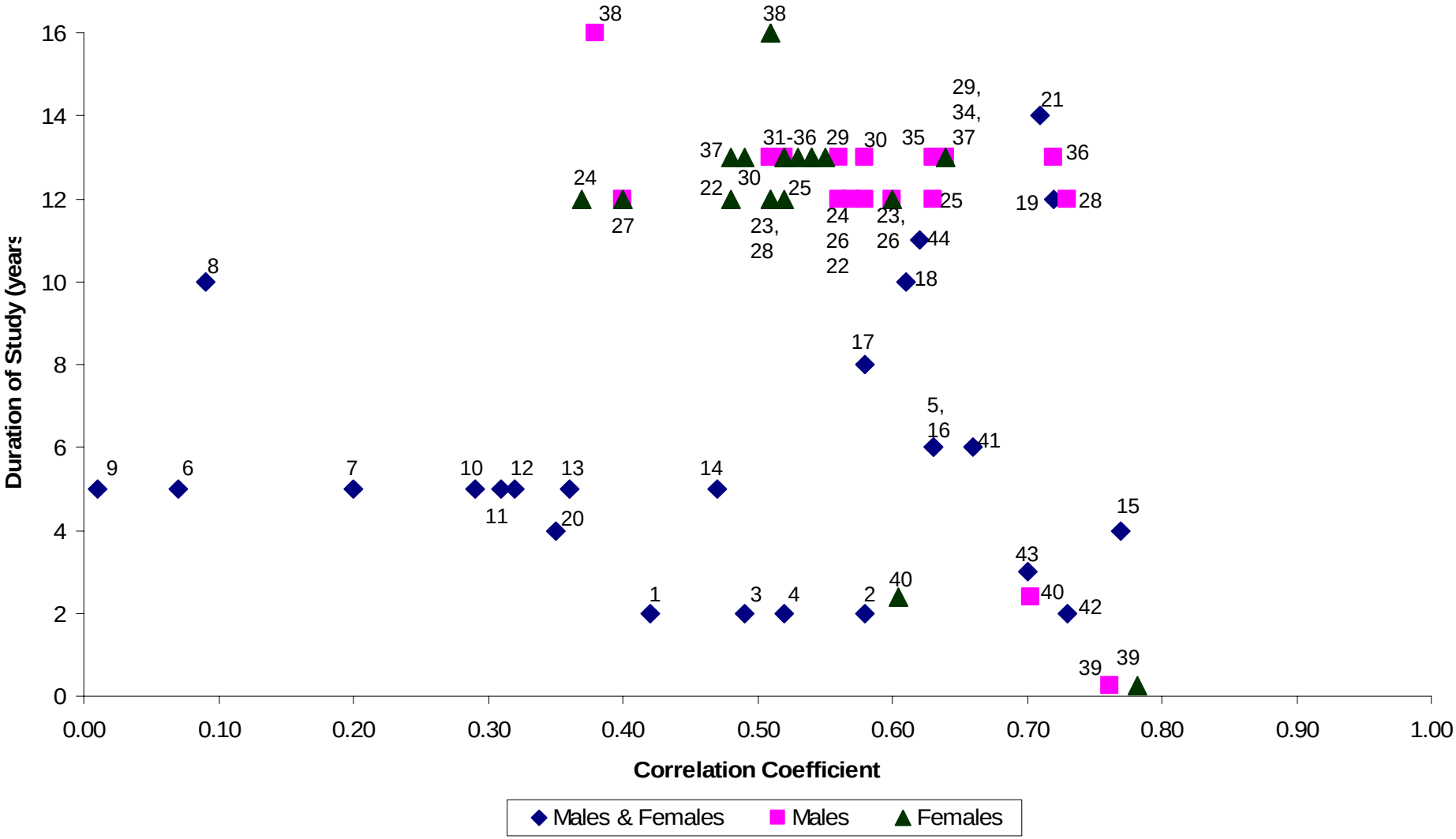

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Figure 6a. Studies of Tracking: Total Cholesterol Levels Based on Duration of Study

Key

	Study, year	Age at start (years)	Age at f/u (years)
1.	Berenson, 1979	5	7
2.	Berenson, 1979	8	10
3.	Berenson, 1979	11	13
4.	Berenson, 1979	14	16
5.	Porkka, 1991	3-18	9-24
6.	Mohler, 1996	5	10
7.	Mohler, 1996	10	14
8.	Mohler, 1996	5	14
9.	Kallio, 1993	0	5
10.	Kallio, 1993	0.17	5
11.	Kallio, 1993	0.33	5
12.	Kallio, 1993	0.50	5
13.	Kallio, 1993	0.75	5
14.	Kallio, 1993	1	5
15.	Guo, 1993	9-21	13-25
16.	Guo, 1993	9-21	15-27
17.	Guo, 1993	9-21	17-29
18.	Guo, 1993	9-21	19-31
19.	Guo, 1993	9-21	21-33
20.	Bastida, 2002	0	4
21.	Twisk, 1997	13-16	27-30
22.	Porkka, 1994	3-18	15-30
23.	Porkka, 1994	3	15
24.	Porkka, 1994	6	18
25.	Porkka, 1994	9	21
26.	Porkka, 1994	12	24
27.	Porkka, 1994	15	27
28.	Porkka, 1994	18	30
29.	Lauer, 1989	7-8	20-25
30.	Lauer, 1989	9-10	20-25
31.	Lauer, 1989	11-12	20-25
32.	Lauer, 1989	13-14	20-25
33.	Lauer, 1989	13-14	26-30
34.	Lauer, 1989	15-16	20-25
35.	Lauer, 1989	15-16	26-30
36.	Lauer, 1989	17-18	20-25
37.	Lauer, 1989	17-18	26-30
38.	Stuhldreher, 1991	11-14	27-30 (mean age 28)
39.	Namboodiri, 1984	<20	<20
40.	Namboodiri, 1984	<20	<20
41.	Kelder, 2002	8.8	14.1
42.	Kelder, 2002	8.8	11.1
43.	Kelder, 2002	11.1	14.1
44.	Eisenmann, 2004	12-18	26.6

Figure 6b. Studies of Tracking: LDL-C Levels Based on Duration of Study

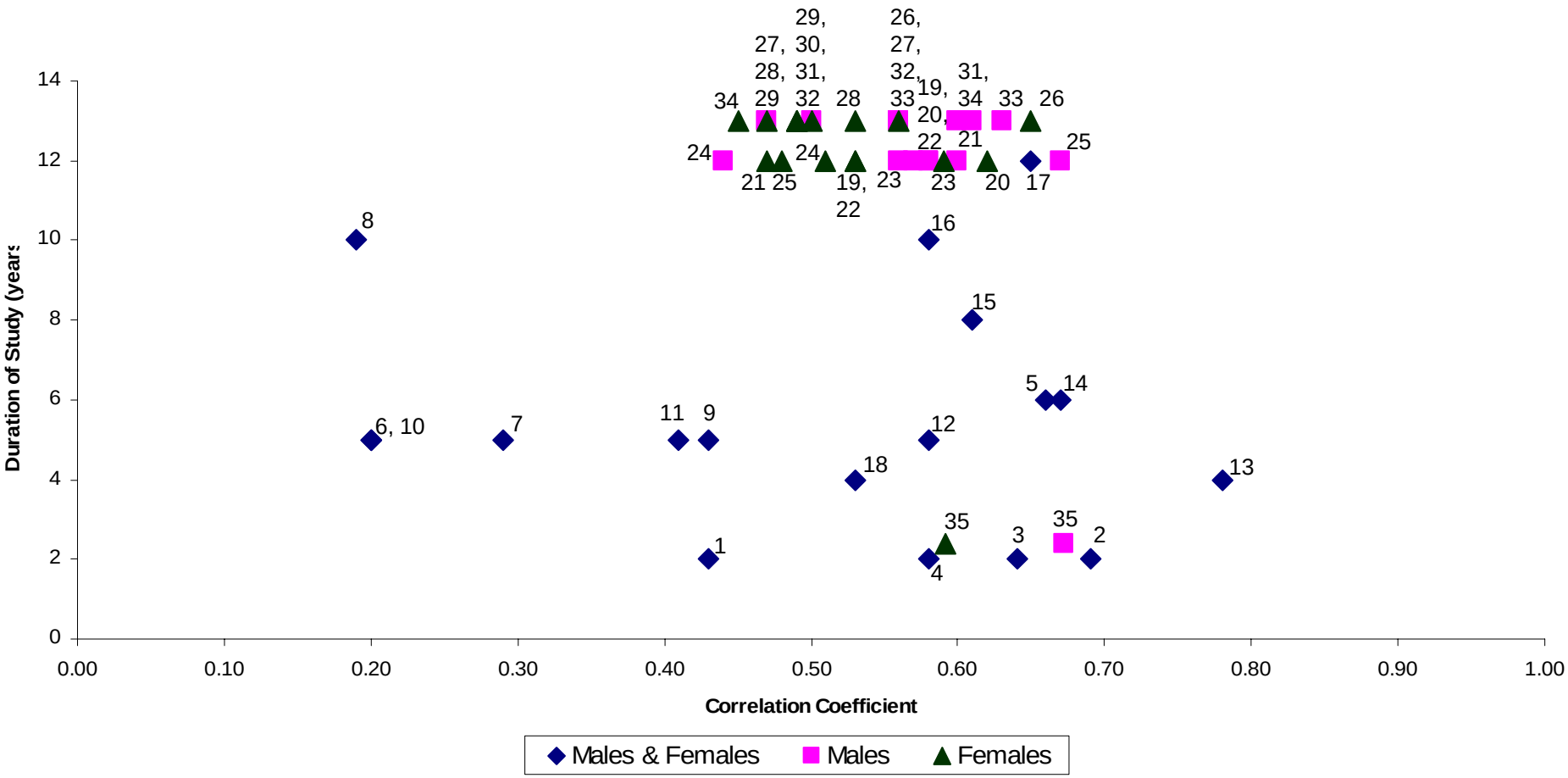

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Figure 6b. Studies of Tracking: LDL-C Levels Based on Duration of Study

Key

	Study, year	Age at start (years)	Age at f/u (years)		Study, year	Age at start (years)	Age at f/u (years)
1.	Berenson, 1979	5	7	24.	Porkka, 1994	15	27
2.	Berenson, 1979	8	10	25.	Porkka, 1994	18	30
3.	Berenson, 1979	11	13	26.	Lauer, 1989	7-8	20-25
4.	Berenson, 1979	14	16	27.	Lauer, 1989	9-10	20-25
5.	Porkka, 1991	3-18	9-24	28.	Lauer, 1989	11-12	20-25
6.	Mohler, 1996	5	10	29.	Lauer, 1989	13-14	20-25
7.	Mohler, 1996	10	14	30.	Lauer, 1989	13-14	26-30
8.	Mohler, 1996	5	14	31.	Lauer, 1989	15-16	20-25
9.	Kallio, 1993	0.17	5	32.	Lauer, 1989	15-16	26-30
10.	Kallio, 1993	0.5	5	33.	Lauer, 1989	17-18	20-25
11.	Kallio, 1993	0.75	5	34.	Lauer, 1989	17-18	26-30
12.	Kallio, 1993	1	5	35.	Namboodiri, 1984	<20	<20
13.	Guo, 1993	9-21	13-25				
14.	Guo, 1993	9-21	15-27				
15.	Guo, 1993	9-21	17-29				
16.	Guo, 1993	9-21	19-31				
17.	Guo, 1993	9-21	21-33				
18.	Bastida, 2002	0	4				
19.	Porkka, 1994	9	21				
20.	Porkka, 1994	3	15				
21.	Porkka, 1994	6	18				
22.	Porkka, 1994	3-18	15-30				
23.	Porkka, 1994	12	24				

Figure 6c. Studies of Tracking: HDL-C Levels Based on Duration of Study

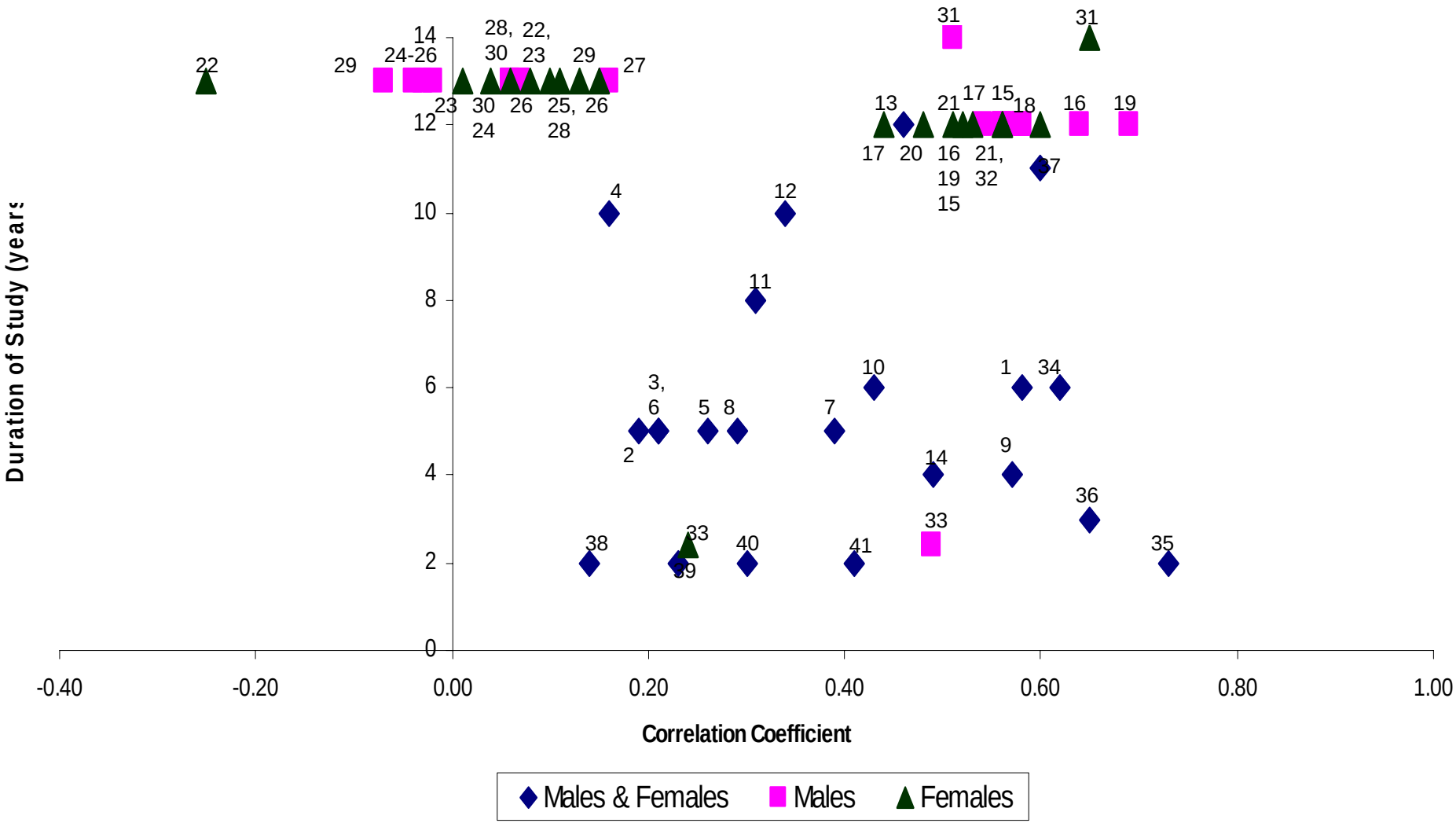

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Figure 6c. Studies of Tracking: HDL-C Levels Based on Duration of Study

Key

	Study, year	Age at start (years)	Age at f/u (years)		Study, year	Age at start (years)	Age at f/u (years)
1.	Porkka, 1991	3-18	9-24	23.	Lauer, 1989	7-8	20-25
2.	Mohler, 1996	5	10	24.	Lauer, 1989	11-12	20-25
3.	Mohler, 1996	10	14	25.	Lauer, 1989	13-14	20-25
4.	Mohler, 1996	5	14	26.	Lauer, 1989	15-16	20-25
5.	Kallio, 1993	0.17	5	27.	Lauer, 1989	13-14	26-30
6.	Kallio, 1993	0.50	5	28.	Lauer, 1989	15-16	26-30
7.	Kallio, 1993	0.75	5	29.	Lauer, 1989	17-18	20-25
8.	Kallio, 1993	1	5	30.	Lauer, 1989	17-18	26-30
9.	Guo, 1993	9-21	13-25	31.	Twisk, 1997	13-16	27-30
10.	Guo, 1993	9-21	15-27	32.	Katzmarzyk, 2001	8-18	20-30
11.	Guo, 1993	9-21	17-29	33.	Namboodiri, 1984	<20	<20
12.	Guo, 1993	9-21	19-31	34.	Kelder, 2002	8.8	14.1
13.	Guo, 1993	9-21	21-33	35.	Kelder, 2002	8.8	11.1
14.	Bastida, 2002	0	4	36.	Kelder, 2002	11.1	14.1
15.	Porkka, 1994	3-18	15-30	37.	Eisenmann, 2004	12-18	26.6
16.	Porkka, 1994	3	15	38.	Berenson, 1979	5	7
17.	Porkka, 1994	6	18	39.	Berenson, 1979	8	10
18.	Porkka, 1994	9	21	40.	Berenson, 1979	11	13
19.	Porkka, 1994	12	24	41.	Berenson, 1979	14	16
20.	Porkka, 1994	15	27				
21.	Porkka, 1994	18	30				
22.	Lauer, 1989	9-10	20-25				

Figure 6d. Studies of Tracking: Triglyceride Levels Based on Duration of Study

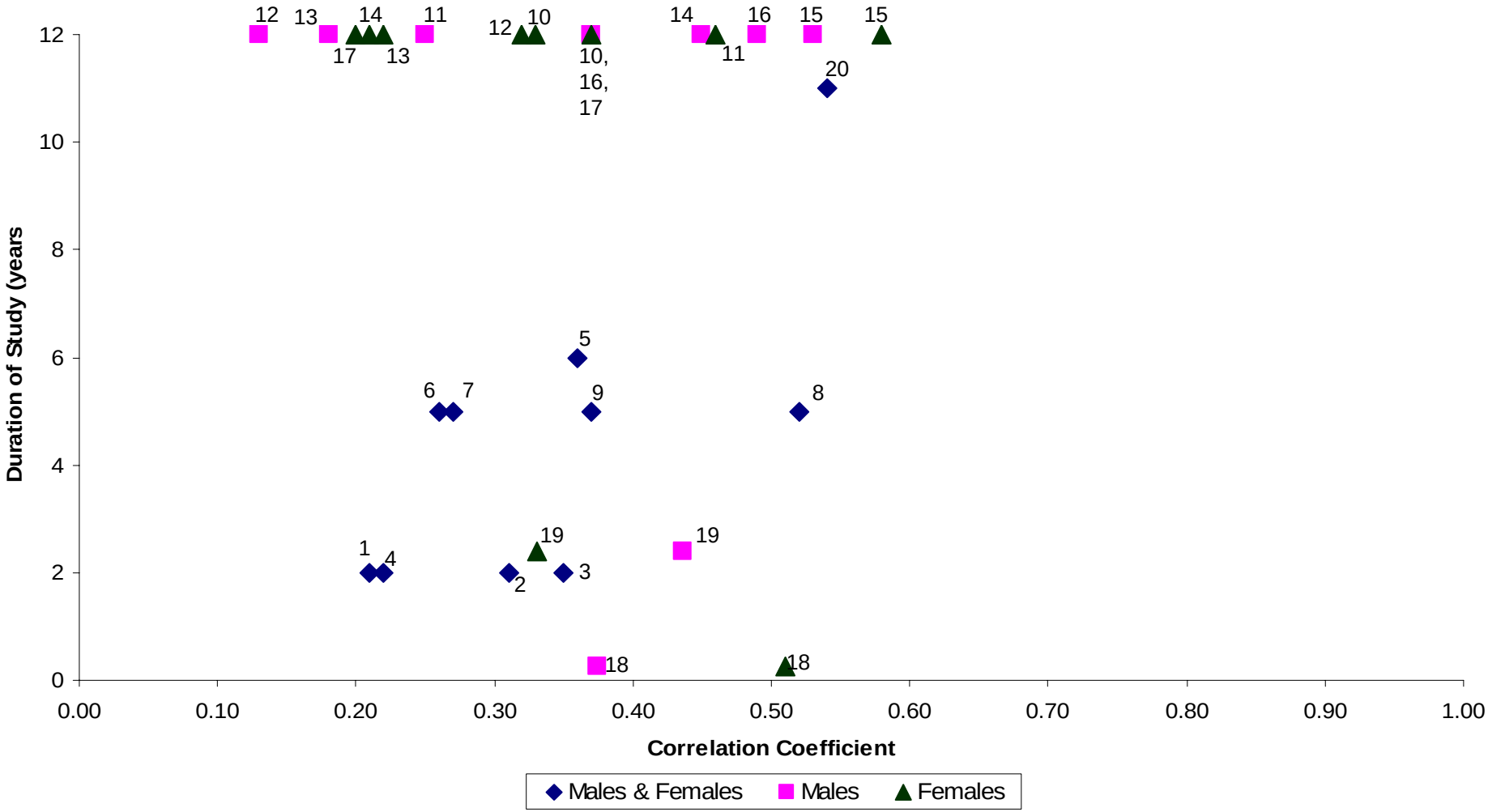

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Figure 6d. Studies of Tracking: Triglyceride Levels Based on Duration of Study

Key

	Study, year	Age at start (years)	Age at f/u (years)
1.	Berenson, 1979	5	7
2.	Berenson, 1979	8	10
3.	Berenson, 1979	11	13
4.	Berenson, 1979	14	16
5.	Porkka, 1991	3-18	9-24
6.	Kallio, 1993	0.17	5
7.	Kallio, 1993	0.50	5
8.	Kallio, 1993	0.75	5
9.	Kallio, 1993	1	5
10.	Porkka, 1994	3-18	15-30
11.	Porkka, 1994	3	15
12.	Porkka, 1994	6	18
13.	Porkka, 1994	9	21
14.	Porkka, 1994	12	24
15.	Porkka, 1994	15	27
16.	Porkka, 1994	18	30
17.	Katzmarzyk, 2001	8-18	20-30
18.	Namboodiri, 1984	<20	<20
19.	Namboodiri, 1984	<20	<20
20.	Eisenmann, 2004	12-18	26.6

Figure 7. Meta-Analysis of Statin Trials in Children With Familial Hypercholesterolemia: Total Cholesterol Reduction

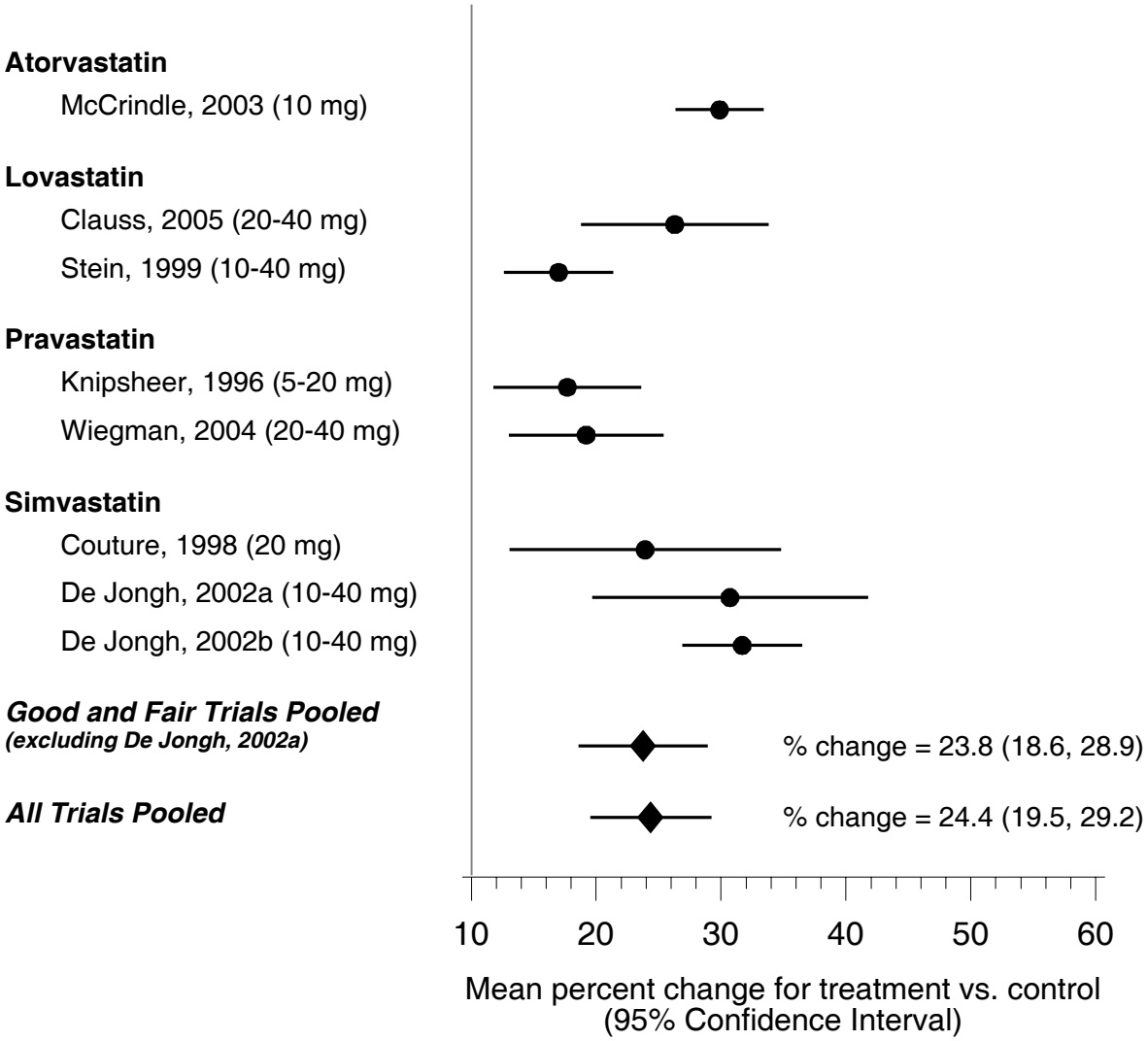

Figure 8. Meta-Analysis of Statin Trials in Children With Familial Hypercholesterolemia: LDL-C Reduction

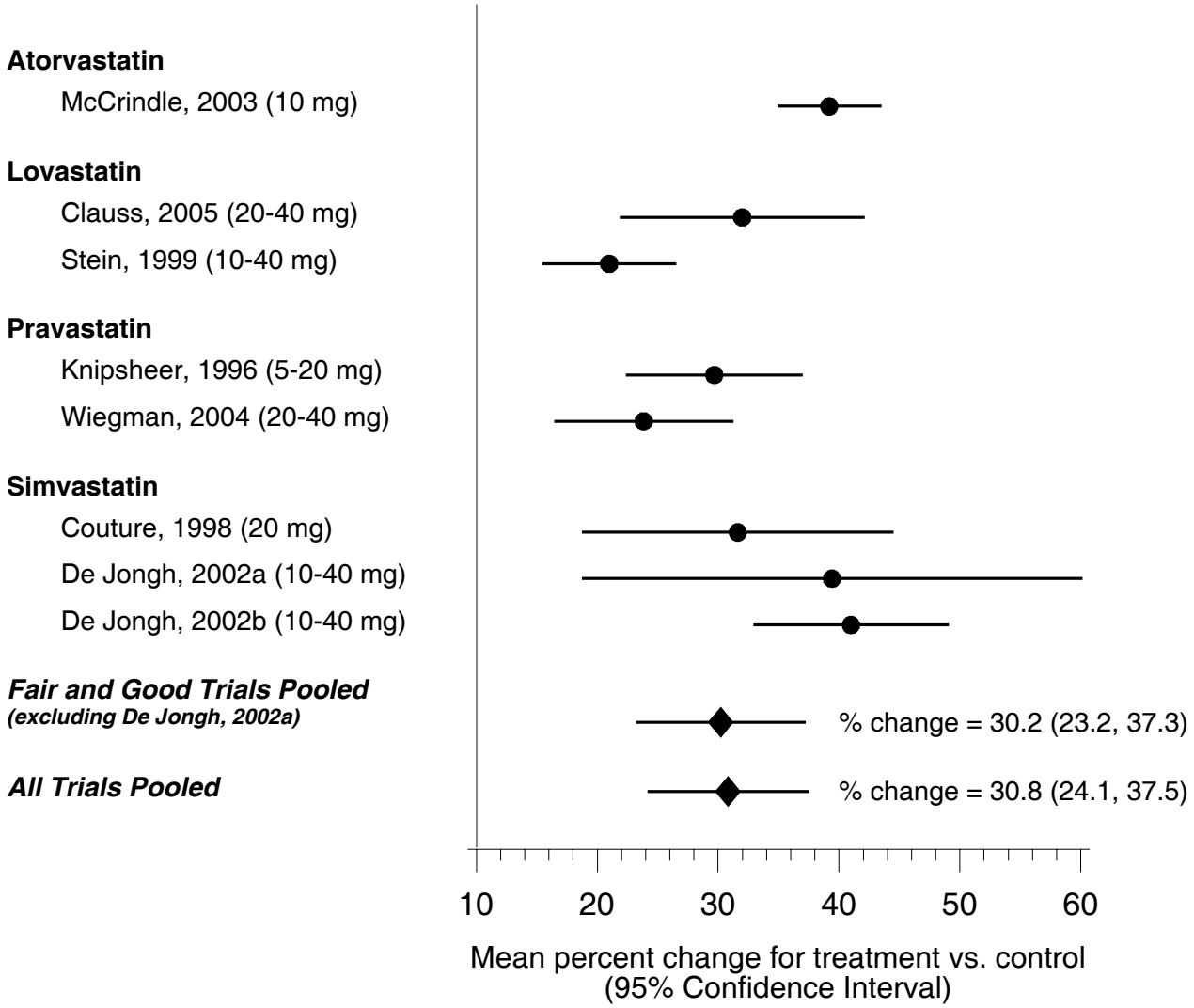

Figure 9. Meta-Analysis of Statin Trials in Children With Familial Hypercholesterolemia: HDL-C Increase

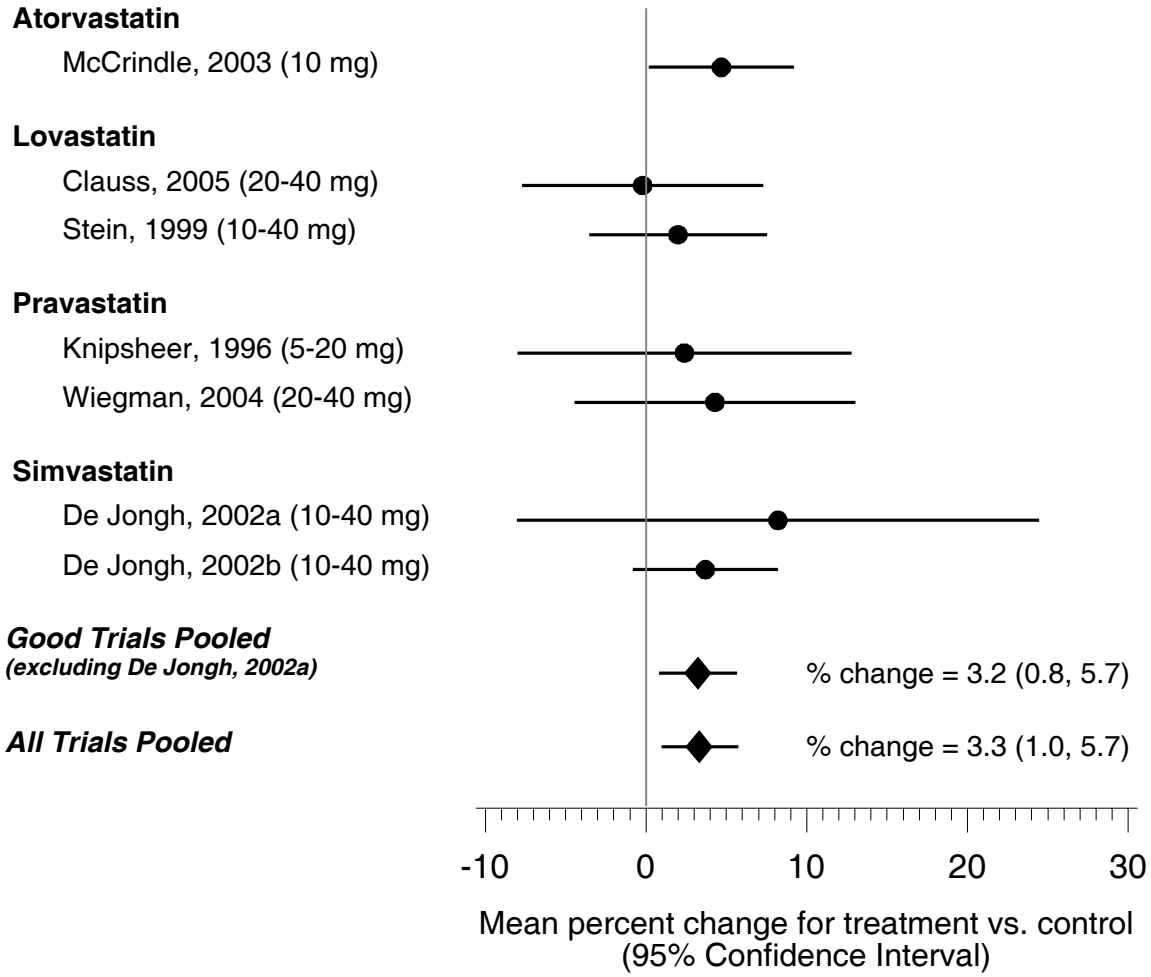

Figure 10. Meta-Analysis of Exercise Trials in Children: Total Cholesterol Reduction

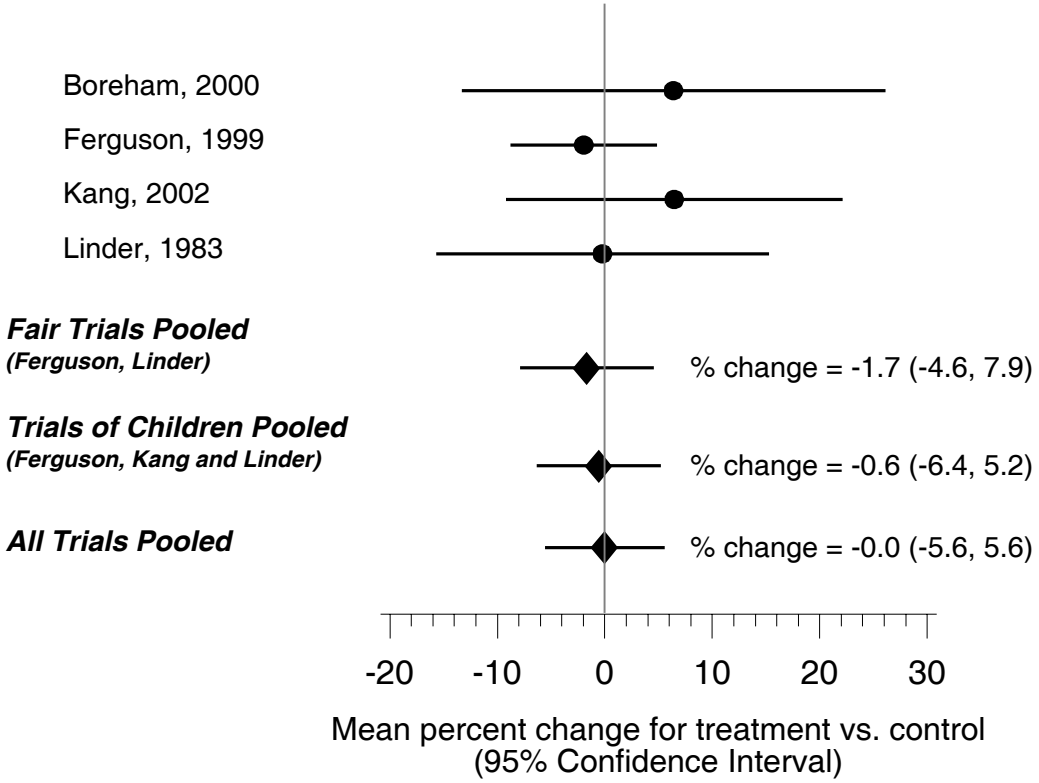

Figure 11. Meta-Analysis of Exercise Trials in Children: LDL-C Reduction

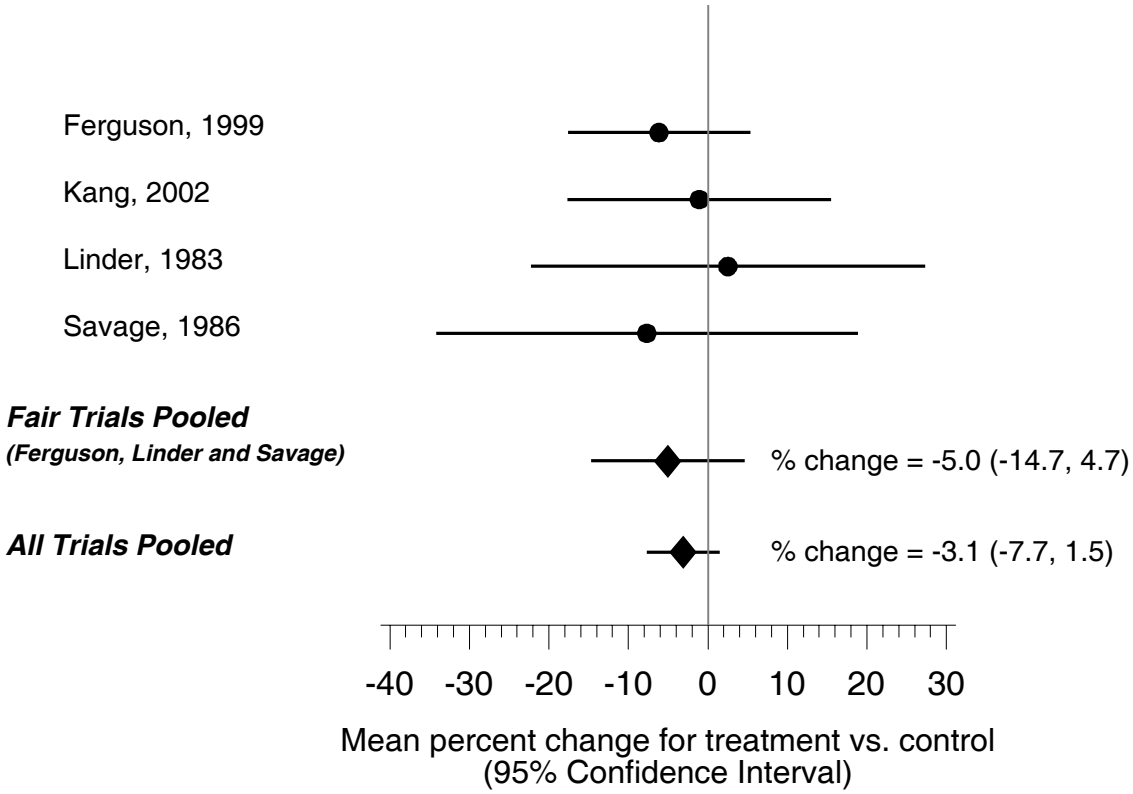

Figure 12. Meta-Analysis of Exercise Trials in Children: HDL-C Increase

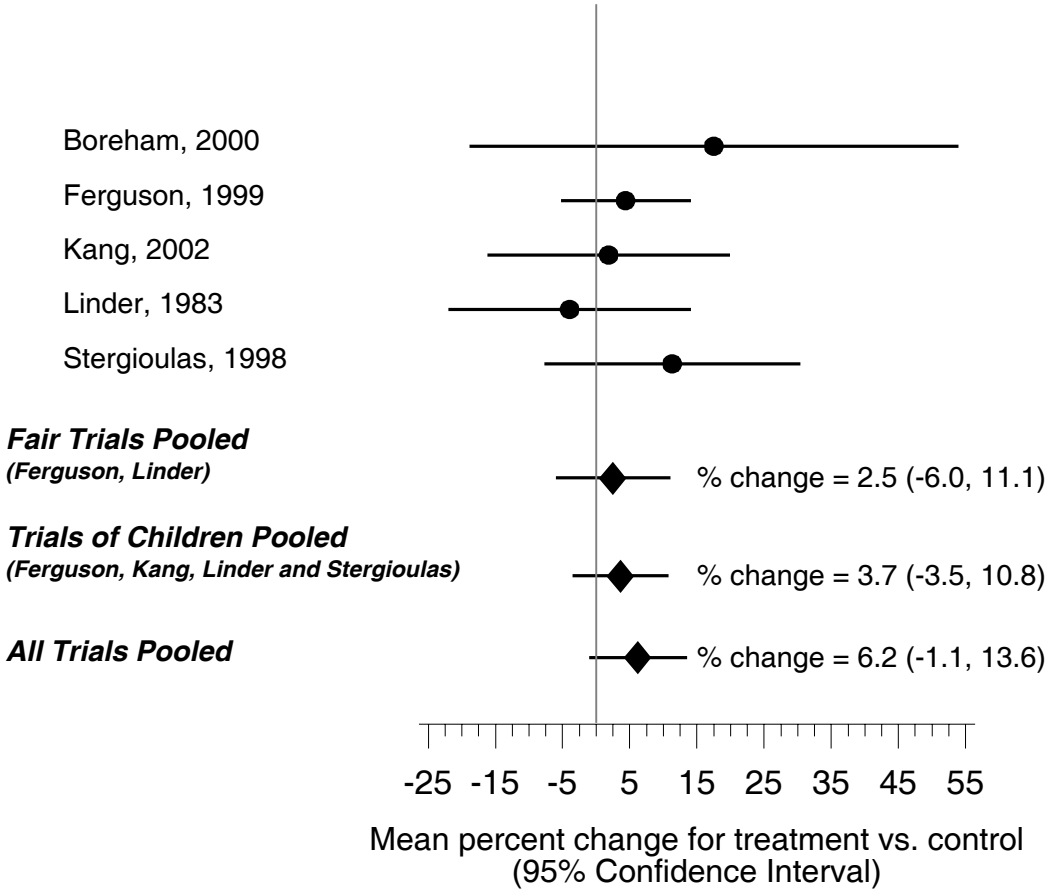

Table 1. Descriptions of Diets in Studies

Name	Patients	Description
American Heart Association endorsed Step I Diet created by National Cholesterol Education Program*[36]	Healthy	Total fat: average of ≤ 30% of total calories Saturated fatty acids: < 10% of total calories Polyunsaturated fatty acids: ≤ 10% of total calories Monounsaturated fatty acids: remaining total fat calories Cholesterol: < 300 mg/day Carbohydrates: about 55% of total calories Protein: about 15-20% of total calories Calories: to promote normal growth and development and to reach or maintain desirable body weight *Intended as the starting point for patients who have high cholesterol levels. Designed to reduce risk of cardiovascular disease by reducing high blood cholesterol levels.*
American Heart Association endorsed Step II Diet created by National Cholesterol Education Program*[36]	High risk	Total fat: same as Step I Saturated fatty acids: < 7% of total calories Polyunsaturated fatty acids: same as Step I Monounsaturated fatty acids: same as Step I Cholesterol: < 200 mg/day Carbohydrates: same as Step I Protein: same as Step I Calories: same as Step I *Intended for people already at the Step I goals or for patients with high-risk cholesterol levels (TC≥240 mg/dL) or who had have had an MI. Designed to reduce risk of cardiovascular disease by reducing high cholesterol levels.*
American Heart Association Prudent diet/1978 Committee Report[239]	High risk	Diet based on AHA's 1973 statement on diet and coronary heart disease for adults. Should produce comparable effects in children, although more research on safety is required. Cholesterol: < 300 mg/day Calories from fat: ≤ 35% of total calories Saturated fat: ≤ 10% of total calories If there is no response to the above diet, the following guidelines are recommended. *For children with familial hypercholesterolemia, ages 1-10:* Fat: 25-30% of total calories Substitute polyunsaturates for saturates to reach a P/S ratio of 1:1 Cholesterol: < 200 mg/day adjusted downward for younger children *Familial triglyceridemia:* Moderate reduction in body weight in relation to the growth curve Further reduction from 1973 statement of carbohydrates and saturated fat intake *Hypercholesterolemia and Hypertriglyceridemia:* Use above familial dietary restrictions. For obesity, calories must also be restricted.

Table 1. Descriptions of Diets in Studies

Name	Patients	Description
Dietary Intervention Study in Children (DISC) Diet[219]	High risk	Total fat: 28% of total energy Saturated fat: < 8% of total energy Polyunsaturated fat: ≥ 9% of total energy Cholesterol: < 75mg/day (not to exceed 150 mg/day) Family oriented, based on social learning and social action theory.
Parent-child Autotutorial Program (PCAT)[220]	High risk	A 10-week educational program for 4-10 year old hypercholesterolic children and their families that incorporates a hands-on and empowerment approach to learning about heart healthy food choices. Includes audio tapes that correspond with picture books for children, recommended methods to assist parents in implementing changes, and hands-on activities for both.

Key

*Since 2000, the American Heart Association no longer uses the terms “Step I” and “Step II” in reference to heart-healthy diets, and have since released new guidelines.

Abbreviations

P/S = Polyunsaturated/saturated, TC = Total cholesterol.

Table 2. Lipid Research Clinics Lipid Levels Iin U.S. Children and Adolescents

Total Cholesterol (mg/dL)*,†

Age (years)	N	Mean	Percentiles 5	10	25	50	75	90	95
Males									
0-4	238	159	117	129	141	156	176	192	209
5-9	1253	165	125	134	147	164	180	197	209
10-14	2278	162	123	131	144	160	178	196	208
15-19	1980	154	116	124	136	150	170	188	203
Females									
0-4	186	161	115	124	143	161	177	195	206
5-9	1118	169	130	138	150	168	184	201	211
10-14	2087	164	128	135	148	163	179	196	207
15-19	2079	162	124	131	144	160	177	197	209

Low-Density Lipoprotein (LDL) Cholesterol (mg/dL)*,†

Age (years)	N	Mean	Percentiles 5	10	25	50	75	90	95
White Males									
5-9	131	95	65	71	82	93	106	121	133
10-14	284	99	66	74	83	97	112	126	136
15-19	298	97	64	70	82	96	112	127	134
White Females									
5-9	114	103	70	75	91	101	118	129	144
10-14	244	100	70	75	83	97	113	130	140
15-19	294	99	61	67	80	96	114	133	141

High-Density Lipoprotein (HDL) Cholesterol (mg/dL)*,†

Age (years)	N	Mean	Percentiles 5	10	25	50	75	90	95
White Males									
5-9	142	57	39	43	50	56	65	72	76
10-14	296	57	38	41	47	57	63	73	76
15-19	299	48	31	35	40	47	54	61	65
White Females									
5-9	124	55	37	39	48	54	63	69	75
10-14	247	54	38	41	46	54	60	66	72
15-19	295	54	36	39	44	53	63	70	76

Table 2. Lipid Research Clinics Lipid Levels Iin U.S. Children and Adolescents

Triglycerides (mg/dL)*,†

Age (years)	N	Mean	Percentiles						
			5	10	25	50	75	90	95
Males									
0-4	238	58	30	34	41	53	69	87	102
5-9	1253	30	31	34	41	53	67	88	104
10-14	2278	68	33	38	46	61	80	105	129
15-19	1980	80	38	44	56	71	94	124	152
Females									
0-4	186	66	35	39	46	61	79	99	115
5-9	118	30	33	37	45	57	73	93	108
10-14	2087	78	38	45	56	72	93	117	135
15-19	2079	78	40	45	55	70	90	117	136

Key

* Adapted from National Heart, Lung, and Blood Institute 1980[14]

† All values have been converted from plasma to serum. Plasma value X 1.03 = serum value.

Table 3. Total Cholesterol Levels by Race*

Race/ Ethnicity	N	Mean mg/dL + SEM†	Percentiles			
			50th	75th	90th	95th
White	2724	162.6 ± 0.537	161	180	198	209
Black	1383	172.9 ± 0.830	171	192	210	225
Asian	177	165.4 ± 2.120	165	181	204	219
Hispanic	1453	167.9 ± 0.734	166	184	203	216
Total ‡	5871	166.4 ± 0.357	165	184	202	215

Key

* Adapted from Resnicow, 1989[55]

† 95% confidence interval = ± 1.96 (standard error of the mean).

‡ Includes unclassified children

Table 4a. Guideline Definitions of High Risk

	AAP* 1998	AHA† 2003	NCEP‡ 1992
Guidelines for High Risk			
LDL ≥ 190 after 1 year low fat and low cholesterol diet			X
LDL > 160 with familial premature heart disease (before 55 years of age)			X
LDL > 160 with ≥ 2 other CVD risk factors in child or adolescent (such as low HDL cholesterol [<35 mg/dL], cigarette smoking, high blood pressure, obesity, or diabetes, etc.)			X
LDL > 110 mg/dL, or TC > 170 mg/dL (borderline risk), TC > 200 mg/dL, or LDL > 130 mg/dL, or TG > 150 mg/dL, or HDL < 35 mg/dL (elevated risk)		X	
Screen if: Parents or grandparents with premature (≤ 55 years old) coronary atherosclerosis or documented MI, angina, peripheral vascular disease, cerebrovascular disease, or sudden cardiac death, or parent with total cholesterol ≥ 240 mg/dL Risk if above is true and: LDL 110-129 mg/dL, or TC 170-199 mg/dL (borderline risk) LDL ≥ 130 mg/dL, or TC ≥ 200 mg/dL (high risk)	X		

Key

*American Academy of Pediatrics, 1998[35]

†American Heart Association[36]

‡National Cholesterol Education Program, 1992[34]

Abbreviations

CVD=Cardiovascular disease, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, MI=Myocardial infarction, TC=Total cholesterol, TG=Triglycerides

Table 4b. Inclusion Criteria for Studies of Children with Familial Hypercholesterolemia

	Treatment trials																				
	Clauss 2005[38]	Couture 1998[66]	Davidson 1996[67]	de Jongh 2002a[68]	de Jongh 2002b[69]	de Jongh 2003[70]	Gylling 1995[38]	Knipscheer 1996[71]	Lambert 1996[72]	Malloy 1978[73]	McCrindle 1997[74]	McCrindle 2002[75]	McCrindle 2003[76]	Stallings 1993[77]	Stein 1999[78]	Sveger 2000[79]	Tonstad 1996a[80]	Tonstad 1996b[81]	Wheeler 1985[82]	Wiegman 2004[83]
Inclusion Criteria																					
LDL values with or without other risk factors																					
LDL 189 - 503 mg/dL and at least 1 parent with LDL ≥ 189 mg/dL not due to secondary causes															X						
LDL 220 - 503 mg/dL and a parent death from CAD with no available lipid values															X						
LDL ≥ 190 mg/dL with TG ≤ 400 mg/dL													X								
LDL > 190 mg/dL and parent with hypercholesterolemia (TC >290 mg/dL) or early CHD death																X					
LDL 158.5 - 398.3 mg/dL					X																
Two fasting LDL levels ≥ 155mg/dL and triglycerides < 350 mg/dL, and 1 parent with definite FH (clinical or molecular diagnosis)																				X	
LDL 160 - 400 mg/dL, and parental history of heterozygous familial hypercholesterolemia	X																				
Fasting LDL cholesterol level before enrollment > 160 mg/dL and family history of hypercholesterolemia or premature CHD in first degree relatives, and minimum												X	X								

Table 4b. Inclusion Criteria for Studies of Children with Familial Hypercholesterolemia

	Treatment trials																				
	Clauss 2005[38]	Couture 1998[66]	Davidson 1996[67]	de Jongh 2002a[68]	de Jongh 2002b[69]	de Jongh 2003[70]	Gylling 1995[38]	Knipscheer 1996[71]	Lambert 1996[72]	Malloy 1978[73]	McCrindle 1997[74]	McCrindle 2002[75]	McCrindle 2003[76]	Stallings 1993[77]	Stein 1999[78]	Sveger 2000[79]	Tonstad 1996a[80]	Tonstad 1996b[81]	Wheeler 1985[82]	Wiegman 2004[83]
Inclusion Criteria (continued)																					
LDL values with or without other risk factors (continued)																					
Fasting serum LDL of ≥ 130 mg/dL while on American Heart Association step 2 diet											X										
LDL > 95th percentile for age/gender				X		X															
LDL > 95th percentile for age/gender or age while on lipid lowering diet		X							X		X										
LDL > 95th percentile for age/gender or age while on lipid lowering diet, with documented family history of hyperlipidemia or hypercholesterolemia in siblings/parents/grandparents				X				X	X												
LDL > 95th percentile for age while on lipid lowering diet, with documented family history of premature CHD < age 50 in first or second degree relatives								X	X												
LDL > 95th percentile for age, while on lipid lowering diet, and history f unsuccessul treatment with BABR.									X												
LDL > 90th percentile for age/gender, with triglycerides ≤ 300 mg/dL			X																		

Table 4b. Inclusion Criteria for Studies of Children with Familial Hypercholesterolemia

	Treatment trials																			
	Clauss 2005[38]	Couture 1998[66]	Davidson 1996[67]	de Jongh 2002a[68]	de Jongh 2002b[69]	de Jongh 2003[70]	Gylling 1995[38]	Knipscheer 1996[71]	Lambert 1996[72]	Malloy 1978[73]	McCrindle 1997[74]	McCrindle 2002[75]	McCrindle 2003[76]	Stallings 1993[77]	Stein 1999[78]	Sveger 2000[79]	Tonstad 1996a[80]	Tonstad 1996b[81]	Wheeler 1985[82]	Wiegman 2004[83]
Inclusion Criteria (continued)																				
LDL values with or without other risk factors (continued)																				
Plasma LDL between 90th - 99th percentile														X						
TC $\geq$ 300 mg/dL while on $\geq$ 4 months of lipid lowering diet										X										
Genetic mutations																				
Diagnosis of FH established in children and in 1 parent mostly by DNA technique							X													
Personal diagnosis by detection of mutation at the LDL receptor gene		X		X		X			X								X			
Other inclusion criteria including combinations																				
TC $\geq$ 301.6 mg/mL and tendon xanthoma in one or both parents and in relatives in a manner compatible with autosomal dominant inheritance																	X			
TC > 290 mg/dL and first degree relative with MI <age 50 (males) or <age 55 (females)																X				

Table 4b. Inclusion Criteria for Studies of Children with Familial Hypercholesterolemia

	Treatment trials																			
	Clauss 2005[38]	Couture 1998[66]	Davidson 1996[67]	de Jongh 2002a[68]	de Jongh 2002b[69]	de Jongh 2003[70]	Gylling 1995[38]	Knipscheer 1996[71]	Lambert 1996[72]	Malloy 1978[73]	McCrindle 1997[74]	McCrindle 2002[75]	McCrindle 2003[76]	Stallings 1993[77]	Stein 1999[78]	Sveger 2000[79]	Tonstad 1996a[80]	Tonstad 1996b[81]	Wheeler 1985[82]	Wiegman 2004[83]
Inclusion Criteria (continued)																				
Other inclusion criteria including combinations (continued)																				
TC > 260 mg/dL and triglyceride levels < 200 dL, and 1 parent had baseline cholesterol > 300 mg/dL, and triglyceride levels < 200 or tendon xanthoma, and autosomal dominant inheritance present in other members																		X		
TC > 259 mg/dL, a type IIa pattern on lipoprotein electrophoresis, and fasting triglyceride < 58.0 mg/dL in the patient, with either similar lipoprotein abnormalities in one of the parents, or premature CHD death in a parent and a similar lipid abnormality in another close relative																			X	

Abbreviations

BABR=Bile acid binding resin, CAD=Coronary artery disease, CHD=Coronary heart diease, CVD=Cardiovascular disease, FCH=Familial combined hyperlipidemia, FH or heFH=Familial hyperlipidemia, LDL=Low density lipoprotein, MI=Myocardial infarction, TC=Total cholesterol, TG=Triglycerides

Table 5a. Cholesterol Tracking by Risk Group at Baseline

Study, n, and Cohort Came	Age at End of Study (years)	Length of Follow-Up (years)	Risk Group at Baseline	Results at Follow-Up for Risk Group
Kallio, 1993[105] n=162 Helsinki, Finland	5	4	TC in top quartile	40% remained in top quartile
Kelder, 2002[3] n=3,659 Child and Adolescent Trial for Cardiovascular Health (CATCH)	13 (8th grade)	4	TC in top quintile HDL in top quintile	55% remained in top (5th quintile); 80% remained in either 4th or 5th quintile 55% remained in top (5th) quintile; 79% remianed in either the 4th or 5th quintile
Laskarzewski, 1979[98] n=108 Cincinnati LRC Princeton School	11-18 11-18	4 3	TC in top decile (13 of 108) LDL in top decile (at 1 yr; 11 of 108)	6 of 13 remained in top decile 3 of 11 remained in top decile
Clarke, 1978[94] n=820 Muscatine	11-25 11-25	6 6	TC in lowest quintile TG in middle quintile	12% were above the 3rd quintile Equally distributed (20% in each quintile)
Guo, 1993[99] n=96 Fels Longitudinal Study	19-21 19-21 19-21 19-21 19-21	10-12 10-12 10-12 10-12 10-12	LDL>2.84 mmol/L LDL>3.1 mmol/L LDL>3.36 mmol/L (130mg/dL) TC>4.8 mmol/L TC>5.2 mmol/L (200 mg/dL)	10% probability of LDL>3.62 mmol/L 17% probability of LDL >3.62 mmol/L 26% probability of LDL>3.36 mmol/L 5% probability of TC>5.69 mmol/L 19% probability of TC> 5.69 mmol/L
Nicklas, 2002[111] and Bao, 1996[92] n=1,169 Bogalusa Heart Study	20-29	15	TC or LDL in top quintile	>40% remained in top quintile
Lauer, 1989[95] n=2,446 Muscatine	20-30 20-30	10-14 10-14	TC>90th percentile at baseline Any TC measurement >90th percentile during the course of study	24-32% had adult TC>90th percentile 42% had adult TC>90th percentile

Abbreviations

HDL=High-density lipoprotein, LDL=Low-density lipoprotein, TC=Total cholesterol, TG=Triglycerides

Table 5b. Cholesterol Tracking by Risk Group at Follow-up

Study	Age at End of Study (years)	Length of Follow-Up (years)	Risk Group at Follow-Up	Derivation of the Risk Group
Kallio, 1993[105] n=162 Helsinki, Finland	5	4	TC>90th percentile	45% had TC>90th percentile at age 12 months, 80% had TC>75th percentile
Porkka, 1994[108] n=883 Cardiovascular Risk in Young Finns Study	15-30	12	Highest quintile of TC	Approximately 3% from 1st quintile, 11% from 2nd, 12% from 3rd and 28% from 4th, 45% from 5th (highest)
Orchard, 1983[112] n= 561 Beaver County Lipid Study	20-24 20-24	9-10 9-10	Adult TC >80th percentile All adults with TC in top quintile	50% were in top quintile at baseline 4% from 1st quintile, 11% from 2nd, 20% from 3rd, 18% from 4th, 48% from 5th (highest)
Stuhldreher, 1991[96] n=295 Beaver County Lipid Study	17-30	16	Top quintile of TC	6% from 1st (lowest) quintile, 13% from 2nd, 19% from 3rd, 21% from 4th, and 40% from 5th (highest)

Abbreviations

TC=Total cholesterol

Table 6. Summary of Studies Evaluating Sensitivity and Specificity of Family History

Study, year	Population	Method	Threshold*	Sensitivity	Specificity	Number Eligible for Screening (based on population of 1,000)†	Number Missed (based on population of 1,000)†
Bell, 1990[115]	1,140 5th graders	Family history of high cholesterol or MI <age 60 in parent or grandparent	non-fasting TC > 200 mg/dL	64%	47%	540	46
	1,140 5th graders	Above, plus family history of stroke, angina or hypertension	non-fasting TC > 200 mg/dL	77%	24%	760	31
Davidson, 1991[116]	1,118 4th graders	Family history from parents (regarding parents, siblings, grandparents, aunts, uncles); early MI defined as < age 56 for men and women (UCI criteria)	TC > 200 mg/dL	41%	68%	330	83
	1,118 4th graders	Parental questionnaire, definition using AAP criteria for early CHD (< age 50 for men, < age 60 for women)	TC > 200 mg/dL	31%	66%	330	96
Dennison, 1989[126]	1,214, ages 4-10, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	fasting TC $\geq$ 95th percentile	38% for Whites; 27% for AA-Blacks	73% for Whites; 65% for AA-Blacks	n/a	n/a
	2,099, ages 11-17, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	fasting TC $\geq$ 95th percentile	59% for Whites; 25% for AA-Blacks	67% for Whites; 56% for AA-Blacks	n/a	n/a
	1,214,ages 4-10, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	fasting LDL $\geq$ 95th percentile	41% for Whites; 20% for AA-Blacks	73% for Whites; 63% for AA-Blacks	n/a	n/a

Table 6. Summary of Studies Evaluating Sensitivity and Specificity of Family History

Study, year	Population	Method	Threshold*	Sensitivity	Specificity	Number Eligible for Screening (based on population of 1,000)†	Number Missed (based on population of 1,000)†
	2,099, ages 11-17, Bogalusa Heart Study	Parental questionnaire asking parental history of any vascular disease (CHD, HTN, diabetes, stroke)	fasting LDL > 95th percentile	37% for Whites; 22% for AA-Blacks	67% for Whites; 56% for AA-Blacks	n/a	n/a
Diller, 1995[117]	232, ages 2-19, Cincinnati MI Hormone Study	Parental questionnaire using NCEP definition of family history of premature CVD	LDL $\geq$ 130 mg/dL	17%	75%	246	207
	232, ages 2-19, Cincinnati MI Hormone Study	Parental questionnaire asking family history of cholesterol > 240	LDL $\geq$ 130 mg/dL	61%	74%	293	99
	232, ages 2-19, Cincinnati MI Hormone Study	Both family history of elevated cholesterol and premature CVD	LDL $\geq$ 130 mg/dL	74%	55%	478	65
	232, ages 2-19, Cincinnati MI Hormone Study	Other indicators: obesity, smoking, use of lipid raising medications, high fat diet, HTN	LDL $\geq$ 130 mg/dL	17.4% for obesity, 9-48% for others	86% for oebsity, 69-95% for others	547	86
	232, ages 2-19, Cincinnati MI Hormone Study	Family history of premature CHD (NCEP definition), TC>240 mg/dL, or any other risk factor (obesity, smoking, lipid raising medication, high fat diet or HTN).	LDL $\geq$ 130 mg/dL	96%	28%	746	13
Gagliano, 1993[118]	224, ages 11-20	Family history of early MI (<age 50 for men, < age 60 for women) or elevated lipids (TC >200 mg/dL), history obtained from adolescent	TC > 85th percentile for gender	36%	69%	320	94

Table 6. Summary of Studies Evaluating Sensitivity and Specificity of Family History

Study, year	Population	Method	Threshold*	Sensitivity	Specificity	Number Eligible for Screening (based on population of 1,000)†	Number Missed (based on population of 1,000)†
	224, ages 11-20	Family history as above, history obtained from parent	TC above the 85th percentile for gender	65%	46%	589	54
Gagliano, 1993[118] (continued)	224, ages 11-20	Use of combined family history from adolescent and parent	TC above the 85th percentile for gender	45%	69%	361	80
Griffin, 1989[119]	1,005, ages 2-13, 8 office practices	Parent and grandparent history of hypercholesterolemia or CHD < age 55	fasting LDL > 95th percentile	46%	NR	n/a	147
	1,005, ages 2-13, 8 office practices	Parent and grandparent history of any risk factor or complication (hypercholesterolemia, diabetes, HTN, gout, obesity and atherosclerosis prior to age 55)	fasting LDL > 95th percentile	78%	NR	n/a	59
	1,005, ages 2-13, 8 office practices	Parent and grandparent history of hypercholesterolemia or CHD < age 55	fasting LDL > 90th percentile	51%	63%	385	48
	1,005, ages 2-13, 8 office practices	Any history of parent or grandparent with a risk factor or complication (hypercholesterolemia, diabetes, HTN, gout, obesity and atherosclerosis prior to age 55)	fasting LDL > 90th percentile	80% 38% for high cholesterol alone 31% for obesity 18% for sudden death 17% for gout 13% for PVD	37%	650	20

Table 6. Summary of Studies Evaluating Sensitivity and Specificity of Family History

Study, year	Population	Method	Threshold*	Sensitivity	Specificity	Number Eligible for Screening (based on population of 1,000)†	Number Missed (based on population of 1,000)†
	1,005, ages 2-13, 8 office practices	Overweight (weight for height > 95th percentile) plus family history of early CHD or hypercholesterolermia	fasting LDL > 90th percentile	57%	NR	n/a	42
Griffin, 1989[119] (continued)	1,005, ages 2-13, 8 office practices	Overweight (weight for height > 95th percentile) plus family history any risk factor or complication	fasting LDL > 90th percentile	84%	31.0%	704	16
Muhonen, 1994[120]	599, ages 14-20, Muscatine, IA	Parental history of high cholesterol	Highest decile of fasting TC	34%	76%	n/a	n/a
	599, ages 14-20, Muscatine, IA	Parental history of high cholesterol	Highest decile of fasting LDL	34%	76%	n/a	n/a
	599, ages 14-20, Muscatine, IA	Parental history of high cholesterol	Lowest decile of fasting HDL	26%	75%	n/a	n/a
O'Loughlin, 2004[127]	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) meds for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) meds for the heart; unknown family history coded as negative	fasting LDL≥109 mg/dL ("borderline")	33%	76%	256	44
	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) meds for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) meds for the heart; unknown family history coded as negative	fasting LDL≥131.5 mg/dL, ("high")	41%	75%	256	12

Table 6. Summary of Studies Evaluating Sensitivity and Specificity of Family History

Study, year	Population	Method	Threshold*	Sensitivity	Specificity	Number Eligible for Screening (based on population of 1,000)†	Number Missed (based on population of 1,000)†
O'Loughlin, 2004[127] (continued)	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) meds for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) meds for the heart; unknown family history excluded	fasting LDL≥109 mg/dL, ("borderline")	42%	70%	n/a	85
	2,217, ages 9, 13, and 16, Quebec	Parental questionnaire asking personal history of 1) high cholesterol 2) meds for cholesterol 3) heart attack, angina, 4) stroke, CVD or PVD or 5) meds for the heart; unknown family history excluded	fasting LDL≥131.5 mg/dL, ("high")	51%	69%	n/a	19
Primrose, 1994[121]	1,012, ages 12-15, Ireland	History of stroke, angina or heart attack in either parent at any age or in 1st degree grandparents, uncles or aunts < age 55. Questionnaires completed by parents	non-fasting TC > 95th percentile according to LRC	33%	72%	293	125
Resnicow, 1993[122]	574, elementary school age	Parental cholesterol ≥240 in 1 parent only with known and reported value by that parent	non-fasting TC > 200 mg/dL	10%	91%	90	106
Rifai, 1996[62]	260, ages 12-20, African American-Black	Family history of early CHD or hyperlipidemia	fasting LDL > 110 mg/dL	10%	NR	365	184

Table 6. Summary of Studies Evaluating Sensitivity and Specificity of Family History

Study, year	Population	Method	Threshold*	Sensitivity	Specificity	Number Eligible for Screening (based on population of 1,000)†	Number Missed (based on population of 1,000)†
Sanchez Bayle, 1992[123]	2,224, ages 2-18, Spain	Parental history of MI	fasting TC>200 mg/dL	7%	96%	49	140
Sanchez Bayle, 1992[123] (continued)	2,224, ages 2-18, Spain	Parental history of MI	fasting LDL>135 mg/dL	9%	96%	49	101
	2,224, ages 2-18, Spain	Parental history of stroke, HTN, diabetes, or hypercholesterolemia (but not MI)	fasting TC>200 mg/dL	14%	90%	98	129
	2,224, ages 2-18, Spain	Parental history of stroke, HTN, diabetes, or hypercholesterolemia (but not MI)	fasting LDL>135 mg/dL	14%	91%	98	95
Shea, 1990[59]	108, ages 4-5, Hispanic, Study of Childhood Activity & Nutrition	AAP definition (maternal hypertension, diabetes, obesity, hyperlipidemia or family history of premature CHD or hyperlipidemia)	fasting TC > 170 mg/dL	57%	59%	493	148
	108, ages 4-5, Hispanic, Study of Childhood Activity & Nutrition	AHA and NIH Consensus Conference definition (history of hyperlipidemia or premature CHD in the child's parent, aunt, uncle or grandparent)	fasting TC > 170 mg/dL	46%	70%	352	185
	108, ages 4-5, Hispanic, Study of Childhood Activity & Nutrition	NCEP guidelines (history of MI or sudden death in the child's parent, aunt, uncle, or grandparent; CHD prior to age 55).	fasting TC > 170 mg/dL	5%	92%	74	324

Table 6. Summary of Studies Evaluating Sensitivity and Specificity of Family History

Study, year	Population	Method	Threshold*	Sensitivity	Specificity	Number Eligible for Screening (based on population of 1,000)†	Number Missed (based on population of 1,000)†
Steiner, 1991[124]	1,001, ages 12-21 (38% Hispanic, 15% Black, 11% Asian, 33.5% White), Kaiser population	AAP 1998 criteria (known hyperlipidemia in parent or sibling, known MI/angina, current corticosteroid use, juvenile diabetes, hypothyroidism, renal/endocrine/hepatic disease in teenager)	non-fasting TC≥200 mg/dL, repeated fasting TC if initial test≥200 mg/dL, repeated a 3rd time if more than 30 mg/dL variability between the 1st two measurements	63%	60%	400	24
Troxler, 1991[125]	110 mostly Hispanic senior high school students	Questionnaires completed with parental assistance; family history in parents or grandparents of high cholesterol or CHD age <55 (AAP)	fastingTC > 75th percentile (4.53 mmol/L)	38%	79%	218	245
Wadowski, 1994[128]	300 African American-Blacks, ages 2-14	Family history of CHD in parent or grandparent at age < 55	fasting TC > 215 mg/dL	59%	72%	327	23

Key

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

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

Abbreviations

AA-Blacks=African-American Blacks, AAP=American Academy of Pediatrics, AHA=American Heart Asssociation, CHD=Coronary heart disease, CVD=Cardiovascular disease, HTN=Hypertension, LDL=Low-density lipoprotein, MI=Myocardial infarction, NCEP=National Cholesterol Education Program, NIH=National Institutes of Health, PVD=Peripheral vascular disease, TC=Total cholesterol

Table 7a. Summary of Risk Factors for Elevated Total Cholesterol in Children and Adolescents

Study	Physical Activity	Aerobic capacity/ cardiovascular fitness	Diet	Family History	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Bonora, 1992[137]					Total body fat, M: **0**	
Bonora, 1996[138]					Total body fat, M: **0**	
Demerath, 2003[139]					**X+**	
DeStefano, 1995[140]			**X+**	**X+**	BMI: **X+***	Parent smokes: **X-***
Douglas, 1996[141]				**X+**	**X+**	
DuRant, 1982[142]				Parent stroke, diabetes, obesity: **X+*** Family history of diabetes, children only:**O*** Family history of diabetes, adolescent only: **X+***		
DuRant, 1983[143]	M: **X+***	M: **0**	General, M: **0** Alcohol, M: **0**			Smoking, M: **0** Television watched per night, M: **X+***
DuRant, 1993[144]	**0**	**0**				
Dwyer, 1994[145]	**0**	**0**			**X-**	
Eisenmann, 2002[146]					SSF, Adolescent, M: **X+***	
Freedman, 1999[18]					Overweight: **X+**	

Table 7a. Summary of Risk Factors for Elevated Total Cholesterol in Children and Adolescents

Study	Physical Activity	Aerobic capacity/ cardiovascular fitness	Diet	Family History	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Giovannini, 1992[148]				CVD: **0** HC parents: **X+**	F: **X+**	
Glassman, 1993[149]					BMI, %ideal weight: **X+*** Obese: **0** BMI in non-obese, HC: **X-**	
Gliksman, 1993[174]			Dietary fat, M: **0**		BMI, M: **X-**	
Howard, 1991[150]			Grain: **X+**			
Jarvisalo, 2001[151]						aIMT, cIMT, HC, DM: **X+** cIMT: **0**
Kunz, 2005[153]						Smoking, M: **X-**
Larsson, 1992[152]				FHx hyperlipidemia: **X+** FHx MI/angina exclusively: **0**		
Macek, 1989[155]		**0**				
Marti, 1989[156]	**0**	**0**				
Muhonen, 1994[120]				Grandfather hx, HC: **X+**		
Resnicow, 1993[122]					BMI: **X+**	

Table 7a. Summary of Risk Factors for Elevated Total Cholesterol in Children and Adolescents

Study	Physical Activity	Aerobic capacity/ cardiovascular fitness	Diet	Family History	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Ribeiro, 2004[159]					Body fatness: **0**	
Shear, 1985[160]				Single parental vascular disease: **0** Parent MI & parent DM or HTN: **X+**		
Simon, 1995[161]	F: **0**	F: **0**				
Suter, 1993[162]					BMI: **0**	
Thorland, 1981[163]	M: **X+***		**0**		Body fatness: **0**	
Tolfrey, 1999[164]	F: **X+**	F: **X+***	P-fat, F: **X+*** Caloric intake & TC, M: **X+**		%Body fat, F: **X+** M: **0**	
Tonstad, 1995[165]						Puberty stage, M: **X-**
Twisk, 2001[166]		Oxygen uptake: **X+***			SSF: **X+***	
Twisk, 1998[167]					BMI, TC: **X+*** SSF, TC: **X+*** Lean Body Mass: **0***	
Twisk, 1996[168]			P/S fat: **X-** Cholesterol: **X+**			Smoking: **X+***
van Lenthe, 1998[169]					Change in S/T, M: **0*** F: **0**	

Table 7a. Summary of Risk Factors for Elevated Total Cholesterol in Children and Adolescents

Study	Physical Activity	Aerobic capacity/ cardiovascular fitness	Diet	Family History	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
van Stiphout, 1985[170]	**0**		Coffee: **0**	TC of parents & TC of children: **X+**	Age 15+: **X+** Age <15: **0**	Menarche: **0** Age 9-16: **X-**
Ward, 1980[171]			**X+**	**X+**		
Wong, 1992[172]	**0**		Extra lean/no hamburger vs lean/regular hamburger: **X+**	High TC: **X+** Premature MI: **0**	BMI: **0**	2-4 hours TV/day: **X+** Age: **0**

Key

X+ positive significant relationship
X- negative significant relationship
0 no significant relationship
* TC/HDL

Abbreviations

aIMT=Abdominal aorta intima medial thickness, cIMT=Cartoid artery intima medial thickness, DM=Diabetes mellitus, Dyslip=Dyslipidemia, F=Female only, FHX=Family history, HC=High cholesterol, HDL=High-density lipoprotein, HTN=Hypertension, HX=History, M=Male only, MI=Myocardial infarction, P-fat=Polyunsaturated fat, P/M=Polyunsaturated/monosaturated fat, P/S=Polyunsaturated/saturated fat, S-fat=Saturated fat, SSF=Sum of skinfolds, S/T=Subscapular/tricep skinfold ratio, T/S=Tricep/suprailliac

Table 7b. Summary of Risk Factors For Elevated LDL in Children and Adolescents

Study	Physical Activity	Aerobic capacity /cardiovascular fitness	Diet	Family History	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Bergstrom, 1997[136]					**X+**	
Bonora, 1992[137]					Total body fat, M: **0**	
Bonora, 1996[138]					Total body fat, M: **0**	
DeStefano, 1995[140]			**X+**	**X+**		
DuRant, 1982[142]				Parent stroke, DM, obesity, LDL/HDL: **X+** FHX of stroke, LDL/HDL, children only: **X-** FHX of DM, LDL/HDL, children only: **0** LDL/HDL, adolescent only: **X+** Obese family member, LDL/HDL, M: **0** LDL/HDL, F: **X+**		
DuRant, 1983[143]	LDL/HDL, M: **X+**	**0**	General, M: **0** Alcohol, M: **0**			Smoking, M: **0** Hours reading/day, LDL/HDL, M: **X+**
DuRant, 1993[144]	**0**				Waist/hip year 1: **X+**	
Eisenmann, 2002[146]					SSF, Adolescents, M: **X+**	
Freedman, 1999[18]					Overweight: **X+**	

Table 7b. Summary of Risk Factors For Elevated LDL in Children and Adolescents

Study	Physical Activity	Aerobic capacity /cardiovascular fitness	Diet	Family History	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Giovannini, 1992[148]				HC parents: **X+**	F: **X+** M: **X-**	
Glassman, 1993[149]					BMI, %ideal weight, in obese: **0***	
					BMI, HC, in non-obese: **X-**	
Gliksman, 1993[174]			PS ratio, LDL/HDL, F: **X+** Dietary fat, LDL, LDL/HDL, M: **0**		BMI, LDL/HDL: **X+**	
Kunz, 2005[153]						Smoking, M: **X-**
Jarvisalo, 2001[151]						cIMT: **0**
Larsson, 1992[152]				FHX, hyperlipidemia: **X+** FHX, MI or angina exclusively: **0**		
Kwiterovich, 1997[154]			Dietary cholesterol, M: **X+** Any single nutrient, F: **0**		BMI at year 3: **X+**	Baseline LDL: **X+** Tanner Stage: **X-**
Macek, 1989[155]		**X-**				
Muhonen, 1994[120]				Grandfather hx of HC: **X+**		

Table 7b. Summary of Risk Factors For Elevated LDL in Children and Adolescents

Study	Physical Activity	Aerobic capacity /cardiovascular fitness	Diet	Family History	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Suter, 1993[162]	VLDL: **X+**	VLDL: **0**	Dietary fat, VLDL: **0**		BMI, VLDL: **0**	
Tolfrey, 1999[164]	F: **X+**	LDL/HDL, F: **X+**	P-fat & LDL, F: **X+** Caloric intake & LDL, M: **X+**		%Body fat, F: **X+**	
Tonstad, 1995[165]			M: **X+**	LDL & parent cholesterol, LDL & non-FH parent's cholesterol: **X+**	%Body fat in those with FH mutation only: **X+**	Puberty stage, M: **X-**

Key

X+, positive significant relationship
X-, negative significant relationship
0, no significant relationship
* TC/HDL

Abbreviations

BMI=Body mass index, cIMT=Cartoid artery intima medial thickness, DM=Diabetes mellitus, F=Female only, FHX=Family history, HC=High cholesterol, HDL=High-density lipoprotein, LDL=Low-density lipoprotein, M=Male only, MI, myocardial infarction, P-fat=Polyunsaturated fat, P/S=Polyunsaturated/saturated fat, SSF=Sum of skinfolds, VLDL=Very low-density Lipoprotein

Table 7c. Summary of Risk Factors for Decreased HDL in Children and Adolescents

Study	Physical Activity	Aerobic capacity /cardiovascular fitness	Diet	Family history	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Andersen, 2003[135]		**X+**			**X+**	
Bergstrom, 1997[136]	**X+**		Fat intake, M: **X+**		BMI: **X-**	
Bonora, 1992[137]					Total body fat, M: **X+**	
Bonora, 1996[138]					Total body fat, M: **X-**	
Demerath, 2003[139]					**X-**	
DeStefano, 1995[140]			**X+**	**X+**	BMI: **X+**	Parent smokes: **X-***
DuRant, 1982[142]				Parent stroke, DM, obesity, LDL/HDL: **X+*** Family history of stroke, LDL/HDL, children only: **X-** Family history of DM, LDL/HDL, children only: **0*** LDL/HDL, adolescent only: **X+*** FHX obesity, LDL/HDL, M: **0** LDL/HDL, F: **X+**		
DuRant, 1983[143]	LDL/HDL, M: **X+***	M: **0**	General, M: **0** Alcohol, M: **0**			Smoking, M: **0** Television watched per night: **X+*** HDL: **X-** Hours reading per day, LDL/HDL, M: **X+**
DuRant, 1993[144]					SSF Year 2: **X+**	

Table 7c. Summary of Risk Factors for Decreased HDL in Children and Adolescents

Study	Physical Activity	Aerobic capacity /cardiovascular fitness	Diet	Family history	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Dwyer, 1994[145]	**0**	**0**			BMI: **X-** SSF: **X+**	
Eisenmann, 2002[146]					SSF, adolescent, M: **X+*** HDL, adolescent, F: **X-**	
Freedman, 1999[18]					Overweight: **X-**	
Fripp, 1985[147]		M: **X+**			BMI, M: **X-**	
Giovannini, 1992[148]				FHX, CVD: **0**	F: **X-**	
Gliksman, 1993[174]			% saturated fat, PS ratio, F: **X+** M: **0**		BMI: **X-**	
Howard, 1991[150]			High fat: **X+**			
Kunz, 2005[153]						Smoking, M: **O**
Jaing, 1995[173]	M**: X+** F: **0**				SSF, change in subscapular thickness: **X+** BMI, F: **X+**	Caucasians ages 5-17: **X-**
Jarvisalo, 2001[151]						cIMT: **0**
Larsson, 1992[152]				FHX MI/angina or angina exclusively, LDL/HDL: **0** Any family history: **0**		
Macek, 1989[155]		**X+**				
Marti, 1989[156]	**0**	**0**			BMI: **X-**	Sexual maturation, M: **X-**

Table 7c. Summary of Risk Factors for Decreased HDL in Children and Adolescents

Study	Physical Activity	Aerobic capacity /cardiovascular fitness	Diet	Family history	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
Muhonen, 1994[120]				Grandfather hx of CHD: **X+** Grandfather hx of high cholesterol, LDL/HDL: **X+**		
Raitakari, 1996[157]	M: **X+** F: **0**				BMI change, F: **X+** SSF: **X+**	
Shear, 1985[160]				Single parental vascular disease: **0** Parent MI & parent DM or HTN: **X+**		
Simon, 1995[161]	F: **0**		P/S fat, PM fat, P-fat: **0** F: **X+**		SSF: **X-** T/S SF, F: **X+**	
Suter, 1993[162]	**X+**	**0**	Dietary fat: **0**		BMI: **0** SSF: **X-**	
Thorland, 1981[163]	M: **X+***		M: **0**		Body fatness, M: **0**	
Tolfrey, 1999[164]		HDL,LDL/HDL, F: **X+***	P-fat, F: **X+***			
Tonstad, 1995[165]				HDL & FH parent HDL: **X+**		Puberty stage, M: **X-**
Twisk, 2001[166]		Oxygen uptake **X+***			SSF **X+***	
Twisk, 1998[167]					BMI: **0** SSF: **0** Lean Body Mass: **0**	
Twisk, 1996[168]	**X+**		Alcohol: **X+**			Smoking: **X-**

Table 7c. Summary of Risk Factors for Decreased HDL in Children and Adolescents

Study	Physical Activity	Aerobic capacity /cardiovascular fitness	Diet	Family history	Overweight or other Biological Composition Measures	Other Biological and Miscellaneous
van Lenthe, 1998[169]					S/T, M: **X-** Change in S/T, F: **0** Change in TC/HDL, M: **0**	
van Stiphout, 1985[170]					Age 15, M: **X-**	

Key

X+ positive significant relationship
X- negative significant relationship
0 no significant relationship
* TC/HDL

Abbreviations

BMI=Body mass index, CHD=Coronary heart disease, cIMT=Cartoid artery intima medial thickness, CVD=Cardiovascular disease, DM=Diabetes mellitus, F=Female only, FHX=Family history, HDL=High-density lipoprotein, HTN=Hypertension, LDL=Low-density lipoprotein, M=Male only, MI=Myocardial infarction, P-fat=Polyunsaturated fat, P/M=Polyunsaturated/monosaturated fat, P/S=Polyunsaturated/saturated fat, SSF=Sum of skinfolds, S/T=Subscapular/tricep skinfold ratio, T/S=Tricep/suprailliac, SF=Saturated fat

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
Statins							
Clauss, 2005[38]	Lovastatin 20 mg/day for 1st 4 weeks then 40 mg/day for remaining 20 weeks vs. placebo	n=54, girls ages 10-17, all post-menarchal	24 weeks	NR	Total cholesterol, LDL, and Apo B were significantly lower after 4 wks (on 20mg) and after 24 wks (on 40mg) compared to placebo. At 24 wks, mean % changes from baseline were: TC: 26.8% for lovostatin vs +5.2 for placebo (p<0.001); LDL: -21.8 for lovastatin vs +4.5 for placebo (p<0.001).		Good
Couture, 1998[66]	Simvastatin 20 mg/day vs. placebo	n=63	6 weeks	AHA Phase 1 diet	Total cholesterol, LDL, and total ApoB levels were significantly lowered by treatment (vs. placebo) at all time measurements (p<0.0001). HDL levels increased in all groups with drug vs. placebo (p=0.003 to 0.30). TG levels decreased (p=0.009 to 0.10).		Fair

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
de Jongh, 2002[68]	Simvastatin 10 mg/day, doubled every 8 weeks up to 40 mg/day vs. placebo	n=50, ages 9-18	28 weeks	NR	Mean absolute change in FMD was higher for treatment group vs. placebo (p=0.05). TC, LDL and TG were all reduced for treament group vs. placebo (p=0.0001, p=0.0001 and p=0.04 respectively).	Treatment group had reductions in mean TC (p=0.0001), LDL (p=0.0001) and TG (p=0.041). No significant changes in lipoproteins for placebo group compared with baseline. FMD increased in the treatment group (p<0.0001) and did not change in the placebo group.	Poor
de Jongh, 2002[69]	Simvastatin 10 mg/day titrating up to 40 mg/day vs. placebo	n=173, ages 10-17	48 weeks of intervention after 4 week run-in	NR	TC and LDL-C, ApoB, and VDL-C reduced at all time points by drug vs. placebo (p<0.001).		Good
Knipscheer, 1996[71]	Pravastatin in 3 active drug groups: 5, 10, or 20 mg/day vs. placebo	n=72	12 weeks, following an 8 wk diet and placebo run-in period.	Carbohydrates 50% of energy, protein 20%; and fat 30%; unsaturated: saturated ratio of 2:1; total cholesterol <300 mg/day	TC, LDL and ApoB100 were significantly reduced in all pravastatin treated groups compared with placebo (p<0.05 for both). HDL increases and TG changes were not significantly different from placebo.	TC, LDL and ApoB100 were significantly reduced in all pravastatin treated groups compared with baseline (p<0.05). HDL increases and TG changes were not significantly different from baseline .	Good

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
Lambert, 1996[72]	Lovastatin at 10, 20, 30, or 40 mg/day (4 active drug groups, no placebo)	n= 69, boys age ≤ 17	8 weeks	Patients counseled by dietician throughout the trial; fat 30% total calories, saturated fat <10%, polyunsaturated fats <10%, cholesterol <125 mg/100 kcal/day or <300 mg/day (whichever less).	Demonstrated a dose response relationship, with improved results up to a dose of 30 mg/day.	All doses reduced total cholesterol, LDC, and ApoB (P ≤ .0001 for all).	Fair

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
McCrindle, 2003[76]	Atorvastatin 10 mg/day vs. placebo	n=187, ages 10-17	26 weeks	NCEP Step 1 diet	TC, LDL-C, TG and ApoB were reduced compared to placebo (p<0.001 for TC, p<0.001 for LDL-C, p=0.03 for TG, p<0.001 for apoB). HDL cholesterol increased for treatment vs. placebo (p=.02).	Reductions in TC, LDL and TG and increase in HDL were significant for simvastatin group. No significant improvements in placebo group.	Good
Stein, 1999[78]	Lovastatin starting at 10mg/day, titrating to 40 mg/day vs. placebo	132 boys, ages 10-17	48 weeks	AHA pediatric diet	TC and LDL-C decreased at all dosages (p<.001). About 6% additional LDL-C lowering occurred with each doubling of lovastatin dosage. No significant changes in HDL-C or triglycerides compared to placebo.		Good
Wiegman, 2004[83]	Pravastatin 40 mg/day vs. placebo	214 ages 8-18	2 years	Instructed to continue a fat restricted diet	TC decreased for pravastatin vs. placebo (56% vs 2%, p<0.001) LDL decreased 57% for pravastatin vs 0% for placebo 9<0.001) No significant differences for HDL or placebo. Carotid IMT decreased for pravastin vs. placebo (p=0.02)		Good

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
Bile-acid Resins							
McCrindle, 1997[74]	Cholestyramine 8 gm/day as pills vs. powder (no placebo)	n=40, ages 10-18	8 weeks each cross-over period	AHA Step II diet	No lipid levels reported prior to cross-over. At end of study, 82% preferred pill, 16% powder, and 2% neither form. Mean compliance was greater for pills (p=0.01).	Reduction in LDL for both pills (p=0.006) and powder (p=0.0001) with no significant difference between forms (p=0.16).	Fair
McCrindle, 2002[75]	Colestipol (5 g/day) + pravastatin 10 mg/day vs. colestipol alone (10g/day)	n=40, ages 8-18	18 weeks each cross-over period	AHA Step II diet	No data reported prior to cross-over.	Reductions in TC and LDL seen with both colestipol only and colestipol plus pravastatin.	Poor
Tonstad, 1996[80]	Colestipol 10 gm/day or 5 gm twice daily vs. placebo	66 adolescents	8 weeks	NCEP diet: fat ≤30% of calories, saturated fat <10%, cholesterol <200 mg/day.	TC and LDL decreased for treatment group vs. placebo (p<0.01 for both). HDL and TG were not signficantly different.		Poor
Tonstad, 1996[81]	Cholestyramine titrating up from 4 gm/day to 8 gm/day vs. placebo	96 boys ages 6-11	1 year	NCEP diet: fat ≤30% of calories, saturated fat <10%, cholesterol <200mg/day.	At 1 year: TC decreased 11.5% in treatment vs 3% in placebo (p<0.001) LDL decreased 18.6% in treatment group vs. 1.5% in the placebo group (p<0.0001). No changes in HDL or TG.		Fair

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
Fibrate							
Wheeler, 1985[82]	Bezafibrate 10-20 mg/kg/day twice daily vs. placebo	14	3 months each cross-over period	Low saturated fat, increased polyunsaturated fat; actual total fat intake of 98g/day (range: 44-148 gm/day)	No data reported prior to cross-over.	Mean plasma TC decreased during bezafirate treatment (p<0.0001) Mean HDL increased (p<0.01). No change in TG.	Poor
Other							
Engler, 2003[224]	Vitamin C 250 mg twice daily vs. Vitamin E 200 IU twice daily vs. placebo	n=15, ages 8-21	6 weeks each cross-over period	Food guide pyramid and NCEP II guidelines	No data given prior to cross-over.	NCEP II diet resulted in an 8% reduction in LDL (p<0.01) from baseline. No other significant differences in lipid levels. Brachial artery FMD improved compared with baseline (p<0.001) in response to diet plus anti-oxidants.	Poor

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
Engler, 2004[234]	Docosahexaenoic acid vs. placebo	20 children ages 9-19	6 weeks each cross-over period, with 6 week wash-out	NCEP II	No data reprted prior to cross-over.	For combined groups, FMD decreased significantly from baseline for both DHA and placebo groups. TC, LDL and HDL increased significantly from baseline for DHA group, but not for placebo group.	Poor
Engler, 2005[234]	Docosahexaenoic acid vs. placebo	20 children ages 9-19	6 weeks each cross-over period, with 6 week wash-out	NCEP II	No data reported prior to cross-over.	For combined groups, there were no significant differences in TC, LDL, HDL or triglycerides. The DHA +diet group had lower LDL subfractions (LDL1 and LDL 3) and higher HDL2 compared to placebo + diet.	Poor

Table 8. Randomized Controlled Trials of Drug Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Drug	Population	Duration of Trial	Baseline Diet	Results		Quality Rating
					Between Group Differences	Within Group Differences	
Malloy, 1978[236]	p-Amnosalicylic acid 150 mg/kg/day up to 8 g/day vs. placebo	20 children ages 5-21	6 months each cross-over period	Restricted in cholesterol (<200 g/day) and saturated fat (<20% of total calories); all participants and parents received monthly dietary counseling	No data reported prior to cross-over.	Mean TC was lower for treatment with diet and PAS-C vs. diet alone (p<.001). Mean fasting serum triglyceride levels decreased 15.7% with PAS-C plus diet (p<.001). Levels in the compliant subgroup were not lower than those of other patients. No difference in HDL with drug treatment.	Poor

Abbreviations

AHA=American Heart Association, ApoA=Apolipoprotein A, ApoB=Apolipoprotein B, DHA=Docosahexaenoic acid, FMD=Flow-mediated dilation, HDL=High-density lipoprotein, HDL-C=High-density lipoprotein cholesterol, IMT=Intima medial thickness, LDL=Low-density lipoprotein, LDL-C=Low-density lipoprotein cholesterol, NCEP=National Cholesterol Education Program, NR=Not reported, PAS-C=P-aminosalicylic acid-cholesterol, TC=Total cholesterol, TG=Triglycerides, VDL-C=Very low-density Lipoprotein cholesterol

Table 9. Randomized Controlled Trials of Diet Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

				Results		
Author, year	**Intervention(s)**	**Population**	**Duration of Trial**	**Between Group Comparisons**	**Within Group Comparisons**	**Quality Rating**
Amundsen, 2002[41]	Plant sterol spread vs. Control spread	38 children	8 weeks each period	No data reported prior to cross-over.	Results combined indicate: TC, LDL, Apo B were decreased for treatment group vs. control. No change in HDL, TG, or Apo A-1.	Fair
Davidson, 1996[67]	58 gram psyllium-enriched cereal vs. placebo cereal	32 children aged 6 - 18 within the Chicago area	6 weeks each period of cross over	No data reported prior to cross-over.	At 6 weeks: TC decreased 8% in psyllium group (p=0.05) vs 3% for placebo (NS). LDL cholesterol decreased 10% in psyllium group (p=0.001) vs 0.5% in placebo group (NS). Response to treatment differed between subjects consuming psyllium during period 1 vs period 2. A period-by-time interaction was found for total cholesterol (p=0.02).	Fair

Table 9. Randomized Controlled Trials of Diet Treatment for Children with Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

				Results		
Author, year	**Intervention(s)**	**Population**	**Duration of Trial**	**Between Group Comparisons**	**Within Group Comparisons**	**Quality Rating**
Gylling, 1995[39]	Rapeseed oil-rich margarine with sitostanol ester vs. Rapeseed oil-rich margarine without sitostanol ester	14 children with HeFH (mostly established by DNA) 7 each group	6 weeks each arm cross over	No data reported prior to cross-over.	TC decreased 11% in sitostanol group vs 0.8% in placebo group (p<0.05). LDL 18% decreased in sitostanol group vs 3% in placebo group (p<0.05). No change in HDL or TG.	Poor
de Jongh, 2003[40]	Sterol-enriched margarine, (15g/day) vs. Identical appearing control spread, non-sterol-enriched (15g/day)	41 prepubertal HeFH, ages 5-12	4 weeks each period cross over	Last 4 weeks: TC and LDL were decreased significantly for sterol group vs placebo (p<0.001 for both). No difference in HDL, TG, or FMD for sterol vs. placebo.		Good
McCrindle, 1998[235]	300 mg tablet of garlic extract (Kwai, Lichtwer Pharma, Berlin, Germany) containing 0.6 mg of allicin placed in a gelatin capsule with inert filler vs identical capsule with gelatin filler only.	30 children with FH, ages 8-18	8 weeks	Relative to placebo, garlic treatment resulted in: TC increase 0.6 mmol/L (p=0.86) LDL-C decrease 0.5mmol/L, p=0.90 HDL increase 9.3 mmol/L, p=0.29 TG decrease 0.72 mmol/L, p=0.70.		Fair

Abbreviations

ApoA-1=Apolipoprotein A-1, ApoB=Apolipoprotein B, FH or HeFH=Familial hyperlipidemia, FMD=Flow mediated dilation, HDL=High-density lipoprotein, LDL=Low-density Lipoprotein, LDL-C=Low-density lipoprotein cholesterol, NS=Not significant, TC=Total cholesterol, TG=Triglycerides

Table 10. Randomized Controlled Trials of Diet Treatment for Children Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Intervention(s)	Control	Population
Dennison, 1993[223]	Psyllium cereal (3 g of water-soluble fiber and 3 gm of water-insoluble fiber per serving). Two 28 gm servings per day.	Placebo cereal with 5 gm of water-insoluble fiber. Two 28 gm servings per day.	25 children ages 5-17 with LDL>110 mg/dL after diet treatment 12 each group
DISC Collaborative Research Group, 1995[219]	Family oriented behavioral intervention to promote dietary adherence. Sessions weekly x 6 weeks, then biweekly x 10 weeks, plus 2 individual visits for children with family members. In second 6 months: 4 group and 2 individual sessions. Years 2 and 3: group individual and maintenance sessions held 4-6 x per year with monthly phone contacts as needed. Used motivational interviewing and stages of change.	Usual care: Public educational publications on heart-healthy eating provided. Parents informed if child blood cholesterol high - no specific recommendations to see physician given. 3-year lipid results provided, with referral as clinically warranted.	663 prepubertal boys and girls, ages 8-10
Gold, 1991[231]	Oat bran supplemented cereal within AHA Step 1 diet	Control cereal within AHA Step 1 diet	49 school age children with TC>185 mg/dL
Kuehl, 1993[227]	MSI= four 90 minute sessions with focus on food preparation. Participants received notebooks with nutrition information and recipes, incentives for attendance and completion of behavioral contracts (eating low fat meal) Multi-session intervention.	SSI=one 90 minute nutrition education session for pt, siblings and parents (slides presentation, low fat food prep and tasting, distribution of fruit and cereal). "Returned for subsequent food sampling with nutritionist present" but no further formal education. Single session intervention.	295 children ages 2-15 with TC $\geq$185

Table 10. Randomized Controlled Trials of Diet Treatment for Children Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

	Results		
Author, year	**Between Group Comparisons**	**Within Group Comparisons**	**Quality Rating**
Dennison, 1993[223]		No pre cross-over results given. No difference for changes in TC, HDL or LDL. TG increased less for psyllium group vs. control (p<0.05).	Poor
DISC Collaborative Research Group, 1995[219]	TC decreased for diet group vs. control in year 1 (p=0.03) and year 3 (p=0.04) LDL decreased in the diet group vs. control at 1 and 3 years (p<0.001 and p=0.02). HDL decreased in diet group vs. control between groups at year 1 (p=0.03) but not year 3 (p<0.75). No significant differences between groups for TG at years 1 or 3. Dietary total fat, saturated fat, and cholesterol intakes were lower in the diet group vs. control.		Good
Gold, 1991[231]	No significant differences between groups in total cholesterol, LDL, HDL, TG or Apo A. Intervention group had decreased ApoB (-9mg/dL) vs. control (2mg/dL), p=0.05.		Poor
Kuehl, 1993[227]		Both groups had improvement in TC from baseline to the 16-week visit (no results given for between group comparison). MSI group also had significantly decreased LDL. Both groups had a significant decreases in the proportion of total calories obtained from fat and the proportion of total calories obtained from protein. Total calorie intake decreased in the MSI group but not the SSI group.	Poor

Table 10. Randomized Controlled Trials of Diet Treatment for Children Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Intervention(s)	Control	Population
Obarzanek, 2001[218]	Counseling intervention, same as DISC above.	Control: Usual care - parents informed child's blood cholesterol high and were given educational materials on heart-healthy eating as available to the public.	663 randomized, 580 at last follow-up visit
Shannon, 1994[220]	Parent-Child AutoTutorial Program (PCAT) included 10 talking book lessons and follow-up paper and pencil games for children with a manual for parents. Counseling treatment: 45-60 minute session with parent, child and registered dietitian, along with take home print materials for both. Dietitian available for phone to answer questions during 3 month period.	At-risk control group.	Ages 4-10 with LDL 107-164 for boys and 112-164 for girls (mg/dL)
Stallings, 1993[77]	Parent-Child AutoTutorial Program (PCAT) 10 sessions total, 1 per week completed in home by child and parents	Usual Care: 1 hour session with registered dietician using AHA guide	44 children ages 4-10 with LDL between 90-99th percentile.

Table 10. Randomized Controlled Trials of Diet Treatment for Children Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

	Results		
Author, year	**Between Group Comparisons**	**Within Group Comparisons**	**Quality Rating**
Obarzanek, 2001[218]	Results for years 1 and 3 are the same as presented in DISC study above Results for years 5 and 7 follow-up presented here. No difference between intervention group and control for LDL at 5 years (p=0.11) or final visit (yr 7) (p=0.25). No difference for TC at 5 or 7 years. No difference for HDL at 5 or 7 years. No differences in TG or LDL/HDL ratio. Intervention group had lower dietary total fat, saturated fat at all points (p<0.001) and lower cholesterol intake at year 5 (p<0.001).		Good
Shannon, 1994[220]	Mean LDL-C decline of PCAT (10.1mg/dL) was greater than in at-risk control (4.1 mg/dL) (p<.05). This represents an 8% decline in the PCAT group. Dietary knowledge scores: increased 3x more in PCAT vs. counseling or at-risk control (p<.001). Lipid intake: Mean grams of total and saturated fat decreased in PCAT/counseling group and increased slightly in at-risk control (p<.05).		Good
Stallings, 1993[77]	No between group differences at either 3 or 6 months for LDL. No results reported for TC, HDL or TG. No differences between groups in knowledge, caloric intake, fat intake. Cholesterol intake was lower in PCAT group vs. control at 6 mo. (p<0.05)	LDL decreased ~10% within both groups at both 3 and 6 months, (p<0.01). Both groups had increases in knowledge at 3 and 6 months compared to baseline (p< 0.001). No difference in caloric intake within groups. Total fat intake decreased in both groups; no change in saturated fat intake; both groups decreased cholesterol intake.	Poor

Table 10. Randomized Controlled Trials of Diet Treatment for Children Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	Intervention(s)	Control	Population
Williams, 1995[229]	Fiber cereal contained 3.2 g soluble fiber per serving. Dose=1 box of cereal per day for 3 weeks, then 2 boxes/day. Children ages 2-5 consumed only 1 box/day throughout study.	Placebo cereal with 0.5/g of fiber, 1 box/day x 3 weeks then 2 boxes per day; children ages 2-5 consumed 1 box per day.	58 with TC>170 mg/dL and LDL>110mg/dL.

Abbreviations

AHA=American Heart Association, Apo A=Apolipoprotein A, Apo B=Apolipoprotein B, HDL=High-density lipoprotein, LDL=Low-density lipopr cholesterol, TG=Triglycerides

Table 10. Randomized Controlled Trials of Diet Treatment for Children Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

	Results		
Author, year	**Between Group Comparisons**	**Within Group Comparisons**	**Quality Rating**
Williams, 1995[229]	TC decreased for fiber vs. Step 1($p<0.05$), LDL decreased for fiber vs. Step 1 ($p<0.01$), no difference in HDL or TG between groups. TC/HDL and LDL/HDL ratios improved ($p<0.001$).	After 12 weeks: Both groups had significant within-group decreases in TC, but decrease for fiber was significantly greater. TC decrease $p<0.01$ within Step I, $p<0.001$ within fiber group. No change in HDL within groups. Fiber group had decrease in LDL ($p<0.01$), No change within step I group. TG decreased for fiber group, with no change within step 1 group.	Poor

Table 11. Randomized Controlled Trials of Exercise Trials for Children and Adolescents Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

					Results		
Author, year	**N**	**Duration of Trial**	**Intervention(s)**	**Control**	**Between Group Comparisons**	**Within Group Comparisons**	**Quality Rating**
Obese Children and Adolescents							
Ferguson, 1999[225]	81 obese children mean age 9.5	4 months each period	Exercise program offered 5 days/week, 40 min per day; children were paid $1/session and given prizes for maintaining a HR>150 bpm. After school transportation was provided.	No exercise training program	Prior to cross-over, no p values reported: TC decreased 6% for intervention group and 7% for control. HDL increased 4% for intervention vs 0% for control. LDL decreased 6% for intervention group vs 12% for control. TG decreased 17% for intervention vs an increase of 12% for control.	For change over 8 months (post-crossover), group x time interaction was significant for triglycerides only (p=0.02) Results also given for combined groups at the end of their intervention periods.	Fair
Kang, 2002[226]	80 obese children ages 13-16	8 months	Physical training (PT) offered 5 days/week for 8 months except when assigned to lifestyle education (LSE). Physical training = individual exercise prescription, 1045 kJ/session (250kcal), mean prescribed HR of 55-60% or 75-80% of peak	Lifestyle education alone.	Comparison of pre-post changes in mmol/L (least-square mean+SEM): No significant change in TC or HDL compared to control. TG decreased for LSE+PT group as compared to control (p=0.003).		Poor

Table 11. Randomized Controlled Trials of Exercise Trials for Children and Adolescents Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	N	Duration of Trial	Intervention(s)	Control	Results		Quality Rating
					Between Group Comparisons	Within Group Comparisons	
Healthy Children and Adolescents							
Boreham, 2000[230]	25 sedentary but healthy female students ages 18-22	7 weeks	7 week stair climbing program, progressing to 6 ascents/day on a public access staircase Mon-Fri (199 steps with a total vertical displacement of 32.8 meters).	No change in activity	Stair climbers had significant improvements compared to control in HDL ($p<0.01$) but not for TC. However, pre-intervention difference in HDL between stair climbing and control group was significant ($p<0.05$).	Pre-post results for stair climbers only in mmol/L, mean +SEM after 7 weeks: TC decreased ($p<0.05$). HDL increased ($p<0.05$). Controls had no signficant changes in lipid levels.	Poor
Linder, 1982[232]	50 healthy boy scouts ages 11-17	8 weeks	Physical conditioning program (PA) designed to increase aerobic capacity.	Usual summer activities.	Post-test physical working capacity increased in the PA group vs control group, $p<0.05$. No difference in TC, LDL, HDL, TG or VLDL between groups.	No significant differences in the change in TC, LDL, HDL, TG, VLDL levels from pre to post.	Fair

Table 11. Randomized Controlled Trials of Exercise Trials for Children and Adolescents Without Identified Familial Hypercholesterolemia or Other Monogenic Dyslipidemia

					Results		
Author, year	N	Duration of Trial	Intervention(s)	Control	Between Group Comparisons	Within Group Comparisons	Quality Rating
Savage, 1986[233]	663 prepube-scent boys	11 weeks	Walking/jogging/running 3 times/week for 11week (total distance of 1.6 km per session). Low intensity group had a training HR of 40% VO2 maximum. High intensity training group had a training HR of 75% VO2 max.	Control subjects were requested to maintain their current activity pattern throughout the study.	No significant differences between groups in the changes of HDL/total cholesterol ratio, TG, or LDL. Change in HDL-C values was significantly greater for the high intensity group ($p<0.05$) but not for the low intensity group as compared to control.	No significant changes in HDL/total cholesterol ratio, TG, or LDL.	Fair
Stergioulas, 1998[228]	58 sedentary high school boys ages 10-14 normal body weight and normal lipids	2 months	Exercise: 2 month training program with four, 60 minute sessions per week. Sessions included warm-up, stretching, and aerobic exercise at 75% of physical work capacity.	No specific training program. Both groups advised not to change dietary habits or physical activity.	No significant differences between groups.	Physical work capacity of exercise group increased at the end of treatment ($p<0.001$). No change seen in control group. HDL increased for intervention group at end of the 2nd treatment month ($p<0.005$) and at the end of the detraining period ($p<0.01$). No change seen in control group.	Poor

Abbreviations HDL=High-density lipoprotein, HR=Heart rate, LDL=Low-density lipoprotein, SEM=Standard error of measure, TC=Total cholesterol, TG=Triglycerides, VLDL=Very low-density Lipoprotein

Table 12. Randomized Controlled Trials of Diet and Exercise for Children Without Identified Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	N	Duration of Trial	Intervention(s)	Control	Results		Quality Rating
					Between Group Comparisons	Within Group Comparisons	
Becque, 1988[221]	36 over-weight children ages. 3 small groups.	20 weeks	1. Diet and behavior change: met with dietician and behavior therapist once/week. ADA exchange program set to elicit the loss 1-2 lbs/week. Behavioral treatment included record keeping stimulus control, changing topography of eating and reinforcing altered behavior. 2. Exercise plus diet and behavior change: same as above, with exercise program 50 minutes 3 days/week.	No change in activity or diet	Post-treatment HDL level for exercise, diet and behavior change group was significantly better from the control and from the diet plus behavior change post-treatment groups (p<0.05) No other between group differences.	Control group had no pre-post differences in HDL, TC or TG (n=14). Diet and behavior change group had no pre-post differences in TC, HDL or TG (n=11). Exercise, diet and behavior change group increased HDL (P<0.05) but did not change TC or TG (n=11).	Fair
Epstein, 1989[217]	56 obese (>20% of ideal weight) children ages 8-12	6 months	Diets were set between 3800-5000/kJ/day and monitored by a nutritionist to maintain nutrient adequacy. Information on diet, exercise, stimulus control, reinforcement, modeling and contingency contracting was presented to parents and their children in eight weekly sessions followed by four monthly sessions.		Results for the two intervention groups (diet or diet+exercise instruction) were combined for total treatment group n=35 and control n=16. TC decreased for intervention vs. control (p=0.03). HDL increased for intervention vs. control, (p=0.007). TG decreased for intervention vs. control (p=0.01).		Poor

Table 12. Randomized Controlled Trials of Diet and Exercise for Children Without Identified Hypercholesterolemia or Other Monogenic Dyslipidemia

Author, year	N	Duration of Trial	Intervention(s)	Control	Results		Quality Rating
					Between Group Comparisons	Within Group Comparisons	
Walter, 1985[222]	1115 4th graders	1 school year (2 hours/ week)	"Know Your Body" curriculum yearly from 4th-8th grade; taught in usual classroom by regular teacher 2 hours/week for entire school year. Teachers trained by research staff in 3 half-day teacher workshops on curriculum implementation. Adherence to teaching protocols monitored by classroom visits from research staff and attendance at training workshops.	Usual cur-riculum	Adjusting for age, gender, race and baseline risk factor level, TC difference between groups was significant (p=0.03). HDL and HDL/TC differences were not significant (p=0.18 and p=0.06 respectively).	At year 1: TC decreased 0.4% in the intervention group vs. a 0.5% increase in control group. HDL decreased 7% in intervention group vs 9% in control group. TC/HDL ratio decreased 9% for intervention vs 6% in control group.	Fair

Abbreviations

ADA=American Dietetic Association, HDL=High-density lipoprotein, TC=Total cholesterol, TG=Triglycerides

Table 13. Adverse Events Reported in Studies of Statins

Author, year, title	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Atorvastatin						
McCrindle, 2003[76]	RCT	187	26 weeks	10-17, mean 14.1	No significant adverse effects; No effect on sexual development.	Increased AST in 1%; Increased ALT in 1%. None withdrew or stopped med as a result of increased transaminases.
Lovastatin						
Clauss, 2005[38]	RCT	54 girls	24 weeks	10-17	None observed; no detectable effect on menstrual cycle length.	NR
Lambert, 1996[72]	RCT	69 boys	8 weeks	<18, mean 12.7	None observed.	Asymptomatic elevations in CK in 3 subjects.

Table 13. Adverse Events Reported in Studies of Statins

Author, year, title	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Stein, 1999[78]	RCT	132	48 weeks	mean 13	No effect on growth; No difference between drug and placebo in testicular volume, Tanner staging, testosterone, or LH level.	DHEAS increased by 18%. Tocopheral decreased. ALT increased in both drug and placebo; no differences between groups at week 48. No consistent changes in AST or CK. Transient CK elevations in response to exercise. Mean CD3 lymphocyte count decreased from baseline of 2.72 + 0.91 $nX10^9$ to 6-months of 2.34 + 0.81 $nX10^9$ (p=0.003). Mean CD4 lymphocyte count decreased from baseline of 1.47 + 0.57 $nX10^9$ to 6-months of 1.26 + 0.50 $nX10^9$ (p=0.010). Mean CD8 lymphocyte count decreased from baseline of 0.89 + 0.34 to 6-months of 0.75 + 0.26 $nX10^9$.
Pravastatin						
Wiegman, 2004[37]	RCT	214	2 years	8-18, mean 13	No impact on growth, endocrine function parameters, Tanner staging scores, onset of menses or testicular volume.	No effects on muscle or liver enzyme levels.
Hedman, 2003[240]	Open-label	20	8 weeks	4-15	Abdominal pain (1), loose stools (1), headache (4), sleep disturbance (2), muscle tenderness or pain at rest (1), muscle tenderness or pain associated with physical training (1).	No effects on serum ALT, CK, or creatinine.

Table 13. Adverse Events Reported in Studies of Statins

Author, year, title	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Knipscheer, 1996[71]	RCT	72	12 weeks	mean 12	Rash, nose bleeding, headache, nausea/vomiting, abdominal pain.	CK abnormal in 8 of placebo, 6 of 5 mg/day, 11 of 10 mg/day and 8 of 20 mg/day groups. Cortisol abnormal in 2 of placebo, 2 of 5 milligrams per day, 5 of 10 milligrams per day, 3 of 20 milligrams per day groups.
Simvastatin						
Couture, 1998[66]	RCT	63	6 weeks	8-17, mean 12.6	None observed.	NR
De Jongh, 2002[68]	RCT	69	28 weeks	9-18, mean 14.6	None observed.	No significant differences between simvastatin and placebo FH groups on ALT, AST, and CK.
De Jongh, 2002[69]	RCT	173	48 weeks	10-17	Abdominal pain (3), chest pain (1), flatulence (1), myalgia (2), headache (4), sleep disorder (1), weight gain (1), pruritus (1).	Increased ALT (3), AST (3), and CK (1).
Dirisamer, 2003[241]	Open-label	20	18 months	10-17, mean 13	Transient headache (2). Myalgia (1) for 2 weeks. Transient gastrointestinal complaints (2).	Slightly higher values of CK (2); Transiently elevated ALAT (GPT) and GCT (1).

Table 13. Adverse Events Reported in Studies of Statins

Author, year, title	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Ducobu, 1992[243]	Open-label	32	24-36 months	<17	Children for whom height (n=12) and weight (n=16) were available remained in the growth percentages they had been in at baseline.	Slight transaminase increase (n=1) and slight CK increase (n=2) were transient. No significant changes detected overall.
Stefanutti, 1999[244]	Non-RCT	16	12 months	7-12, mean 8.75	No adverse effects were observed with diet alone or with diet plus simvastatin. Patients showed good compliance with the treatment.	NR
Various or unspecified statins						
Sinzinger, 2004[242]	Descriptive	22 profes-sional athletes	8 years	15-27, mean 24.1	Muscle pain reported in 84% of periods of statin therapy. Mean time of onset of muscle pain was 8.3 days.	Elevated CK in 3 subjects. No increase in liver enzymes.
De Jongh, 2003[70]	Cross-sectional	69	NR	10-18, mean 15.3	No differences between the children with FH and their healthy peers on health-related quality of life and anxiety.	Not assessed.

Abbreviations

ALAT=Alanine aminotransferase, ALT=Alanine transaminase, AST=Aspartate aminotransferase, CK=Creatine kinase, DHEAS=Dehydroepiandrosterones, GCT=Glucose challenge test, GPT=Glutamic-pyruvic transaminase, FH=Familial hyperlipidemia, LH=Luteinizing hormone, NR=Not reported, RCT=Randomized controlled trial

Table 14. Adverse Events Reported in Studies of Bile-acid Binding Resins

Author, year, title	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Cholestyramine					
Curtis, 1991[245]	1	2 years	7	Loss of dental enamel noted. This was presumed due to low pH (2.4) of cholestyramine mixed with Kool-Aid (and swished by child in his mouth for 15 min before swallowing)	Serum calcium, phosphorus, folate, B12 were normal
Farah, 1977[246] Farah, 1977[247]	20	16 days	4-23, mean 15	Febrile gastroenteritis in 1 patient after 7 days treatment resulting in discontinuation of therapy.	Serum folate decreased significantly in females. 7/11 females had folate measured after treatment and results only reported in aggregate by gender. SGOT increased in 2 patients (32 and 41 IU/dL), and persisted 6 months. Transient LDH increases (>60 IU/dL) in 2. No fat-soluble vitamin malabsorption.
Glueck, 1973[263]	20 on diet +BABR	6 months with additional 12-18 months follow-up for growth	7-21	10 of 12 routinely took the suggested dose of cholestyramine. Weight gain and growth progressed during the 12 and 18 month follow-up period along normal growth percentile	No consistent changes in any of the laboratory safety tests (CBC, liver function tests, BUN, calcium, phosphorous, total protein, electrolytes and carbon dioxide). No evidence for hypercholoremic acidosis at any time.
Glueck, 1974[262]	30 on diet + BABR	average follow-up of 6 months	5-21	NR	Plasma vitamins A and E remained within the normal range and paralleled at higher levels the 25th to 75th percentile distirbution for vitamin A and E in normal children.

Table 14. Adverse Events Reported in Studies of Bile-acid Binding Resins

Author, year, title	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Glueck, 1977[260]	16 (same children as Glueck 1973 above)	16 children followed for 18 months; 12 for 24 months; 7 for 30 -36 months	9-17	11 of 16 had good adherence. 5 children dropped out after 2 years because of poor palatability of the drug. 1 child had persistent constipation. None had nausea. 5 complained that resin was gritty, had poor palatability. 1 complained of chronic fatigue	CBC, liver function tests, vitamin A and E, calcium, phsophorus, blood urea nitrogen, fasting blood sugar levels did not vary signficantly over time when compared to baseline levels on diet only.
Glueck, 1986[261]	33	4.3 years	mean 10.3	Height and weight percentiles at completion were unchanged from baseline. No abnormal growth patterns noted. Sexual maturation was normal. None had unusual infections or extra school sick days. None of the girls had ammenorrhea; though 1 competitive cross-country runner had persistently irregular periods. No depression, suicide attempts or traumatic deaths. 4 children exhibited transient refusal to follow diets and/or take bile acid-binding resins.	NR
Koletzko, 1992[251]	35 on diet; 14 on diet + BABR	Diet: mean 17.5 mos. Diet+BABR: mean 27.9 months	2-17, mean 7.9	No serious side effects were noted with both forms of treatment (diet/ diet + BABR). Normal growth. Mild gastrointestinal symptoms occurred in "very few" patients.	NR
Liacouras, 1993[252]	87	Up to 62 months	mean 10.6	12 nausea, 2 abdominal bloating, 1 severe constipation. 73% complained of poor palatability	No elevated prothrombin times.

Table 14. Adverse Events Reported in Studies of Bile-acid Binding Resins

Author, year, title	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
McCrindle, 1997[74]	40	28 weeks	10-18	Minor gastrointestinal complaints were frequent but did not result in any drop-out	NR
Tonstad, 1996[81]	96	1 year	6-11 mean 8	Growth and bone age were normal. One case of intestinal obstruction caused by adhesions in 1 patient. Unpalatability, headaches, and vomiting were reasons for withdrawals.	Folate deficiency occurred in most subjects with cholestyramine, and vitamin D levels decreased significantly for those not taking a multi-vitamin. No other significant differences in nutrient levels. Hemoglobin and liver enzymes were unchanged.
Tonstad, 1998[255]	96	1 year	6-11 mean 8	22/36 treatment and 26/36 placebo participants completed the trials thought secondary to unpalatability of drug.	During cholestyramine treatment, plasma total homocysteine increased in subjects with the C677T mutation in one or both alleles but not in subjects with the CC genotype.
West, 1973[256]	19	Up to 20 months		Some had impaired fat absorption without diarrhea. Growth was normal. None developed anemia.	Serum folate decreased in all patients. Hemoglobin, prothrombin time, serum calcium, alkaline phosphates, and serum vitamin A concentrations were unchanged.
West, 1975[257]	18	1 to 2.5 years	1-14	No child developed diarrhea, and growth was normal.	Folate deficiency and decreased red cell folate. Prothrombin time remained normal in all patients. There was a significant decrease in mean serum levels of vitamins A and E and inorganic phosphorus. Levels of serum iron, vitamin B12, plasma calcium, and protein did not change significantly.
West, 1975[258]	45	2-8 years	1-16	Adherence was poor due to unpalatability of cholestyramine.	Folate deficiency, steatorrhoea, and reduction in serum levels of vitamins A and E and of inorganic phosphorus although not to abnormally low values.

Table 14. Adverse Events Reported in Studies of Bile-acid Binding Resins

Author, year, title	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
West, 1980[259]	35	1-8 years	1-17, mean 8.4	Almost all children expressed some dislike of cholestyramine, and a few complained of transient gastric fullness. No patient had persistent constipation, loss of appetite or diarrhea. Nausea, dizziness and malaise in a female aged 18. One boy died of intercurrent infection 10 months after starting meds, not stated whether related to treatment.	NR

Table 14. Adverse Events Reported in Studies of Bile-acid Binding Resins

Author, year, title	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Colestipol					
Groot, 1983[248]	33	16 weeks	NR	5 withdrew due to unpalatability.	NR
Hansen, 1992[249]	30	8.5 years (diet); 5.5 years (diet followed by diet + BABR)	1-17	One child's height/age decreased below -2 SD. Growth was normal in other children	NR
Harvengt, 1976[250]	3	Up to 36 months	6, 11, 18	No hepatic dysfunction, renal function, or hematologic side effects observed. Mild gastrointestinal complaints (flatulence, constipation) during first 3 months, but disappeared despite continued treatment. No steatorrhea.	Low iron without anemia in one. Serum uric acid level increased during treatment but did not reach abnormal values. Serum vitamin B12 and folic acid content were not impaired after 2 and 3 years on colestipol. Prothrombin time values were not abnormally prolonged.
McCrindle, 2002[75]	40	36 weeks	9-18, median 14	18% reported constipation, 21% had stomachache, 11% had headache, 6% had muscle aches. Compliance was 57-66% overall and was similar among treatment groups and dose groups.	NR

Table 14. Adverse Events Reported in Studies of Bile-acid Binding Resins

Author, year, title	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values
Schwarz, 1980[253]	23	Up to 24 months	5-17, mean 12	6 subjects complained of poor palatability. 1 patient developed Reynauld's phenomenon during therapy but continued treatment without recurrence of symptoms.	Serum vitamins A and E decreased significantly after 18-24 months of colestipol. No changes in 25-hydroxycholecalciferol, folic acid or prothrombin time.
Tonstad, 1996[80]	66	52 weeks	mean 13.2	8 had gastro-intestinal side effects, including constipation, dyspepsia, flatulence, nausea, decreased appetite, abdominal pain. Growth was normal.	Low-dose colestipol (10 g/day) reduced concentrations of serum folate after 8 weeks. Serum vitamin E and carotenoids decreased proportionally with decreases in cholesterol. Vitamin D did not change significantly, but decreased more in subjects who were more compliant after 1 year.
Tonstad, 1996[254]	27	6 months for colestipol; mean 6 years for diet	10-16	Growth was normal. Two had difficulty swallowing the tablets; one had difficulty with flatulence; one had abdominal discomfort.	NR

Abbrevations

BABR=Bile acid binding resin, BUN=Blood urea nitrogen, CBC=Complete blood count, LDH=Lactate dehydrogenase, NR=Not reported, SGOT=Serum glutamic-oxalocetic transaminase

Table 15. Adverse Events Reported in Studies of Other Drugs and Combinations

Author, year, title	Drug	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Baker, 1982[54]	Probucol	Open-label trial	7	15-21 months	6-21	Nausea in one patient; Growth and development were normal.	No significant changes in endocrine, hepatic, or hematological investigations. Levels of total T1 and T4, and of free T1 and T4 did not change.	Well tolerated
Becker, 1992[264]	Sitosterol and bezafibrate, in sequence and in combination	Open-label trial	7	3 months sitosterol; 3 months bezafibrate; 24 months sitosterol + bezafibrate	mean 8.4	Two had decreased appetite for the first 2 weeks on sitosterol. Ultrasounds of gallbladder found no abnormalities.	Sitosterol: slight, significant decrease in hemoglobin (-5%) and ALP (-19%). Bezafibrate: ALP remained lower; iron increased by 26%. Combination: transferrin increased 20% and reached abnormal levels in 2; all other lab values normal.	Children and parents reported a high degree of acceptance and compliance during all treatments.
Brun, 1980[265]	Dextrothy-roxine (D-T4)	Descrip-tive	6	12 weeks	7-12	NR	With D-T4 treatment, the secretion of both TSH and T3 in response to TRH was abolished. An increase in the basal level of T3 was observed after treatment with D-T4. The high circulating levels of D-T4 and possibly of D-T3 after chronic administration of D-T4 may be responsible for the saturation of pituitary nuclear T3 receptors, resulting in the suppression of the TRH-induced TSH response.	NR

Table 15. Adverse Events Reported in Studies of Other Drugs and Combinations

Author, year, title	Drug	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Colletti, 1993[266]	Niacin	Retro-spective	21	1-19 months, average 8.1	4-14	18 of 21 patients reported some adverse effect: flushing 71%, itching 19%, abdominal pain 14%, nausea 14%, headache 14%, constipation 5%. One subject developed febrile illness with serum aminotransferase >400 IU/L two months after starting niacin. Niacin at 1000 mg/day-sustained release was considered a possible cause of hepatitis.	Reversible serum aminotransferase elevations (dose related) in 6 patients: 4 with crystalline and 2 with sustained release form of niacin.	18 of 21 patients reported some adverse effect. Drug was discontinued in 1 subject due to poor compliance.
Malloy, 1978[73]	P-amnosali-cylic acid	RCT	20	6 months	5-21, mean 12	No indicators of drug toxicity reported, other than mild gastric irritation that remitted with oral antacid treatment.	Normal SGOT, SGPT, ALP, bilirubin, and glucose levels in fasting serum; normal TSH and thyroxine. Triiodothyronine levels were slightly below normal for 2 in active drug and 1 on placebo.	Compliance was >50% for 11 subjects, <50% for 9 subjects.

Table 15. Adverse Events Reported in Studies of Other Drugs and Combinations

Author, year, title	Drug	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
McDuffie, 2002[267]	Orlistat	Observa-tional	20	3 months	mean 14.6	Effects were generally mild, limited to gastrointestinal effects related to increased fat excretion, and resolved within the first 6 weeks of treatment.	A small but significant drop in 25-hydroxy vitamin D levels was seen at 1 month. 3 subjects required additional vitamin D supplementation despite the prescription of a daily multivitamin containing vitamin D. TSH, free thyroxine, glycosylated hemoglobin, calcium, phosphorous, magnesium, zinc, measures of iron stores did not change significantly.	Subjects who completed treatment (85%) reported taking 80% of prescribed medication. Only one subject (5%) cited intolerance of adverse effects as reason for withdrawal.
Stein, 1989[268]	Diet + drug or combined drugs: BABR; BABR + niacin; lovastatin or simvastatin	Cross-sectional	30	1-9 years	1-20, mean 5.5	No adverse clinical or biochemical side effects were noted on the HMG CoA reductase inhibitor.	Resin + niacin together produced elevated AST and ALT and clinical symptoms of hepatotoxicity in one subject. Niacin in this subject was associated with a significant rise in liver enzymes, suppression of albumin, and clinical symptoms of hepatotoxicity.	NR

Table 15. Adverse Events Reported in Studies of Other Drugs and Combinations

Author, year, title	Drug	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Steinmetz, 1981[269]	Fenofibrate	Descrip-tive	17	18 months	4-19	NR	4 of 17 subjects had increased ALT (at least 100%) and AST (at least 80%). Uric acid decreased significantly (mean change -20%). Bilirubin decreased significantly (mean change -19%). Inorganic phosphates decreased slightly but significantly. Albumin was unchanged. ALP decreased by mean 15%. GGT decreased slightly (by 1.5 U/l). ALT increased by 9 U/l. AST increased by 11 U/l.	NR
Wheeler, 1985[82]	Bezafibrate	RCT	14	3 months	4-15, mean 10.9	Growth was satisfactory throughout trial. No other reports of adverse effects	One child had high alk phos after 3 months of bezafibrate. Another child had slight transient rise in ALT during first 2 months on bezafibrate but values were normal by end of 3rd month.	All subjects declared preference for this drug over cholestyramine used previously.

Abbreviations

ALP=Alkaline phosphate, ALT=Alanine transaminase, AST=Aspartate aminotransferase, BABR=Bile acid binding resin, NR=Not reported, SGOT=Serum glutamic-oxalocetic transaminase, SGPT=Serum glutamic-pyruvic transaminase, TRH=Thyroid releasing hormone, TSH=Thyroid stimulating hormone

Table 16. Adverse Events Reported in Studies of Low Fat Diet

Author, year, title	Study Design	N	Duration	Age (years)	Growth	Adverse Effects of Treatment	Laboratory Values
Cetta, 1994[279]	Retro-spective	63	2 years	2-16, mean 7.8	Normal height. Weight loss in 2 females: 1 with anorexia nervosa, 1 with a more restrictive vegetarian diet.	NR	NR
Copperman, 1995[270]	Cross-sectional	54	NA	mean 10.8	NR	NR	Normal intake of energy, minerals, or vitamins D and E.
DISC Collaborative Research Group, 1995[219]	RCT	663	3 years	mean 9.4	Normal	NR	Intake was low for vitamin E and zinc.
Feoli-Fonseca, 1998[282]	Retro-spective	16	23 years reviewed; mean follow-up 6.76 years	infants (<1 year) with familial chylo-micro-nemia	Normal	2 children had severe abdominal pain, and another had acute pancreatitis after using an oral contraceptive agent.	Abnormal values were observed for serum iron, alkaline phosphatase, and total calcium. All erythrocyte folate and albumin levels were within normal range.

Table 16. Adverse Events Reported in Studies of Low Fat Diet

Author, year, title	Study Design	N	Duration	Age (years)	Growth	Adverse Effects of Treatment	Laboratory Values
Jacobson, 1998[280]	Observa-tional	138	3 years	2-15	Normal	NR	NR
Kaistha, 2001[285]	Cross-sectional	80	N/A	9.9	NR	NR	More children with hyperlipidemia than controls ($p<0.05$) consumed below 75% of the RDA/DRI for vitamin E and calories.
Kuehl, 1993[227]	RCT	295	33 weeks	mean 7	Normal	NR	Iron intake maintained at over 87% and calcium intake at over 81% of the RDA throughout the study.
Lavigne, 1999[281]	RCT	663	Mean follow-up 36.2 months	8-10	NR	No adverse effects of treatment in academic function, psychological symptoms, or family function.	NR

Table 16. Adverse Events Reported in Studies of Low Fat Diet

Author, year, title	Study Design	N	Duration	Age (years)	Growth	Adverse Effects of Treatment	Laboratory Values
Lifshitz, 1989[278]	Observa-tional	40	Mean time since diagnosis: 20.1 months (with growth failure); 3.9 months (without growth failure)	mean 7.7	8 (20%) of 40 patients had growth failure. Three had nutritional dwarfing with no progression of puberty. The other 5 had a drop in body weight without linear growth alterations.	NR	The 3 patients with nutritional dwarfing consumed <60% of required energy, <50% RDA of vitamins B6, D, folacin, zinc, iron, calcium, and magnesium, and <66% of RDA for vitamins A and B12, niacin, and phosphorus. Only vitamins E and C were adequately consumed.
McKenzie, 1996[274]	Prospec-tive cohort	300	3 months	4-10	NR	NR	74% failed to consume two thirds of the RDA for vitamin D.
Moreno, 1998[275]	Descrip-tive	42	6 months	7-15	NR	NR	Lymphocyte T subset counts (CD3, CD4, and CD8) showed significant decreases after 6 months but were within normal ranges.

Table 16. Adverse Events Reported in Studies of Low Fat Diet

Author, year, title	Study Design	N	Duration	Age (years)	Growth	Adverse Effects of Treatment	Laboratory Values
Obarzanek, 2001[218]	RCT	663	4 years	mean 9.5	Normal height, BMI, and sexual maturation	NR	No abnormalities in serum ferritin, red blood cell folate, serum retinol and zinc.
Rose, 1976[277]	Descrip-tive	16	16 followed for 1 year; 9 for >1 year	1 month to 20 years	Normal	None observed	NR
Sanchez-Bayle, 1994[276]	Observa-tional	451	6-24 months	2-18	Normal	NR	NR
Sanchez-Bayle, 2003[283]	Prospec-tive	144	Mean 7.42 years	2-13, mean 5.5	Normal height. Increase in weight	NR	NR

Table 16. Adverse Events Reported in Studies of Low Fat Diet

Author, year, title	Study Design	N	Duration	Age (years)	Growth	Adverse Effects of Treatment	Laboratory Values
Segall, 1970[272]	Observa-tional	5	10 days	6-15	1 child lost 1.4 kg, another child gained 1.2 kg	NR	In all subjects, serum triglyceride increased after 3-6 days on the high-carb diet. TG levels fell on resumption of a diet containing 45% carbohydrates.
Tershakovec, 1998[284]	RCT	261	12 months	3.9-9.9	Normal	None noted.	NR
Tonstad, 1996[271]	Cross-sectional	185	N/A	7-16	Normal	Normal behavioral and emotional scores.	NR
Witschi, 1978[273]	Observa-tional	91	3 week diet period	Adoles-cents	Normal	NR	NR

Abbreviations

BMI=Body mass index, DRI=Dietary reference intakes, NA=Not applicable, NR=Not reported, RCT=Randomized controlled trial, RDA=Recommended daily allowance, TG=Triglycerides

Table 17. Adverse Events Reported in Studies of Dietary Supplements

Author, year, title	Dietary Supplement	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Amundsen, 2002[41] (some data from Amundsen 2004)	Plant sterol ester spread 18.2 g/day of spread corresponding to 1.6 g/day of sterol esters.	RCT	38	8 weeks	mean 10.5	None observed.	ALT increased 16.8% (p = 0.04). After adjustment for lipid changes, lycopene was 8.1% lower (p=0.015) in treatment than in control group. lipid-adjusted serum retinol levels were 15.6% (p<0.001) higher in treatment than control groups. Lipid-adjusted lathosterol levels increased by 96% ; sitosterol increased by 48%	Children consumed 18 g/day of spread. 1 subject withdrew because the amount of spread was too large.
Amundsen, 2004[287]	Plant sterol ester spread (20 g of spread per day, corresponding to 1.76 g/day of plant sterol), some children took fish oil supplements or vitamins	Open-label trial, following RCT above	37	26 weeks	mean 9.6	NR	Lipid-adjusted lathosterol levels were stable; sitosterol levels were 77% higher compared to control period of RCT. Lipid-adjusted retinol levels were 11% higher at the end of the open label period as compared to control. No changes in lycopene or lutein. Lipid-adjusted serum a-carotene increased in the open label period following a decrease in the trial period.	Children consumed slightly less spread (14 g/day vs 18 g/day during trial).

Table 17. Adverse Events Reported in Studies of Dietary Supplements

Author, year, title	Dietary Supplement	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Becker, 1993[288]	Diet plus sitosterol pastils, then diet plus sitostanol	Open-label trial	9	10 months: 3 sitosterol 7 sitostanol	mean 11.9	Growth was normal. No abnormalities in liver and gallbladder. No changes in stool pattern.	Diet phase: ALT decreased. Sitosterol: alk phos and carotene decreased. Sitostanol: ALP and carotene returned to initial values; transferrin increased slightly and serum bile acid levels decreased, but were within normal range. No changes in hemoglobin, leukocyte count, platelet count, calcium, phosphate, lipase, iron, creatinine, and creatinine kinase.	All 9 subjects completed the study; good compliance with all treatments.
Clarke, 1990[289]	Fish oil 5 g/day	Observa-tional	11	6 months	11-21	8 of 11 subjects had episodes of epistaxis that caused 2 to withdraw. One subject had asymptomatic occult blood in the stool on one occasion; the bleeding time was normal.	No evidence of liver dysfunction. All prothrombin and partial thromboplastin times and platelet counts were normal.	2 (18.2%) of 11 subjects withdrew due to epistaxis.

Table 17. Adverse Events Reported in Studies of Dietary Supplements

Author, year, title	Dietary Supplement	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Dennison, 1993[223]	Psyillium fiber 6 g/day	RCT	25	4-5 weeks	mean 11.1	No changes in sub scapular or triceps skin-fold thicknesses. Height and weight growth were normal.	None of vitamin or mineral levels tested were decreased.	Compliance was 82% for both cereals.
Glassman, 1990[290]	Psyillium fiber 5 g/day	Descrip-tive	36	8.1 months	9-17, mean 9.7	No abdominal distention or cramping, constipation, diarrhea, or excessive flatus production.	No changes in serum zinc, copper, or hemoglobin concentrations; hematocrit; mean corpuscular volume; or prothrombin and partial thromboplastin times.	All patients tolerated both regimens well.
Gulesserian, 2002[291]	Rapeseed oil substitution for all fats and food preparation	Descrip-tive	17	5 months	4-19, median 12.7	NR	NR	The diet was well accepted; no patient withdrew due to dislike of the oil.

Table 17. Adverse Events Reported in Studies of Dietary Supplements

Author, year, title	Dietary Supplement	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Gylling, 1995[39]	Rapeseed oil-rich margarine substitution of fats (24 g/day) with sitostanol (3 g/day)	RCT	14 HeFH, 1 HoFH	6 weeks	2-15, mean 9.1	NR	NR	Reported good compliance; well tolerated. Children noted no difference in taste between the two margarines.
Laurin, 1991[294]	Soy-protein beverage	RCT	10	4 weeks	mean 7.9	Growth and development were normal.	NR	Reported good control over mean dietary intake; similar percentages of protein energy were consumed as a dairy source in the soy-protein and cow-milk diet groups.

Table 17. Adverse Events Reported in Studies of Dietary Supplements

Author, year, title	Dietary Supplement	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
McCrindle, 1998[235]	Garlic extract	RCT	30	8 weeks	8-18, mean 14	The most common effects were headache and upset stomach, and were similar between garlic and placebo groups. 1 patient on garlic had unpleasant body odor, but had been working concomitantly on a garlic farm during the study.	Serum albumin level (+2.0 g/L, p=0.002) and hemoglobin (+5.2 g/L, p=0.02) with garlic.	1 patient was unable to swallow the capsules and withdrew. Compliance was similar between garlic and placebo groups. 86% vs 93% (p=0.34).
Mietus-Snyder, 1998[292]	Vitamins E (400 IU) and C (500 mg) twice daily	Non-randomized controlled trial	11	6 weeks	6-21, mean 12.5	No adverse effects of antioxidant vitamin therapy reported.	NR	All subjects tolerated the study well.
Sanchez-Bayle, 2001[293]	Fiber tablets (50% wheat bran, 50% pectin) 100-150 mg/kg/day	Observational	53	3 months	4-18, mean 7.3	Two children reported abdominal discomfort and soft stools.	NR	Generally well tolerated; 2 withdrew due to abdominal discomfort

Table 17. Adverse Events Reported in Studies of Dietary Supplements

Author, year, title	Dietary Supplement	Study Design	N	Duration	Age (years)	Adverse Effects of Treatment	Laboratory Values	Compliance/ Tolerance
Schlierf, 1978[295]	Sitosterol	RCT	15	3 months	8-20	Not reported.	NR	Good compliance.
Zavoral, 1983[296]	Locust bean gum (LBG)	Non-RCT cross-over trial	11	8 weeks	10-18	Increased rectal gas for 1 to 2 weeks while on the LBG-containing products.	No change observed in the white blood cell counts, serum calcium, or SGOT determinations.	Children ate the prescribed amount of LBG food products.

Abbreviations

ALP=Alkaline phosphatse, ALT=Alanine transaminase, HeFH=Familial hyperlipidemia, HoFH=Familial homozygous hyperlidpidemia, NR=Not reported, RCT=Randomized controlled trial, SGOT=Serum glutamic-oxalocetic transaminase

Table 18. Summary of Systematic Evidence Review

Arrow	Key question	Level and Type of Evidence	Quality of Evidence	Conclusions
1	Is screening for dyslipidemia in children effective in delaying the onset and reducing the incidence of CHD-related events?	None		
2	What is the accuracy of screening for dyslipidemia in identifying children at increased risk of CHD-related events and other outcomes?			See below.
2a	What are abnormal lipid values in children?	II-2	Fair to Poor	Normal values for lipids in children are currently defined according to population levels (percentiles). NCEP recommendations are based on LRC data, which defines the 95th percentile for TC as 200 mg/dL and for LDL as 130 mg/dL. There are more recent studies suggesting that age, gender, racial differences and temporal trends shift these cut points. The NCEP has defined levels of LDL for which drug treatment (LDL≥190mg/dL or LDL≥160mg/dL with family history of early CHD), further evaluation, diet therapy and testing (LDL>130mg/dL) and diet therapy with increased surveillance (LDL110-129mg/dL) are recommended.
2b	What are the appropriate tests? How well do screening tests (non-fasting total cholesterol, fasting total cholesterol, fasting lipid panel) identify individuals with dyslipidemia?	II-2, II-3.	Poor	The most appropriate test is one that accurately predicts future risk and benefit from treatment. In the general population of children there have not been adequate studies to determine these characteristics. Data from few studies suggest that TC above the 95th percentile predicts LDL above the 95th percentile with 44-69% sensitivity. TC minus HDL might be a more sentivitive 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.

Table 18. Summary of Systematic Evidence Review

Arrow	Key question	Level and Type of Evidence	Quality of Evidence	Conclusions
2c	How well do lipid levels track from childhood to adulthood?	II-2. Longitudinal cohort studies.	Good	Serial correlations measured in individual children over time are higher for TC (r=0.38-0.78) and LDL (r=0.4-0.7) than for HDL and TG. Approximately 40-55% of children with elevated lipids (by percentile) will continue to have elevated lipids on follow-up as older children. In two studies that followed children/adolescents to young adulthood (between ages 20-30), 40-45% continued to have elevated lipids.
2d	What is the accuracy of family history in determining risk?	II-2. Studies of diagnostic test accuracy.	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.
2f	What are other important risk factors?	II-2. Cross-sectional and longitudinal cohort studies.	Good for family history; Good for obesity; Poor for all other risk factors.	Evidence from epidemiologic cross-sectional and cohort studies establish a statistical association between family history and overweight and elevations in lipids. There is inadequate evidence to show the magnitude of the effect of overweight on lipids, or the impact that incorporating weight measures into a screening tool could have. Multiple other risk factors (diet, physical inactivity, aerobic capacity/fitness, puberty level and smoking) have not been evaluated adequately to assess their contribution to dyslipidemia in children or their usefulness as screening tools.
2e	What are effective screening strategies for children (including frequency of testing, optimal age for testing)?	I, III. One RCT and multiple descriptive studies of screening programs.	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.

Table 18. Summary of Systematic Evidence Review

Arrow	Key question	Level and Type of Evidence	Quality of Evidence	Conclusions
3	What are the adverse effects of screening including false positives, false negatives, labeling, etc?	I, II-3, III.	Fair	Studies demonstrate lack of parental compliance with screening and follow-up recommendations. Reasons for non-compliance include concern about test accuracy, lack of proof that intervention makes a difference in children, concern about upseting the child, refusal by the child, inconvenience, or decision to institute a diet themselves and have child rechecked subsequently.
4	In children and adolescents, what is the effectiveness of drug, diet, exercise, and combination therapy in reducing the incidence of adult dyslipidemia, and delaying the onset and reducing the incidence of CHD-related events and other outcomes (including optimal age for initiation of treatment)?	None		
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)?	I. RCTs in familial hypercholesterolemia patients (drugs and diet) and general populations of children (diet and exercise)	Good quality studies with fair external validity for drug therapy. Fair to poor for diet and exercise treatments.	Statins are effective for reducing TC and LDL in children with familial hypercholesterolemia. It is not clear how this efficacy translates to children with milder and/or non-familial forms of dyslpidemia. Diet supplements (psyllium, oat, sterol margarine) and counselling were marginally effective in both FH/FCH children and adolescents and those without identified monogenic dyslipidemia. Exercise treatments showed minimal to no improvements in children without monogenic dyslipidemia.

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	N	Demographics	Duration of follow-up	Age at start	Age at follow-up	Fasting serum levels?
Bogalusa Heart Study; Bogaulsa, LA						
Bao, 1996[92]	1169	64% white, 36% black, 50% M; 50% F	15 years but dates given are 15-17 years post start	5-14 years	(calc)	Yes
Freedman, 1985[17]	1052	49% M; 51% F 55% white, 45% black	8 years	2.5-14 years		Yes
Berenson, 1979[93]	1052	212 for TC; 154 for LDL, HDL and TG	2 years	5 years	7 years	Yes
	1,052	281 for TC; 247 for TG; 245 HDL and LDL	2 years	8 years	10 years	Yes
	1,052	323 for TC; 270 for LDL, HDL and TG	2 years	11 years	13 years	Yes
	1,052	241 for TC; 200 for LDL, HDL and TG	2 years	14 years	16 years	Yes
Child and Adolescent Trial for Cardiovascular Health Cohort Study; Multi-centered in U.S.						
Kelder, 2002[3]	3,659 at grade 8 (3rd follow-up point); HDL done on a random 30% of population	51% M, 49% F; 71% White, 13% AA, 13% Hispanic, 3% other	6 years	3rd grade (mean age 8.8 years)	8th grade (mean age 14.1 years)	No
	4,019	same	2 years	3rd grade (mean age 8.8 years)	5th grade (mean age 11.1 years)	No

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	Correlation coefficients				Other Outcome	Adjusted? If so, for what?	Comments
	TC	LDL	HDL	TG			
Bogalusa Heart Study; Bogaulsa, LA *continued*							
Bao, 1996[92]	0.4-0.6	0.4-0.6	0.2-0.4	0.1-0.4		No	
Freedman, 1985[17]	0.54-0.63	0.55-0.71	0.25-0.43			No, but values given are race and sex specific	Lipids appear to track better in black M vs. black F or whites
Berenson, 1979[93]	0.42	0.43	0.14	0.21		Yes for year 1, race, sex height at year 1, change in weight/height, change in ht. (MV regression)	Alphalipoprotein = HDL
	0.58	0.69	0.23	0.31		No	
	0.49	0.64	0.30	0.35		No	
	0.52	0.58	0.41	0.22		No	
Child and Adolescent Trial for Cardiovascular Health Cohort Study; Multi-centered in U.S. *continued*							
Kelder, 2002[3]	0.66	NR	0.62	NR			
	0.73	NR	0.73	NR			

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	N	Demographics	Duration of follow-up	Age at start	Age at follow-up	Fasting serum levels?
Child and Adolescent Trial for Cardiovascular Health Cohort Study; Multi-centered in U.S. *continued*						
Kelder, 2002[3]	3,659	same	3 years	5th grade (mean age 11.1 years)	8th grade (mean age 14.1 years)	No
Muscatine Study; Muscatine, IA						
Clarke, 1978[94]	7,371	3,521 M; 3,850 F	2 years	5-16 years		
	3,268	1,558 M; 1,710 F	4 years	6-14 years		
	816	408 M; 408 F	6 years	8-12 years		
Lauer, 1989[95]	2,446	1,167 M; 1,279 F	12-14 years	8-18 years	20-30 years	Yes (LRC method)
	99	55 M; 54 F	same	7-8 years	20-25 years	
	612	292 M; 311 F	same	9-10 years	20-25 years	
	1,018	476 M; 542 F	same	11-12 years	20-25 years	
	339	490 M; 551 F	same	13-14 years	20-25 years	

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	Correlation coefficients: TC	LDL	HDL	TG	Other Outcome	Adjusted? If so, for what?	Comments
Child and Adolescent Trial for Cardiovascular Health Cohort Study; Multi-centered in U.S. *continued*							
Kelder, 2002[3]	0.7	NR	0.65	NR		No	% remaining in highest quintile for 3rd grade to 5th grade: 59% for TC; 63% for HDL. % remaining in lowest quintile for 3rd grade to 5th grade: 59% for TC; 60% for HDL. For 3rd to 8th grade: lowest 53% for TC, 52% for HDL; highest 55% for TC, 55% for HDL.
Muscatine Study; Muscatine, IA *continued*							
Clarke, 1978[94]	0.68			0.44		No	
	0.63			0.4		No	After 4 years, 40% of those in the highest quintile for TG remained in that quintile.
	0.61			NA		No	After 6 years, 50% of those originally in the highest quintile for TC remained in that quintile.
Lauer, 1989[95]							Paper reports percent variability of adult lipids according to tobacco, alcohol and OCP use.
	M: 0.56, F: 0.64	M: 0.56, F: 0.65	M: 0.07, F: -0.25	NA		No	
	M: 0.58, F: 0.49	M: 0.56, F: 0.47	M: 0.07, F: 0.01	NA		No	
	M: 0.51, F: 0.54	M: 0.47, F: 0.53	M: -0.04, F: 0.06	NA		No	
	M: 0.51, F: 0.52	M: 0.47, F: 0.49	M: -0.02, F: 0.11	NA		No	

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	N	Demographics	Duration of follow-up	Age at start	Age at follow-up	Fasting serum levels?
Muscatine Study; Muscatine, IA *continued*						
Lauer, 1989[95]	1,041	155 M; 184 F	same	13-14 years	26-30 years	
	767	352 M; 415 F	same	15-16 years	20-25 years	
	568	263 M; 305 F	same	15-16 years	26-30 years	
	615	299 M; 316 F	same	17-18 years	20-25 years	
	479	233 M; 246 F	same	17-18 years	26-30 years	
Beaver County Lipid Study, Beaver County, PA						
Stuhldreher, 1991[96]	295	48.7 M	16 years	11-14 years	27-30 (mean age 28)	Yes for follow-up values; baseline values measure calorimetrically by the ferric chloride-sulfuric acid method

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	Correlation coefficients				Other Outcome	Adjusted? If so, for what?	Comments
	TC	LDL	HDL	TG			
Muscatine Study; Muscatine, IA *continued*							
Lauer, 1989[95]	M: 0.52, F: 0.52	M: 0.50, F: 0.49	M: 0.16, F: 0.08	NA		No	
	M: 0.64, F: 0.53	M: 0.60, F: 0.49	M: -0.03, F: 0.15	NA		No	
	M: 0.63, F: 0.55	M: 0.56, F: 0.50	M: 0.06, F: 0.10	NA		No	
	M: 0.72, F: 0.54	M: 0.63, F: 0.56	M: -0.07, F: 0.13	NA		No	
	M: 0.64, F: 0.48	M: 0.61, F: 0.45	M: 0.06, F: 0.04	NA		No	
Beaver County Lipid Study, Beaver County, PA *continued*							
Stuhldreher, 1991[96]	M: 0.38; F: 0.51	NA	NA	NA		No	

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	N	Demographics	Duration of follow-up	Age at start	Age at follow-up	Fasting serum levels?
Lipid Research Clinics Program, multi-centered, U.S.						
Namboodiri, 1984[97]	103	56 M, 47 F	0-30 months (median 3 months)	<20 years	<20 years	Yes, LRC
	105	55 M, 50 F	7-52 months (median 29 months)	<20 years	<20 years	Yes, LRC
	102	54 M, 48 F	7-102 months (not explicitly stated)	<20 years	<20 years	Yes, LRC
Laskarzewski, 1979[98]	108	46% M; 54% F; 81% White, 18% Black, <1% Asian.	7 years	7-14 years	14-21 years	Yes, LRC
Fels Longitudinal Study; Cincinnati, OH						
Guo, 1993[99]	96	NR	4 years	9-21 years	13-25	Yes, LRC
	96	NR	6 years	9-21 years	15-27	
	96	NR	8 years	9-21 years	17-29	
	96	NR	10 years	9-21 years	19-31	
	96	NR	12 years	9-21 years	21-33	
Baumgartner, 1991[100]	69	27 F; 42 M 100% White	unclear	12-18 years	up to age 21 years	Yes, LRC

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	Correlation coefficients				Other Outcome	Adjusted? If so, for what?	Comments
	TC	LDL	HDL	TG			
Lipid Research Clinics Program, multi-centered, U.S. *continued*							
Namboodiri, 1984[97]	M: 0.762, F: 0.782	NA	NA	M: 0.374, F: 0.510		Not reported, but paper states that "correlations were also computed with the advariate adjusted lipid values; the results were generally similar."	
	M: 0.703, F: 0.604	M: 0.672, F: 0.592	M: 0.488, F: 0.241	M: 0.436, M: 0.331		As stated above	
	M: 0.593, F: 0.604	NA	NA	M: 0.363, F: 0.522		As stated above	
Laskarzewski, 1979[98]	0.68	0.61	0.53	0.39			
Fels Longitudinal Study; Cincinnati, OH *continued*							
Guo, 1993[99]	0.77	0.78	0.57				
	0.63	0.67	0.43				
	0.58	0.61	0.31				
	0.61	0.58	0.34				
	0.72	0.65	0.46				
Baumgartner, 1991[100]	M: 0.63, F: 0.56	M: 0.60, F: 0.52	M: 0.43, F: 0.79	M: 0.58, F: 0.53			Used Foulkes-Davis tracking index (using Dallal program), TC, TG, LDL for boys and TC, HDL for girls were statistically significant.

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	N	Demographics	Duration of follow-up	Age at start	Age at follow-up	Fasting serum levels?
Aerobics Center Longitudinal Study, Cooper Institute, Dallas Texas						
Eisenmann, 2004[110]	48	12 F; 36 M Mean weigh 61.5kg	11 yrs	12-18 years (mean age 15.8)	mean age 26.6	Yes
NON-U.S. COHORTS						
Amsterdam Growth & Health Study						
Twisk, 1997[101]	181		14 years	13-16 years		Yes
Kindergarten Study, Basel, Switzerland						
Mohler, 1996[102]	NR	NR	5 years	5 years	10 years	No, capillary blood morning sample not fasting
	NR	NR	4 years	10 years	14 years	No
	249	NR	9 years	5 years	14 years	No
Quebec, Canada						
Vobecky, 1988[103]	88 at risk children	41 M, 47 F	9 years	3-36 months	9-11 years	Yes (LRC method)
Quebec Family Study						
Katzmarzyk, 2001[104]	147	76 M, 71 F	12+1.5 years	8-18 years		Yes

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	Correlation coefficients				Other Outcome	Adjusted? If so, for what?	Comments
	TC	LDL	HDL	TG			
Aerobics Center Longitudinal Study, Cooper Institute, Dallas Texas *continued*							
Eisenmann, 2004[110]	0.62	NR	0.6	0.54	TC:HDL ratio 0.78	length of follow-up used as a covariate	
NON-U.S. COHORTS *continued*							
Amsterdam Growth & Health Study *continued*							
Twisk, 1997[101]	tracking coefficient: 0.71	NA	tracking coefficient: M: 0.51, F: 0.65	NA			
Kindergarten Study, Basel, Switzerland *continued*							
Mohler, 1996[102]	0.07 (NS)	0.2	0.19				
	0.2	0.29	0.21				
	0.09 (NS)	0.19	0.16				
Quebec, Canada *continued*							
Vobecky, 1988[103]	OR for TC≥200 mg/dL: 4.35 (1.78-10.63)	OR for LDL>125 mg/dL: 3.88 (1.85-8.14)	OR for HDL<40mg/dL: 2.10 (0.89-4.97)				
Quebec Family Study *continued*							
Katzmarzyk, 2001[104]	NA	NA	M: 0.58, F: 0.56	M: 0.37, F: 0.20	TC/HDL ratio: M: 0.51, F: 0.57	Yes, initial age and length of follow-up period	

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	N	Demographics	Duration of follow-up	Age at start	Age at follow-up	Fasting serum levels?
Helsinki, Finland						
Kallio, 1993[105]	162	NR	5 years	birth	5 years	Cord blood sample at birth, scalp vein sample at 2,4,6,9,12 mos, non-fasting
	162	NR		2 months	5 years	
	162	NR		4 months	5 years	
	162	NR		6 months	5 years	
	162	NR		9 months	5 years	
	162	NR		12 months	5 years	
Toledo Area Study; Toldeo, Spain						
Bastida, 2002[106]	38	21 F, 17 M	4 years	births	4 years	12 hour fast for 4 year olds, cord blood sample at birth
Cardiovascular Risk in Young Finns Study; mulit-centered in Finland						
Porkka, 1991[107]	2,236	47.6% M	6 years	3-18 years		Yes
Porkka, 1994[108]	883	414 M, 469 F	12 years	3-18 years	(15-30 years)	Yes
	187	97 M; 90 F	12 years	3 years	15 years	Yes
	160	74 M; 86 F	12 years	6 years	18 years	Yes

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	Correlation coefficients				Other Outcome	Adjusted? If so, for what?	Comments
	TC	LDL	HDL	TG			
Helsinki, Finland *continued*							
Kallio, 1993[105]	0.01	NA	NA	NA		No	
	0.31	0.43	0.26	0.26			
	0.29	NR	NR	NR			
	0.32	0.2	0.21	0.27			
	0.36	0.41	0.39	0.52			
	0.47	0.58	0.29	0.37		No	
Toledo Area Study; Toldeo, Spain *continued*							
Bastida, 2002[106]	0.35	0.53	0.49	NR			
Cardiovascular Risk in Young Finns Study; mulit-centered in Finland *continued*							
Porkka, 1991[107]	0.63	0.66	0.58	0.36		No	
Porkka, 1994[108]	M: 0.58, F: 0.48	M: 0.58, F: 0.53	M: 0.58, F: 0.53	M: 0.37, F: 0.33		No	M showed more tracking than F
	M: 0.60, F: 0.51	M: 0.62, F: 0.57	M: 0.64, F: 0.51	M: 0.25, F: 0.46		No	
	M: 0.56, F: 0.37	M: 0.60, F: 0.47	M: 0.56, F: 0.44	M: 0.13, F: 0.32		No	

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	N	Demographics	Duration of follow-up	Age at start	Age at follow-up	Fasting serum levels?
Cardiovascular Risk in Young Finns Study; mulit-centered in Finland *continued*						
Porkka, 1994[108]	156	77 M; 79 F	12 years	9 years	21 years	Yes
	149	64 M; 85 F	12 years	12 years	24 years	Yes
	115	51 M; 64 F	12 years	15 years	27 years	Yes
	116	51 M; 65 F	12 years	18 years	30 years	Yes
Eno, East Finland						
Fuentes, 2003[109]	82	49 M, 33 F	8 years	7 years	15 years	Yes

Abbreviations M = Male; F = Female

Evidence Table 1. Tracking of Serum Lipid Levels

Study, year arranged by cohort	Correlation coefficients				Other Outcome	Adjusted? If so, for what?	Comments
	TC	LDL	HDL	TG			
Cardiovascular Risk in Young Finns Study; mulit-centered in Finland *continued*							
Porkka, 1994[108]	M: 0.63, F: 0.52	M: 0.58, F: 0.53	M: 0.56, F: 0.60	M: 0.18, F: 0.22		No	
	M: 0.57, F: 0.60	M: 0.56, F: 0.59	M: 0.69, F: 0.52	M: 0.45, F: 0.21		No	
	M: 0.40, F: 0.40	M: 0.44, F: 0.51	M: 0.57, F: 0.48	M: 0.53, F: 0.58		No	
	M: 0.73, F: 0.51	M: 0.67, F: 0.48	M: 0.54, F: 0.56	M: 0.49, F: 0.37		No	
Eno, East Finland *continued*							
Fuentes, 2003[109]	Yes	NA	NA	NA		Gender, body weight, parental education, family history of obesity, family history high cholesterol, family history CVD and BMI	TC decreased more steeply in boys than in girls from age 7 to 15, but no statistically significant age-gender interaction was found.

Abbreviations M = Male; F = Female

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Andersen, 2003[135]	Randomly-selected Danish children ages 9 and 15	1020	To determine whether the number of participants with multiple coronary heart disease (CHD) risk factors exceeded the number expected from a random distribution. To establish whether and to what extent clustering of risk factors occurs in Danish children and adolescents.	Cardiovascular fitness: Estimated from maximal power output in a cycle test with progressively increasing workload until exhaustion. Anthropometric measures: SSK (biceps, triceps, subscapular and suprailiac) BMI Venous blood samples: Following overnight fast Risk factors defined as: TC, HDL, TG, serum insulin and blood pressure
Bergstrom, 1997[136]	Healthy Swedish adolescents aged 14 to 17.	879	To assess the relationship between physical fitness and BMI and suggested cardiovascular risk indicators of lipids, insulin, ferritin and blood pressure; as well as physical activity and dietary intake.	Activity: Self-report 7-day records and questionnaire. Physical training and other physical exercise graded on a 6-graded scale. Cardiovascular fitness: 3 km running test Anthropometric: BMI, SSF (biceps, triceps, subscapular, suprailiac skinfolds) Diet: Self-report 7-day record Blood: lipids, insulin, ferritin Blood pressure Chronic disease history
Bonora, 1992[137]	18 yr old males, Verona Italy	1293	To evaluate the relation of either total body fat or body fat localization in several risk factors for atherosclerosis (serum lipids, insulin, and blood pressure)	Body mass index (obese = BMI of >27) Waist and hip circumferences (body fat distribution) Total body fat or fat free mass (electrical resistance) Serum cholesterol (HDL, LDL, & Total) Triglycerides Insulin Blood pressure Smoking, alcohol use, physical activity

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Andersen, 2003[135]	X	NE	Those who had a high level of cardiovascular risk factors (4 or 5 risk factors) had a physical fitness level 1.2 standard deviations lower than mean values for the population. Authors conclude study found clustering of risk factors for metabolic syndrome.	NE
Bergstrom, 1997[136]	X	Physical activity: + correlated HDL, boys only (0.008, 95%CI, 0.001,0.014)	Positive relationship between running time and TG Boys: 0.014, 95%CI, 0.000,0.028 Girls: 0.016, 95%CI, 0.005,0.027	Fat intake: + correlate HDL boys only (0.013, 95%CI, 0.003,0.023) inverse correlate TG girls only (-0.013, 95%CI, -0.022,-0.003) Iron intake: Inverse correlate ferritin boys only (-37.995, 95%CI, -73.237,-2.752)
Bonora, 1992[137]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Andersen, 2003[135]	NE	BMI: Those who had a high level of cardiovascular risk factors (4 or 5 risk factors) had a BMI 1.6 standard deviations higher than mean values for the population. Risk factors included TC, HDL, TG, serum insulin and blood pressure.
Bergstrom, 1997[136]	NE	BMI inversely related to HDL (boys -0.027, 95%CI, -0.044,-0.009; girls -0.019, 95%CI,-0.031,-0.007) BMI + related to LDL (boys 0.037, 95%CI, 0.003,0.071; girls 0.036, 95%CI 0.006,0.067) BMI + related to insulin (boys 0.383, 95%CI, 0.193,0.572; girls 0.305, 95%CI, 0.128,0.483) Degree of adiposity is the most important factor in explaining differences between lipid and insulin values between adolescents with different levels of fitness.
Bonora, 1992[137]	NE	Total body fat is independently associated with: HDL, HDL/TC, TG, insulin, systolic blood pressure, diastolic blood pressure ($p<.001$). Not significant for total cholesterol or LDL. Total body fat is a better predictor of risk than waist/hip ratio (body fat localization).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Andersen, 2003[135]	NE	NE
Bergstrom, 1997[136]	NE	NE
Bonora, 1992[137]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Bonora, 1996[138]	Healthy Italian men in Verona, Italy aged 18 or 38. Subset of those in the Verona Young Men Artherosclerosis Risk Factors Study. Our focus is on the 18 year old population only.	188	To examine to what extent differences in total body fat content, regional fat distribution, and lifestyle contribute to differences in the cardiovascular risk profile of middle-age vs young men.	Activity: Questionnaire on physical activity at work and during leisure time, classification into light, moderate and intense Anthropometric: BMI, waist circumference, hip circumference, estimate of fat-free mass and total body fat (body electrical resistance) Blood sample after overnight fast: TC, HDL, TG. LDL calculated. Hypertriglyceridemia: TG > 250 mg/dL. Hypercholesterolemia: TC >240 mg/dL. HDL: abnormal if < 35 mg/dL. Insulin measured by Hales and Randle method. Smoking Daily alcohol intake: Grams consumed per day Blood pressure: Hypertension defined as systolic $\geq$ 160 mmHg and/or diastolic $\geq$ 95mmHg
Demerath, 2003[139]	5th grade children in 14 rural West Virginia counties	1338	To examine the feasibility and utility of conducting a school-based obesity and cardiovascular disease risk factor screening program in a rural Appalachian population.	Anthropometric measures: BMI Blood samples: Whole blood from finger prick, with portable Cholestech LDX analyzers to measure TC and HDL-C.
DeStefano, 1995[140]	Schoolchildren in rural Wisconsin aged 5 to 15	2726 for multi-variate analysis	To evaluate determinants, especially dietary, of serum lipid concentrations in schoolchildren in a community-wide screening.	Family history: Brief questionnaire completed by parents or children Anthropometric measures: BMI Diet: brief questionnaire completed by parents or children. Most diet questions open-ended with questions on consumption during past week or during average day. Venous blood samples after 12 hour overnight fast: TC, HDL, calculated LDL

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Bonora, 1996[138]	X	Not included in multiple linear regression analysis	Not included in multiple linear regression analysis	NE
Demerath, 2003[139]	X	NE	NE	NE
DeStefano, 1995[140]	X	NE	NE	TC and LDL: Associated with butter and egg consumption HDL: Associated with butter and lard, negative association with vegetable shortening, whole grain bread Triglycerides: Associated with magerine, nonfat milk; negative association with eggs. TC:HDL ratio: no strong association with diet

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Bonora, 1996[138]	NE	Only muliple linear regression analysis results reported here. BMI, waist/hip ratio, and insulin levels strongly intercorrelated. BMI predicted TG (30% of this risk factor variability). Std coefficient 0.48, t-value 3.1, p<0.005.
Demerath, 2003[139]	NE	TC: Greater risk of high TC among obese vs non-overweight (OR 2.4, p< 0.05), sensitivity 50%, specificity 71% HDL: Lower among obese vs non-overweight (OR 5.3, p<0.05), sensitivity 66%, specificity 73%
DeStefano, 1995[140]	TC and LDL: strong association with family history of hypercholesterolemia (r=0.184 and 0.174, respectively) TC:HDL ratio: associated with having 1st degree relative with hypercholesterolemia.	Increased BMI: Related to adverse levels of all lipids and lipoproteins (TC, LDL, HDL, TG). BMI: Associated with TC:HDL ratio

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Bonora, 1996[138]	NE	NE
Demerath, 2003[139]	NE	NE
DeStefano, 1995[140]	NE	Parent who smokes: negative association with TC:HDL ratio

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Douglas, 1996[141]	Youth aged 5 - 19, predominantly African American and Hispanic, who live in an inner city environment.	506	To determine whether adding the criterion of obesity to family history would increase the yield of screening	Family history: Data collected at appointment. Anthropometric: BMI Diet: Question from HANES-1 Blood samples: Nonfasting cholesterol (TC, TG) via finger stick. Those with elevated TC were asked to return for a fasting lipid profile via venipuncture (TC, TG, HDL). Elevated TC: 170 mg/dl Elevated TG: 100 mg/dl

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Douglas, 1996[141]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Douglas, 1996[141]	Predictor of higher cholesterol vs no family history (p<0.001). Odds ratio of those with family history of hypercholesterolemia having high cholesterol: 2.28 (95% CI=1.70 to 2.86). Sensitivity of family history as screening tool: 24% Use of family history of CVD, hypertension, myocardial infarction, stroke produced similar results. Specificity: 88% Positive predictive value: 51% Negative predictive value: 69%	Obesity defined as BMI > 20% above ideal BMI. Predictor of higher cholesterol: correlation to non-fasting TC: p<0.001. OR of obese screenees having hypercholesterolemia: 1.74 (95% CI=1.34 - 2.14). Multiple linear regression analysis: obesity related to hypercholesterolemia when controlling for age and family history (p<0.001). Sensitivity in screening for hypercholesterolemia: 42% Specificity: 71% Positive predictive value: 41% Negative predictive value: 72% **Predictive value of family history and obesity combined: Sensitivity: 49%, Specificity: 64%, Positive predictive value: 41%, Negative predictive value: 71%**

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Douglas, 1996[141]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
DuRant, 1982[142]	Black children and adolescents aged 7 - 15 who were economically disadvantaged and participated in a 6-week organized community recreation program	84	To evaluate the influence of a family history of CHD and CHD risk factors on the TC/HDL and LDL/HDL ratios in a group of black children and adolescents	Family history: Family health questionnaire re: 1st and 2nd degree relatives administered to parent. Anthropometric measures: Triceps skinfold thickness Diet: 24-hour intake history Venous blood samples: Drawn after 12-hour fast, TC, TG, HDL. LDL calculated.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
DuRant, 1982[142]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
DuRant, 1982[142]	Parental CHD risk factors with significant effects on LDL/HDL and TC/HDL: stroke, diabetes mellitus, obesity. Stroke and age, diabetes and age, and obesity and age interactions in TC/HDL, LDL/HDL. Children with family history of stroke: <LDL/HDL; this difference was less apparent in adolescents. For TC/HDL, from childhood to adolescence > increase for those with a family history for stroke. Non-stroke history: small < in TC/HDL from childhood to adolescence. No difference in LDL/HDL or TC/HDL between children with and without family history of diabetes. Both > in adolescents with family history of diabetes, < in those without this history. Males: LDL/HDL same in those with/without obese family member. Females: higher LDL/HDL in those with obese family member. From childhood to adolescence, those with an obese family member showed > LDL/HDL vs those without an obese family member. Obesity, age, sex interaction effect on TC/HDL, with males with obese family members <TC/HDL from childhood to adolescence. Females with an obese family member had the highest TC/HDL levels, which increased from childhood to	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
DuRant, 1982[142]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
DuRant, 1983[143]	Middle class white males aged 11 -17 recruited from local boy scout troops.	50	To examine the relationship between reported physical activity levels and HDL, LDL /HDL ratio, and TC/LDL among white male adolescents.	Activity: Questionnaire of usual level of physical activity (hours watching tv, reading and studying, team sports during previous school year, sports/activities performed $\geq$ 3 days/week continuously for $\geq$ 1 hour at a time, days of jogging per week, days bike riding per week) Exercise capacity tested by mechanically braked bicycle ergometer. Anthropometric: Weight, height, relative body weight (Weight-for-height index) triceps skinfold, resting pulse, blood pressure Diet: 48-hour diet history kept by parents, with dietary recall completed by a registered dietician. Blood sample after 12 hour fast: TC, HDL, LDL Other: Cigarettes smoked per day, alcohol consumed per week.
DuRant, 1993[144]	4 and 5 year old African American, Hispanic and Caucasian children in the Texas Studies of Child Activity and Nutrition (SCAN) program.	123	To examine relationships among indicators of physical activity, physical fitness, and body composition with serum lipid and lipoprotein levels in young children.	NA

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
DuRant, 1983[143]	X	Days jogged per week: 2nd strongest predictor of TC/HDL (r=0.29); strongest predictor of LDL/HDL (r=-0.32)	Maximum exercise capacity not related to lipid levels.	Not significant in multiple regression
DuRant, 1993[144]	X	TC: Not significant LDL: Not significant TG: Negative correlation with mean activity level	TG: negative correlation with percentage of time in higher activity level, work load.	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
DuRant, 1983[143]	NE	NE
DuRant, 1993[144]	NE	TG: positive correlation with sum of skinfolds at year 1 and 2, and with waist/hip ratio and heart rate at year 2. TSC: at year 2, correlated with year 1 waist/hip ratio, but year 2 waist/hip ratio not significant LDL: correlated with year 1 waist/hip ratio HDL: correlated with sum of skinfolds at year 2 LDL/HDL ratio: positive correlation with year 1 waist/hip and year 2 sum of skinfolds TSC/HDL ratio: positive correlation with year 1 waist/hip and year 2 sum of skinfolds

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
DuRant, 1983[143]	Age: Strongest predictor of HDL (r=-0.42), and TC/HDL (r=0.38) Height: 3rd strongest predictor of HDL (r=-0.31) Systolic blood pressure: predictor of TC/HDL (r=0.30); of LDL/HDL (r=0.23)	Television watched per night: 2nd strongest predictor of HDL-(r=-0.42), 3rd strongest predictor of TC/HDL Hours spent reading per day: 2nd strongest predictor of LDL/HDL (r=0.27) Smoking and alcohol use not significant in multiple regression.
DuRant, 1993[144]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Dwyer, 1994[145]	Australian schoolchildren aged 7 - 15	1919	To relate objective measures of fitness to standard CHD risk factors on a large representative sample of children, to assess overall associations and determine whether threshold effects are present.	Endurance fitness: physical work capacity on a Monark bicycle ergometer. Measure for fitness analysis: ratio of work capacity to lean body mass. Anthropometric: BMI, skinfold thickness at 4 sites Serum lipids: measured after 12 hour fast. Lipid Research Clinic procedures followed. Plasma total cholesterol, triglycerides and HDL determined.
Eisenmann, 2002[146]	Runners between age 8 and 15 who consistently placed within the top 5 finishers of road races 10 km or more by age and gender.	54	To examine age- and sex-associated variation in subcutaneaous andipose tissue (SAT) and its association with blood lipoproteins among adolescent distance runners.	Activity: Self-reported running volumes Anthropometric: SUM6: subcutaneous measures of triceps, biceps, subscapular, supra-iliac, abdominal and medial calf. TER: (trunk-to-extremity ratio) ratio of 3 trunk skinfolds to sum of 3 extremity skinfolds. SAT: (subcutaneous adipose tissue) TER regressed on SUM6, residuals retained to represent an index of relative SAT independent of overall subcutaneous fatness Venous blood samples: following 12 hour fast and 24 hours after last bout of exercise. TC, TG, HDL-C, LDL-C.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Dwyer, 1994[145]	X	Not significant for TC or HDL.	Not significant for TC or HDL.	NE
Eisenmann, 2002[146]	X	All subjects very active: self-reported mean training volumes 1503 (males) and 1865 (females) km per year .	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Dwyer, 1994[145]	NE	BMI TC - Negative correlation (p<.01) HDL - Negative correlation (p<.001) TG - correlated (p<.001) Sum of skinfolds: TG - correlated (p<.001) HDL - correlated (p<.001)
Eisenmann, 2002[146]	NE	Increase in SUM6: associated with > in LDL-C, TG and TC:HDL in adolescent males (p<0.05) In adolescent females: associated with < in HDL-C and > in TG (p<0.05). TER not significant.

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Dwyer, 1994[145]	NE	NE
Eisenmann, 2002[146]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Freedman, 1999[18]	5 - 17 year old males and females examined in 7 cross-sectional studies conducted by the Bogalusa Heart Study between 1973 and 1994.	9167	To examine the relationship of cut points for overweight derived from several national studies (Quetelet index, >95th percentile) to adverse risk factor levels and risk factor clustering.	Anthropometric: Quetlet index/BMI (kg/m2). Triceps and subscapular skinfolds. Overweight: defined as Quetlet index above the smoothed 95th percentile of combined data from 5 national surveys conducted between 1963 and 1994. Blood samples: TC, TG, LDL, HDL. High level of TC: >200 mg/dL, TG: $\geq$ 130 mg/dL, LDL: 130 mg/dL. HDL: <35 mg/dL considered low.
Fripp, 1985[147]	Males aged 15 -17 recruited from the 10th grade in a regional public high school who tested as having low-moderate to moderate levels of physical fitness	37	To evaluate the interrelationship between aerobic capacity, ponderosity, and atherosclerotic risk factors by examining exercise duration, maximum oxygen consumption, body mass index, systolic and diastolic blood pressure, and levels of plasma lipids of male adolescents with low-to-moderate levels of physical fitness.	Family history questionnaire. Aerobic capacity: progressive treadmill test. Anthropometric: BMI, ponderal index. Venous blood samples after overnight fast: TC, TG, LDL-C, HDL-C, LDL-B.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Freedman, 1999[18]	X	NE	NE	NE
Fripp, 1985[147]	X	NE	HDL-C higher with increased exercise duration (p<.05) Triglyceride level lower with increased exercise duration (p<.05).	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Freedman, 1999[18]	NE	Overweight: defined as Quetlet index above the smoothed 95th percentile of combined data from 5 national surveys conducted between 1963 and 1994. TC: Overweight children 2.4x more likely to have elevated TC LDL-C: 3.4 x more likely TG: 7.1 x more likely HDL-C: 3.4x more likely to be <35mg/dL Use of overweight as screening tool could identify 50% of school children who had 2 or more risk factors. Sensitivity for TC: 24% TG: 47% LDL: 28% HDL: 25%
Fripp, 1985[147]	NE	BMI: positive association with triglyceride level ($p<.05$); negative association with HDL-C ($p<.05$).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Freedman, 1999[18]	NE	NE
Fripp, 1985[147]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Giovannini, 1992[148]	Schoolchildren in 2 small towns near Milan, Italy	361	To investigate how levels of pediatric lipoprotein are influenced by nutritional and familial factors in a northern Italian population.	Family history: Parent report of 1st and 2nd degree history of atherosclerotic complications. Anthropometric: weight $\underline{>}$ 20% of ideal labeled as obese 3-day diet record Blood samples: TC, HDL-C, TG, ApoB, ApoAI. LDL calculated by Friedwald's formula.
Glassman, 1993[149]	Retrospective chart review of 98 children referred for evaluation and treatment of obesity or Type IIA hyperlipoproteinemia at the Children's Nutrition Center, NY Medical College.	98	To determine whether inclusion of obesity to the current AAP criteria significantly enhances their predictive value in identifying children with hypercholesterolemia.	Family history: obtained from medical record Anthropometric measures: BMI, percent ideal body weight [(actual weight/height appropriate weight)x100]. Obesity defined as BMI 20.5 or body weight >120% of ideal. Venous blood samples after 14 hour fast: TC, TG, HDL-C. LDL-C calculated as difference between TC and HDL-C.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Giovannini, 1992[148]	X	NE	NE	Higher TC/HDL-C ratio in the lower quartile of polyunsaturated fatty acid intake (survey data, no p value reported)
Glassman, 1993[149]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Giovannini, 1992[148]	CVD not significant for TC, LDL Hypercholesterolemic parents: associated with higher TC and LDL, although not predictive of TC>200 mg/dl or LDL >120 mg/dl. Family history of CVD: Sensitivity TC>200: 0.19, LDL>140: 0.09 Specificity: 0.83, 0.91 + predictive value: 0.34, 0.30 - predictive value: 0.69, 0.69 of Family history of HC: Sensitivity 0.22 0.13 Specificity 0.85 0.93 + predictive value: 0.47 0.52 - predictive value: 0.65 0.65 Family history of CVD + HC: Sensitivity 0.20 0.11 Specificity 0.86 0.93 + predictive value: 0.61 0.64 - predictive value: 0.48 0.48	TC: higher for obese girls (p<0.01) TG: higher for obese girls and boys (p<0.01) HDL-C: lower for obese girls (p<0.001) LDL-C: higher for obese girls (p<0.001) ApoB: higher for obese girls (p<0.001) and boys (p<0.1) ApoA1: not significant LDL-C/ApoB: lower in obese boys (p<0.1)
Glassman, 1993[149]	NE	Obesity defined as BMI 20.5 or body weight >120% of ideal. 36/45 (80%) obese children had cholesterol levels >90th percentile (suggesting > risk for hypercholesterolemia in this group). If obesity was added to AAP criteria, 66/80 hypercholesterolemic subjects would have been identified. This would also improve sensitivity of the standards (70 vs 87%, p<0.02) and negative predictive value (45 vs 30%, p<0.02) BMI and percent ideal weight not correlated with TC/LDL-C in obese subjects. BMI inversely correlated with TC (p<0.005) and LDL-C (p<0.002) in non-obese, hypercholesterolemic patients.

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Giovannini, 1992[148]	NE	NE
Glassman, 1993[149]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Gliksman, 1993[174]	Healthy Australian schoolchildren aged 12 and 15 (subgroup of 1985 ACHPER sample survey)	1017	To report on differences in dietary variables and serum lipids by age, sex, and ethnic origin in a national cohort of Australian children.	Anthropometric: BMI Diet: 24 hour diet record Blood sampling after 12 hour fast with procedures from LRC. TC, TG, HDL. LDL calculated. Socioeconomic status: As linked to postal code. Ethnic origin: Determined by parent birth country
Howard, 1991[150]	Children aged 7-18 years in Spokane, WA	78	To answer 6 research questions: Is there a difference in: 1) Physical measurements and different diets 2) Physical measurements and blood pressures 3) Physical measurements and parental smoking status 4) Physical measurements and family history of CD or no CD 5) Relationships exercise and physical measurements 6) Physical measurements and Type A personality	Bloomsday Cardiovascular Fitness Questionnaire; Coronary Risk Profile (family history and other demographics); Diet Habit Survey: Type of diet: 1) meat 2) dairy 3) fats and oil 4) grains 5) sweets 6) salt Four classifications of fat intake: American diet (40% from fat), Phase I (30% fat), II (25% fat), and III (20% fat). Physical measurements: total serum cholesterol and HDL-C level, weight, and blood pressure

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Gliksman, 1993[174]	X	NE	NE	In multiple regression analysis, socioeconomic and gender-based lipid differences could be explained by differences in diet. Significant differences of dietary fat intake based on ethnic origin were not reflected in serum lipid differences. Girls: Dietary fat variables were more important predictors of serum lipids than BMI. (%kJ saturated fat: TG, HDL; PS ratio: TG, HDL, LDL/HDL) Boys: BMI was a more important predictor of serum lipids than dietary fat.(Dietary fat not associated with TC, TG, HDL, LDL, LDL/HDL)
Howard, 1991[150]	Multiple one way ANOVAs	Walk and run: Pearson correlations only	Correlation only	American diet of meat had significantly lower weight percentiles than Phase II diets (p =0.03). American diet of fat had significantly higher HDL-C percentiles than those in Phase I, II, or III (p=0.001). American grain diet (>13 yrs) had higher cholesterol percentiles than subjects in Phase II (p=0.01). Phase I diet (>13 yrs) higher cholesterol than subjects in Phase II (p=0.01). American grain diet lower weight percentiles than Phase 1 (p=0.01).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Gliksman, 1993[174]	NE	Girls: Dietary fat variables were more important predictors of serum lipids than BMI. BMI negatively associated with HDL. Positive association with TG and LDL/HDL. Boys: BMI was a more important predictor of serum lipids than dietary fat. TC and HDL: Negative association with BMI. TG and LDL/HDL: Positive association with BMI.
Howard, 1991[150]	Family history of heart disease and high blood pressure: Chi square tests only	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Gliksman, 1993[174]	In multiple regression analysis, age did not explain socioeconomic and gender-based differences in serum lipids.	NE
Howard, 1991[150]	Blood pressure: Mann-Whitney U statistics only	Stress/personality characteristics: No need to excel had higher weight percentiles than those with some, a fair or a great need to excel (p=0.04, p=0.01, p=0.001 respectively). Non-competitive subjects had a higher weight percentile than those who were somewhat competitive or very competitive (p=.0.05, p=0.001 respectively). Smoking: T-tests only

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Jiang, 1995[173]	Bogalusa, LA, 5-30 yr olds (age 5 - 17 reported here)	4136	To assess whether circulating insulin is a major contributor to adverse lipid profiles during the transition from adolescence to adulthood	Serum total cholesterol, triglycerides, VLDL, HDL, LDL, plasma glucose, plasma insulin. Obesity (skinfold thickness), smoking, alcohol and life style and health habits survey
Jarvisalo, 2001[151]	Males and females ages 8-14 yrs Non-controls from outpatient clinic of the Department of Pediatrics, Turku University Central	88	To examine the feasibility of measuring aIMT in children and to study its value in distinguishing high-risk children from healthy controls compared with a more established marker of subclinical atherosclerosis	Abdominal aorta (aIMT) and carotid artery thickness (cIMT) ; blood pressure; serum total, LDL and HDL cholesterol; triglycerides; glucose
Kunz, 2005[153]	Boys with mean age 14.5 recruited from 8 schools in Innsbruck, Austria.	336	To compare coronary risk factors of smoking and non-smoking boys; to gather information on whether boys who start smoking early have different baseline charactoristics impacting coronary risk.	TG, HDL-C, TC, gluclose, LDL-C (Friedman's formula), coagulometric and chromogenic assays, radioimmunoassays, blood cell counts. Cardiovascular endurance (PWC-170 bicycle ergometer test), handgrip strength, average weekly hours in sports, forced expiratory vital capacity and peak flow. Self report of medical histoy, sports activities, alcohol consumption, smoking habits of self and parents.
Kwiterovich, 1997[154]	Boys and girls with elevated LDL age 8 - 10 at baseline of 3 year study	663	To examine the effects of dietary intake of fat and cholesterol, sexual maturation and BMI on LDL-C on boys and girls with elevated LDL-C levels.	Fasting serum LDL-C, total cholesterol, triglycerides, HDL-C, dietary intake, height, weight, Tanner stage.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Jiang, 1995[173]	X	NE	NE	NE
Jarvisalo, 2001[151]	X	NE	NE	NE
Kunz, 2005[153]	X	NE	NE	NE
Kwiterovich, 1997[154]	X	NE	NE	For boys, LDL-C decreased by 0.696 mg/dL for each 10 mg/4.2 MJ decrease in dietary cholesterol (p<.05). For girls, no single nutrient was significant, but there was a treatment group effect (p<.05)

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Jiang, 1995[173]	NE	NE
Jarvisalo, 2001[151]	NE	NE
Kunz, 2005[153]	NE	NE
Kwiterovich, 1997[154]	NE	BMI For both genders, BMI at 3 years and LDL at baseline were significant and positive predictors of LDL

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Jiang, 1995[173]	Fasting insulin level: + association with VLDL cholesterol independent of age, sex, glucose concentration, obesity, cigarette smoking, and alcohol intake; - association with HDL in whites aged 5 to 17. Although fasting insulin level along with other variables was shown to be a significant predictor of lipoprotein measures, it can account for only a small part of the variability of lipoprotein cholesterol level (R2 values were low).	NE
Jarvisalo, 2001[151]	Multivariate regression model results: aIMT associated with group (diabetes and HC) (p=0.001), age (p=0.014), diastolic blood pressure (p=0.75). cIMT was associated with group (diabetes and HC) (p=.0.001) and diastolic blood pressure (p=0.046). No association with serum total, LDL and HDL cholesterol, triglycerides or glucose	NE
Kunz, 2005[153]	NE	Smoking TC and LDL-C lower in smokers after adjustment for age, size, weight, BMI. HDL-C: No significant difference between smokers and non-smokers after adjustment for weight or BMI TG: No difference
Kwiterovich, 1997[154]	NE	Sexual development Males: LDL lower at Tanner Stage 4+ than Stage 1 (p<.01) Females: LDL lower at Tanner Stage 4+ than Stage 1 (p<.05)

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Larsson, 1992[152]	7 year old students in Sweden	147 with family history; 148 controls	To compare lipid measures in 7 year old children who have a family history of myocardial infarction/angina pectoris before age 55 or hyperlipidemia to children without this family history.	Family history: Parents completed a family history questionnaire Venous blood samples: Drawn after overnight fast, TC, HDL-C, TG. LDL calculated.
Macek, 1989[155]	Students aged 16 - 18. Treatment group recruited from high school where 5 hours a day was devoted to swimming and athletics. Controls, recruited from a similar school, had lower activity levels, were 1.7 years older and similar in height and therefore viewed as comparable.	93	To investigate differences in CHD risk factors in groups of trained and untrained adolescents.	Family history: Parents completed World Health Organization Questionnaire for CHD history. Maximal aerobic power: cycle ergometer following WHO criteria. Anthropometric: percentage body fat. Venous blood samples following overnight fast: TC, HDL-C, LDL-C, Apo-A, Apo-A1, Apo-B, TG.
Marti, 1989[156]	15 year-old boys and girls from 40 Finnish schools	1142	To examine the associations between frequency of leisure time exercise and cardiovascular risk factors in adolescents.	Leisure time exercise: self-report using a 5 category question. Aerobic fitness: Self-report of distance covered during 12 minute run. Anthropometric: BMI, Tanner scale for sexual maturity Blood samples: serum TC, HDL, serum thiocyanate. Smoking measured by self-report in 13 questions

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Larsson, 1992[152]	X	NE	NE	NE
Macek, 1989[155]	X	NE	TC: not significant HDL-C higher vs controls (p<0.05); significant relationship with Vo2 max (p<0.001) Apo-A1 higher vs controls (p<0.01) Apo-A higher vs controls (p<0.01) LDL-C lower vs controls (p<0.001) Apo-B lower vs controls (P<0.001) TG lower vs controls (p<0.001); significant relationship with Vo2 max (p<0.001)	NE
Marti, 1989[156]	X	No relationship between leisure time exercise and TC or HDL.	No relationship between aerobic fitness and HDL or TC.	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Larsson, 1992[152]	TC, LDL, LDL/HDL for those with family history of hyperlipidemia vs controls (p<0.001). No difference in these lipids among those with family history for myocardial infarction or angina pectoris exclusively vs controls. HDL, TG: No significant difference between those with any family history vs controls	NE
Macek, 1989[155]	NE	NE
Marti, 1989[156]	NE	HDL: Inversely related to BMI for boys and girls (p<0.01) and sexual maturation for boys (p<0.01).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Larsson, 1992[152]	NE	NE
Macek, 1989[155]	Gender: Girls had higher HDL-C (p<.001)	NE
Marti, 1989[156]	NE	Smoking: Inversely related to HDL for boys (p<0.01) and girls (p<0.05)

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Muhonen, 1994[120]	9th through 12th grade students aged 14 to 20 in Muscatine, LA.	599	To determine the utility of a school-based family history questionnaire to identify adolescents with adverse coronary risk factor levels.	Family history: HFTQ questionnaire, history of heart attack, angina, bypass surgery, hypertension and obesity; morbidity and mortality in parents and grandparents Anthropometric measures: TSF thickness Venous blood samples after overnight fast: TC, HDL, TG. LDL calculated
Raitakari, 1996[157]	Finnish children and adolescents aged 3-18 years, pulled from the national population register	714	To analyze the effect of changes in physical activity and other determinants of HDL-C on HDL-C levels.	Physical activity index: questionnaire of leisure-time physical activity using intensity X estimated duration X monthly frequency, the range was 0-225. Anthropometric measures: subscapular skinfolds, height, and BMI. Smoking: self-report of smoking status and frequency. Blood samples: serum total cholesterol, triglycerides, high-density cholesterol, and insulin.
Resnicow, 1993[158]	Data obtained from Know Your Body school health promotion program 1984 - 1991, including 29 elementary schools in 8 states. Convenience sample; half of schools from low-income, inner-city neighborhoods.	11,370	To examine the relationship between BMI, systolic blood pressure (SBP), and total plasma cholesterol along with the implications of using obesity as a criterion for blood pressure screening in an ethically diverse sample of 11,370 schoolchildren.	Anthropometric: Quetelet's BMI (kg/m2) Blood samples: Non-fasting finger-stick. TC. High TC defined as 200mg/dL

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Muhonen, 1994[120]	X	NE	NE	NE
Raitakari, 1996[157]	X	Boys: HDL-C was significantly correlated with physical activity, with a correlation coefficient of 0.20 ($p<0.001$) Girls: Physical activity did not significantly correlate with HDL-C.	NE	NE
Resnicow, 1993[158]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Muhonen, 1994[120]	Parent history of CHD: >BMI, <ApoA1 Grandfather history of CHD: <ApoA1, >HDL, >BMI Grandfather history of high cholesterol: >TC, >LDL, >ApoB, >LDL/HDL ratios Grandmother history: Not significant	NE
Raitakari, 1996[157]	NE	Changes in subscapular skinfold thickness correlated to changes in HDL-C for both boys and girls ($p<0.05$ for both). BMI change was correlated with a change in HDL-C for girls only ($p<0.001$), BMI cut-off not defined.
Resnicow, 1993[158]	NE	26% of subjects with BMI's in the top decile and elevated SBP had TC levels $\geq$ 200 mg/dL. This was approximately twice the rate of high TC observed among overweight children with normal SBP (14%), normal-weight children with normal SBP (11%), and normal-weight children with elevated SBP (13%).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Muhonen, 1994[120]	NE	NE
Raitakari, 1996[157]	NE	NE
Resnicow, 1993[158]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Ribeiro, 2004[159]	Healthy, treatment-free children aged 8 to 15 in 17 primary and 13 high schools an urban and rural area of Porto, Portugal.	1533	1) To determine the coexistence of CVD risk factors high blood pressure (HBP), percentage of high fat body mass (%HFM), and high total cholesterol (HTC) 2) To study the relationship between physical activity (PA) and biological risk factors clustering (HBP, %HFM, HTC).	Activity: Physical activity index (PAI) self-report questionnaire on activities $\geq$ 15 minute duration in past week. Intensity catagories based on metabolic equivalents. Risk factor: $\leq$ 25th percentile of PAI adjusted for age & sex. PAI divided into quartiles. Anthropometric: BMI, tricipital skinfold, subscapular skinfold, percentage fat mass (%FM) estimated via Slaughter, et al (skinfold and maturational stage measurements). Risk factor HFM: above 75th percentile for age and sex. Blood: Capillary samples from earlobe after $\geq$ 12 hour fast for plasma TC. High TC (HTC): $\geq$ 75th percentile adjusted for age, sex. Blood pressure: Systolic and diastolic measured in right arm. Risk factor HBP: SBP or DBP $\geq$ 75th percentile adjusted for age, sex.
Shear, 1985[160]	Children aged 5 to 17 residing in Bogalusa, LA, and their biological parents. Part of the 4th cross-sectional survey of the Bogalusa prospective cohort study.	3312	To assess the relationship between parental history of vascular disease (heart attack, stroke, diabetes mellitus and hypertension) and risk factors variables for cardiovascular disease in their offspring.	Family history: Parent or guardian self-report on questionnaire Venous blood samples: 12 hour fasting. TC, TG, LDL, VLDL, HDL

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Ribeiro, 2004[159]	X	PAI and percent of subjects with biological risk factors Male: PAI 1st quartile, 59.1% had risk factors, 4th quartile, 41.3% had risk factors (p=0.010) Female: Not significant. PAI quartiles and 1 and 2 - 3 biological risk factors: no statistical significance.	NE	NE
Shear, 1985[160]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Ribeiro, 2004[159]	NE	Percentile high fat mass and HBP: Highest observed odds ratio for clustering. Females: OR 2.6, CI 1.8-3.8 Males: OR 1.9, CI 1.3-2.8. Percentile high fat mass and high TC: No significant clustering.
Shear, 1985[160]	Multivariate analysis: No significant effect for a single parental vascular disease. Combination of parental heart attack with parental diabetes ($p<0.0001$) and parental heart attack with parental hypertension ($p<0.01$) significant in relationship to overall risk factors in children. Risk factors: TC, TG, LDL, HDL, blood pressure	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Ribeiro, 2004[159]	About half of subjects had ≥ 1 biological risk factor. HTC and HBP: Clustering significant in females (OR 1.6, CI 1.0-2.4)	NE
Shear, 1985[160]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Simon, 1995[161]	Premenarchal Black and white girls aged 9 and 10 in Richmond, CA; Cincinnati, OH; and Washington, DC	1397	To determine the correlates of serum HDL-C in 9 and 10 year old girls.	Activity: Television viewing per week Anthropometric: BMI. Sum of skinfolds (triceps, subscapular, suprailiac). Tanner staging for sexual maturation. Diet: 3-day diet record Blood sample: HDL
Suter, 1993[162]	Boys and girls aged 10 - 15 recruited from a private school in Calgary.	97	1) To describe lipid levels, physical activity, fitness and diet of healthy Canadians aged 10 - 15. 2) To evaluate if predictive power of physical activity for serum lipid levels exists for this population as it does in adults. 3) To adjust the relationship between activity and blood lipids for confounding factors.	Activity: 7-day recall with metabolic equivalents (MET) and additive 7-day physical activity index (PAIND) calculated. Substance use and oral contraceptives: assessed in private interview with trained counselor. Cardiovascular fitness: submaximal test using bicycle ergometer. Anthropometric: obtained by 1 measurer with high reliability; sum of skinfolds and BMI included. Diet: analysis of 3-day food records. Venous blood samples after overnight fast: TC, TG, VLDL-C, LDL-C, HDL-C, Apo A-1, Apo B, lipoprotein (a).

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Simon, 1995[161]	X	Not significant after multivariate adjustment for television viewing and pubertal maturation.	NE	Ratio of polyunsaturated fat/saturated fat intake and polyunsaturated fat/monosaturated fat intake as well as total fat intake showed no significant association with HDL in multivariate analysis. Polyunsaturated fat intake associated with higher HDL ($p<.05$). Each 10% > in polyunsaturated fat intake was associated with > of 3.4 mg/dL.
Suter, 1993[162]	X	Multiple linear regression analysis: significant predictor for HDL-C, Apo A-1, TG and VLDL-C.	Cardiovascular fitness not significant for TG, HDL, VLDL.	Multiple linear regression analysis: dietary fat intake not a predictor of TG, HDL, VLDL.

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Simon, 1995[161]	NE	Changes in subscapular skinfold thickness correlated to changes in HDL-C for both boys and girls ($p<0.05$ for both). BMI change was correlated with a change in HDL-C for girls only ($p<0.001$), BMI cut-off not defined.
Suter, 1993[162]	NE	Multiple linear regression analysis: BMI not significant predictors of TG, LDL, VLDL. Gender is a modifying factor of the relationship between subcutaneous body fat and TG or VLDL-C levels. Bivariate analysis: High sum of skinfolds more closely related to an unfavorable lipid profile in girls than boys.

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Simon, 1995[161]	NE	NE
Suter, 1993[162]	NE	Alcohol: 7/97 reported use, all in very small amounts. No statistical significance. Smoking: No subjects smoked. Oral contraceptives: No subjects used.

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Thorland, 1981[163]	8 - 11 year old boys recruited from elementary schools and sports clubs in Ann Arbor, MI.	55	Compare lipid levels of pre-adolescent boys who have high or low intensity of physical activity and high or low levels of body fatness.	Activity: 5-day records with time-motion analysis. Parents observed or got information from children on activities and intensity. Anthropometric: Skinfold measurements at 6 sites, underwater weighing to assess relative fatness, fat weight, and lean body weight. Diet: 5 day record. Parents recorded food items and amounts consumed by child each day. Consumption away from home based on child report. Venous blood samples after overnight fast and 36 - 40 hours after exercise: TC, TG
Tolfey, 1999[164]	Healthy 10 year old boys and girls in England	71	To identify independent contributions from predictor variables of habitual physical activity, peakV02, percent body fat, and dietary composition are related to prepubertal children's lipid-lipoprotein profile.	Activity: estimated through 4-day continuous heart rate measurement of cardiovascular stress. PAHR-25 (Total time spent 25% above resting heart rate), PAHR-50 (50% above heart rate) and mean heart rate over collection period. Cardiovascular fitness: Peak VO2 measured from cycle ergometer test to volitional exhaustion with expired air collection. Anthropometric: Skin fold, body mass, estimated percent body fat. Sexual maturity assessed by parent and child responses to Tanner drawings. Diet: 7-day diary completed by parent Venous blood samples: Following 11-12 hour fast and no structured exercise 48 hours prior to sampling. TC, TG, HDL-C, , VLDL-C, LDL-C, TC/HDL-C and LDL-C/HDL-C derived from concentration. NCEP performance criteria met.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Thorland, 1981[163]	X 2-way ANOVA and stratification	HDL/TC ratio larger in more active vs less active boys ($p<0.05$). Triglyceride lower in more active boys ($p<0.05$).	NE	Not significant
Tolfey, 1999[164]	X	Girls: Habitual physical activity (HPA) related to lipid-lipoprotein profile ($p<0.05$) (Bivariate analysis). 1 of 3 main predictor variables for girls in multiple regression analysis, accounting for 18% of unique variance in TC and 22.6% in LDL. Boys: HPA related to TC/HDL-C and LDL-C/HDL-C ($p<0.05$ for both) in bivariate analysis. Not significant in multiple linear regression.	Girls: VO2 related to lipid-lipoprotein profile ($p<0.05$) in bivariate analysis. Multivariate analysis: in TG: VO2 accounted for 22.7% of unique variance in HDL-C: accounted for 24.8% of unique variance in LDL-C/HDL-C: accounted for 22.5% of unique variance in TC/HDL-C: accounted for 24.2% of unique variance Boys: Not significant	Girls: Polyunsaturated-saturated fatty acid ratio accounted for 10.3% of LDL-C variance and 7.9% of TC/HDL-C variance Boys: TC: Daily energy intake accounted for 15.4% of variance and 22% of LDL variance

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Thorland, 1981[163]	NE	Body fatness not significant.
Tolfey, 1999[164]	NE	Multivariate analysis: TC: % body fat accounted for 12.1% of unique variance, girls only LDL: % body fat accounted for 21.2% of unique variance, girls only Boys: % body fat not significant

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Thorland, 1981[163]	NE	NE
Tolfey, 1999[164]	NE	TG: Higher in girls ($p<0.01$) than boys, and the only gender difference in lipid-lipoprotein profile.

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Tonstad, 1995[165]	Boys and girls aged 6 to 16 with heterozygous FH in Norway referred to lipid clinic or identified through screening families with known FH. FH diagnosis: LDL receptor mutation or 1 prior TC >6.7 mmol/L and if a parent had tendon xanthomas and/or TC ≥ 7.8 mmol/L with triglyceride levels <3.0 mmol/L prior to treatment with lipid-lowering drugs.	164	To compare lipid levels and family history of premature cardiovascular disease in children with FHC210G, null alleles, or no detected mutation, while taking into account parental lipid levels, apoE polymorphism, and anthropometric and dietary characteristics.	Family history: Parental history of cardiovascular disease based on hospital or physician report. Parental lipid levels before treatment obtained from charts. History of early cardiovascular disease in 2nd degree relatives based on family report. Substance use: Those ≥ age 12 asked about smoking in absence of parents. Alcohol use self-reported (age 11+). Cardiovascular fitness: Anthropometric measures: Sum of skinfolds: triceps and subscapular sites. Percent body fat calculated from sex-specific regression equation with age and sum of skinfolds. Sexual maturation: Tanner scale. Diet: Dietary instruction following National Cholesterol Education Program guidelines. No specific weight-loss plans. Unexpected 24-hour diet recall at clinic visit, 4-day diet record. Venous blood: Samples following 8-10 hour fast. TC, TG, HDL. LDL calculated by Friedwald formula.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Tonstad, 1995[165]	X	NE	NE	Boys: LDL correlated with 24-hour recall cholesterol intake (p=.04) TG correlated with 24-hour recall sucrose intake (p=.004)

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Tonstad, 1995[165]	Multiple regression analysis: LDL related to FH parent's cholesterol levels, percent body fat, pubertal stage, and non-FH parent's cholesterol level (p<.01), together explaining 40% of variance in LDL (CI 25%-55%). HDL related to FH parent's HDL and to pubertal stage, explaining 17% (95%CI, 6% - 31%) of variance in HDL.	Multiple regression analysis: LDL related to percent body fat. Boys TG related to percent body fat and percent dietary energy from sucrose Girls TG related to percent body fat, explaining 7% of variance (95%CI, 0.2% - 27%)

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Tonstad, 1995[165]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Twisk, 2001[166]	Subjects were from the longitudinal Amsterdam Growth and Health Study, who ranged in age from 12-15 years at the initial screening and a mean age of 27 years at the final follow-up	181	To investigate the development of biological CHD risk factor clustering and to analyze the influence of lifestyle parameters on this clustering	Biological: Blood - 10 ml for cholesterol and HDL-C testing; Other - blood pressure; Skinfold thickness was measured using four skinfolds: triceps, biceps, subscapular, and suprailiac; cardiopulmonary fitness - maximal oxygen uptake relative to body weight Lifestyle: dietary intake - questionnaire of fat intake, carbohydrate intake, Keys-score, and alcohol intake; smoking - questionnaire of amount of tobacco smoked per week; physical activity - time spent on physical activities in relation to school and work, organized & unorganized sports, other leisure time activities, etc were measured during a structured interview.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Twisk, 2001[166]	X	Physical activity was inversely related to the clustering score (RR = 0.89, p<0.01)	NE	Heavy alcohol consumption was inversely related to the clustering score (RR = 0.79, p=0.01) but only for males. There was a weak inverse relationship for fat intake (RR = 0.95, p=0.05) and a weak positive relationship for carbohydrate intake (RR 1.05, p=0.05)

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Twisk, 2001[166]	NE	Skinfolds and oxygen uptake were significantly related to TC:HDL ($p<0.01$, $p<0.05$, respectively).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Twisk, 2001[166]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Twisk, 1998[167]	Males and females initially age 13. Participants healthy students in Amsterdam secondary school.	181	To analyze longitudinal relationships between BMI/SSF and biological and lifestyle risk factors for CHD.	Six repeated measurements over 15 years, starting at age 13. Activity: Structured interview assessing total time in activities, with a total weighted activity score covering the 3 months prior. Substance use: alcohol use measured by self-report with diet. Smoking behavior questions in separate questionnaire. Cardiovascular fitness: maximal oxygen uptake measured on a maximal test using a treadmill with speed of 8 km/h and increasing slope. Anthropometric measures: BMI, sum of 4 skinfolds (triceps, biceps, subscapular, suprailiac). Lean body mass [(100-%body fat)xbody weight] (body fat estimated from SSF) Diet: cross-check dietary history interview Venous blood samples: TC, HDL

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Twisk, 1998[167]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Twisk, 1998[167]	NE	TC male: related to SSF (B=0.12, CI 0.07-0.18, p<0.01) TC female: related to SSF (B=0.07, CI 0.03-0.11, p<0.01) TC: related to BMI (B=0.05, CI 0.02-0.08, p<0.01). No relationship with lean body mass. HDL and SSF; HDL and BMI; HDL and lean body mass: no significant relationship TC:HDL ratio: related to SSF (B=0.08, CI 0.05-0.12, p<0.01); to BMI (B=0.04,CI 0.01-0.07, p<0.01); no relationship with lean body mass.

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Twisk, 1998[167]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Twisk, 1996[168]	Subjects were from the longitudinal Amsterdam Growth and Health Study, who ranged in age from 12-15 years at the initial screening and a mean age of 27 years at the final follow-up	181	To investigate the relationship between the longitudinal development of TC, HDL, and TC:HDL ratio and the evolution of lifestyle measures .	Biological: Blood - 10 ml for cholesterol , HDL-C, and ratio of TC to HDL-C testing; Skinfold thickness was measured using four skinfolds: triceps, biceps, subscapular, and suprailiac; cardiopulmonary fitness - maximal oxygen uptake relative to body weight Lifestyle: dietary intake - fat intake, ratio of polyunsaturated fatty acids and saturated fatty acids, carbohydrate intake, cholesterol intake, and alcohol intake; smoking - questionnaire of amount of tobacco smoked per week; physical activity - time spent on physical activities in relation to school and work, organized & unorganized sports, other leisure time activities, etc were measured during a structured interview.
vanLenthe, 1998[169]	Initial recruitment from 1st and 2nd grade of a secondary school in Amsterdam, the Netherlands who were invited to participate in a study on growth, development and risk indicators for cardiovascular disease.	182	To investigate the association between the change in a central pattern of body fat and blood pressure and lipoprotein levels in healthy males and females age 13 - 27.	Anthropometric measures: Trunk skinfold measurements (subscapular, suprailiac) and extremity measures (biceps, triceps) used to create a subscapular/triceps skinfold ratio (S/T ratio) as an indicator of central pattern of body fat. Venous blood samples: Non-fasting TC, HDL. Calculated TC/HDL.

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Twisk, 1996[168]	X	Daily physical activity was positively related to HDL levels (p=0.38)	NE	TC is inversely influenced by the ratio of intake of polyunsaturated fatty acids to saturated fatty acids (p=0.001) but is positively correlated with the intake of cholesterol (p=0.002). As well, the key scores are positively correlated with TC levels (p<0.001). TC:HDL ratio was positively correlated with the intake of carbohydrates (p=0.022). Alcohol consumption was positively related to HDL levels (p=0.001) and negatively related to TC:HDL ratio (p=0.005). No other dietary parameters were found to be significant for TC, HDL, or TC:HDL ratio.
vanLenthe, 1998[169]	X	NE	NE	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Twisk, 1996[168]	NE	NE
vanLenthe, 1998[169]	NE	Males: >S/T associated with < HDL (Beta -0.14, CI -0.24 to -0.05, p<0.05). No association between change in S/T and change in TC/HDL Females: No significant association between change in S/T and lipoprotein levels (TC, HDL).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Twisk, 1996[168]	NE	Smoking: inversely related to HDL (p=0.007) and positively related to TC:HDL ratio (p=0.003)
vanLenthe, 1998[169]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
van Stiphout, 1985[170]	Residents of a suburban Dutch community aged 5 to 19 who were a subset of those invited to participate in a study of risk factor for cardiovascular disease (EPOZ).	458	To identify the distribution and determinants of serum total cholesterol and HDL in children from a general Dutch population.	Activity: Self-report via questionnaire by children over 10 Oral contraceptives: Females age 10+ were asked about Anthropometric measures: Quetelet index (ratio of body weight over height squared). Females age 10+ asked about menstruation Diet: Self-report via questionnaire. Coffee and alcohol used assessed Venous blood samples: non-fasting, TC, HDL of children and parental TC Smoking: Children aged 10+ asked about in questionnaire
Ward, 1980[171]	74 volunteer families from a previous study on cord blood cholesterol. 74 children evaluated at age 2.5 years.	74	To identify familial and environmental variables related to cholesterol levels in children at age 2.5.	Child measures taken at age 2.5 Anthropometric measures: Triceps skinfolds Diet: Mother provided written diet record for child for 3 weekdays. Dietary history and food frequency record obtained for each parent. Blood samples: 5-ml cholesterol, hemocrit

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
van Stiphout, 1985[170]	X	TC: No relationship to physical activity level	NE	TC: No relationship to coffee consumption.
Ward, 1980[171]	X	NE	NE	Stepwise multiple regression: TC: Previous breast-feeding (vs formula), current dietary poly-unsaturated/saturated fatty acid ratio, maternal alcohol and fat consumption, paternal cholesteryl esters, and maternal hemocrit (r=0.53). Free cholesterol: similar predictor variable set (r=0.52) Esterified cholesterol of children: predicted by history of breast-feeding, child's current protein and caloric intake, maternal total and esterified cholesterol, and proteinuria during pregnancy (r=0.69).

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
van Stiphout, 1985[170]	TC: For both fathers and mothers positively related to TC of children ($p<0.001$ except for males in quartile 2, where $p< 0.005$).	Body weight and Quetelet index: + relationship with TC for males and females > age 15 ($p< 0.05$). No relationship for those < 15 years of age. Body weight: Negative relationship with HDL in males age 15+ ($p<0.05$ for quartile 3, $p<0.01$ for quartile 4). Quetelet index: Similar negative relationship as body weight. (No p value given)
Ward, 1980[171]	In stepwise multiple regression TC: related to paternal cholesteryl esters and maternal hemocrit ($r=0.53$) Free cholesterol: similar predictor variable set ($r=0.52$) Esterified cholesterol of children: predictors included maternal total and esterifies cholesterol ($r=0.69$)	NE

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
van Stiphout, 1985[170]	Age: Decrease in total cholesterol between ages 9 and 16 Menarche: No relationship with TC	NE
Ward, 1980[171]	NE	NE

Evidence Table 2. Risk Factors

Study, year	Population and Setting	N	Aims	Measures Used
Wong, 1992[172]	Pediatric-office-based cholesterol screening program in 2-20 year old children; 87% white, 4% Hispanic, 2% Asian, 7% other	1081	To evaluate the importance of family history factors and television viewing habits of children for hypercholesterolemia.	Total cholesterol, height, weight, blood pressure. Family medical history questionnaire, dietary habits, exercise, TV viewing.

NA = Not applicable, NE = Not evaluated, RR = Risk ratio, X = Indicates that an adjusted analysis is present (sensitivity analysis).

Evidence Table 2. Risk Factors

Study, year	Adjusted Analysis	Results		
		Activity	Aerobic Capacity / Cardiovascular Fitness	Diet
Wong, 1992[172]	X	Exercise and activities were not associated with cholesterol level status. Watching 2-4 or >4 hrs of television daily to have cholesterol level of 200 mg/dL or higher (p<.01).	NE	Families who used only extra-lean or no hamburger (vs lean or regular hamburger) were more likely to have children with a cholesterol level of 200 mg/dL or higher (RR 2.5, p<.01). Other dietary habits (type of milk, skin or no skin on chicken, etc) were not associated with cholesterol level status.

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Family History**	**Overweight or other Biological Composition Measures**
Wong, 1992[172]	Family history of a high cholesterol level but not premature myocardial infarction was associated with an increased likelihood of high cholesterol (RR 1.62, p<.05).	BMI not associated with cholesterol level status.

Evidence Table 2. Risk Factors

	Results *continued*	
Study, year	**Other Biological**	**Other Miscellaneous**
Wong, 1992[172]	Age and blood pressure level were not associated with cholesterol level status.	NE

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Bachman, 1993[175]	Routine screening via family history questionnaire at pediatric appointments Kaiser Permanente medical Center, ages 2-18	1160 children ages 2-18	Random serum cholesterol test at Kaiser Permanente Regional laboratory using methods approved by the CDC.	Any 1st or 2nd degree relative (parent, sister, brother, uncle, aunt, grandparent) with heart attack, angina or stroke <age 55; and parental high cholesterol
Bell, 1990[115]	Screening event via schools in Scotsdale AZ	1140 fifth grade students	Non-fasting capillary blood samples (Autoclix) collected; total cholesterol measured by wet-chemistry methods using three Abbott Vision analyzers.	Survey of parents for: history of heart attach, stroke, angina, high cholesterol, smoking and high blood pressure in child's parents and grandparents. Age at first occurrence for heart attack, stroke, angina
Bistritzer, 1995[176]	Hospital-based screening of children of father hospitalized for myocardial infarction < age 40 Israel	107 children (ages 2-20) of 40 men (age 31-41) and women	Fasting venous samples, IL Monarch analyser	Family history determined from father's histories of MI or CHD (coronary artery stenosis > 70% of 1+ major branches) before age of 40. Fathers were patients particular Israeli hospital.

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Bachman, 1993[175]	Of 1160 who completed questionnaires, 529 (46%) had positive family history of CHD prior to age 55 or high cholesterol; 369 (70%) of these had a random cholesterol level drawn as recommended. 93 subjects had TC>185mg/dL; 58 of these (62%) completed follow-up testing for lipid panel. Of the 58 who had a panel drawn, 25 (43%) had LDL>126mg/dL and were offered a 3 or 6 week nutrition program. Of the 25, 9 (35%) enrolled in the program.	NR	
Bell, 1990[115]	1201 returend parental permission and family history forms. 34 children were absent or refused testing. 27 samples were hemolyzed or inadequate. Thus, 1140 students had cholesterol samples measured. 25% had TC>185 mg/dL (4.75 mmol/L) and 13% had levels greater than 200 mg/dL (5.2 mmol/L). Family history of parent or grandparent with high cholesterol, hypertension or vascular disease had the highest sensitivity (77%) but lower specificity (24%). Parent or grandparent high cholesterol had sensitivity of 53% and specificity of 62%. The group with negative familiy history included 40% of all the levels greater than 185 mg/dL and 36% of all the levels greater than 200 mg/dL.	NR	
Bistritzer, 1995[176]	3 men died from MI and 3 refused to participate, so 34 men remained. 8 (24%) had normal values. 26 (77%) had 1+ abnormal values including: TC > 6.24 mmol/l, TG > 2.55 mmol/l, LDL-C > 4.42 mmol/l, HDL-C < 0.91 mmol/l. 6 were obese (BMI > 30 kg/m2) 15 mothers (38%) had significant hyperlipidemia (TC > 6.24 mmol/l, TG > 2.55 mmol/l, LDL-C > 4.42 mmol/l, HDL-C < 0.91 mmol/l, or combination). 6 of the mothers were obese. Children' s mean values: TC 4.68 mmol/l, TG 1.40 mmol/, LDL-C 3.00 mmol/l, HDL-C 1.18 mmol/l. Altogether 42% of the children had significant hyperlipidemia (above 95%ile). 1 child was obese (BMI > 27 kg/m^2).	NR	

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Boulton, 1979[131]	Screened samples of children various ages taken from a cohort study, a preschool health program, and a school-based screening program	200 2 year olds; 385 4 year olds; 230 students ages 8-17	2 year olds had non-fasting capillary samples; 4 year olds had fasting capillary samples; school children had fasting venous samples	Family history obtained from parents of children with TC and/or LDL >95th percentile for age; early CHD defined as <65 yrs, hypercholesterolemia in a parent was defined as a TC>251.5 mg/dL
Davidson, 1989[177]	School-based screening, 4th graders	420 of 786 invited children participated	Capillary testing, Kodak CT-60 analyzer; repeated with serum test (Reflotron analyzer) for those with TC>200 mg/dL	Sibling, parent or grandparent history of MI, bypass surgery, stroke, diabetes, high blood pressure, smoking and high cholesterol
Dennison 1994[133]	Otsego County, NY population survey	10,457 children ages 2-19	N/A	Questionnaire asking household adults >age 20 to completed information about cardiovascular disease, early cardiovascular disease (<age 60) in sibling or parent, history of "high cholesterol" diagnosed by a physician, and whether blood cholesterol was measured in the past 2 years

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Boulton, 1979[131]	Case finding rate was greatest for the older age group: For 2 year olds, 15 were >95th percentile with 12 having family history of early CHD; For preschoolers, 20 had TCD>95th percentile, 9 with family history of early CHD; For primary school, 4 children had TC>95th percentile, 2 of whom had family history of CHD; For secondary school, 7 students had TC>95th percentile of whom 5 had family history information and all had a family history of early CHD.	NR	Population and method differences make comparisons of these three groups (ages 2, 4 and 8-17) problematic)
Davidson, 1989[177]	33% of children the upper decile of cholesterol levels had a family history of early < age 56 MI in grandparents, none had family history of early CHD in parents. 83% of those asked to return were confirmed to have TC>185mg/dL	Cost <$2 per test.	
Dennison 1994[133]	Most of the family history of early coronary heart disease was not due to coronary heart disease in the parents (only 5.8% had parents with early coronary heart disease). Children living in two-parent households were more likely to report a known family history of early coronary heart disease than children living in single-parent households (41.8% vs 25.8%, p<0.001) and twice as likely to have known parental hypercholesterolemia (18.8% vs 9.5%, p<0.001). Authors adjusted their estimate of children qualifying for cholesterol screening in order to account for the younger age (<55 yrs) for definition of early coronary heart disease used by the NCEP. With this adjustment, 29% of children from 2-parent families (reduced from 41.8%), and 18.4% of children from one-parent families (reduced from 25.8%) would qualify for lipoprotein analysis. Overall 38% of this population would qualify for cholesterol screening. 35% of children had incomplete or unavailable family health history and/or unknown parental cholesterol status.	NR other than, "parents who belonged to an HMO were much more likely to have had their cholesterol levels measured than parents with private group insurance, Medicaid, or no health insurance.	

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Dennison, 1989[126]	Bogalusa	2127 children ages 3-17	Lipid Research Clinic protocol	Questionnaire completed by parent/guardian, asking whether child's natural mother or father had a history of "high blood pressure," heart attack," "stroke," or "sugar diabetes." Four years later a questionnaire asked parent's age at first heart attach for 108 of the 144 parents who had previously reported a history of heart attack.
Diller, 1995[117]	Cincinnati Myocardial Infarction and Hormone (CIMIH) Family Study	241 families and 501 children ages 2-19	A singleTC and LDL-C determined in a CDC and NHLBI standardized laboratory.	Screening indicators were: history in parent or grandparent of documented myocaridal infarction, angina, pectoris, peripheral vascular disease, sudden death, angiographically demonstrated coronary artery disease, ballon angioplasty, or coronary bypass grafting before age 56. Discretionary indicators were: HTN, obesity, diabetes, smoking, steroid use, high fat diet.
Faigel, 1992[178]	Mass screening of college students	9,938 students ages 17-21	Students required to submit cholesterol results upon matriculation; those >200 mg/dL (95th percentile approximately) were referred to student health for lipid profile	AAP criteria (heart disease, CAD or stroke prior to age 50)

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Dennison, 1989[126]	Only 40% of white children and 21% of black children with elevated LDL levels (>95th percentile) had a parental history of vascular disease.	NR	
Diller, 1995[117]	Prevalence of screening indicators was 47.8%. Prevalence of discretionary indicators was 54.7%. 9.9% had high LDL-C (≥130mg/dL)and 15.1% had borderline LDL-C levels (110-130mg/dL). Of the 58 children with elevated (borderline or high) LDL-C, 7 had no identifiable screening indicators, 38 had at least one of the discretionary indicators. Diet alone would have identified 29 children with elevated LDL-C values. Parental cholestoler concentration >240 mg/dL would have identified 31 children with elevated LDL-C.	NR	
Faigel, 1992[178]	427 of the 873 students with cholesterol levels >200 mg/dL completed fasting lipid profile; 344 of these had abnormal levels (TC>200, TG>180; LDL>160 or HDL<30). Others had testing done by their PCP (data not included). 43 of the 344 students with abnormal lipid profiles met AAP criteria with family history of early CHD.	Cost per case identified was $212.	

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Gagliano, 1993[118]	All new patients at an adolescent/young adult clinic associated with a children's hospital	224 of 248 new patients participated	Total cholesterol obtained at time of visit; those with TC>185mg/dL (85th percentile) advised to have repeat fasting lipid panel (Kodak Ektachem 700)	Questionnaire administered to patient by physician; positive if any member of the family (1st and 2nd degree relatives) had early myocardial infarction (<50 for men, <60 for women) or elevated lipids; negative if no history or unknown. Parent interviewed if present at clinic visit.
Garcia, 1989[179]	Routine surveillance of pediatric patients age 3-18	6500 ages 3-18 (mean 6.4 years)	Non-fasting venipuncture with Reflotron analyzer, confirmed with fasting lipid profile if >200 mg/dL (95th percentile)	Family history of premature MI or known hypercholesterolemia
Goff, 1991[186]	Routine screening at well-child visits in the office of 4 pediatricians.	Ages 4-19	Non-fasting capillary bloodsample with Reflotron analyzer	NR
Griffin, 1989[119]	Routine screening of children in pediatric office practices.	1,005 children ages 2-13	Non-fasting serum cholesterol: commercial laboratories or physicin offices (desk-top analyzers). Children with TC>175mg/dL (75th percentile) were asked to return for fasting lipid panel.	Parent or grandparent with hypercholesterolemia, sudden death, gout, peripheral vascular disease, any family history of obesity. Any family history of coronary artery disease, various combinations.

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Gagliano, 1993[118]	Family history based on adolescent interview had 36.4% sensitivity and 69.1% specificity for hypercholesterolemia (TC>185mg/dL); family history based on parent interview was 65% sensitive and 45.7% specific; combined history was 45% sensitive and 69% specific. Of the adolescents with elevated cholesterol levels, 16 (48%) would have been missed if screening was performed only based on family history (including 1 of 2 patients with cholesterol >240 mg/dL). Of the 33 patients with TC>185 mg/dL, only 13 (39%) returned for fasting lipid profile. Of these 13 patients, 6 had LDL>125 mg/dL, HDL<35, or TC/HDL>4.5.	NR	
Garcia, 1989[179]	552 (8.5%) had cholesterol > 200mg/dL; Of those 487 completed the fasting lipid profile and 375 had LDL>130 (95th percentile); Of these 42 had LDL>190mg/dL; 90 had LDL between 160-189 mg/dL and 243 were between 130-159mg/dL	NR	
Goff, 1991[186]	In 12 month period, 138 or 791 boys (18.5%) and 100 of 165 girls (16.3%) had TC screening values that exceeded the 90th percentile for gender. In ther first 6 months, 238 patients were identified. 37% of boys and 38% of girls received follow-up by a second cholesterol check, a lipoprotein analysis or both. Overall, 37.4% of those with sex-sepcific TC > 90th percentile and 43% of those with sex-specific TC >95th percentile had f/u within 6 months	NR	
Griffin, 1989[119]	Using a family hisotry of early coronary arter disease or hhpercholesterolemia (parent or granparent) would have detected 51% of children with elevated LDL-C.	NR	

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Hammond, 1994[180]	Routine screening of children in seven primary schools in Cantebury England selected from a range of socioeconomic backgrounds	593 295 (50%) ages 5-6; 298 (50%) ages 8-9	Non-fasting venipuncture	NR
Heyden, 1991[181]	Cholesterol education and screening in 5 North Carolina high schools, ages 15-17 USA	1910 tested in 1987 1845 tested in 1988	Reflotron instruments (Boehringer-Mannheim Diagnostics, Indianapolis, Indiana), using a finger stick blood sample	NR
Lannon 1992[130]	Routine screening of all children at well-child visits in six-member pediatric practice	439, ages 2-15	Capillary testing, Kodack DT-60 analyzer, if high advised to return for fasting lipid panel (LRC approved lab)	NR

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Hammond, 1994[180]	Of 593 consent forms, 443 parents (74.7%) gave positive parental consent. Of the 443, 13 children (2.9%) were absent for the venipuncture, 21 children (4.7%) refused, for 17 (3.8%) there was a technical failure, 2 (.05%) felt unwell or unspecified. Venus sample obtained from 390 (88%). 375 (84.6%) were usable for analysis.	NR	Paper looks at feasibility of testing; no data on levels. Note significant difference in failure rate of phlebotomists. Lower parental response rates were from schools with lower socioeconomic backgrounds.
Heyden, 1991[181]	In both males and females, the 2 schools that included teacher involvement had significant decreases in cholesterol levels over a one year period. Males in first school (n= 219) levels decreased from 145.1 to 129.7 ($p<0.05$). Males in second school (n=261) levels decreased from 151.1 to 131.6 ($p<0.05$). Females in first school (n=280) levels decreased from 162.7 to 143.3 ($p<0.05$). Females in second school (n=321) levels decreased from 165.2 to 151.7 ($p<0.05$). There were no significant differences in the 3 other schools that did not include teacher involvement.	NR	Paper examines methods of cholesterol education. Interventions: teacher involvement plus testing vs no teacher involvement plus testing. Teacher involvement described as: discussing cholesterol, nutrition, heart disease; demonstrated how to read package labels; counseled on cafeteria food choices, follow up discussion after testing, etc. Testing occurs first in 1987, then again to evaluate methods in 1988.
Lannon 1992[130]	Of 439 screened, 134 (31%) had TC>175 or LDL>110 mg/dL (AAP criteria). Of those with abnormal screening tests, 63 (47%) returned for lipid panel; of those returning, 54 (86%) were confirmed to have hypercholesterolemia. Of those 134 children, 23 (17%) had negative family history and thus would have not been screened according to AAP/NCEP criteria.	Cost of lipid profile $13	

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Lansing, 1990[182]	Mass screening at state fair	69 people ages 2-19	Capillary testing, Reflotron analyzer.	Not part of screening program
Manchester, 1989[183]	RCT of mass screening of college students vs. selective screening (all sophomores with family history of heart disease)	735 of a total 1,117 students ages 17-19.	Non-fasting blood sample, Kodak Ektachem analyzer; confirmed for those with TC>180 mg/dL (75th percentile)	Any relative with CAD or stroke
Muhonen, 1994[120]	Mass screening of high school students grades 9-12 in Muscatine, IA	599 students from a total of 1,024 students, ages 14-20	fasting venous blood sample, LRC processing methods	Students completed family history questionnaire at home, with help of parents. Family history assessed for parent or grandparent with fatal or nonfatal MI, angina, bypass surgery, HTN, high cholesterol or obesity. Classifications: no CHD, early CHD (between ages 30-55 for at least one parent or grandparent); later CHD (after age 55 in at least one parent or grandparent); and unsure (incomplete forms, missing information or unsure about at least one parent or grandparent.

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Lansing, 1990[182]	Well-accepted. 3 found to have moderate risk, 3 to have high risk (not defined)	Cost per person found with elevated cholesterol was $40 (includes adult cases); $140 per person who visited his/her physician.	
Manchester, 1989[183]	735 (62%) of students had cholesterol tested; no difference in family history between those who had cholesterol measured and those who did not, although the aim was to get those with family history. 60 students had confirmatory measurement; 50 remained over 180mg/dL. Only 10% of those with a risk factor chose to participate.	Cost per case confirmed was $121 for mass screening vs $624 for selective screening.	
Muhonen, 1994[120]	Of 1,024 targeted students, 599 had both family history questionnaire and lipid measurements completed. 19% indicated a parental history of hyperlipidemia; 26% had unsure responses. 2.5% had a parental history of early CHD.	NR	

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Polonsky, 1993[184]	Pediatric lipid clinic at Children's Hospital Medical Center, Cincinnati, OH	182 mean age 9 (18 months - 20 years)	Fasting levels of TC, HDL-C and TG were drawn at the clinic and analyzed at the one central laboratory.	NR
Resnicow, 1993[122]	School-based screening in 4 elementary schools, grades 1-6	1166	Non-fasting capillary samples analyzed with Kodak Ektachem DT 60.	Questionnaire sent home to parents asking them about their cholesterol levels (asked to provide specific value if known)
Rifai, 1996[62]	African American adolescents at the Adolescent medicine and Ambulatory Clinic: 260 of 201 enrolled	260, ages 12-20 years (74% female)	fasting venous samples, Ektachem 700 analyzer, CDC certified lab.	Questionnaire completed by patients
Shea, 1990[59]	Columbia Study of Childhool Activity and Nutrition (recruited mainly from General pediatrics Group Practic at Presbyterian Hospital, New York)	108 Hispanic children who had lipids measured	fasting venous blood samples analyzed for TC and HDL-C and TG in a Columbia University research laboratory calibrated to Centers for Disease Control standards.	Posi5tive if child's mother had HTN, diabetes, obesity, hyperlipidemia or family hsitory of premature CHD or hyperlipidemia. No data on risk factors obtained from the fathers. Also positive if history of hyperlipidemia, premature CHD, MI or sudden death in child's parent or aunt, uncle, or grandparents

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Polonsky, 1993[184]	16 (9%) subjects had normal lipid levels and classifications. Of those (59 subjects, 32%) with elevated LDL-C levels, 16 had concurrent elevated TG or depressed HDL-C. In the TG:HDL-C group (54 subjects) 46 had TG > 95th percentile. For subjects with HDL-C below the 5th percentile, 5 had borderline TG (75th to 95th percentile) and 3 had normal TG levels.	NR	
Resnicow, 1993[122]	Using a parental cut point of 200 mg/dL, 34% of children would have been screened. 40.3% and 48.5% of children with TC values >170 mg/dL and >200 mg/dL would have been identified. Using NCEP/AAP recommended parental cut-point of 240 mg/dL, 9% of children would have been screened and 10.3% of children with TC values >170 mg/dL and 200 mg/dL would have been identified. If clinicians screen only children with one parent who reports a total cholesterol≥240mg/dL, between 90-93% of children with elevated total cholesterol (≥170) would be missed.	NR	
Rifai, 1996[62]	37% of population would have met NCEP/AAP criteria for screening. Of 95 patient meeting screening criteria 25 (26%) had LDL>110 mg/dL (75th percentile); 11(12%) had LDL>130mg/dL (90th percentile). 66% of those with LDL>110mg/dL and 60% of those with LDL>130mg/dL would have been missed under current screening guidelines, even including those with unknown family history.	NR	
Shea, 1990[59]	Using AAP definition of family history, sensitiviy was 57% and specificity was 59% . When family history defined according to NIH consensus conference and the AHA, senstiivity was 46% and specificity was 70%. 12 of 106 would have been misclassified on the basis of TC level (LDL-C would have placed them in another risk category).	NR	

Evidence Table 3. Screening Strategies

Study, year	Venue	N	Laboratory Method	Family History Determination Method & Definition
Skovby, 1991[185]	Copenhagen school system	2085, ages 6-8	Non-fasting capillary blood sample obtained between 8am-12pm.	Parents completed a questionnaire on incidence of chest pains or coronary occlusions in themselves or their parents, siblings, aunts, uncles including age. Positive family history defined as angina pectoris or myocardial infarction <age 50 in men and <age 60 in women.
Steiner, 1991[124]	Kaiser Permanente Teenage Health Centers in Los Angeles, CA	1001, 12-21 years old	Random serum cholesterol test performed at one central laboratory.	Questionnaires were completed about risk factors and family history. Used AAP criteria from 1985 and 1988.
Sveger, 2000[79]	School-based questionnaire, with lipid levels in those who were high risk and their parents, ages 10-11	4000 quest-ionnaires; 2199 (55%) were returned	Blood samples collected after overnight fast from high risk child and parent(s). Centrifugation serum was separated and frozen at -20^{o} C for later analysis.	Family history questionnaire that asked parents whether they or the child's grandparents has suffered premature CAD (before age 50 in father or grandfathers; or before age 55 in the mother or grandmothers). Definition of genetically linked dyslipidemias: 1) LDL-C > 189.48 mg/dL + parent has hypercholesterolemia or died of premature CAD. Hypercholesterolemia in parent = above, or if TC > 290.03 mg/dL + myocardial infarction occurred before age 50 (male) or 55 (female) in first degree relative 2) child has increase of LDL-C + apolipoprotein B, or only apolipoprotein B, and a parent with hypercholesterolemia and/or hypertriglyceridaemia.

Evidence Table 3. Screening Strategies

Study, year	Screening Results	Cost	Comments
Skovby, 1991[185]	3025 questionnaires distributed, 2657 returned, 2166 consented to screening with capillary blood measurement. Of the 2,657 questionnaires completed, 398 families (15%) disclosed a history of early cardiovascular disease.	NR	
Steiner, 1991[124]	Only 30 of 64 (sensitivity = 47%, specificity = 74%) subjects with hypercholesterolemia were identified by the 1985 AAP criteria, while 40 of the 64 (sensitivity = 62%, specificity = 60%) subjects were identified by the 1988 AAP criteria. Combining the two criterias (1985 & 1988 AAP criteria) 44 of the 64 (sensitivity = 69%, specificity = 53%) subjects were identified.	NR	
Sveger, 2000[79]	Family history of premature CAD in parents or grandparents was identified in 208 families. 182 agreed to participate. Blood samples obtained from 175. 89 children had normal tests (LDL-C $\leq$ 131.48 mg/dL, HDL-C $\geq$ 34.80 mg/dL, TG $\leq$ 124 mg/dL, apolipoprotein B $\leq$ 1.00 g/l, and Lp(a) $\leq$ 300 mg/l. Of the remaining: 48 had isolated increase in Lp(a). 23 had non-hereditary abnormalities of low LDL or high HDL cholesterol or apolipoprotein B. 15 were suspected to have genetically determined dyslipidaemias or a combination of risk factors: possible familial hypercholesterolemia in 4; possible familial combined hyperlipidemia in 5; hereditary low HDL in 3; combination of high LDL and Lp(a) in 3. Also, possible familial hypercholesterolemia was detected in 8.	NR	

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Amundsen, 2002[41]	Diet	Randomized, double-blind crossover Oslo, Norway	To assess effect of SE-enriched spread on serum lipids, lipoproteins, carotenoids, fat-soluble vitamins, and physiologic variables in children with FH aged 7 - 12 years.	Study period: 25 weeks with run-ins and washouts Two 8 week treatment periods.	Subjects recruited from patient register at Lipid Clinic of National Hospital in Oslo, Norway

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Amundsen, 2002[41]	Not specifically noted. Implied: 1. Parent with hypercholesterolemia 2. Diagnosed with "definite" or "possible" heterozygous FH 3. Healthy, with no clinical symptoms of hypercholesterolemia	38 2 non-study-related drop-outs; 1 drop out because the amount of spread required to be consumed was too large.	Mean age: 10.5 ± 1.7 50% female Cholesterol (mmol/L) total: 7.01 ± 1.26 LDL: 5.39 ± 1.42 HDL: 1.37 ± 0.32 Triacyglycerol (mmol/L) 0.56 ± 0.22

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Amundsen, 2002[41]	Exposure: In a double-blind crossover, with two 8-week interventions, 38 children with FH consumed 18.2 ± 1.5 g SE spread/day, corresponding to 1.60 ± 0.13 g SE spread, or a control spread. Blood samples were analyzed at the start and end of each diet period. Subjects consumed a recommended American Heart Association Step I diet during both intervention periods.	Measures: Plasma total, LDL and HDL cholesterol Triacylglycerol apolipoprotein (apo) A-1 and apo B Serum concentrations of carotenoids, retinol, and a-tocopherol Blood analyses	Main Clinical Outcomes: 1. Plasma LDL decreased by 10.2% (p=0.003) with treatment vs control. 2. Total cholesterol and apolipoprotein B concentrations decreased by 7.4% (p=0.007 and p=0.020, respectively) with treatment vs control. 3. No changes with treatment in HDL, triaclglycerol or apolipoprotein A-I. 4. Serum concentration of lipid-adjusted lycopene decreased by 8.1% (p=0.015) with treatment, with no other carotenoid changes. 5. Lipid-adjusted retinol and a-tocopherol concentrations increased by 15.65% (p<0.001) and 7.1% (p=0.027), respectively. 6. Alaninetransaminase increased with treatment, which was explained by a significantly lower starting concentration in the treatment vs control period.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Amundsen, 2002[41]	ALT increased in SE diet 16.8% (p = 0.04). No subjects had plasma concentration of ALT outside the reference concentration at any time. Starting concentration of ALT was significantly lower in the SE diet period compared to control. Serum levels of lycopene and B-carotene decreased with SE. After adjustment for lipid changes, differences in B-carotene disappeared; lypocene concentration was still 8.1% lower (p=0.015) in SE compared to control. Serum levels of retinol were higher in SE, and after lipid standardization: 15.6% (p<0.001) higher than control. After lipid standardization,) a topopherol was 7.1% higher in SE than in control (p=0.027). Authors note results may be influenced by different starting concentrations in SE spread than control.	Small N Many children used supplements or vitamins during the study. These variables were not analyzed separately. FH was confirmed by mutation analysis in only 25/38 subjects. Some included children may not have had FH, as baseline total and LDL cholesterol concentrations were significantly higher in the confirmed FH group.	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Becque, 1988[221]	Diet and exercise combination	RCT of exercise, diet and behavior change. Michigan	To determine the incidence of coronary heart disease risk factors and the effects of a 20 week diet and exercise intervention program on risk factors including serum lipids.	20 weeks	Recruited via advertisements in local newsletters and newspapers.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Becque, 1988[221]	Inclusion criteria: 1. Body weight and triceps skinfold greater than the 75th percentile according to NHANES data	36 obese adolescents randomly assigned to three groups: diet plus behavior (n=11), exercise plus diet and behavior change (n=11) or control (n=14).	Girls (n-21): mean age 12.8+0.3 year. Height 156.3+1.5 cm weight 71.3+3.6 kg boys (n=15) mean age 12.7+0.05 year. Height 157.4+2.3 weight 70.8+4.7 kg.

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Becque, 1988[221]	Control group was encouraged not to change their basic lifestyle Diet plus behavior change: subjects met with dietician and behavior therapist once/week. Moderate dietary restriction based on ADA exchange program with caloric intake set to elicit the loss of 0.45-0.90 kg/week (1-2 lbs/week). Behavioral treatment included record keeping stimulus control, changing topography of eating and reinforcing altered behavior. Exercise plus diet and behavior change: diet and behavior were same as above, exercise program was 50 minutes 3 days/week. Each session included warm-up and aerobic activity, increasing from 15-40 minutes per session of the course of the fist 7-8 weeks. HR maintained at 60-80% of age-predicted maximum.	TG, HDL, TC systolic and diastolic BP body weight, % fat and maximum to uptake	Results in mg/dL and reported as mean+SEM post treatment vs post-control. When NS stated means even within group changes were not significant. Control group (n=14): TG increased 117.8+15.8 to 122.2+13.6, NS HDL increased 29.5+1.6 to 32.0+1.5, NS TC decreased 1776.9+10.7 to 167.1+9.0, NS Exercise, diet and behavior change group (n=11) TG: decreased 135.8+16.5 to 91.6+18.4, NS HDL increased 35.3+2.3 to 43.4+2.2 ($p<0.05$ for within group difference, $P<0.05$ for between group difference in post-intervention levels). TC decreased 170.6+10.2 to 149.3+9.2, NS Diet and behavior change group (n=11) TG decreased 117.3+13.9 to 99.9 +17.4, NS HDL increased 34.5+2.7 to 38.4+3.0, NS TC decreased 181.2+12.3 to 171.9+11.4, NS

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Becque, 1988[221]	NR		Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Boreham, 2000[230]	Exercise	RCT of stair climbing. Belfast, Ireland	To evaluate the effects of a 7 week progressive stair-climbing program on cardiorespiratory fitness and lipid levels in young women	7 weeks	Previously healthy female student volunteers ages 18-22, sedentary but previously healthy.
Clauss, 2005[38]	Drug	RCT	NR	24 weeks	Post-menarchal girls with heFH

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Boreham, 2000[230]	Responded that they exercised or played sport on one or no occasions each week. Students at the University of Belfast.	25 people enrolled; data reported on 22 women who completed the study.	22 females, ages 18-22
Clauss, 2005[38]	HeFH; baseline LDL required was 160-400 mg/dL and parental history of familial hypercholesterolemia.	54 girls ages 10-17 at least 1 years post-menarche	54 girls ages 10-17

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Boreham, 2000[230]	Stair-climbing group underwent a 7 week program, progressing from one ascent/day in week 1 to 6 ascents/day in weeks 6-7 on a public access staircase Monday-Friday. Staircase was 199 steps with a total vertical displacement of 32.8 meters. Subjects were instructed to distributed their efforts evenly over the working day and to log completed ascents (ie: could be done in separate short bursts). Completed ascents were 75% of the target over the 7 weeks period. Control group was asked to maintain their normal lifestyle over the experimental period.	1. Serum lipids 2. Cardiorespiratory fitness (VO2 maximum and HR) 3. Anthropometry	Pre-post results in mmol/L, mean + SEM after 7 weeks Stair climbers: TC decreased 4.93+0.25 to 4.53+0.24, p<0.05 within group HDL increased 1.24+0.09 to 1.48+0.14, p<0.05 but p<0.01 for interaction between groups and p<0.05 for pre-intervention differences between this group and the control.
Clauss, 2005[38]	Lovastatin 20 mg for 1st 4 weeks, then 40 mg thereafter	Serum lipids, apo-B	Mean % change from baseline at week 24 in ITT population: TC: -22.4 for lovastatin vs +3.6 for placebo LDL: -29.2 for lovastatin vs +2.5 for placebo HDL +2.4 for lovastatin vs +4.8 for placebo TG: -22.7 for lovastatin vs -3.0 for placebo Apo B: -24.4 for lovastatin vs +6.4 for placebo

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Boreham, 2000[230]	None reported	3 subjects (2 controls and 1 stair climber) withdrew because of illness or academic pressures.	Poor
Clauss, 2005[38]	"Adverse reactions to lovastatin were generally mild and transient." Patients treated with lovastatin had an adverse experience profile generally similar to that of patients treated with placebo. In this limited controlled study, there was no detectable effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on lovastatin therapy."	Unpublished data from lovastatin package insert and confirmed through contact with Merck, Inc.	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Couture, 1998[66]	Drug	RCT Laval University Lipid Research Clinic, Quebec City, Canada	To determine whether the nature of the LDL receptor mutation effects the response to simvastatin. To describe the different responses to simvastatin of plasma lipids, lipoproteins, and apoprotein levels among 3 genetically differentiated groups of heterozygous FH children and adolescents.	6 weeks	FH patients at university research clinic

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Couture, 1998[66]	1. Heterozygous FH patients with 1of 3 mutations in the LDL receptor gene. 2. Aged 8 - 17 3. Weight $\geq$ 27 kg 4. Plasma levels persistently above 95th percentile for age and sex while maintaining a lipid-lowering diet. 5. No concomitant conditions, such as diabetes, anorexia, thyroid disorders	63	37 boys and 26 girls Aged 8-17, mean 12.55

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Couture, 1998[66]	Individual screening with medical history, physical exam, interview with dietician, and blood sampling 6 weeks prior to study entry. All lipid-lowering medications discontinued at screening entry. Four weeks placebo run-in, followed by randomization to double-blind active treatment, 20 mg/d simvastatin or placebo for 6 weeks at 3:1 ratio. Compliance verified by tablet count at weeks 0, 2, 4, and 6. Patients questioned about adverse or unusual signs or symptoms at all clinic follow-up visits (weeks 0, 2, 4, and 6). Patients counseled by dietician to follow American Heart Association phase I diet throughout trial.	Total Cholesterol HDL cholesterol LDL cholesterol apoA-I apoB apoE genotypes triglycerides BMI	Compared to placebo, drug reduced total cholesterol, LDL, and total apoB levels at all time measurements ($p<0.0001$). HDL levels increased in all groups with drug versus placebo ($p=0.003$ to 0.30), and triglyceride levels decreased ($p=0.009$ to 0.10). Multiple regression analyses suggested that 42% of the variation of LDL response to drug is due to variation in the mutant LDL receptor locus, apoE genotype, and BMI; 35% of variation in HDL response was due to gender and baseline HDL level.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Couture, 1998[66]	None reported	Small sample size	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Davidson, 1996[67]	Diet	Double-blind, randomized cross-over study	To investigate the hypocholesterolemic effect of psyllium-enriched cereal in children with documented hyperlipidemia.	6 weeks of treatment in each condition (8 weeks diet stabilization, 6 weeks treatment 1, 6 weeks wash-out, 6 weeks treatment 2)	Children aged 6 - 18 with in the Chicago area with hypercholesterolemia recruited by family screening and public appeal.
de Jongh, 2002[69]	Drug	Double-blind, placebo controlled multi-center RCT 9 international sites	To evaluate LDL-cholesterol-lowering efficacy, overall safety, tolerability and the influence of growth and pubertal development of simvastatin in a large cohort of boys and girls with heterozygous familial hypercholesterolemia (heFH).	48 weeks of intervention after 4 week run-in	173 boys and girls with heFH

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Davidson, 1996[67]	1. Males and premenarcheal females aged 6 - 18. 2. LDL > 90th percentile for age and sex at baseline. 3. Height and weight ≤ 75th percentile 4. No chronic medical condition, such as diabetes. 5. Triacylglycerol ≤ 300 mg/dL 6. Any lipid-lowering agents, including dietary fiber supplements, discontinued ≥ 6 weeks before 1st qualifying blood draw	25-32 randomized ; 2 dropped due to inability to consume amount of cereal required, 1 discontinued for noncompliance, 2 discontinued for family problems. Of the 27 who completed study protocol, 2 excluded from analysis because baseline LDL varied markedly	25 children, ages 6-18. Gender and mean age not reported, although females were premenarchal.
de Jongh, 2002[69]	1. Age 10 - 17 2. LDL-C 158.55 - 398.3 mg/dL 3. Parent with confirmed diagnosis of heFH. 4. Boys: Tanner stage II or above Girls: postmenarchal for at least 1 year before study initiation Exclusion: homozygous familial hypercholesterolemia, secondary hyperlipidemia	173	98 boys and 75 girls

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Davidson, 1996[67]	8 week NCEP diet stabilization followed by blood sampling and random assignment to active or control cereal for 6 weeks. 6 week wash-out, then 6 week crossover treatment period. Active: 58 g of psyllium-enriched cereal daily. Each serving had 3.2 g soluble fiber. Control: matching placebo cereal without psyllium. Subjects instructed to consume two 28-g boxes of cereal daily for a total daily dose of 6.4 soluble fiber from psyllium. Dietary compliance assessed by cereal box count every 3 weeks, questioning of children individually and with parents, and by 3 day dietary records. Subjects on NCEP diet throughout study.	Fasting lipid profile (baseline, ever 6 weeks, week 19) Compliance assessment Dietary assessment (including computerized nutrient analysis at weeks -8, -1, 6, 12, and 19)	Psyllium cereal vs control reduced total (12.1 mg/dL, p=0.03) and LDL cholesterol (10.9 mg/dL, p=0.01). LDL-cholesterol decreased 7% in active vs control groups. Response to treatment differed between subjects consuming psyllium during period 1 vs period 2. A period-by-time interaction was found for total cholesterol (p=0.02). Subjects consuming psyllium had an average decrease in total cholesterol of 19.1 mg/dL during the 1st period and 5.6 mg/dL during the 2nd period; LDL decreased 17.1 mg/dL during the 1st period and 5.2 mg/dL during the 2nd period.
de Jongh, 2002[69]	After 4 week placebo/diet run-in, randomization to active treatment or matching placebo in 3:2 ratio and stratified by sex. Simvastin (drug) started at 10mg/day and increased at 8 week intervals to 20 and then 40 mg/day for the remainder of the study (period 1, 24 week duration) and for a 24 week extension (period 2). Office visits every 4 weeks. Menstrual cycle monitored throughout study period and Tanner staging used to assess pubertal development.	Total cholesterol, triglycerides, LDL-C, HDL-C, ALT, AST, CK, apoB, apoA-1, adrenal hormones, gonadal hormones, pituitary hormones and FSH. In girls, *B* -human chronic gonadotropin was measured each visit.	LDL-C reduced at all time points by drug vs placebo (p<0.001). At 24 weeks, LDL-C reduced 38.4% to 125.29 mg/dL in drug vs 1.2% reduction in placebo (p<0.001). Total-C, VLDL-C, and apoB also reduced vs placebo at all time points (p<0.001). TGs reduced at weeks 8, 16 and 48. HDL-C and apoA-1 increased for all weeks, and were only significant relative to placebo at week 24 (p<0.05). No changes in either treatment group noted in either treatment group at week 24 or 48.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Davidson, 1996[67]	None reported. "Only one child complained of gastrointestinal effects with slight abdominal bloating"	8/25 subjects who completed the study were < 80% compliant during 1 or both treatment periods. Response to treatment differed between subjects consuming psyllium between period 1 and 2. Small sample size.	Fair
de Jongh, 2002[69]	No serious adverse effects. In period 1, 1 discontinuation, due to mononucleosis. In period 2, 4.7% of drug vs 3.4% of placebo reported $\geq$ 1 drug-related clinical AE. (Difference not significant). Total drug group clinical adverse effects included: abdominal pain (3), chest pain (1), flatulence (1), mylgia (2), headache (4), sleep disorder (1), weight gain (1), pruitus (1). Total drug group lab adverse effects: increased ALT (3), increased AST (3), increased CK (1). No deleterious effects on growth or pubertal development.	223 assessed for eligibility, 175 randomized - 69 to placebo, 106 to control. 5 of placebo discontinued: 1 lost to follow-up, 2 withdrew consent, 2 for other reasons. 5 of drug discontinued: 1 to mononucleosis, 1 to protocol deviation, and 3 to consent withdrawal. 101/106 drug completed period 1 and 83/106 completed period 2 (78%). 56/69 placebo(81%) completed period 2.	Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
de Jongh, 2002[68]	Drug	RCT with an additional arm of non-FH controls. USA.	To determine whether simvastatins improves endothelial function in children with familial hypercholesterolemia (FH)	28 weeks; dosage doubled every 8 weeks	HeFH patients ages 9-18
de Jongh, 2003[40]	Diet	Double blind randomized cross-over trial	To determine whether prepubertal HeFH children are characterized by impaired endothelial function and whether short-term intervention with plant sterols can improve endothelial dysfunction.	4 weeks each period, 2-6 week run-in, 6 week wash-out between treatment periods	41 prepubertal HeFH children between ages 5-12 and 20 non-FH controls. The Netherlands.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
de Jongh, 2002[68]	Children with heterozygous FH as defined by: 1. LDL>95 percentile for age/gender; 2. Documented family history of hyperlipidemia with LDL>95 percentile for age/gender after treatment; 3. Personal diagnosis by detection of mutation at the LDL receptor gene	50 heterozygous FH children plus 19 non-affected controls	FH simvastatin group Mean age: 14.6+2 Female gender: 13 (42%) Race: NR. FH placebo group Mean age: 14.6+2.5. Female gender: 11 (50%) Race: NR.
de Jongh, 2003[40]	Children with HeFH selected as follows: 1) LDL>95 percentile for age and gender; 2) documented family history of hyperlipidemia with LDL>95th percentile for age and gender prior to treatment or 3) personal diagnosis of FH by detection of mutation in the LDL receptor gene. Excluded if : girls post-menarchal, boys with Tanner stage later than stage 1, smoking, current use of vasoactive medications or dietary supplements, any other serious illness (HTN, DM).	41 children with HeFH.	mean age 8.2 years 20 males, 21 females

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
de Jongh, 2002[68]	50 heterozygous FH children randomized to simvastatin or placebo in 3:2 ratio. An additional 19 healthy non-FH siblings also used as controls.	1. FMD (flow mediated dilitation) of brachial artery at baseline and 28 weeks. 2. TC, TG, LDL, HDL; 3. AST, ALT, CK at each visit for safety; 4. Height, weight and BP.	Mean absolute change in FMD was higher in the FH simvastatin group vs FH placebo group: 3.9%+4.3% vs. 1.2%+3.9%, p=0.05. Mean absolute reduction in TC mmol/l (FH simva -2.16+1.04 vs -FH placebo 0.05+1.17, p=0.0001); increase in HDL mmol/l (FH simvastatin 0.05+0.17 vs FH placebo -0.05+0.22, P=0.080); decreased in LDL (FH simva -2.13+0.99 vs FH placebo -0.05+1.06 mmol/l, p=0.0001); and decrease in TG (FH simvastatin -0.19+0.37 vs FH placebo -0.10+0.54 mmol/l, p=0.041).
de Jongh, 2003[40]	All HeFH children also were on a low-saturated -fat, low-cholesterol diet (step I).	Endothelial function by flow-mediated filation (FMD) at R brachial artery.	Mean+sd in mmol/L for HeFH children randomized to placebo vs plant sterol spread (baseline data are combined for both P and S groups): TC decreased from 7.30+1.51 to 7.06 for placebo vs 6.27+1.12 for sterol group, p<0.001. LDL decreased from 5.68+1.51to 5.4$\pm$1.137 for P vs 4.58+1.13 for sterol group, p<0.001 HDL increased from 1.25+1.25 to 1.29+0.29 in P vs 1.31+0.31 in S, p=0.594. TG increased from 0.74(range 0.46-2.20) to 0.90+0.40 vs. 0.85+0.36, p=0.476. FMD was significantly lower in the FH placebo group than in the healthy controls (7.2%+3.4% vs 10.1%+4.2%, p<0.005) with no difference in baseline vessel size. Among the HeFH children, FMD in the P and sterol treated groups were not significantly different (7.2%+3.4% P vs 7.7%+4.1%, p=0.592). Again, baseline vessel size between P and S were similar.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
de Jongh, 2002[68]	"In the present cohort, no toxicity or serious adverse or side effects wre reported by the children during the course of this study. However, the duration of the present study is too short to draw conclusions with regard to the saftey of long-term use of simvastatin in children."	28 in FH simvastatin group, 22 in FH placebo group, 19 non-FH controls.	Poor
de Jongh, 2003[40]	"FH children did not report any adverse effects throughout the study."	Compliance was 97% in both P and S groups based on returned empty tubs of margarine.	Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Dennison, 1993[223]	Drug	randomized cross-over trial of psyllium	To assess whether psyllium was effect at lowering TC and LDL values in children beyond the reduction achieved by diet alone	4-5 weeks each period with a 2 week wash-out period between	children ages 5-17 with LDL>110 mg/dL already being treated with diet, recruited from Pediatric Lipid Control Center and from private pediatricians in the vicinity.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Dennison, 1993[223]	Children with LDL>110 mg/dL after treatment with diet.	25 children began the study; 4 did not return for the final blood drawing (3 because of parental difficulties - timing, logistics; 1 boy because he refused to eat the cereal and have his blood redrawn); 1 second blood sample was lost.	11 males; 9 females age 11.1+3.8 years

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Dennison, 1993[223]	Diet consisted of <30% calories as total fat, <10% as saturated fat and <200 mg dietary cholesterol/day. Total calories enough to ensure adequate growth. Subjects instructed to eat two 28gm servings (1 0z or 2/3 c each) of the control cereal (5 mg water-insoluble wheat fiber per serving) or the psyllium cereal (3 gm of water-insoluble fiber and 3 game water-soluble fiber per serving). Cereals were similar in appearance and provided by same manufacturer.	1. Dietary intake (food diary kept by subjects and their parents) 2. Serum lipid levels 3. Serum levels of vitamin D, folic acid, vitamin A, vitamin E, calcium, iron, TIBC and transferrin saturation 4. Height, weight, subscapular and triceps skin-fold thickness	Results for psyllium vs control cereal (also given are results for each group, change from baseline with the control and psyllium cereals separately). Values are in mmol/L, mean +SEM. TC decreased by 0.01+0.10, NS HDL increased 0.03+0.04, NS TG decreased 0.68+0.32, p<0.05 LDL increased 0.10+0.11, NS Serum iron was higher after the psyllium cereal than after the control (92 vs 75 mg/dL, p=0.04). No changes in subscapular or triceps skin-fold thicknesses. Height and weight increased equally during consumption of control and psyllium cereals. None of vitamin or mineral levels tested were lower after the psyllium cereal.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Dennison, 1993[223]	One child (a 17 year old girl reported a transient increase in loose stools (3 /day) with the control cereal with resolved with discontinuation and reappeared with a second challenge of the control cereal and resolved post discontinuation. Compliance was 82% for both cereals.	baseline lipid levels not different significantly for those (n=5) who did not complete the study. Most families were unaware of which cereal was in use (2/3 of children or parents incorrectly identified the psyllium containing cereal).	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
DISC Collaborative Research Group, 1995[219]	Diet	RCT 6 centers	To assess the efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol to decrease low-density lipoprotein cholesterol (LDL-C) levels in children	3 years	Prepubertal boys and girls recruited from public and private elementary schools, by mass mailings to members of an HMO, and from pediatric practices

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
DISC Collaborative Research Group, 1995[219]	1. Girls aged 7 years, 10 months - 10 years 1 month; boys aged 8 years, 7 months - 10 years, 10 months 2. Average of 2 screening LDL-C values ≥ 80th and < 90th percentile for age and sex. 3. No medication or medical condition that could effect growth or blood cholesterol 4. No behavior problems in child or family likely to reduce adherence 5. Prepubertal 6. No plans to move within the 3 study years	663 (362 boys, 301 girls)	Mean age: boys 9.7 girls 9.0

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
DISC Collaborative Research Group, 1995[219]	Randomized to diet (334) or usual care (329). Diet: Behavioral intervention to promote adherence to a diet providing 28% of energy from total fat, less than 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75/mg (1000 kcal) per day of cholesterol (<150 mg/day). Family oriented, based on social learning and social action theory. 1st visit: eating pattern assessed and personalized program developed. In the 1st 6 months: 6 weekly and then 5 biweekly group sessions augmented by 2 individual visits of children with their family members. In the 2nd 6 months, 4 group and 2 individual sessions. Years 2 and 3: group individual and maintenance sessions held 4-6 x per year with monthly phone contacts between sessions. Usual care: Public educational publications on heart-healthy eating provided. Parents informed if child blood cholesterol high - no specific recommendations to see physician given. 3-year lipid results provided, with referral as clinically warranted.	Height and serum ferritin levels at 3 years LDL-C, total serum cholesterol levels, triglycerides, HDL-C, dietary assessment, skinfold thickness, body circumferences, and blood pressure at 1 and 3 years. Red blood cell folate, serum zinc, retinol, and albumin at 3 years Annual Tanner staging, height, weight and psychosocial assessments	At 3 years, dietary total fat, saturated fat, and cholesterol levels decreased significantly in the diet group compared to control (p<.001 for all). LDL-C decreased in diet and control groups by 15.4 mg/dL and 11.9 mg/dL, respectively. With adjustment for baseline level and sex and imputing values for missing data, mean differences between the groups was -3.23 mg/dL (95% CI -5.6 - 0.5 mg/dL) (p=.02). No differences between groups in adjusted mean height, serum ferritin levels, or other safety outcomes.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
DISC Collaborative Research Group, 1995[219]	No differences between groups in adjusted mean height, serum ferritin levels, or other safety measures. Serum ferritin decreased in both groups and the intervention group had slightly lower mean ferritin concentrations than did usual care at year 3 (p=0.08). In both groups, mean ferritin concentrations remained above the 75th percentile for age and sex. Risk of consuming less than 2/3 of the RDA was significant for vitamin E at all visits (baseline OR: 1.009; year 1 OR: 1.007; year 3 OR: 1.007; p<0.0001 for all visits); for zinc at all visits for boys (baseline OR: 1.004, p<0.05; year 1OR: 1.003, p<0.02, and year 3 OR: 1.004, p<0.003) and girls (baseline OR:1.007, p<0.001: year 1 OR: 1.008, p< 0.0006 and year 3 OR: 1.005, p < 0.003).	Authors state randomization yielded comparable treatment groups, although baseline diet group had lower polyunsaturated fat (p=.03), higher vitamin B6 (p=.04) zinc (p=.02), a higher proportion with household income < $20,000 (p=.002), and scored higher on the Child Depression Inventory (p=.09) Low drop-out rate	Good*

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Engler, 2003[224]	Drug	RCT	To determine the effects of antioxidant vitamin therapy and the NCEP-II diet on endothelial functions well as on surrogate biomarkers for oxidative stress and inflammation.	6 months	Not reported

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Engler, 2003[224]	1. Children aged 8 - 21 with hyperlipidemia. 2. FH (LDL >130 mg/DL and a parent diagnosed) or FCH (LDL >130 mg/dL, or triglycerides >150 mg/dL or both, and at least 1 parent presenting with any of these phenotypes). 3. No systematic illness with or without secondary hyperlipidemia. 4. No current smoking.	15 (8 boys, 7 girls). 4/19 19 were excluded due to noncompliance with vitamin therapy.	Not reported

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Engler, 2003[224]	After 6 weeks of adherence to NCEP-II diet, patients randomized to 6 weeks of vitamin C (250 mg) and vitamin E (200 IU) twice daily or placebo. Following 6 weeks of wash-out, patients crossed-over to alternate treatment group for 6 weeks. All followed NCEP-II diet throughout the trial with the support of nutritional counseling. Dietary intake assessed with 3 non-consecutive 24-hour recalls at each visit. Nutrient intake assessed. Compliance with supplements determined through pill counts. Blood and urine samples obtained at baseline and every 6 weeks.	Brachial artery baseline diameter, flow-mediated dilation, cholesterol (total, LDL, VLDL, HDL), triglycerides, lipoprotein, OxLDL antibody titer, OxLDL-E06 levels, ADMA, F2-isoprostanes, C-reactive protein, urinary 8-OH-2'dG, blood pressure, BMI	Antioxidant vitamin therapy and NCEP-II diet improved FMD of the brachial artery compared with baseline ($p<0.001$) without an effect on biomarkers for oxidative stress (antibodies to epitopes of oxidized LDL, F2-isoprostanes, 8-hydroxy-2'-deoxyguanosine), inflammation (C-reactive protein), or levels of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide. The primary effect of the NCEP-II diet was an 8% reduction in LDL ($p<.001$), with no other significant effects of diet or antioxidants on other lipid levels or biomarkers of oxidative stress, inflammation or ADMA.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Engler, 2003[224]	None reported	Very small sample size No demographic/setting description	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Engler, 2004[234]	Drug	Randomized cross-over trial	To determine whether diet (NCEPII) plus placebo or diet plus docosahexaenoic acid (DHA) affects endothelial function in children with FH or FCH.	6 weeks each pase with 6 week washout period between	Not reported

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Engler, 2004[234]	Children ages 8-21 with FH or FCH. FH characterized by LDL>130mg/dL and parent diagnosed with the disorder. FCH was characterized by elevated levels of LDL (>130 mg/dL) or triglycerides (>150 mg/dL) or both, and a parent presenting with 1 of these 3 phenotypes. Excluded were those with chorinc systemic illness with or without secondary hyperlipidemia and current smoking.	20 subjects ages 9-19, 12 with FH and 8 with FCH.	baseline BMI for entire group = 21±4; no race data reported

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Engler, 2004[234]	After 6 weeks of adherence to NCEP-II diet, pts were randomized to 6 weeks of placebo or DHA (all continued on diet). Subsequently, following a 6 week washout period, the groups crossed over.	Primary outcome was brachial artery flow-mediated dilation. Secondary outcomes were lipid levels	Cross-over results presented in aggregate. However, the repeated measures anova indicated no main effect or order and no order by phase interaction "indicating that presenting DHA first or placebo first had no effect." FMD increased after DHA supplementation compared to placebo ($p<0.012$) TC was higher for DHA plus diet compared to diet plus placebo: 297+81 vs. 286+85 mg/dL TC increased for DHA plus diet compared to diet alone: 263+79 vs. 297+81mg/dL (pre-post comparison, not randomzied, $p>0.006$). LDL was higher for DHA plus diet compared to placebo plus diet: 229±85 vs. 216±98 mg/dL. HDL was lower for DHA plus diet compared to placebo plus diet: 51±13 vs. 52±11 mg/dL. TG were lower for DHA plus diet compared to placebo plus diet: 119+71 vs. 131+94 mg/dL

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Engler, 2004[234]	Not Reported		Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Engler, 2005[236]	Drug	Randomized cross-over trial	To determine whether diet (NCEPII) plus placebo or diet plus docosahexaenoic acid (DHA) affects endothelial function in children with FH or FCH.	6 weeks each pase with 6 week washout period between	Not reported

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Engler, 2005[236]	Children ages 8-21 with FH or FCH. FH characterized by LDL>130mg/dL and parent diagnosed with the disorder. FCH was characterized by elevated levels of LDL (>130 mg/dL) or triglycerides (>150 mg/dL) or both, and a parent presenting with 1 of these 3 phenotypes. Excluded were those with chorinc systemic illness with or without secondary hyperlipidemia and current smoking.	20 subjects ages 9-19, 12 with FH and 8 with FCH.	baseline BMI for entire group = 21±4; no race data reported

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Engler, 2005[236]	After 6 weeks of adherence to NCEP-II diet, pts were randomized to 6 weeks of placebo or DHA (all continued on diet). Subsequently, following a 6 week washout period, the groups crossed over.	Lipoprotein subclass profile	Results report an shift toward larger, more buoyant LDL and HDL particles without significant changes in quantitative total cholesterol amount. Cross-over results presented in aggregate. LDL was higher for HAD+diet compared to placebo + diet (226+86 vs 216+92). LDL-1 and LDL-3 had signficant differences vs. placebo. HDL-2 was significantly higher for DHA+diet vs placebo +diet as compared to diet alone. No significant change in HDL overall, or in triglycerides.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Engler, 2005[236]	Not Reported		Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Epstein, 1989[217]	Diet and exercise combination	RCT	To assess the effects of weight change over 6 months on serum lipid changes	6 months	Community

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Epstein, 1989[217]	1. Children ages 8-12 2. One child and one natural parent who were >20% of ideal weight for age, sex and height. 3. Child's triceps skinfolds >95th percentile for age and sex 4. No history of psychiatric contact for the children	56 children randomly assigned to diet (n=18), diet plus life-style exercise (n=19) or no treatment control (waiting list) (n=19).	mean age 10.5 in treatment groups, 10.3 in control % overweight: 42 in treatment group, 50 in control group

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Epstein, 1989[217]	Diets were set between 3800-5000kJ/day and monitored by anutrtionis to maintain nutrient adequacy. Information on diet, exercise, stimulus control, reinforcement, modeling and contingency contracting was presented to parents and their children in eight weekly sessions followed by four monthly sessions.	Weight, height, fitness, and serum lipids	Results for the two intervention groups (diet or diet+exercise instruction) were combined for total treatment group n=35 and control n=16. 51/56 completed the trial. 9 did not have 6 month serum data because they refused venipuncture. Values given as mean (SD) in mmol/L after 6 months: Change in total cholesterol was -0.27 (0.47) for intervention vs +0.09(0.50) for control, p=0.03 Change in HDL was 0.20 (0.16) for intervention vs +0.06 (0.13) for control, p=0.007 Change in triglycerides was -0.55 (0.53) for intervention vs -0.12 (0.30) for control, p=0.01 Change in weight -3.6 kg (-17.4% change in percent overweight) for intervention vs +5.2 kg (-0.8% change in % overweight).

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Epstein, 1989[217]	NR other than 9 children refusing venipuncture.		Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Ferguson, 1999[225]	Exercise	Randomized cross-over trial of 4 months of exercise training (ET)	To examine the effect of exercise training on obese children	8 weeks	Obese children living in community near the Medical College of Georgia; recruited via community fliers and community/hospital newspapers

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Ferguson, 1999[225]	Inclusion criteria: children need to have a triceps skinfold>85th percentile for gender, ethnicity and age and not be involved in any other weight control or exercise program, and not be restricted as to physical activity; all females were menarchal	81 children; 2 were dropped for medical reasons prior to randomization. 79 children randomized.	Mean age, s.d= 9.5+1.0 yrs mean height= 141.9+8.7 cm mean weight= 57.6+17.7 kg black=44 subjects; white=37 subjects; Asian=1 subject 26 boys and 53 girls

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Ferguson, 1999[225]	2 days diet recall Exercise program offered 5 days/week; children were paid $1/session for each day of attendance and given prizes for satisfactory participation (maintaining a HR>150 bpm). Transportation was provided to the program after school. Each session was 40 minutes long with 20 minutes of aerobic activity and 20 minutes of games that were designed to assure continuous activity.	TC, HDL, LDL, TG, LDL-C size, Lp (a), ApoA-1, APoB, insulin, glucose, GHb(%), %fat and submaximal HR.	Results at months 4 (prior to cross-over) in mmol/L, least square mean+s.e. TC: ET group (n=40) decreased from 4.29+0.08 to 4.04+0.08; control group (n=37) decreased from 4.63+0.08 to 4.27+0.08. HDL: ET group (n=40) increased from 1.14+0.03 to 1.19+0.03 vs control group did not change (n=37) 1.35+0.03 to 1.35+0.03 LDL: ET group (n=39) decreased 2.48+0.08 to 2.33+0.08 vs control group decreased 2.79+0.08 to 2.45+0.08 TG: ET group (n=39)decreased 1.15+0.01 to 0.95+0.01 vs control group (n=36) increased 0.98+0.01 to 1.10+0.01 Lp (a): ET group (n=37)0.15+0.01 to 0.13+0.01 vs control group (n=37) decreased 0.16+0.01 to 0.12+0.01g/L Apo A-1: ET group (n=39) increased 1.10+0.03 to 1.24+0.04 vs control (n=37) decreased 1.31+0.03 to 1.28+0.03 ApoB: ET group (n=39) decreased 0.77+0.01 to 0.76+0.02 vs control (n=37) decreased 0.79+0.01 to 0.74+0.02. Results significant for the change in TG ("p-0.02 for the group x time interaction over entire 8 months). Results also given for both groups at the end of the cross over

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Ferguson, 1999[225]	NR	76 children tested at month 4; 70 children tested at month 8. 3 subjects withdrew from the group that had no exercise in the first 4 months; 3 children withdrew from each group during the 2nd 4 month period.	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Gold, 1991[231]	Diet	RCT	To evaluate serum apolipoprotein and lipid profile effects of an oat bran supplemented low-fat diet in children with elevated serum cholesterol.	4 weeks	School-age children in the U.S.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Gold, 1991[231]	1. Cholesterol level over 185 mg/dL	49	Mean age: 10 years

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Gold, 1991[231]	Subjects given American Heart Association Step 1 Guidelines (fat intake limited to 30% of total calories and cholesterol to 300 mg/day), then randomized to control or oat bran supplemented (OBS) groups. OBS consumed an estimated 38 grams of oat bran/day in the form of cereals and snack bars for 4 weeks.	ApoA1, apoB, total cholesterol, LDL, HDL, and triglycerides	OBS had decreased apoB (-9mg/dL) vs control (2mg/dL), p=0.05. No significant differences between groups in total cholesterol, apoA, LDL, HDL, or serum triglycerides.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Gold, 1991[231]	No adverse side effects or symptoms reported.	No information on compliance, withdrawals, intent-to-treat. Very brief write up.	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Gylling, 1995[39]	Diet	Randomized cross-over trial of diet	To assess the effect of sitosterol rapeseed margarine vs. rapeseed margarine without sitosterol	6 weeks each arm	14 children with HeFH Helsinki, Finland

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Gylling, 1995[39]	Diagnosis of FH established in children and in one parent mostly by DNA technique	14 children with HeFH and 1 child with HoFH (2 yr old)	7 boys, 7 girls Mean age 9.1+1.1 yr (2-15)

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Gylling, 1995[39]	Children were randomized to replace 24 grams of their normal daily fat intake by the same amount of a rapeseed oil-rich margarine with or without sitostanol ester (M vs MS) . All children had previously been advised to use a low animal fat-low cholesterol diet rich in monoenic fatty acids for years. Protocol results in daily consumption of 3 grams of free sitostanol in MS group.	TC, VLDL, IDL, LDL, HDL, HDL/LDL ratio, HDL2, HDL3, phospholipids and subfractions, triglycerides and subfractions.	Results combined after cross over, p-value assumed given notation of "significant change between groups." mean+SE in mmol/L, pre values were combined. TC: decreased from 7.68+0.36 to 7.62+0.32 in M group vs 6.81+0.34 in MS group (10.6% lower in MS group, p<0.05). LDL decreased from 5.64+0.35 to 5.47+0.30 in M group vs 4.65+0.32 in MS group (15% lower in MS group, p<0.05). VLDL increased from 0.21+0.05 to 0.26+0.06 in M group vs 0.25+0.07 in MS group (3.8% lower in MS group, NS). HDL increased from 1.17+0.07 to 1.20+0.07 in M group vs 1.25+0.08 in MS group (4.2% higher in MS group, NS). TG increased from 0.87+0.10 to 1.03+0.13 in M group, vs 0.92+0.12 in MS group, (10.7% lower in MS group, NS). Data reported separately for HoFH boy

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Gylling, 1995[39]	Children noted no difference in taste between the two margarines. Report "good compliance," and "well tolerated."		Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Kang, 2002[226]	Exercise	RCT of exercise. Atlanta, GA	To test whether high intensity physical training would have a favorable effect on components of the insulin resistance syndrome in obese adolescents	8 months	Obese 13-16 year old youths were recruited.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Kang, 2002[226]	Inclusion criteria: 1) triceps skin-fold greater than the 85th percentile for gender, ethnicity and age 2) no involvement in any other weight control or exercise program 3) no restriction with respect to ability to engage in physical activity.	80 obese youths enrolled in two cohorts and randomized within gender and sex to one of three groups: lifestyle education alone (LSE); LSE+moderate intensity physical training (PT); and LSE + high intensity PT.	White boys: n=10, mean age 14.5years. white girls: n=15, mean age 15.3yr. black boys: n=16, mean age 14.1yr. black girls: n=39, mean age 15.2 yr.

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Kang, 2002[226]	Physical training was offered 5 days/week for 8 moths except during the weeks that they were assigned to lifestyle education (LSE). Physical training program involved an individual exercise prescription based on baseline treadmill test, designed for 1045 kJ/session (250kcal) regardless of whether it was high/moderate intensity. The intensities corresponded to a mean prescribed HR of 55-60% peak for moderate intensity group and 75-80% of peak for high intensity group.	1. TC, HDL, LDL, Lp (a), apo A1, ApoB, glucose, insulin, triacylglycerol 2. Percentage of body fat 3. Systolic and diastolic BP	Pre-post changes in mmol/L least-square mean+SEM: TC: LSE alone increased 0.24±0.10 vs LSE+PT decreased 0.03±0.09, p=0.066. HDL: LSE alone decreased 0.03±0.04 vs Lse+PT decreased 0.03±0.04, p=0.958. VLDL: LSE alone increased 0.12+0.04 vs LSE+PT decreased 0.04+0.04, p<0.001 TG: LSE increased 0.12+0.08 vs LSE+PT decreased 0.22+0.08, p=0.002 Lp (a): LSE increased 2.45+4.79 mg/dL vs LSE+PT increased 9.88+4.32, p=0.263 Apo A1: LSE increased 10.51+4.31 vs LSE+PT increased 12.40+3.90, p=0.748 ApoB: LSE decreased 1.03+3.29 vs LSE+PT decreased 0.30+2.97, p=0.868.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Kang, 2002[226]	Not Reported		Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Knipscheer, 1996[71]	Drug	double-blind, randomized placebo controlled study, children stratified by age. 4 arms (3 doses of pravastatin, 1 placebo)	To assess the safety, tolerability and efficacy of pravastatin for HeFH	12 weeks, following an 8 week diet and placebo run-in period.	Lipid clinic The Netherlands

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Knipscheer, 1996[71]	Children with "known heterozygous FH" were eligible. HeFH defined as plasma LDL above 95th percentile for age and sex during lipid-lowering diet AND hypercholesterolemia in siblings, parents or grandparents, or clinical manifestations of premature atherosclerosis prior to age 50 in 1st/2nd degree relatives. Exclusions: 1. Major surgery within the past 3 months 2. Use of medications interfering with lipid metabolism (anticonvulsants, oral contraceptives, corticosteroids, fibric acid derivatives or immunosuppressants). 3. Hepatic or renal dysfunction	72 children with HeFH	25 male; 47 female 66/72 White; 5/72 Black. Mean age 11.9-12.1 across 4 groups.

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Knipscheer, 1996[71]	Pravastatin 5, 10 and 20 mg/day	1. TC, LDL, HDL, TG, Apo B100 2. TSH, cortisol, ACTH before and after treatment period 3. Physical exam at entry and final visit. ALT, AST, T bilirubin, CK, Alk phos.	1. Compliance was 93% 2. At week 12: TC and LDL were significantly reduced in all pravastatin treated groups compared with baseline ($p<0.05$). LDL: 5 mg/day - 20% decrease; 10 mg/day - 20% decrease; 20 mg/day - 30% decrease (from baseline LDL levels of 247.49 mg/dL for P, 239.75 mg/dL for 5mg/day, 235.89 mg/dL for 10 mg/day and 259.01 mg/dL for 20 mg/day. TC: 5 mg/day - 18% decrease; 10 mg/day - 18% decrease; 20 mg/day - 25% decrease (from baseline TC of 301.63 mg/dL for P, 297.76 mg/dL for 5 mg/d, 235.89 mg/dL for 10 mg/d, and 317.09 mg/dL for 20 mg/day. (all numbers estimated from graph). Plasma LDL cholesterol levels were not reduced below the 95th percentile for sex and age, except for 2 children in the 20mg pravastatin group, and 1 child each in the 5 and 10 mg pravastatin groups. Plasma HDL showed a mean increase of 11% (from baseline of 46.4 mg/dL) in the 20 mg pravastatin group ($p<0.001$), but was unchanged in the other groups. TG did not change as compared from baseline in any group. Plasma VLDL and Apo B100 levels were reduced in all pravastatin treatment groups ($p<0.05$ and $p<0.001$ respectively).

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Knipscheer, 1996[71]	Total number adverse events P- 9, 5 mg/day - 3, 10 mg/day - 6, 20 mg/day - 1. List: rash, fatigue (P only), nose bleeding, headache, diarrhea (P only), dyspepsia (P only), nausea/vomiting, abdominal pain, myalgia (P only). Laboratory safety measurements did not show significant changes in any of the groups between the end of the treatment period and baseline. However CK abnormal in 8 of P , 6 of 5mg/day, 11 of 10 mg/day and 8 of 20 mg/day. Cortisol abnormal in 2 of P, 2 of 5 mg/d, 5 of 10 mg/d, 3 of 20 mg/d.		Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Kuehl, 1993[227]	Diet	RCT of parental and family education USA	To identify and characterize a family-based group intervention to lower plasma cholesterol in children.		Children with TC ≥185 ages 2-15 (mean 7)

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Kuehl, 1993[227]	Children referred by physicians who participated in a seminar on the risk factors for atherosclerosis in children, identification and management of high cholesterol in children. 14 pediatric practices referred 295 children.	295 children randomized to either a single session intervention (SSI) or a multi-session intervention (MSI)	SSI group: mean age 6.6 gender: NR race: NR MSI group: mean age 7.6 gender NR race NR

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Kuehl, 1993[227]	1. SSI=one 90 minute nutrition education session for patient, siblings and parents (slides presentation, low fat food prep and tasting, distribution of fruit and cereal). "Returned for subsequent food sampling with nutritionist present" but no further formal education. 2. MSI= four 90 minute sessions with focus on food preparation for breakfast, snack, lunch and dinner. Received notebooks with nutrition information and recipes, incentives for attendance and completion of behavioral contracts (eating low fat meal)	1. TC, TG, LDL, HDL 2. Caloric intake 3. Diet composition 4. Nutritional intake of calcium and iron 5. Growth	Both groups had improvement in TC from baseline to the second visit: TC: MSI group TC (n=90) decreased from 207.9±3.2 to193±3.0 (p<0.0001; SSI group (n=87) TC decreased from 206.1±3.3 to 198.5±3.3 (p<0.01). HDL: MSI group decreased 53.7±1.4 to 51.6±1.4 (p<0.08). SSI group NR. LDL: MSI group decreased 137.0±3.6 to 124.9±3.3 (p<0.0001); SSI group NR. TG: MSI group decreased from 88.5±6.8 to 83.5±5.1 (p NS); SSI group NR. Both groups had a significant decreased in the proportion of total calories obtained from fat. Both groups had a significant increase in the proportion of total calories obtained from protein. Total calorie intake decreased in the MSI group but not in the SSI group: MSI 1464±34 to 1348±31 (p<0.002); SSI group 1358±33 to 1306±32 (p=NS).

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Kuehl, 1993[227]	Both groups maintained iron intake at over 87% and calcium intake at over 81% of the RDA throughout the study. % RDA of iron reported baseline to visit 2: MSI 103±5 to 98±5 (pNS); SSI 87± 4 to 90±4 (p=NS). All patients "grew linearly with a mean height increase of 2.0±0.3 inches in the MSI group and 2.0±0.1 in the SSI group. Both groups had a mean weight increase of 4.1 lbs. Growth parameters not significantly different between the two groups.	Large and unequal drop out rates (35% for SSI and 16% for MSI) and analysis only use those who completed the second blood draw (215 of original 295); ie not intention to treat. No assessment of intervention fidelity. 18% of MSI and 20% of SSI had plasma TC values <170 and were excluded from the analyses because they didn't meet the initial referral criteria of TC ≥ 185.	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Lambert, 1996[72]	Drug	RCT of drug multicenter: 6 sites in Canada	To determine the efficacy, safety and tolerance of short-term administration of lovastatin in a male pediatric population with severe FH, and to evaluate dose-response relationship.	8 weeks of randomization to meds vs. placebo; 4 wk run-in for both groups.	Boys aged 17 or younger with heterozygous FH

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Lambert, 1996[72]	1. Weight 27 kg or more 2. Plasma LDL above 95th percentile for age while on lipid-lowering diet 3. History of unsuccessful treatment with bile acid-binding resins 4. Family history of atherosclerosis at or before age 50 5. Documented family history of hyperlipidemia with LDL > 95th percentile for age and sex before treatment or a personal diagnosis of FH substantiated by LDL receptor activity or mutation. 6. No significant concomitant conditions 7. Weight and height not 3 - 97th percentile for age	69 randomized, 17 to 10 mg/day group 18 to 20 mg/day group 19 to 30 mg/day group 15 to 40 mg/day group	10 mg/day group Mean age: 12.5 (2.4) Female gender: 0 Race: 94.1% white 20 mg/day group Mean age: 12.7 (1.6) Female gender: 0 Race: 100% white 30 mg/day group Mean age: 13.3 (2.7) Female gender: 0 Race: 94.7% white 40 mg/day group Mean age: 12.9 (2.7) Female gender: 0 Race: 93.3% white

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Lambert, 1996[72]	After pre-study visit and lab tests, all lipid-lowering medications were discontinued at least 8 weeks before study start, with no lipid-lowering therapy allowed other than that permitted by study protocol. Placebo given weeks -4 to 0, followed by randomization to double-blinded active treatment of lovastatin at 10, 20, 30 or 40 mg/day for 8 weeks. Medication dispensed at weeks -4, 0, and 4. Compliance verified by tablet count at weeks 0, 4 and 8. Clinic follow-up visits at weeks -4, -2, 0, 2, 4, 6, and 8. Complete physical exam at weeks 0 and 8. Ophthalmologic exam during placebo period and within 8 weeks of study exit. Patients continuously counseled by dietician to follow lipid-lowering diet throughout the trial. Daily food records completed by patients for 3 consecutive days and reviewed by a dietician at weeks -4, 0, 4, and 8.	Total cholesterol LDL Apolipoprotein B Safety Compliance	All doses reduced total cholesterol, LDC, and ApoB ($P \leq .0001$ for all). Mean percent change from placebo to end of treatment varied from -17% to -29% for total cholesterol values, from -21% to -36% for LDL, and from -19% to -28% for ApoB. Dose response relationship, with improved results up to a dose of 30 mg/day. Drug well-tolerated. Increased aspartate aminotransferase concentrations, with no evidence of a dose-response relationship, and no value exceeding 2x the upper limit of normal. No change in alanine aminotransferase. Three patients had $\geq$ asymptomatic elevations in creatine kinase, which spontaneously returned to normal, with no action required regarding the drug. 85% of patients took at least 70% of the prescribed dose during the active treatment period.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Lambert, 1996[72]	No serious clinical adverse effects reported	No separate control group: patients served as own controls	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Linder, 1983[232]	Exercise	RCT Augusta, GA	To determine the effect of an 8-week physical conditioning program on the serum lipid and lipoprotein levels in healthy white male adolescents.	8 weeks	Volunteers from middle income families, all subjects were members of Boy Scout troops. Any boys with health problems and those taking medication were excluded.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Linder, 1983[232]		50 healthy boys randomly assigned to either control (n=21) or physical conditioning (n=29).	boys ages 11-17; all white

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Linder, 1983[232]	Subjects in the physical conditioning group were required to participate in 4 days/week of exercise. This program consisted of 3 days of an alternating walk-jog program (60 seconds each) and 1 day of competitive team soccer or rugby (min 1 hour). Jogging segments were run at a rate that increased the subject's pulse rate to 80% of the maximum pulse rate reached during individual working capacity testing at baseline. Subjects in the control group participated in their usual summer activities.	1. 48 hour dietary history kept by parents and subjects 2. Height, weight, triceps skin fold, resting pulse rate, blood pressure, relative body weight calculated using Weight-for-Length Index. 3.	1. Physical working capacity increased in the PA group from pre to post (16.2+3.4 to 18.7+3.5 kpm/min/kg) as compared to the control group (16.4+3.3 to 16.3+2.9 kpm/min/kg). $p<0.05$ for the difference between the PA and control groups post-test results. 2. No significant differences were noted in weight, height, skinfold, BP or resting pulse rate, dietary components 3. There were no significant differences in the change in serum cholesterol levels from pre to post or between groups. Total cholesterol: PA group 148.14+22.39 pre to 147.23+26.49 post vs control group 149.45+24.87 pre to 148.22+29.34 post mg/dl LDL: PA group 93.90+20.93 to 97.25+22.86 vs control group 95.20+23.36 to 101.00+33.44 mg/dL HDL: PA group 41.33+8.39 to 37.38+7.87 vs. control group 40.20+8.39 vs 37.94+8.59 VLDL: PA group 15.38+8.15 to 14.47+8.28 vs control group 14.55+10.77 vs 13.89+10.68 Triglycerides: PA group 84.14+29.47 to 84.00+25.40 vs control group 81.70+28.71 vs 87.17+34.12

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Linder, 1983[232]	NR	No sessions were missed due to illness; any sessions missed for vacation were completed under parental supervision; 1 day per week was offered as a make-up day. 39 of 50 subjects completed the post-tests; 8 of the 29 subjects in the physical conditioning group were excluded because they failed to fulfill adequately all the requirements of the exercise program. 3 of the 21 subjects in the control group failed to return for follow up testing and were not included in the final analysis.	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Malloy, 1978[73]	Drug	Single-blind random assignment pattern with cross-over at 6 months - drug USA	To determine the effect of *p* -aminosalicylic (PAS) on serum cholesterol and triglycerides in 3 lipoprotein classes in children and adolescents with severe familial hypercholesterolemia.	6 months each condition (drug and placebo); follow-up at 12, 18, and 24 months for some. 4 month run-in period for all prior to randomizatio n.	Children aged 5 to 21 years with severe familial hypercholesterolemia; asting triglycerides were normal and electrophoresis of serum in agarose gel showed a predominant narrow liporptien band of beta moility in all patients.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Malloy, 1978[73]	1. Severe familial hypercholesterolemia 2. Consistently elevated serum cholesterol while on ≥ 4 month diet restricted in cholesterol and saturated fats 3. No disorders known to contribute to secondary hyperlipidemia 4. No other serious disorder 5. No medications other than PAS 6. One parent with proven and one other in kindred with hypercholesterolemia.	20 enrolled	Median age: 12 years Female gender: 45%

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Malloy, 1978[73]	Dietary cholesterol and saturated fats restricted 4 months prior to and throughout the study. Subjects and their parents received monthly dietary counseling. Single-blind assignment to active drug (150 mg/kg/day, up to 8 gm/day) or placebo during first 6 months. Dose adjusted monthly for change in body weight. After 6 months, the alternate agent (placebo or active drug) was given for 6 months. Composite index of compliance for each subject based on interviews, tacit drug inventories, and tests for PAS metabolites. Monthly clinic visits including clinical exam.	1. Serum cholesterol 2. Triglycerides 3. LDL 4. HDL 5. TSH	1. Mean serum cholesterol levels for all subjects were 14% lower during the 6 months of treatment with diet and PAS-C vs diet alone (p<.001).Those in the compliant subgroup decreased 19.5% below control levels with PAS-C (p<.001) 2. Mean fasting serum triglyceride levels of all patients were within the normal range with diet alone, and decreased 15.7% when PAS-C was added (p<.001). Levels in the compliant subgroup were not lower than those of other patients, suggesting a smaller dose of PAS-C may be maximally effective. 3. In paired samples of serum from 8 subjects, LDL decreased in all and the mean content of serum cholesterol in the LDL fraction declined 24% below control levels during treatment with drug (p<.002). 4. No difference in HDL with drug 5. No difference in TSH with drug

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Malloy, 1978[73]	No indicators of drug toxicity reported, other than mild gastric irritation that remitted with oral antacid treatment.	Single-blind randomization No separate control group: patients served as own controls Only 11/20 subjects were > 50% compliant LDL change evaluated for 8 subjects only	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
McCrindle, 1997[74]	Drug	Randomized crossover patients recruited from 2 lipid disorder clinics	To compare acceptability, compliance and effectiveness of two forms of cholestyramine resin in treatment of hypercholesterolemia in children.	28 weeks	2 pediatric lipid clinics; children with familial hypercholesterolemia

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
McCrindle, 1997[74]	1. Age 10 - 18 years 2. 1 or more parent with heterozygous familial hypercholesterolemia type IIA or IIB 3. Fasting serum LDL of 130 mg/dl or more while on American Heart Association step 2 diet 3. No contraindications to use of cholestyramine 4. No lipid-lowering agents other than those in study protocol	40	43% female 2 siblings from 6 families 3 siblings from 1 family Median age at enrollment: 13 (10-18) Median age at diagnosis: 9.5 (0.1-17.2)

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
McCrindle, 1997[74]	6 week washout period followed by random assignment in pairs to either 8 grams/day of cholestyramine powder (4 gram packets) or pills (1 gram tablets) for an 8 week period. Drug dispensed with random over count, and subjects instructed to return unused drug at end of drug period. Subject completed log book during the 1st week on amount of drug taken, acceptability and adverse effects, with questionnaire at weeks 4 and 8. After the first 8 week course of medication and assessment, there was another 6 week wash-out, followed by crossover to the alternate form of medication and assessment.	Baseline assessment: self-administered questionnaire on attitudes, health beliefs and perceptions re: hypercholesterolemia, detailed medical and family history, food frequency questionnaire. Fasting lipid profile Complete blood cell count Serum chemistry determinations Physical exam Dietary assessment Questionnaire on ease of drug use and compliance	Reduction in LDL for both pills (-10% +/- 20%, p=0.006) and powder (-15% +/- 17%, p=0.0001) with no significant difference between forms (p=0.16). At end of study, 82% preferred pill, 16% powder, and 2% neither form. Mean (+/-SD) compliance as assessed by amount of medication taken was greater for pills (61% +/- 31% than powder (50% +/- 30%, p=0.01). Form of medication increased compliance by at least 25% for 16 patients (42%), 13 in favor of pills and 3 of powder. Compliance not associated with patient attitudes or perceptions of hypercholesterolemia, demographics, family history, previous experience with lipid-lowering medications or lipid-profile parameters.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
McCrindle, 1997[74]	38/40 (95%) completed both medication periods Authors noted minor gastrointestinal complaints were frequent but did not result in any drop-out	No control group Small sample size At baseline, pill group had perception of increased importance of diet	Fair*

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
McCrindle, 1998[235]	Diet	Randomized trial	To determine compliance, safety, and efficacy of therapy with garlic extract in lowering cholesterol levels in children and adolescents with hypercholesterolemia	8 weeks	Lipid clinic, Toronto, Canada

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
McCrindle, 1998[235]	Children between ages 8-18 Positive family history of hypercholesterolemia or prematrues atherosclerotic cardiovascular disease in first-degree relative Minimum fasting TC >185 mg/dL Participating in a dietary counseling program Compliance with NCEP Step II diet for at least 6 months Excluded: secondary dyslipidemias, hisotry of major surgery or illness within 3 months of enrollment	30 randomized to either garlic supplement or identical placebo	16 males, 14 females Mean age 14.0±2.3 years

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
McCrindle, 1998[235]	1 whole 300 mg tablet of garlic extract (Kwai, Lichtwer Pharma, Berlin, Germany) containing 0.6 mg of allicin placed in a gelatin capsule with inert filler. One bulb of Chinese-grown garlic provides the same amount of allicin as that provided by 6 tablets of garlic extract. Placebo consisted of identical gelatin capsule with inert filler only.	Compliance Fasting TC, LDL-C, HDL-C, TG, and Apo A-1, Apo B-100	Relative to placebo, garlic treatment resulted in: TC increase 0.6 mmol/L (p=0.86) LDL-C deccrease 0.5mmol/L, p=0.90 HDL increase 9.3 mmol/L, p=0.29 TG decrease 0.72 mmol/L, p=0.70

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
McCrindle, 1998[235]	At the end of study, 13% of placebo group and 21% of garlic group reported adverse effect (p=0.66), the most common being headache. Upset stomach was also reported by both groups at the mid-oint questionnaire. No effects on hight, wieght or blood pressure. Serum albumin level and hemoglobin levels increased in the garlic treated group (p=0.002 for albumin and p=0.02 for hemoglobin) Compliance 78±22% of expected for placebo and 72±21% for garlic group.		Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
McCrindle, 2002[75]	Drug	Randomized cross-over trial	To determine the short-term safety and effectiveness of combination drug therapy in children	18 weeks each period	Lipid clinic, Toronto, Canada
McCrindle, 2003[76]	Drug	RCT of drug 20 centers world-wide (US, Canada, Europe, South Africa); open label.	To determine the safety and efficacy of atorvastatin (10 to 20 mg) in children and adolescents with familial hypercholesterolemia (FH) or severe hypercholesterolemia	26 weeks of treatment or placebo, then all subjects recieved 26 weeks of treatment	Children aged 10 to 17 with FH or severe hypercholesterolemia

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
McCrindle, 2002[75]	1. Children between ages 8-18 2. Positive family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease in first-degree relatives 3. Minimum fasting LDL cholesterol level before enrollment > 160.5 mg/dL 4. Participation and compliance in dietary counseling program for at least 6 months. 5. No secondary cause for hyperlipidemia, no major surgery or serious illness within past 3 months.	40 randomized to either colestipol 10grams/day alone or colestipol 5 grams/day +pravastatin 10 mg/day	11 girls, 25 boys median age 14, range 9-18 BMI 22-25 kg/m2
McCrindle, 2003[76]	1. Known FH or severe hypercholesterolemia and LDL-C≥190mg/dL or LDL-C ≥ 160 mg/dL and a family history of FH or documented premature CV disease in a 1st or 2nd degree relative; 2. TG ≤ 400 mg/dL; 3. ≥ Tanner stage II; 4. Not premenarche, pregnant or breastfeeding; 5. Testicular volume > 3cm^3 after age 12; 6. Weight between 10th and 95th percentile for age; 7. No liver or kidney disease; 8. No known sensitivity to statins	187 randomized, 140 to drug 47 to placebo	Atorvastatin group Mean age: 14.1 (2.0) Female gender: 32% Race: W: 94% B: 1.4% A: 1.4% Placebo group Mean age: 14.1 (2.2) Female gender: 28% Race: W: 87% B: 2.4% A: 2.4%

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
McCrindle, 2002[75]	colestipol 10grams/day (10 tablets) alone vs colestipol 5 grams/day (5 tablets) plus pravastatin 10 mg/day (1 tablet) for first 18 week period, followed by 8 week wash-out period and then each group crossed over to the other treatment for the second 18 week period.	Acceptability Compliance LDL, total cholesterol, Apo-B 100, triglycerides	No data reported prior to cross-over. Results as mean change +SD in mg/dL Total cholesterol: -0.63+0.80 for C vs -1.06+1.10 for C+P, p=0.041 LDL: -0.65+.80 for C vs -1.07+1.06 for C+P, p=0.066 HDL: +0.01+0.18 for colestipol vs +0.03+0.13 for C+P, p=0.63 Triglycerides +0.11+0.68 for colestipol vs -0.07+0.72 for C+P, p=0.28 Apo A-1 (g/L) +0.06+0.16 for C vs +0.07+0.13, p=0.81 Apo B-100 (g/L): -0.19+0.24 for C vs -0.26+0.31 for C+P, p=0.48
McCrindle, 2003[76]	After a 4 week baseline/placebo phase in which subjects were instructed to follow the NCEP step 1 diet, those whose LDL-C remained $\geq$ 160 mg/dL and had TG $\leq$ 400 mg/dL at week -2 were randomly assigned in 3:1 ratio to receive 26 weeks double blind treatment with drug (10mg/d) or placebo. Drug could be titrated to 20 mg/d at week 4 for those not at LDL-C $\leq$ 130 mg/dL. Those completing double-blind were eligible to continue treatment for 26 weeks with open label atorvastatin (10 mg/d).	1. Change in LDL-C, total cholesterol, triglycerides, HDL, and apolipoprotein B from baseline to week 26 2. Safety as measured through week 52 by standard blood measurements, safety laboratories, blood pressure, pulse and physical examination	1. LDL-C reduced compared to placebo (-40% vs -0.4%, p<.001). At week 26, change in total cholesterol greater in drug group than in placebo (-32% vs -1.5%; p<.001), as well as changes in triglycerides (-12% vs + 1.0%; p=0.03) and apolipoprotein B (-34% vs +0.7%; p<.001). HDL cholesterol decreased with drug vs placebo (+2.8% vs -1.8%; p=.02). 2. Drug tolerated as well as placebo. Incidence of treatment-related adverse events during double-blind: 7% in drug vs. 4% in placebo group (p=.7) Most adverse effects were mild or moderate. Drug had no effect on sexual development.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
McCrindle, 2002[75]	Symptoms reported at the end of the study in the final preference questionnaire showed that the majority of patients had no symptoms. 18% reported constipation with colestipol vs 0% with the combination vs 3% who had it with both, 12% reported bloating/gas with colestipol alone vs 0% with combination (3% had it with both). 21% had stomach ache with colestipol alone vs 0% with combination vs 0% with both. 11% had headache with colestipol vs 0% with combination vs. 3% with both regimens. 6% had muscle aches on colestipol along vs 3% with combination vs 0% with both regimens.		Poor
McCrindle, 2003[76]	No significant adverse effects documented		Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Obarzanek, 2001[218]	Diet	RCT 6 clinical centers in the USA	To evaluate the long-term safety and efficacy of a cholesterol-lowering diet in children with elevated LDL	4 years; treatment changed at 6 months, 12 months, and at 2 and 3 years.	Prepubertal girls aged 7.8 - 10.1 years and boys aged 8.6 - 10.8 years were recruited from schools, an HMO, and pediatric practices.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Obarzanek, 2001[218]	1. Average of 2 LDL-C values in 80th - 98th sex-specific percentiles for 8 - 10 year old children in a fasting state 2. No medical conditions or medications that could effect growth or serum cholesterol, behavioral problems or onset of pubertal maturation.	663 randomized, 334 to intervention 329 to control	Intervention group Mean age: 9.5 (.74) Female gender: 46% Race: 86.5% of entire study sample white Control group Mean age: 9.5 (.70) Female gender: 44% Race: 86.5% of entire study sample white

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Obarzanek, 2001[218]	Randomized to dietary intervention or control group. Intervention: Dietary behavioral intervention that promoted adherence to a diet with 28% of energy from total fat,< 8% from saturated fat, up to 9% from polyunsaturated fat, and <75 mg/1000 kcal cholesterol per day. Control: Usual care - parents informed child's blood cholesterol high and were given educational materials on heart-healthy eating as available to the public. Annual examinations for study-wide measurements. Intervention: 1st six months: 6 weekly and then 5 biweekly group sessions led by nutritionists and behaviorists, and 2 individual sessions with nutritionist. 2nd six months: 4 group and 2 individual sessions. 2nd and 3rd years: group and individual maintenance sessions held 4 - 6 x/year, with monthly phone contacts between group sessions. 4th year: individualized approach with motivational interviewing and stage of change. 2 group events and 2 individual visits annually, with individual phone contacts "as appropriate".	1. Dietary intake 2. Serum LDL-C, height, serum ferritin 3. Serum total cholesterol, HDL-C, LDL-C/HDL-C, triglycerides, red blood cell folate, serum retinol and zinc, sexual maturation	1. Reductions in dietary total fat, saturated fat were greater in intervention than in control throughout the intervention period (p<.001). Differences in dietary cholesterol intake between intervention and usual care groups were significant at 1, 3, and 5 years (all p<.001), but not at the last visit. At 1 and 3 years energy intake was lower in intervention vs control (p=.01 and p<.0001, respectively) 2. At 1, 3, and 7 years follow-up, intervention had 4.8 mg/dL, 3.3 mg/dL, and 2.0 mg/dL lower LDL-C than control, respectively. Mean adjusted differences between the 2 groups were significant at 1 and 3 years (p<.001 and p<.02, respectively), but not at 5 years (p=.11) or the last visit (p=.25). No significant differences in height or serum ferritin. 3. Total serum cholesterol lower in intervention than usual care at 1 (p<.001) and 3 years (p=.04), but not at 5 or 7 years. HDL-C was higher in control than intervention at 1 year (p=.03), with no difference at years 3, 5 or 7. No differences seen in LDL-C/HDL-C or triglycerides. Serum retinol was higher in the intervention group at 3 (p 7(p=.02) years. There were no other differences between groups in nutritional biochemical measures. There were r differences in weight or measures of sexual maturation, o intake of recommended vitamins and minerals.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Obarzanek, 2001[218]	No differences at any data collection point in height or serum ferritin or any differences in an adverse direction in red blood cell folate, serum retinol and zinc, sexual maturation or body mass index.	Higher proportion of intervention vs control had household income < $20,000 (15.1% vs. 5.9%; p=.002). Secondary analyses suggests this may have effected results. 87.5% participated in final follow-up Only 1.3 of 4 scheduled intervention visits per subject were achieved in the final year. Intention to treat analysis conducted Dietary intake based on self-report and may be biased.	Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Savage, 1986[233]	Exercise	RCT Omaha, Nebraska	To compare the serum lipid and lipoprotein response to identical exercise training in young children and adults.	11 weeks	Subjects recruited by media from Omaha, Nebraska metropolitan area

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Savage, 1986[233]	Inclusion criteria: 1. Prepubescent boys (no pubic hair as confirmed by parents) or adult males ages 30-45. 2. No regular (≥3x/week) aerobic exercise program within the last 3 months. 3. No medical contraindications 4. Medical examination and clearance by a physician within the last year. 5. Non-smoker.	Subjects were randomly divided in to high, low and control groups (n=8 for Low, n=12 for High, n=10 for control).	Ages for boys not listed, all prepubescent

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Savage, 1986[233]	Training consisted of walking/jogging/running 3 times/week for 11 week for a total distance of 1.6 km per session. Participants had a 1 week period of accommodation preceding the training period. Low intensity group had a training HR of 40% VO2 max. High intensity training group had a training HR of 75% VO2 max. Control subjects were requested to maintain their current activity pattern throughout the study.	1. Serum lipids 2. Cardiorespiratory fitness (modified Bruce ETT), VO2 max. 3. Body composition: weight, height, skinfold thickness, body density 4. Dietary intake for 3 days.	For boys only: results as pre-post for low (L), high (H) treatment groups and control (C) mean+sd. HDL/cholesterol (%): Low group decreased 36+3.9 to 28+2.8; High group decreased 40+1.4 to 32+2.0; Control group 32+2.0 to 32+2.3. NS Triglycerides (mg/dL): Low group increased 50+2.1 to 55+3.5; High group increased 53+3.6 to 69+8.6; Control group increased 68+8.1 to 81+5.8. NS LDL (mg/dL): Low group increased 109+20.0 to 123+23.2; High group increased 88+3.8 to 92+3.6; Control group decreased 96+7.8 to 93+8.8. NS All post values were the average of two measurements taken on day 1 and day 2 post-completion of the training regimen. No significantly differences at p=0.05 by ANCOVA.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Savage, 1986[233]	NR		Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Shannon, 1994[220]	Diet	RCT	To assess effects of a home-based, parent-child autotutorial (PCAT) dietary education program on the dietary knowledge, lipid consumption, and plasma LDL of 4 to 10 year old children with elevated plasma LDL-C.	3 month follow-up	Children aged 4 -10 with elevated plasma LDL-C identified through a cholesterol screening program open to those served in 9 pediatric practices in suburban Philadelphia. USA

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Shannon, 1994[220]	1. Age 3.9 - 9.9 years 2. 85% to 130% ideal body weight for height 3. No history of disease that would explain hypercholesterolemia 4. No medications that would affect blood lipids 5. Boys: mean fasting plasma LDL-C 107 - 164 mg/dL. Girls: 112 - 164 mg/dL. Not at risk control group: 1 through 4, and TC at screening test below 60th percentile	342	Average age: 6.3 Girls: 50% Boys: 50% White: 76.8% African-American: 6.75% Other: 2%

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Shannon, 1994[220]	Randomization into(1) Parent-child autotutorial program (PCAT) (n=88), (2) individual dietary counseling (n=86) or (3) at-risk-control groups (n=87) using permuted blocks within strata design with an adaptive allocation procedure to balance 1st order interactions with season and pediatric practice. Adjustment made to select a comparable control group among children "not at risk" (n=81). After initial assessment, PCAT treatment included 10 talking book lessons and follow-up paper and pencil games for children with a manual for parents. Counseling treatment: 45-60 minute session with parent, child and registered dietitian, along with take home print materials for both. Dietitian available for phone to answer questions during 3 month period.	Dietary knowledge Lipid intake Plasma LDL-C level Weight and height	Dietary knowledge scores: increased 3x more in PCAT vs counseling or at-risk control (p<.001). Lipid intake: Mean grams of total and saturated fat decreased in PCAT and counseling and increased slightly in at-risk control (p<.05). At-risk control knowledge and diet did not differ from that of not-at-risk group. Mean LDL-C decline of PCAT (10.1mg/dL) was greater than in at-risk control (4.1 mg/dL) (p<.05). This represents an 8% decline in the PCAT group.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Shannon, 1994[220]	Not Reported	At baseline, mean calorie intake of at-risk control group greater than in other groups ($p<.05$).	Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Stallings, 1993[77]	Diet	Randomized pilot study USA	To determine the effectiveness of a home-based dietary education program vs usual care in LDL, gain in knowledge of heart-healthy eating, and change in consumption of dietary fat	6 months. PCAT is a 10-week lesson program; families got that and nothing else for 6 months. Usual care families got 1 visit with a dietician and nothing else for 6 monhts. Assessments (serum and diet) at 3 and 6 months.	Healthy children aged 4 to 10 with high LDL cholesterol referred to a research center.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Stallings, 1993[77]	1. Plasma LDL between 90th - 99th percentile	44 randomized, 20 to PCAT 24 to usual care	PCAT group Mean age: 8.3 (2.5) Female gender: 40% Race: NR Placebo group Mean age: 7.7 (2.2) Female gender: 42% Race: NR

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Stallings, 1993[77]	After assessment and instruction to parents on use of measurements, randomized to PCAT or Usual Care. PCAT: 10 lessons, 1 per week completed in home by child and parents. Registered pediatric dietitian explained use of the program for self-education. Usual care: 1 hour session with registered pediatric dietitian who provided standardized guidance using an American Heart Association booklet. Assessment at 3 and 6 months	1. Change from baseline in LDL cholesterol response 2. Gain in knowledge of heart healthy eating patterns 3. Change in consumption patterns of dietary fats	1. No differences between groups at each time period; within both groups 3 and 6 month values were different from baseline (p<.01). Both groups maintained a decrease of about 10% over 6 months. 2. Knowledge scores of the 2 groups did not differ during the study. Both groups had increases in knowledge at 3 and 6 months compared to baseline (p< 0.001). 3. Calories: No difference between or within groups at each time period. Total fat: No difference between groups at each time period. Within both groups, 6 month values different from baseline (p<0.05). Saturated fat: No difference between or within groups at each time period. Cholesterol: At 6 months, PCAT lower than Usual Care (p<0.05). Within both groups, 3 month values lower than baseline (p<0.05). At 6 month follow-up, Usual Care higher than at baseline (160 vs 89).

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Stallings, 1993[77]	Not Reported	86% completed 3 month follow-up. 68% completed 6 month follow-up. Drop -out in specific variable data-sets was higher - EG: 66% completed knowledge test at 6 months. High drop-out rate with resulting small N's in many comparisons. Dietary data based on self-report.	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Stein, 1999[78]	Drug	RCT of drug 14 pediatric clinics in the USA and Finland	To assess the lipid-lowering efficacy, biochemical safety, and effect on growth and sexual development of lovastatin in adolescent boys with HeFH	48 weeks	Boys aged 10 - 17 years with HeFH recruited from 14 pediatric outpatient clinics

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Stein, 1999[78]	1. Followed American Heart Association (AHA) pediatric diet for at least 4 months 2. LDL-C 189 mg/dL - 503 mg/dL 3. At least 1 parent had an LDL-C of at least 189 mg/dL not due to secondary causes or LDL-C values were 220 - 503 mg/dL or their LDL-C values were 220 - 503 mg/dL and a parent died of CAD with no available lipid values. 4. No homozygous FH, underlying disorders known to produce secondary LDL-C elevations 5. No disorders affecting triglyceride-rich lipoproteins 6. After the trial began, FDA requested only subjects who had Tanner stage 2 at entry be included in the trial. 7. No delayed puberty shown by testicular volume $\leq$ 3 cm after age 12 8. Weight $\geq$ 32 kg and between 10th - 95th percentile for age	132 randomized, 67 to drug 65 placebo	Lovastatin group Mean age: 13.3 (0.3) Female gender: 0% Race: 93% of all were white Placebo group Mean age: 13.1 (0.3) Female gender: 0% Race: 93% of all were white

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Stein, 1999[78]	All received formal dietary reinstruction, were monitored, and determined to be stable following a AHA pediatric diet for at least 8 weeks before randomization. Placebo was administered week -4 to week 0. All subjects continued diet instruction, monitoring, and evaluation throughout the study. Randomized to drug: Lovastatin, starting at 10 mg/day, with a forced titration at 8 and 16 weeks to 20 and 40 mg/day, respectively. 40 mg/day weeks 25 - 48. Randomized to placebo: Matching placebo tablets	1. LDL-C 2. Growth 3. Sexual development 4. Biochemical, nutritional and endocrine parameters	1. Lovastatin: reductions in LDL-C and total cholesterol at all dosages (p<.001 vs placebo) and in apoB at 40 mg/day. About 6% additional LDL-C lowering occurred with each doubling of lovastatin dosage. No significant changes in HDL-C or triglycerides compared to placebo. No changes in either group in Lp (a). During weeks 24-48, lovastatin reduced LDL-C and apo B 25% and 22%, respectively. No significant changes in other lipids or apoliproteins. 2. Drug had no significant effect on growth parameters at 24 or 48 weeks 3. No difference between drug and placebo in testicular volume, Tanner staging, testosterone, or LH level. DHEAS increased 18% in the drug group compared to 5% in the placebo group. (p=.03) 4. Reduction of tocopherol in drug group at week 48 (p=.002), consistent with decrease in LDL-C. In both groups, increase in ALT from baseline, with no differences between groups at week 48 (p=.20), although increase was significant for each group (drug, P<.001; placebo, P=.008). No consistent changes in AST or CK. Report of infrequent, sporadic, nonsustained CK elevations in response to exercise.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Stein, 1999[78]	1 drug and 2 placebo subjects discontinued due to adverse effects. No clinically significant adverse effects.		Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Stergioulas, 1998[228]	Exercise	RCT Greece	To investigate how physical exercise on a bicycle ergometer influences serum high-density lipoprotein cholesterol and prostacyclin levels	2 months	Sedentary high school boys aged 10 - 14 years recruited from the random population study sample examined in the survey of the Greek Secretariat of Sports in 1993.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Stergioulas, 1998[228]	1. Resident of Peania 2. Lipids and prostanoids between normal concentrations (Szamosi et al) 3. Body weight between normal values (8 -10 kg lower the height)	58 randomized, 38 to exercise 20 to control	Exercise group Mean age: 11.9 (0.5) Female gender: 0% Race: Control group Mean age: 12.1 (0.6) Female gender: 0% Race:

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Stergioulas, 1998[228]	4 month lead-in phase. Randomized to exercise intervention or control. Exercise: 2 month training program with four, 60 minute sessions per week. Sessions included warm-up, stretching, and aerobic exercise at 75% of physical work capacity. Control: No specific training program. Both groups advised not to change dietary habits or physical activity. Blood samples taken at baseline, after 15 days of training, after 1st and 2nd training month, at end of 1st month of detraining.	1. Physical work capacity 2. HDL-C 3. 6-keto-PGF1a concentration	1. Physical work capacity of exercise group increased at the end of treatment ($p<0.001$). No change seen in control group. 2. Exercise group had higher HDL-C at end of the 2nd treatment month ($p<0.005$) and at the end of the detraining period ($p<0.01$). No change seen in control group. 3. Exercise group had higher 6-keto-PGF1a concentration at end of 2nd treatment month compared to baseline ($p<0.001$) and lower 6-keto-PGF1a concentration at end of the detraining period compared to the end of the 2nd treatment month ($p<0.001$). No change seen in control group.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Stergioulas, 1998[228]	None reported.	Very high attrition/drop-out rate: intervention 20/38 (53%) dropped control 10/20 (50%) dropped. Detraining period not defined. Four month lead-in phase not described. No analyses of between group differences.	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Tonstad, 1996[80]	Drug	Double-blind RCT of colestipol 10g once per day or 5 g twice per day versus placebo	Effectiveness of colestipol in treating FH.		67 adolescents Norway

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Tonstad, 1996[80]	Adolescents age 10-16 referred to lipid clinic; all had two or more TC ≥239.75 mg/dL and TG≤116.01 mg/dL.	74 targeted, 67 agreed to participate	37 boys (58%); 29 girls mean age 13.2 Tanner stage 2.6

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Tonstad, 1996[80]	All subjects instructed to follow a diet: 30% calories from fat; <10% from saturated fat and <200 mg cholesterol/day. Assessed with 4 day weighed food record. Subjects randomized to drug treatment got either colestipol 10g once per day or 5g twice per day x 8 weeks. Open label trial after 8 weeks in which placebo group started colestipol for 52 weeks; colestipol group continued on colestipol.	1. Fasting TC, TG, HDL, calculated LDL, apolipoproteins A-I and B, serum carotenoids. 2. Compliance 3. Diet 4. Growth	After 8 weeks: 1. TC decreased by 14% in colestipol (8.16±1.47 pre vs. 6.99±1.46 post) vs 1% in placebo (7.69±1.26 pre vs 7.57±1.34 post), p≤0.01; LDL decreased by 19.5% in colestipol (6.58±1.3 pre vs 5.27±1.29 post) vs 1% in placebo (6.13±1.18 pre vs. 6.01±1.32 post), p≤0.01. HDL was not significantly different (colestipol 1.12±0.25 pre vs 1.19±0.35 post vs placebo 1.12±0.20 vs 1.18±0.23). TG were not significantly different (colestipol 0.99±0.61pre; 1.15±0.90 post vs placebo 0.96±0.66 pre vs 0.84±0.36 post). 2. Compliance was 68% in colestipol group vs 76% in placebo group NS. 3. intakes of major nutrients and vitamins were similar in the groups 4. Linear growth velocity was within reference range for Norwegian adolescents. 1 patient lost ≥1 kg during the study (24.5 kg/m2 pre and 21.3 kg/m2 post).

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Tonstad, 1996[80]	Total of 7 subjects dropped out 4 in colestipol; 3 in placebo. 5 patients dropped out because they refused to swallow the drug; 2 dropped out because they had unexpectedly low lipid concentrations at randomization. 8 girls did not agree to continue in the open phase. Of 51 in open phase, 42 completed 1 year. 8 subjects in colestipol group had GI side effects attributed to the drug: 2 had constipation that improved with temporary dose reduction; 1 had dyspepsia and 1 had flatulence throughout entire study; 2 had intermittent nausea, 1 had temporary decrease in appetite; 1 had abdominal pain improved with dose reduction.	placebo group was older and more advanced Tanner stage ($p<0.05$)	Poor

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Tonstad, 1996[81]	Drug	Random assignment to double-blind comparison Norway	To determine the efficacy and safety of cholestyramine therapy in young children with familial hypercholesterolemia	2 years: 1 year of diet for everyone; 1 year randomized treatment phase	Boys aged 6 to 11 years and girls aged 6 to 10 years with familial hypercholesterolemia in a referral lipid clinic

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Tonstad, 1996[81]	1. Familial hypercholesterolemia diagnosed if TC > 260 mg/dl and triglyceride levels < 200 mg/dl, if 1 parent had baseline cholesterol ≥ 300 mg/dl and triglyceride levels < 200 mg/dl, or tendon xanthoma, or if autosomal dominant inheritance present in other members. 2. Prepubertal girls aged 6 - 10, and prepubertal boys aged 6 - 11 who completed an initial medical evaluation and dietary session and had a parent who understood the diet. 4. Height velocity score standard deviation score > -2.0. 3. Those taking lipid-lowering drugs were required to discontinue doing so at least 4 weeks before study start 4. Secondary hyperlipidemia ruled out by clinical and lab examination.	96 randomized, 36 to drug 36 to placebo	Drug group Mean age: NR Female gender: 44% Race: NR Placebo group Mean age: NR Female gender: 33% Race: NR

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Tonstad, 1996[81]	After 1 year of a low-fat, low-cholesterol diet, children with LDL $\geq$ 190 mg/dl or $\geq$ 160 mg/dl in the presence of familial premature cardiovascular disease were randomly assigned to a double-blind comparison of 8 gm cholestyramine or placebo for 1 year. Dieticians reinforced the diet at each visit. Dietary composition assessed by a 7 day record, evaluated by FIBER. Assigned dose 8 gm/day, following 1 week build-up phase of 4 gm/day. Follow-up visits scheduled after 2, 5, 7, 9 and 12 months. Compliance assessed by counting leftover packages at each visit.	1. Serum LDL 2. Height velocity 3. Erythrocyte folate 4. Total plasma homocysteine 5. Serum fat-soluble vitamins 6. Side-effects	1. Serum cholesterol decreased in drug group vs placebo after 2, 9 and 12 months ($p<0.001$) LDL decreased by -16.9% to -18.6% vs 0 to 1.5% ($p=0.0001$). Change in HDL level was no significant, and mean triglyceride levels remained unchanged in both groups. Apolipoprotein B levels were reduced in drug vs placebo groups ($p=0.0001$). 2. No difference in mean height velocity standard deviation scores in those who hadn't started puberty 3. No significant differences reported 4. Total homocysteine level increased in drug group, and was negatively correlated with levels of erythrocyte and serum folate after 1 year. 5. In drug group vs placebo, mean levels of 25-hydroxyvitamin D decreased ($p=0.04$) 6. In drug group, one girl had low folate and elevated homocysteine levels, and there was one case of intestinal obstruction caused by adhesions

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Tonstad, 1996[81]	In the drug group, folate defiency occurred in one subject, in whom the total homocysteine level increased concurrently. With the exception of modest decreases in levels of vitamin D during the winter, other nutritional deficiencies were not observed. No adverse effects on growth and bone age evident.	1. High attrition: only 22/36 (61%) in drug group and 26/36 (72%) in placebo completed the study. 2. Only about half the children were able to take cholestyramine in the amount prescribed, primarily because of unpalatability.	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Walter, 1985[222]	Diet and exercise combination	Randomized trials of school-based interventions	To assess the feasibility and effectiveness of a curriculum focused on nutrition, physical fitness, and smoking prevention in elementary schools	5 years	2,283 4th graders from 22 elementary schools in the Bronx, NY.

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Walter, 1985[222]	Assume all children at each school were eligible	1,563 (68.5% participated in baseline examination. 1,115 of these (71.3%)were available at 1 year for follow up assessments. Final n: 805 intervention and 310 control	mean age=9.1 years male 51.4% race: black 48.9% Hispanic 23.2% white 24.6% 3.3% other (Asian or Pacific origin primarily) median family income $22,126

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Walter, 1985[222]	Intervention schools received the "Know Your Body" curriculum each year starting in 4th grade and continuing until 8th grade; taught in usual classroom by regular teacher 2 hours/week for entire school year. Teachers trained by research staff in 3 half-day teacher workshops on curriculum implementation. Adherence to teaching protocols monitored by classroom visits from research staff and attendance at training workshops. Curriculum based on social learning, encouraging adoption of healthy behaviors: AHA prudent diet/AHA Committee Report (1978); regular exercise program; resisting social pressures to smoke. Curriculum materials included: teacher guides, student workbooks and worksheets, health passports, videotapes, posters and calendars.	1. HDL, TC 2. Serum thiocyanate ponderosity index (derived from height and weight measurements) 3. Triceps skinfold thickness 4. Post-exercise pulse recovery rate (recovery index). 5. Systolic and diastolic BP	1. Plasma TC: control (170.1 mg/ml±25.6 at baseline vs 171±28.3 at 1 year; intervention 173.3±26.6 at BL vs 172.7+27.7 at year 1). This is a 0.4% decrease in the intervention group compared with 0.5% increase in control group. 2. Plasma HDL: control 56.8±12.8 at BL vs 60.5+12.3 at 1 year; intervention 54.4±11.3 at BL vs 59.5±13.5 at 1 year. 3. TC/HDL ratio control 3.1±0.8 at BL vs 2.9±0.7 at 1 year; intervention 3.3±1.2 at BL vs 3.0±0.8 at 1 year. Adjusting for age, gender, race and BL risk factor level, TC difference between Intervention and Control groups at 1 year was -3.1 (p=0.032); HDL difference was +1.0 (p=0.175); ratio difference was -0.10 (p=-0.063). Intervention was successful in reducing systolic and diastolic BP.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Walter, 1985[222]	Significant impact on the classroom teacher (time away from usual material)	Screening for risk factors was also done in control school children.	Fair

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Wheeler, 1985[82]	Drug	DB randomized cross-over trial	To evaluate the use of benafibrate for lower cholesterol in children.	6 months: 3 month arm of either placebo or medication.	14 children with FH
Wiegman, 2004[37]	Drug	RCT of drug Netherlands	To determine the 2-year efficacy and safety of pravastatin therapy in children with familial hypercholesterolemia (FH)	2 years	FH children ages 8 to 18 recruited from academic medical referral setting

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Wheeler, 1985[82]	Diagnosis of FH established by TC>259.09 mg/dL, a type IIa pattern on lipoprotein electrophoresis and normal fasting TG (<58 mg/dL) in the patient; with either similar lipoprotein abnormalities in one of the parents or premature CHD death in a parent and a similar lipid abnormality in another close relative.	14 children; all had previously been treated with dietary measures (inadequate to control cholesterol), had been recommended cholestyramine but refused to take it.	NR
Wiegman, 2004[37]	1.Parent with clinical or molecular diagnosis of FH; 2.Two fasting samples with LDH-C levels of 155 mg/dL or more and triglyceride levels below 350 mg/dL; 3.Adequate contraception for sexually active girls; 4. No drug treatment for FH or use of plant sterols; 5. No homozygous FH; 6. No hypothyroidism; 7. No abnormal levels of muscle or liver enzymes.	214 randomized, 106 to drug 108 to placebo	Pravastatin group Mean age: 13.0 Female gender: 57% Race: NR Placebo group Mean age: 13.0 Female gender: 57% Race: NR

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Wheeler, 1985[82]	1. Children asked not to change their diets 2. 10-20 mg/kg/day given bid (in 100 mg tablets) given for 3 months	1. TC, HDL, TG 2. Urine bezafibrate to assess compliance.	1. Mean plasma TC on bezafibrate was 22% lower than while on placebo (7.8±1.0 vs 10.0±1.6, p<0.0001) and 16% lower than in the period before the trial (7.8±1.0 vs. 9.3±1.5,p<0.001). 2. Mean HDL rose 15% while on bezafibrate compared with placebo (p<0.01); increased 25% compared with pre-trial values (p<0.001). 3. Mean plasma TG fell 23% while on bezafibrate compared with placebo (pNS), and 33% compared with pre-trial values (p<0.05). 4. In all but one case bezafibrate was detected in the urine on all measurements during the active drug phase, and in none of the measurements while on placebo.
Wiegman, 2004[37]	After initiation of a fat restricted diet for 3 months or more and encouragement of regular physical activity, randomized to pravastatin 20 - 40 mg/day or placebo. Evaluated every 6 months for 2 years.	1. Change from baseline mean carotid IMT 2. Growth, maturation and hormone level measurements 3. Changes in muscle and liver enzyme levels	1. Pravastatin: trend toward regression, mean [SD], -0.010 [0.48]mm; p=.049. Placebo: trend toward progression, 0.005 [0.044]mm;p=.28. Mean change in IMT between the groups significant, p=.02. Greater reduction in mean LDL with pravastatin vs placebo (-24.1% vs 0.3% respectively, p<.001. 2. No differences observed in growth, endocrine function parameters, Tanner staging scores, onset of menses or testicular volume. 3. No differences observed in muscle or liver enzyme levels.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Wheeler, 1985[82]	1. One child had high alk phosphatase at the end of 3 months of bezafibrate (had a slight intercurrent infection, and values returned to normal) 2. Another child had slight transient rise in alanine transaminase during first 2 months on bezafibrate but values were normal by end of 3rd month 3. growth was satisfactory throughout trial 4. no other reports of adverse effects	All children declared a strong preference for this drug as compared with cholestyramine used previously. No results prior to cross-over. No wash out period between cross over periods.	Poor
Wiegman, 2004[37]	No significant differences between groups for "all endocrine functionp arameters." In the placebo group, 1 child developed extreme CPK elevation which returned to normal 1 week after stopping the study regimen. In the placebo group, AST elevation (more than 3-fold) occured twice. Elevations in CPK occured 4 times in the treatment group and three times in the placebo group. "No adverse effects on growth, sexual maturation, hormone levels, or liver or muscle tissue."	2 year follow-up Well-designed	Good

Evidence Table 4. RCTS of Treatment

Author, year	Type of Intervention	Type of Study/ Setting	Aims	Duration of Trial	Population/ Setting
Williams, 1995[229]	Diet	Randomized single blind trial of psyllium	to compare fiber enriched Step I diet to usual Step I diet to lower cholesterol in children with borderline high and high blood cholesterol levels	12 week	Children ages 2-11 referred to lipid clinic

Evidence Table 4. RCTS of Treatment

Author, year	Main eligibility criteria	Enrolled	Demographics
Williams, 1995[229]	Serum cholesterol >170 mg/dL and LDL >110 mg/dL	58 children	5% of children had a parent and 52% had a grandparent with premature onset of CHD (<55 yrs); 48% had a parent with blood cholesterol >200 mg/dL

Evidence Table 4. RCTS of Treatment

Author, year	Interventions	Outcomes Assessed	Results
Williams, 1995[229]	Age 2-11 years (mean age in Step I group 94.7mo (n=24); in fiber group 82.5mo n=26)	1 box of cereal per day x 1st 3 weeks, then 2 boxes/day. Children age 2-5 consumed only 1 box/day throughout study. Fiber group cereal contained 3.2 g soluble fiber per serving; control cereal contained 0.5 g soluble fiber per serving. Both identical boxes, manufacturer.	Lipoprotein results n=50; anthropometric and lipid results N=49. After 12 weeks: 1. TC 196 mg/dL step I (-5.5%) vs 197mg/dL (-9.6%) fiber group; p<0.05 between groups, p<0.01 within Step I, p<0.001 with fiber. 2. HDL 49.6+8.8 mg/dL step I (+1.5%) vs 45.01+13.57mg/dL (+4%) fiber group, NS between groups or within groups. 3. LDL 124.3+25 step I (-6.4%) vs. 126.76 (-15.7%); p<0.001 between groups, NS change in step I group, p<0.01 for change in fiber group. 3. TG 113.9+47 mg/dL step I (-15.3%) vs 128.9+55mg/dL (-8.9%) fiber group (p<0.001 between groups; NS change within groups) 4. TC/HDL and LDL/HDL ratios also had significant improvements (-17.9% and -21.1% respectively) in the fiber group vs -4.7% and -7.4% in Step I group, P<0.001 for between group difference.

Evidence Table 4. RCTS of Treatment

Author, year	Adverse Effects	Comments	Quality Rating
Williams, 1995[229]	Growth velocity, height, weight skinfold thickness and BMI were monitored and no differences between treatment and control group were noted.	Authors state that 8 children who did not complete the study were no significantly different than the remaining 50.	Poor

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Statins				
Clauss, 2006[38]	Lipid-lowering Effects of Lovastatin in Post-menarchal Girls with heterozygous Familial Hypercholesterolemia	RCT in Post-menarchal girls with heFH	NR	24 weeks
Couture, 1998[66]	Association of specific LDL receptor gene mutations with differential plasma lipoprotein response to simvastatin in young French Canadians with heterozygous familial hypercholesterolemia	RCT Laval University Lipid Research Clinic, Quebec City, Canada	To determine whether the nature of the LDL receptor mutation affects the response to simvastatin. To describe the different responses to simvastatin of plasma lipids, lipoproteins, and apoprotein levels among 3 genetically differentiated groups of heterozygous FH children and adolescents.	6 weeks
de Jongh, 2002a[68]	Early statin therapy restores endothelial function in children with familial hypercholesterolemia	RCT with an additional arm of non-FH controls. USA.	To determine whether simvastatins improves endothelial function in children with familial hypercholesterolemia (FH)	28 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Statins			
Clauss, 2006[38]	HeFH; baseline LDL required was 160-400 mg/dL and parental history of familial hypercholesterolemia.	54 girls ages 10-17 at least 1 years post-menarche	-
Couture, 1998[66]	1. Heterozygous FH patients with 1of 3 mutations in the LDL receptor gene. 2. Aged 8 - 17 3. Weight $\geq$ 27 kg 4. Plasma levels persistently above 95th percentile for age and sex while maintaining a lipid-lowering diet. 5. No concomitant conditions, such as diabetes, anorexia, thyroid disorders	63 FH patients at university research clinic	37 boys and 26 girls
de Jongh, 2002a[68]	Children with heterozygous FH as defined by: 1. LDL>95 percentile for age/gender; 2. Documented family history of hyperlipidemia with LDL>95 percentile for age/gender after treatment; 3. Personal diagnosis by detection of mutation at the LDL receptor gene	50 heterozygous FH children plus 19 non-affected controls. 28 in FH simvastatin group, 22 in FH placebo group, 19 non-FH controls.	HeFH patients ages 9-18. FH simvastatin group Mean age: 14.6+2 Female gender: 13 (42%) Race: NR. FH placebo group Mean age: 14.6+2.5. Female gender: 11 (50%) Race: NR.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Statins		
Clauss, 2006[38]	Lovastatin 20 mg for 1st 4 weeks, then 40 mg thereafter	"Adverse reactions to lovastatin were generally mild and transient." Patients treated with lovastatin had an adverse experience profile generally similar to that of patients treated with placebo. In this limited controlled study, there was no detectable effect on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on lovastatin therapy."
Couture, 1998[66]	Individual screening with medical history, physical exam, interview with dietician, and blood sampling 6 weeks prior to study entry. All lipid-lowering medications discontinued at screening entry. Four weeks placebo run-in, followed by randomization to double-blind active treatment, 20 mg/d simvastatin or placebo for 6 weeks at 3:1 ratio. Compliance verified by tablet count at weeks 0, 2, 4, and 6. Patients questioned about adverse or unusual signs or symptoms at all clinic follow-up visits (weeks 0, 2, 4, and 6). Patients counseled by dietician to follow American Heart Association phase I diet throughout trial. Routine hematology and blood chemistry test results were obtained at week -6 and 6.	Patients were questioned about any adverse or unusual signs or symptoms, but none were suggested. Compliance to the prescribed medication was assessed weekly by tablet counting, and there was no significant difference in compliance among the mutation groups.
de Jongh, 2002a[68]	50 heterozygous FH children randomized to simvastatin or placebo in 3:2 ratio. An additional 19 healthy non-FH siblings also used as controls.	There were no significant differences with regard to safety measurements (ALT, AST, and CK) between simvastatin and placebo FH groups, and no adverse events were reported.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Statins		
Clauss, 2006[38]	NR	
Couture, 1998[66]	NR	
de Jongh, 2002a[68]	Not reported.	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
De Jongh, 2002b[69]	Efficacy and safety of statin therapy in children with familial hypercholesterolemia	Double-blind, placebo controlled multi-center RCT 9 international sites	To evaluate LDL-cholesterol-lowering efficacy, overall safety, tolerability and the influence of growth and pubertal development of simvastatin in a large cohort of boys and girls with heterozygous familial hypercholesterolemia (heFH).	48 weeks of intervention after 4 week run-in
De Jongh, 2003[70]	Quality of life, anxiety and concerns among statin-treated children with familial hypercholesterolemia and their parents	Cross-sectional study; lipid clinic, Amsterdam	To determine whether statin therapy influenced the quality of life and anxiety levels of the FH children and their parents, and to assess the specific FH-related concerns of these families.	0 (cross-sectional survey)
Dirisamer, 2003[70]	The effect of low-dose simvastatin in children with familial hypercholesterolemia: a 1-year observation	Single-center, open-label, diet-controlled study.	To investigate the efficacy and safety of low-dose simvastatin for 1 year in children and adolescents (aged 10-17) with FH. Safety assessment included weight, height, and lab values.	18 months: 3-month diet, followed by drug therapy

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
De Jongh, 2002b[69]	1. Age 10 - 17 2. LDL-C 4.1 - 10.3 mmol/L 3. Parent with confirmed diagnosis of heFH. 4. Boys: Tanner stage II or above Girls: postmenarchal for at least 1 year before study initiation Exclusion: familial hypercholesterolemia, secondary hyperlipidemia	173	98 boys and 75 girls
De Jongh, 2003[70]	Children who had received 1 year of statin therapy and their parents were recruited from the Paedriatric Lipid Clinic of the Emma Children's Hospital of the University of Amsterdam. Inclusion criteria: age 10-18 y, LDL >158 before statin therapy and one parent diagnosed with FH.	69 children from 51 families	Mean age 15.3 47.8% female
Dirisamer, 2003[70]	Boys and girls aged 10-17 with LDL >190 and a BMI between 5th and 85th percentile for age were included.	20	Mean age 13.0, range 10-17 60% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
De Jongh, 2002b[69]	After 4 week placebo/diet run-in, randomization to active treatment or matching placebo in 3:2 ratio and stratified by sex. Simvastatin (drug) started at 10mg/day and increased at 8 week intervals to 20 and then 40 mg/day for the remainder of the study (period 1, 24 week duration) and for a 24 week extension (period 2). Office visits every 4 weeks. Menstrual cycle monitored throughout study period and Tanner staging used to assess pubertal development.	223 assessed for eligibility, 175 randomized - 69 to placebo, 106 to control. 5 of placebo discontinued: 1 lost to follow-up, 2 withdrew consent, 2 for other reasons. 5 of drug discontinued: 1 to mononucleosis, 1 to protocol deviation, and 3 to consent withdrawal. No serious AEs. Total drug group clinical AEs included: abdominal pain (3), chest pain (1), flatulence (1), myalgia (2), headache (4), sleep disorder (1), weight gain (1), pruritus (1). Total drug group lab AEs: increased ALT (3), increased AST (3), increased CK (1). No deleterious effects on growth or pubertal development.
De Jongh, 2003[70]	Children had been treated with statins for 1 year prior to the study. The children and their parents were administered questionnaires during a visit to the Lipid Clinic while an investigator explained the questionnaire and stayed in the room. The instruments used: the NO AZL Children's Quality of Life (TACQoL), the Trait Anxiety Inventory for children, and a specific FH survey. A random sample of 200 healthy Dutch children aged 12-16 served as a control for the TACQoL and Trait Anxiety Inventory surveys.	There were no significant differences between the children with FH and their healthy peers on the health-related quality of life and anxiety questionnaires.
Dirisamer, 2003[70]	Simvastatin dosage begin at 5 mg/day for patients with LDL < 220, and 10 mg/day for patients with LDL >220. If a range for LDL of 150-170 was not reached within the first 8 weeks, the daily dosage was increased stepwise up to 20 mg/day. Safety was assessed at follow-up visits every 4-8 weeks. Each time patients were questioned about any adverse or unusual signs or symptoms. Lab parameters include routine hematology and biochemistry, including blood urea nitrogen, creatinine, electrolytes, total protein, albumin, fasting glucose, complete blood count, AST, ALT, alkaline phosphatase, CK, and total and direct bilirubin.	3 patients had abnormal levels of safety parameters: 2 patients (one receiving 5 mg/day and the other 10 mg/day) showed slightly higher values of CK. One (10 mg/day) expressed transiently elevated concentrations of ALAT (GPT) and GCT. Two boys (one 5 mg/day and the other 10 mg/day) suffered from headache in the morning of the first days treatment but which disappeared after a couple of days. One girl (5 mg/day) reported myalgia for about 2 weeks. Two other patients (one male 10 mg/day, one female 5 mg/day) had gastrointestinal complaints, which both resolved after 2 days without changing the medication. There was no difference in mean BMI between baseline and 1 year.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
De Jongh, 2002b[69]	101/106 drug completed period 1 and 83/106 completed period 2 (78%). 56/69 placebo(81%) completed period 2.	
De Jongh, 2003[70]	Not reported.	Methods of data collection of control subjects was not adequately described.
Dirisamer, 2003[70]	"Simvastatin was well tolerated. Side-effects were few and equally distributed among the three dosage periods."	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Ducobu, 1992[243]	Simvastatin use in children	Open-label	To describe the long-term efficacy and safety data (24-36 months) in 32 hypercholesterolemic children younger than 17 years.	24-36 months
Hedman, 2003[240]	Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia	Open-label clinical follow-up trial Finland	To determine the single-dose pharmacokinetics and the lipid-lowering effect and safety of short-term use of pravastatin in children with heterozygous FH.	8 weeks
Knipscheer, 1996[71]	Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia	double-blind, randomized placebo controlled study, children stratified by age. 4 arms (3 doses of pravastatin, 1 placebo) Lipid clinic, The Netherlands	To assess the safety, tolerability and efficacy of pravastatin for HeFH	12 weeks, following an 8 week diet and placebo run-in period.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Ducobu, 1992[243]	Male or female children with total cholesterol >300 mg/dL after diet therapy for 6 months.	32	Age <17 22 (68.8%) male 10 (31.2%) female
Hedman, 2003[240]	1. Age 4 or older 2. Total serum cholesterol > 6 mmol/L despite dietary interventions 3. Diagnosis of FH confirmed by LDL receptor mutation analysis or lymphocyte test 4. Healthy, with no use of cholesterol lowering medication before study	20	13 girls and 7 boys with heterozygous FH. Age range: 4.9 - 15.6 years.
Knipscheer, 1996[71]	Children with "known heterozygous FH" were eligible. HeFH defined as plasma LDL above 95th percentile for age and sex during lipid-lowering diet AND hypercholesterolemia in siblings, parents or grandparents, or clinical manifestations of premature atherosclerosis prior to age 50 in 1st/2nd degree relatives. Exclusions: 1. Major surgery within the past 3 months 2. Use of medications interfering with lipid metabolism (anticonvulsants, oral contraceptives, corticosteroids, fibric acid derivatives or immunosuppressants). 3. Hepatic or renal dysfunction	72 children with HeFH	25 male; 47 female 66/72 White; 5/72 Black. Mean age 11.9-12.1 across 4 groups.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Ducobu, 1992[243]	Children under age 10 started simvastatin at an initial dose of 5 mg/day. Titration to 10 mg daily after 4 weeks and to 20 mg after another 4 weeks was possible. Older children began on 10 mg/day, increased to 20 mg/day after 6 weeks, and if necessary to 40 mg/day after an additional 6 weeks. Mean dose: 16 mg/day.	Transaminases, alkaline phosphatase, and creatinine phosphokinase were measured at weeks 4, 12, 26, 52, 78, and 104, No significant changes were detected. Transient increases in 1 transaminase, and 2 CPK measurements. Growth: Children for whom height (n=12) and weight (n=16) were available remained in the growth percentages they had been in at baseline.
Hedman, 2003[240]	10 mg pravastatin orally per day for 8 weeks.	Few transient adverse events. No increase in serum alanine aminotransferase, creatine kinase, or creatinine. Adverse events reported in questionnaires: abdominal pain (1), loose stools (1), headache (4), sleep disturbance (2), muscle tenderness or pain in rest (1), muscle tenderness or pain associated with physical training (1). All symptoms mild and disappeared during first 4 weeks of treatment.
Knipscheer, 1996[71]	Pravastatin 5, 10 and 20 mg/day	Total number adverse events P- 9, 5 mg/day - 3, 10 mg/day - 6, 20 mg/day - 1. List: rash, fatigue (P only), nose bleeding, headache, diarrhea (P only), dyspepsia (P only), nausea/vomiting, abdominal pain, myalgia (P only). Laboratory safety measurements did not show significant changes in any of the groups between the end of the treatment period and baseline. However CK abnormal in 8 of P , 6 of 5mg/day, 11 of 10 mg/day and 8 of 20 mg/day. Cortisol abnormal in 2 of P, 2 of 5 mg/d, 5 of 10 mg/d, 3 of 20 mg/d.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Ducobu, 1992[243]	Author states "well tolerated"	This study was published only as a letter
Hedman, 2003[240]	Author states "well-tolerated without any clinical significant side effects"	Duration only 8 weeks. Dose too low to achieve therapeutic response except for 2 patients - therefore, AE's associated with a therapeutic dose were not adequately assessed.
Knipscheer, 1996[71]	Compliance was 93%	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Lambert, 1996[72]	Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin	RCT of drug multicenter: 6 sites in Canada Boys aged 17 or younger with heterozygous FH	To determine the efficacy, safety and tolerance of short-term administration of lovastatin in a male pediatric population with severe FH, and to evaluate dose-response relationship.	8 weeks
McCrindle, 2003[76]	Efficacy and safety of Atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial	RCT of drug 20 centers world-wide (US, Canada, Europe, South Africa) Children aged 10 to 17 with FH or severe hypercholesterolemia	To determine the safety and efficacy of atorvastatin (10 to 20 mg) in children and adolescents with familial hypercholesterolemia (FH) or severe hypercholesterolemia	26 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Lambert, 1996[72]	1. Weight 27 kg or more 2. Plasma LDL above 95th percentile for age while on lipid-lowering diet 3. History of unsuccessful treatment with bile acid-binding resins 4. Family history of atherosclerosis at or before age 50 5. Documented family history of hyperlipidemia with LDL > 95th percentile for age and sex before treatment or a personal diagnosis of FH substantiated by LDL receptor activity or mutation. 6. No significant concomitant conditions 7. Weight and height not 3 - 97th percentile for age	69 randomized, 17 to 10 mg/day group 18 to 20 mg/day group 19 to 30 mg/day group 15 to 40 mg/day group	10 mg/day group Mean age: 12.5 (2.4) Female gender: 0 Race: 94.1% white 20 mg/day group Mean age: 12.7 (1.6) Female gender: 0 Race: 100% white 30 mg/day group Mean age: 13.3 (2.7) Female gender: 0 Race: 94.7% white 40 mg/day group Mean age: 12.9 (2.7) Female gender: 0 Race: 93.3% white
McCrindle, 2003[76]	1. Known FH or severe hypercholesterolemia and LDL-C>190mg/dL or LDL-C > 160 mg/dL and a family history of FH or documented premature CV disease in a 1st or 2nd degree relative; 2. TG < 400 mg/dL; 3. >Tanner stage II; 4. Not premenarche, pregnant or breastfeeding; 5. Testicular volume > 3cm3 after age 12; 6. Weight between 10th and 95th percentile for age; 7. No liver or kidney disease; 8. No known sensitivity to statins	187 randomized, 140 to drug 47 to placebo	Atorvastatin group Mean age: 14.1 (2.0) Female gender: 32% Race: W: 94% B: 1.4% A: 1.4% Placebo group Mean age: 14.1 (2.2) Female gender: 28% Race: W: 87% B: 2.4% A: 2.4%

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Lambert, 1996[72]	After pre-study visit and lab tests, all lipid-lowering medications were discontinued at least 8 weeks before study start, with no lipid-lowering therapy allowed other than that permitted by study protocol. Placebo given weeks -4 to 0, followed by randomization to double-blinded active treatment of lovastatin at 10, 20, 30 or 40 mg/day for 8 weeks. Medication dispensed at weeks -4, 0, and 4. Compliance verified by tablet count at weeks 0, 4 and 8. Clinic follow-up visits at weeks -4, -2, 0, 2, 4, 6, and 8. Complete physical exam at weeks 0 and 8. Ophthalmologic exam during placebo period and within 8 weeks of study exit. Patients continuously counseled by dietician to follow lipid-lowering diet throughout the trial. Daily food records completed by patients for 3 consecutive days and reviewed by a dietician at weeks -4, 0, 4, and 8.	No serious clinical adverse effects reported. Three patients had > asymptomatic elevations in creatine kinase, which spontaneously returned to normal, with no action required regarding the drug.
McCrindle, 2003[76]	After a 4 week baseline/placebo phase in which subjects were instructed to follow the NCEP step 1 diet, those whose LDL-C remained > 160 mg/dL and had TG < 400 mg/dL at week -2 were randomly assigned in 3:1 ratio to receive 26 weeks double blind treatment with drug (10mg/d) or placebo. Drug could be titrated to 20 mg/d at week 4 for those not at LDL-C < 130 mg/dL. Those completing double-blind were eligible to continue treatment for 26 weeks with open label atorvastatin (10 mg/d).	No significant adverse effects documented. Incidence of treatment-related adverse events during double-blind: 7% in drug vs. 4% in placebo group (p=.7) Most adverse effects were mild or moderate. Drug had no effect on sexual development. Labs: 1% on atorvastatin had elevated AST, and 1% had elevated ALT.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Lambert, 1996[72]	Drug well-tolerated. 85% of patients took at least 70% of the prescribed dose during the active treatment period.	No separate control group: patients served as own controls
McCrindle, 2003[76]	Drug tolerated as well as placebo.	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Sinzinger, 2004[242]	Professional athletes suffering from familial hypercholesterolemia rarely tolerate statin treatment because of muscular problems.	Descriptive study in professional athletes with FH; Austria	To monitor the experiences of 22 adolescent and young-adult professional athletes with FH, in whom treatment with statins was attempted.	8 years
Stefanutti, 1999[244]	Diet only and diet plus simvastatin in the treatment of heterozygous familial hypercholesterolemia in childhood	Non-randomized controlled trial	To investigate the effect of hypolipidemic treatment - low cholesterol diet only (group A) or diet plus 10 mg/day simvastatin (Group B).	12 months

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Sinzinger, 2004[242]	Patients were considered as professional athletes when they had attended an Austrian championship at any age class during the last 2 years or were playing gin the top two leagues of their respective discipline. All were suffering from FH as diagnosed at the receptor level. Testing for anabolic steroids was done in all athletes to exclude any possible influence.	22	Mean age 24.1 (range 15 - 27) 31.8% female
Stefanutti, 1999[244]	Pediatric patients with heterozygous FH	16	Age 7-12, mean 8.75 7 (44%) males 9 (56%) females

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Sinzinger, 2004[242]	No drugs including vitamins were taken for at least 4 weeks. The lowest available dose of statin was used as a starting dose. Subjects were given atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin. Switching patients who tolerated a statin occurred only if they did not achieve target values. The shortest duration of treatment before switching was 8 weeks. Safety was assessed by blood samples for CK and liver enzymes (GOT, GPT, gamma-GT) drawn regularly	Among 87 periods of attempted statin therapy, the treatment was tolerated only 16% of the time. Muscle pain (weakness, cramps, aches, others) was reported in 84% of periods of statin therapy. The mean time of onset of muscle pain was 8.3 days (range 2 to 18 days). Only two of the 22 subjects tolerated each of four statins (lovastatin, pravastatin, atorvastatin, and simvastatin. Two other patients tolerated atorvastatin and fluvastatin, but experienced muscle pain on lovastatin, pravastatin, and simvastatin. Three patients had elevated CK with one or more statins. An increase in liver enzymes was not observed in any of the athletes.
Stefanutti, 1999[244]	Patients were submitted to a 3-month washout (free diet). Then they were given an AHA Step 2 diet for 6 months: cholesterol <=200 mg/day, saturated fats <=10% of calories, total fats <=30% of total calories. After 6 months they were divided in two groups, matched for sex, age, and body mass index: Group A (n=8) received only the diet. Group B (n=8) was given 10 mg/day simvastatin. Followup lasted 1 year for both groups.	No adverse effects were observed during the therapeutic approach with diet, and with diet plus simvastatin, on relatively long-term treatment.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Sinzinger, 2004[242]	When initiating a statin therapy, only 3 out of 22 athletes (11%) tolerated the chosen drug. Another 3 patients tolerated at least one statin. Only two athletes tolerated all the statins used.	
Stefanutti, 1999[244]	Patients showed good compliance with the treatment.	Small sample size

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Stein, 1999[78]	Efficacy and safety of Lovastatin in adolescent males with heterozygous familial hypercholesterolemia	RCT of drug 14 pediatric clinics in the USA and Finland	To assess the lipid-lowering efficacy, biochemical safety, and effect on growth and sexual development of lovastatin in adolescent boys with HeFH	48 weeks
Wiegman, 2004[37]	Efficacy and safety of statin therapy in children with familial hypercholesterolemia	RCT of drug Netherlands FH children ages 8 to 18 recruited from academic medical referral setting	To determine the 2-year efficacy and safety of pravastatin therapy in children with familial hypercholesterolemia (FH)	2 years

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Stein, 1999[78]	1. Followed American Heart Association (AHA) pediatric diet for at least 4 months 2. LDL-C 189 mg/dL - 503 mg/dL 3. At least 1 parent had an LDL-C of at least 189 mg/dL not due to secondary causes or LDL-C values were 220 - 503 mg/dL or their LDL-C values were 220 - 503 mg/dL and a parent died of CAD with no available lipid values. 4. No homozygous FH, underlying disorders known to produce secondary LDL-C elevations 5. No disorders affecting triglyceride-rich lipoproteins 6. After the trial began, FDA requested only subjects who had Tanner stage 2 at entry be included in the trial. 7. No delayed puberty shown by testicular volume $\leq$ 3 cm after age 12 8. Weight $\geq$ 32 kg and between 10th - 95th percentile for age	132 randomized, 67 to drug 65 placebo	Lovastatin group Mean age: 13.3 (0.3) Female gender: 0% Race: 93% of all were white Placebo group Mean age: 13.1 (0.3) Female gender: 0% Race: 93% of all were white
Wiegman, 2004[37]	1.Parent with clinical or molecular diagnosis of FH; 2.Two fasting samples with LDH-C levels of 155 mg/dL or more and triglyceride levels below 350 mg/dL; 3.Adequate contraception for sexually active girls; 4. No drug treatment for FH or use of plant sterols; 5. No homozygous FH; 6. No hypothyroidism; 7. No abnormal levels of muscle or liver enzymes.	214 randomized, 106 to drug 108 to placebo	Pravastatin group Mean age: 13.0 Female gender: 57% Race: NR Placebo group Mean age: 13.0 Female gender: 57% Race: NR

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Stein, 1999[78]	All received formal dietary reinstruction, were monitored, and determined to be stable following a AHA pediatric diet for at least 8 weeks before randomization. Placebo was administered week -4 to week 0. All subjects continued diet instruction, monitoring, and evaluation throughout the study. Randomized to drug: Lovastatin, starting at 10 mg/day, with a forced titration at 8 and 16 weeks to 20 and 40 mg/day, respectively. 40 mg/day weeks 25 - 48. Randomized to placebo: Matching placebo tablets	1. 1 drug and 2 placebo subjects discontinued due to AE's. No clinically significant AE's. 6 withdrew in lovastatin, 1 due to AEs: increased bruising and purpura 16 withrew in placebo, 2 due to AEs: skin rash and myalgia 2. Drug had no significant effect on growth parameters at 24 or 48 weeks 3. No difference between drug and placebo in testicular volume, Tanner staging, testosterone, or LH level. DHEAS increased 18% in the drug group compared to 5% in the placebo group. (p=.03) 4. Reduction of tocopherol in drug group at week 48 (p=.002), consistent with decrease in LDL-C. In both groups, increase in ALT from baseline, with no differences between groups at week 48 (p=.20), although increase was significant for each group (drug, P<.001; placebo, P=.008). No consistent changes in AST or CK. Report of infrequent, sporadic, nonsustained CK elevations in response to exercise.
Wiegman, 2004[37]	After initiation of a fat restricted diet for 3 months or more and encouragement of regular physical activity, randomized to pravastatin 20 - 40 mg/day or placebo. Evaluated every 6 months for 2 years.	No differences between groups in changes in height, weight, BMI, body surface area, testis volume, liver and muscle enzymes, and endocrine function parameters (corticotropoin, cortisol, DHEA-S, FSH, LH, thyrotropin, 17b-estradiol, testosterone), and Tanner Stage. One child had an asymptomatic but extreme CPK elevation (16400 U/L) after 168 of placebo treatment. CPK level decreased to normal within 1 week of stopping treatment. No differences observed in growth, endocrine function parameters, Tanner staging scores, onset of menses or testicular volume. 3. No differences observed in muscle or liver enzyme levels.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Stein, 1999[78]	6 withdrew in lovastatin, 1 due to AEs: increased bruising and purpura 16 withrew in placebo, 2 due to AEs: skin rash and myalgia	Good
Wiegman, 2004[37]	Tablet counting revealed that 84% of tablets were taken; mean visit attendance per child was 95% of all study visits.	2 year follow-up Well-designed

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Bile-acid binding resins				
Curtis, 1991[245]	Loss of dental enamel in a patient taking cholestyramine	Case report	Report of a case of extensive loss of dental enamel in a young boy, thought to be attributed to mixing the cholestyramine in Kool-Aid and swirling the mixture in the mouth before swallowing.	2 years of treatment with cholestyramine
Farah, 1977[246]	A study of the dose-effect relationship of cholestyramine in children with familial hypercholesterolemia.	Descriptive study Lipid clinic, Johns Hopkins Hospital	1) To determine the optimal dose of cholestyramine required in children to significantly lower their LDL and cholesterol; 2) to relate this dose to their body weight and pre-treatment levels of LDL and cholesterol; 3) to study the effectiveness of a dose given twice daily; and 4) to monitor for potential side-effects, such as fat soluble vitamin malabsorption.	21 days

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Bile-acid binding resins			
Curtis, 1991[245]	N/A	1	7-year-old boy, LDL 240 mg/dL.
Farah, 1977[246]	Children and young adults with HeFH were identified through screening children of affected parents followed at the Lipid Research Clinic.	20	Mean age 15 y

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Bile-acid binding resins		
Curtis, 1991[245]	The family was instructed to follow AHA Step 1 diet, and an aerobic exercise program. After 6 months the patient's LDL was 255 mg/dL, and so was given 4g of cholestyramine daily twice daily for the next 2 years. The parents stated that they had mixed the cholestyramine in Kool-Aid to improve the taste, and the patient stated that he had "swished" the mixture in his mouth for 10 to 15 minutes before swallowing.	After 2 years, the parents noted a change in the color of the patient's teeth, and a subsequent dental examination revealed extensive loss of enamel. Serum calcium, phosphorus folate, and vitamin B12 values were normal. Results of a radioactive bone mineral analysis were normal. KoolAid has a pH of 2.9 after water is added; the pH decreases to 2.4 after cholestyramine is added.
Farah, 1977[246]	13 patients were maintained on an outpatient isocaloric diet (<200 mg cholesterol with polyunsaturated: saturated fat ratio of 2.0). The diet was continued for 21 days. After 5 days, cholestyramine was started at 1 g/day and increased by 1 g/day up to a total of 16 g/day given twice daily. In another group, 7 children received the same dietary treatment, and started on a dose of cholestyramine predicted by a regression based on post-diet level of LDL: either 4 g, 8 g, or 16 g/day.	None of the patients on cholestyramine demonstrated any significant side-effects such as fat-soluble vitamin malabsorption.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Bile-acid binding resins		
Curtis, 1991[245]	NR	Case report
Farah, 1977[246]	NR	Reports on different AEs in the same study as Farah, 1997 below.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Farah, 1977[247] (See Farah, 1977 above)	Dose-effect relation of cholestyramine in children and young adults with familial hypercholesterolemia	Descriptive study Lipid clinic, Johns Hopkins Hospital	1) To determine the minimum dose of cholestyramine required to lower significantly the plasma LDL cholesterol and total cholesterol in young patients with FH; 2) to relate this dose to their body-weight and pretreatment concentrations of LDL cholesterol and total cholesterol; 3) to study the effectiveness of the dose given twice daily; 4) to monitor for immediate side-effects such as gastrointestinal symptoms and folate deficiency.	21 days: 5 days of baseline evaluation followed by a 16-day period of drug treatment.
Glueck, 1973[263]	Pediatric familial type II hyperlipoproteinemia: therapy with diet and cholestyramine resin	Noncomparative clinical study	To evaluate the effects of diet and diet plus cholestyramine on cholesterol and LDL in 36 children with familial type II hyperlipoproteinemia from 18 kindreds with documented familial type II.	6 months with additional 12-18 months follow-up for growth

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Farah, 1977[247] (See Farah, 1977 above)	Criteria for FH were the presence of xanthomas and hyperbetalipoproteinaemia in the parent, or the transmission of hypercholesterolemia and hyperbetalipoproteinemia through many generations. The latter conditions were defined by concentrations of plasma total and LDL cholesterol above 95th percentiles, adjusted for age and sex. The pattern of inheritance of hyperlipidemia was not indicative of familial combined hyperlipidemia in any of these kindreds; none of the affected members had type-III hyperlipoproteinemia. Secondary causes of hyperlipoproteinemia were excluded in each patient by tests of thyroid, renal, and liver function.	20	Mean age 15 ±5 S.D. years
Glueck, 1973[263]	36 children aged 7-21 from 18 kindreds with well-documented familial type II hyperlipoproteinemia were studied. These children had been originally found to b e heterozygous for familial type II hyperlipoproteinemia. Excluded secondary hypercholesterolemia.	36, including 20 on diet plus cholestyramine	Age 7-21

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Farah, 1977[247] (See Farah, 1977 above)	Patients had been treated for a minimum of 6 weeks on a therapeutic outpatient diet. NIH-type II diet was calculated daily for each of the children during admission to the metabolic unit. Average cholesterol intake was 159 mg/day (range 118-200) with mean ratio of polyunsaturated to saturated fats of 2.1 (range 1.9 to 2.2). Thirteen patients were given cholestyramine, with dose increased by 1 g daily until a total dose of 16 g/day was achieved. Mean dose of cholestyramine = 11 g/day.	In one patient, febrile gastroenteritis developed after 7 days of treatment with cholestyramine, and resulted in therapy being stopped. Mean serum-folate among 15 patients before treatment was 9.0 ng/mL, and did not differ significantly between males (mean 9.8 ng/mL, N=5) and females (mean 8.6, N=10). Serum folate was measured after treatment in 11 patients. Analysis by sex showed an upward trend for 4 males but a significant decrease in serum-folate in 7 females. SGOT increased in 2 patients (by 32 and 41 i.u./L). Two other patients had significant increases in LDH (>70 I.U./L). These results were not accompanied by any significant changes in other tests of hepatic function. The increases in SGOT persisted for 6 months then became normal. Increases in LDH were only transient. No other abnormal chemical measurements were observed.
Glueck, 1973[263]	Children and their parents were instructed to ingest a low cholesterol type II diet (<300 mg/day), and were seen monthly thereafter. At monthly visit, diet adherence was reviewed with a written 24-hr diet recall, separately with the children and their mothers. After 6 months of diet, the children were arbitrarily separated into two groups, diet responders (n=11, LDL < 170 mg/dl) and diet non-responders (n=25, LDL 170+ mg/dl). 20 of the diet non-responders then received cholestyramine therapy (12 g/day) in addition to diet, and were seen monthly with review of adherence. Safety measures at monthly visits included height, weight, blood pressure, physical exam, drug and diet adherence. Lab tests were obtained at every other visit, including full hemogram, liver function tests, blood urea nitrogen, calcium, phosphorous, total protein (albumin/globulin), electrolytes, and carbon dioxide.	10 of 12 routinely took the suggested dose of cholestyramine. Weight gain and growth progressed during the 12 and 18 month follow-up period along normal gwoth percentile. No consistent changes in any of the laboratory safety tests (CBC, liver function tests, BUN, calcium, phosphorous, total prtein, electrolytes and carbon dioxide). No evidence for hypercholoremic acidosis at any time.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Farah, 1977[247] (See Farah, 1977 above)	One subject stopped cholestyramine therapy due to febrile gastroenteritis.	
Glueck, 1973[263]	Of the 20 children on cholestyramine, 10 routinely took the suggested dose and also adhered to diet. 10 others had good diet adherencew but did not consistently take the full cholestyramine dose.	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Glueck, 1974[262]	Plasma vitamin A and E levels in children with familial type II hyperlipoproteinemia during therapy with diet and cholestyamine resin	Noncomparative clinical study	To evalute the short-term effectgs of diet and diet plus cholestyramine on plasma vitamin A and E levels in 46 children with familial type II hyperlipoproteinemia, and in 36 normal children.	average follow-up of 6 months
Glueck, 1977[260]	Therapy of familial hypercholesterolemia in childhood: diet and cholestyramine resin for 24 to 36 months	Noncomparative clinical study	To determine whether a higher dose of cholestyramine (16 mg/day) would provide a more substantial cholesterol level-lowering effect.	16 children followed for 18 months; 12 for 24 months; 7 for 30 -36 months
Glueck, 1986[261]	Safety and efficacy of long-term diet and diet plus bile acid-binding resin cholesterol lowering therapy in 73 chlidren heterozygous for familial hypercholesterolemia	Observational study	To examine the safety and efficacy of long-term diet and diet plus BABR therapy for pediatric familial hypercholesterolemia in 73 children heterozygous for familial hypercholesterolemia	4.3 years

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Glueck, 1974[262]	Diagnoses of hypercholesterolemia and hyperbetalipoproteinemia were made in 46 children, aged 5-21, from 19 kindreds with famlial type II hyperlipoproteinemia. These children were heterozygous for familial type II and the primary nature of their hyperbetalipoproteinemia was confirmed by exclusion of common diosrders which produce secondary hypercholesterolemia. 36 normocholesterolemic siblings of the hypercholesterolemic children were also studied.	46; of whom 30 were on diet plus BABR	Age 5-21
Glueck, 1977[260]	Sixteen children heterozygous for familial hypercholesterolemia (aged 9-17) from six kindreds with well-documented familial hypercholesterolemia were studied. Their ascertainment, the nature of their hypercholesterolemia, their response to diet, and their short-term response to cholestyramine resin (12g/day) have been previously described. (see Glueck, 1973)	16 (same children as in Glueck 1973 above, who were on diet plus cholestyramine)	Age 9-17
Glueck, 1986[261]	The 73 children were heterozygous for familial hypercholesterolemia as defined by primary elevations of total and/or low-density lipoprotein cholesterol equal to or more than the age, sex, and race-specific 95th percentile, absence of secondary causes of hypercholesterolemia, and at least 2 similarly affected first degree relatives.	73, including 33 on diet plus resin therapy	mean age 10.3

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Glueck, 1974[262]	Children were instructed to ingest a low cholesterol Type II diet. Diets were not supplemented with adidtional vitamins A, D, K, or E. Diet adherence was reviewed at monthly visits. The 46 hypercholesterolemi children were maintained on the diet for an average of 4 months per child, then divided into two groups: 16 whose TC & LDL normalized, and 30 whose TC and LDL did not normalize on diet. These 30 were then placed on cholestyramine in addition to the diet (12 g/day) and seen at monthly intervals, with average followup of 6 months on diet and cholestyramine.	Plasma vitamins A and E remained within the normal range and paralleled at higher levels the 25th to 75th percentile distirbution for vitamin A and E in normal children.
Glueck, 1977[260]	In this study, at month 13 of the 6-month Glueck 1973 study, the dose of cholestyramine was increased to 16 g/day and the children were followed up subsequently for an additional 1-2 years. The children were seen in the outpatient research clinic every 4-6 weeks. At each visit, adherence was reviwed using 24-hour diet recall. Drug adherence was determined by packet count. Assessment of AES included clinical symptoms and questions about constipation, nausea, flatulence, overall palatability of the resin, and fatigue. 16 children were followed up for months 13-18, 12 for months 19-24, 7 for 25-30, and 31-36.	1 child had persistent consitipation. None had nausea. 5 complained that resin was gritty, had poor palatability. 1 complained of chronic fatigue. CBC, liver function tests, vitamin A and E, calcium, phsophorus, blook urea nitrogen, fasting blood sugar levels did not vary signficantly over time when compared to baseline levels on diet only.
Glueck, 1986[261]	73 children heterozygous for familial hypercholesterolemia were compared with 39 normal healthy children wfrom a local pediatric practice, matched for sex and age at entry, who were ingesting habitual diets without modifications by family or physicians. Height and weight were obtained in both groups of children. HeFH children were put on a modified type II diet. Dietary adherence was assessed at each visit. BABR therapy (cholestyramine or colestipol, 8 to 20 g/day) was not started until the children had been on diets alone for at least 4 months. No hypocaloric regimens were recommended, and supplemental fat-soluble vitamins were not given. Serum folic acid levels were not systematically measured.	Height and weight percentiles at completeion were no unchanged from baseline. No abnormal growth patterns noted. Sexual maturation was normal. None had unusual infections or extra school sick days. None of the girls had ammenorrhea; though 1 competitive cross-country runner had persistently irregular periods. No depression, suicide attempts or traumatic deaths.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Glueck, 1974[262]	NR	
Glueck, 1977[260]	11 of 16 had good adherence. 5 children dropped out after 2 years because of poor palatability of the drug.	
Glueck, 1986[261]	4 children exhibited transient refusal to follow diets and/or take bil acid-binding resins.	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Groot, 1983[248]	The effects of colestipol hydrochloride on serum lipoprotein lipid and apolipoprotein B and A-1 concentrations in children heterozygous for familial hypercholesterolemia	Non-randomized, cross-over placebo controlled. in children ages 7-15 with heterozygous familial hypercholesterolemia type II-A The Netherlands	To evaluate the effects of colestipol vs. placebo on serum lipoprotein lipid concentrations in heterozygous hypercholesterolemic patients consuming a type II-A diet	16 weeks
Hansen, 1992[249]	Growth during treatment of familial hypercholesterolemia	Descriptive study Pediatric lipid clinic, Denmark	To observe somatic growth in children treated for FH.	8.5 years in 13 (diet); 5.5 years in 17 patients (diet followed by diet + colestipol)

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Groot, 1983[248]	Inclusion criteria: 1. One parent with hypercholesterolemia or who had died from cardiovascular disease. 2. Serum cholesterol levels >6.2 mmol/l and serum triglycerides normal (<1.5 mmol/L) after a low fat breakfast. 3. No disease associated with secondary hyperlipidemia; no hypertension.	33 children Two comparable groups were formed with respect to age, sex and serum cholesterol concentration. One group given placebo then colestipol (8 weeks of each); the other group given colestipol then placebo.	Not given
Hansen, 1992[249]	Children with FH were followed in a pediatric lipid clinic for at least one year from 1970-1987. Several children were ascertained through a neonatal pilot screening program. The diagnosis of FH was based on increased concentrations of serum total and low-density lipoprotein cholesterol in the child, in one of the parents and in other members of a pedigree compatible with autosomal dominant inheritance of type IIa hyperlipidemia. Secondary hyperlipidemia was excluded by obtaining normal results on laboratory tests of thyroid, renal, hepatic, and glucose metabolism.	30	Age range 1/17, median 4.5 53% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Groot, 1983[248]	Placebo was silicagel stained with FeCl3. Dose of colestripol or placebo was 5 g at AM and 5 gm at dinner for children <40 kg; and 10 gm at breakfast and 5 gm at dinner for children >40kg. Mean dose was 0.34+0.08 (mean+sd) g/kg/body weight/day.	NR
Hansen, 1992[249]	Dietary counseling was provided by the physician in the lipid clinic. 17 children additionally received colestipol at 125-250 mg/kg/day in 1-2 daily doses.	Among all 30 children, the SD scores for both height/age and weight/age decreased by approximately 0.4 during dietary treatment ($p<0.05$), but were not affected by treatment with colestipol. The addition of colestipol to the dietary regimen of 17 children did not cause any statistically significant change of growth. No child decreased to below -2 SD during dietary treatment. During treatment with colestipol the height/age, but not the weight/age, of only one child decreased below -2 SD. A deficit of 0.4 SD score for a 10-year-old boy corresponds to approximately 1.8 kg in weight and 2.4 cm in height.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Groot, 1983[248]	5 children withdrew because they didn't like the taste of the medication: 2 in the group that started with colestipol and 3 in the group that started with placebo.	
Hansen, 1992[249]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Harvengt, 1976[250]	Colestipol in familial type II hyperlipoproteinemia: a three-year trial	Non-randomized, single-blind trial with placebo lead in phase 13 patients aged 6 to 61 with familial type II hyperlipoproteinemia	To evaluate the effects of colestipol on serum cholesterol in patients with primary type II hyperlipoproteinemia.	Up to 36 months of treatment, following 6-wk placebo
Koletzko, 1992[251]	Treatment of hypercholesterolemia in children and adolescents	Descriptive study, lipid clinic, Germany	To study the effects of outpatient treatment with diet alone or with combined diet and drug therapy in pediatric outpatients. With genetic hypercholesterolemia.	Diet: 4-70 months (mean 17.5 months) Combined therapy, mean observation period was 27.9 months

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Harvengt, 1976[250]	Inclusion criteria: Hypercholesterolemia or tendon xanthomas or both. Type II lipoproteinemia was defined by serum cholesterol and triglyceride levels, agarose lipoprotein electrophoresis pattern, clinical signs (corneal arcus, xanthomas), and familial study.	Included 3 children: ages 6, 11, and 18	3 pediatric patients: 1 male aged 6 2 females age, 11 and 18
Koletzko, 1992[251]	Diagnosis of primary genetic hypercholesterolemia was based on a positive family history suggestive of dominant inheritance and on at least two fasting blood tests with results for total cholesterol, LDL cholesterol, and in the case of familial combined hyperlipidemia, triglycerides also, exceeding the 95th percentile for age and sex as well as a positive result of lipoprotein electrophoresis.	35 on diet only 14 on diet + BABR	Mean age 7.9 (range 2-17.6)

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Harvengt, 1976[250]	All patients followed a diet less than 300 mg cholesterol daily with polyunsaturated-saturated fatty acid ratio >1,8. Patients were given an inert cellulose powder as placebo for 6 weeks. Colestipol was then given before meals in 5 gm t.i.d.	There were only 3 children in this study, and no AEs were observed in them except for low iron level without anemia was seen in an 18-yr-old female. No hepatic dysfunction, renal function, or hematologic side effects were observed. The prothrombin time values were not abnormally prolonged during colestipol medication. Fasting blood sugar increased from 74 mg/dl (placebo) to 88.5 mg/dl after 18 months of treatment, but returned to baseline values after 3 years. Serum uric acid level increased during treatment but did not reach abnormal values. There was no steatorrhea in patients receiving colestipol. Serum vitamin B12 and folic acid content were not impaired after 2 and 3 years on colestipol. Serum iron concentration was low in one pediatric patient, without hematologic signs of anemia. "There was some increase in weight in the two children." Mild gastrointestinal complaints (flatulence, constipation) were described during the first 3 months of treatment, which disappeared despite continuation of treatment.
Koletzko, 1992[251]	Diet focused on limiting intake of saturated fatty acids to $\leq$10% of energy and replacing them with poly- and monounsaturated. Fats as well as reducing cholesterol intake to $\leq$100 mg/1000kcal. 14 patients, whose serum TC and LDL remained severely increased despite diet, additionally received cholestyramine 2-4 times daily (mean daily dose 0.36 g/kg) in addition to continued diet therapy.	No serious side effects were noted with both forms of treatment (diet/ diet + BABR). "Mild gastrointestinal symptoms occurred in very few patients." Percentile values for weight and length remained unchanged in all patients with the exception of three overweight children whose weight fell by more than 5 percentage points but remained above the 50th percentile.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Harvengt, 1976[250]	NR	
Koletzko, 1992[251]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Liacouras, 1993[252]	Use of cholestyramine in the treatment of children with familial combined hyperlipidemia	Observational Philadelphia Lipid clinic	To report the experience with cholestyramine in children over a 10 year period.	Varied, 0-62 months
McCrindle, 1997[74]	Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: A randomized, crossover trial	Randomized crossover Patients recruited from 2 lipid disorder clinics	To compare acceptability, compliance and effectiveness of two forms of cholestyramine resin in treatment of hypercholesterolemia in children.	28 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Liacouras, 1993[252]	Referred to Lipid Heart Clinic at Children's Hospital of Philadelphia (87 of 673 children referred met criteria) Heterozygous FH (HeFH) was diagnosed if the plasma LDL-cholesterol level was above the 98th percentile in both the child and an affected parent and if total cholesterol levels were greater than 300 mg/dL in another 1st degree family member. Familial combined hyperlipidemia (FCHL) was diagnosed when both the child and an affected parent had a plasma LDL-cholesterol or triglyceride level above the 90th percentile and a first degree relative had documented hyperlipidemia and at least one affected family member had a plasma triglyceride value >90th percentile. Exceptions: 2 children were included in the study because of a strong family history of premature heart disease.	87	85 met criteria for HeFH (n=36) or FCHL (n=51). 2 others were included because of family history; thus 87 children were treated with cholestyramine. FCHL group: Average age 10.4+3.9 years; male/female ratio 18/19 HeFH group: average age 10.7+4.3 years; male/female ratio 13/12.
McCrindle, 1997[74]	1. Age 10 - 18 years 2. 1 or more parent with heterozygous familial hypercholesterolemia type IIA or IIB 3. Fasting serum LDL of 130 mg/dl or more while on American Heart Association step 2 diet 3. No contraindications to use of cholestyramine 4. No lipid-lowering agents other than those in study protocol	40	43% female 2 siblings from 6 families 3 siblings from 1 family Median age at enrollment: 13 (10-18) Median age at diagnosis: 9.5 (0.1-17.2)

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Liacouras, 1993[252]	All children had failed diet alone. All continued to adhere to a Step 1 NCEP diet. Cholestyramine given as Questran, initially as 4 gm/day in 2 divided doses; then increased in increments of 4 gm/day every 8-12 weeks up to 16 gm/day unless LDL levels dropped to <130 mg/dL or side effects occurred. In four patients the dose was increased to greater than 16 gm/day. All patients were given a multivitamin at hospital.	Of the 62 who continued more than 1 month on the drug, 15 had an adverse effect: 12 nausea, 2 abdominal bloating, 1 severe constipation. 73% complained of poor palatability No instances of elevated prothrombin times.
McCrindle, 1997[74]	6 week washout period followed by random assignment in pairs to either 8 gm/day of cholestyramine powder (4 gm packets) or pills (1 gm tablets) for an 8 week period. Drug dispensed with random over count, and subjects instructed to return unused drug at end of drug period. Subject completed log book during the 1st week on amount of drug taken, acceptability and adverse effects, with questionnaire at weeks 4 and 8. After the first 8 week course of medication and assessment, there was another 6 week wash-out, followed by crossover to the alternate form of medication and assessment.	38/40 (95%) completed both medication periods Authors noted minor gastrointestinal complaints were frequent but did not result in any drop-out

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Liacouras, 1993[252]	73% complained of poor palatability After cholestyramine therapy was initiated 7 pts (8%) failed to return for follow-up visits, 18 (21%) began medication but discontinued it within 1 months, 62 (71%) continued to take medication >1 months and complete f/u visits	Unclear duration of treatment; post treatment values represent lipoprotein profiles taken at the time of maximum decrease of LDL (6-12 months). No intention-to-treat analysis
McCrindle, 1997[74]	At end of study, 82% preferred pill, 16% powder, and 2% neither form. Mean (+/-SD) compliance as assessed by amount of medication taken was greater for pills (61% +/-31% than powder (50% +/- 30%, p=0.01). Form of medication increased compliance by at least 25% for 16 patients (42%), 13 in favor of pills and 3 of powder.	No control group Small sample size At baseline, pill group had perception of increased importance of diet

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
McCrindle, 2002[75]	A Randomized Crossover Trial of Combination Pharmacologic Therapy in Children with Familial Hyperlipidemia.	Randomized cross-over trial Lipid clinic, Toronto, Canada	To determine the short-term safety and effectiveness of combination drug therapy in children	18 weeks each period
Schwarz, 1980[253]	Fat-soluble vitamin concentrations in hypercholesterolemic children treated with colestipol	Pre/post Longitudinal Outpatient clinic of Washington University Lipid Research Center from 1973 to 1978.	To determine whether long-term administration of colestipol hydrochloride to hypercholesterolemic children along with a diet low in cholesterol is effective in reducing plasma total and LDL, and to learn if changes in plasma concentrations of vitamins A, D, E, K or folic acid occur during therapy. Also assessed effect of drug on calcium metabolism by sequential determination of serum total and ionized calcium, phosphorus, alkaline phosphatase, and parathyroid hormone.	Up to 24 months

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
McCrindle, 2002[75]	1. Children between ages 8-18 2. Positive family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease in first-degree relatives 3. Minimum fasting LDL cholesterol level before enrollment >4.15 mM/L 4. Participation and compliance in dietary counseling program for at least 6 months. 5. No secondary cause for hyperlipidemia, no major surgery or serious illness within past 3 months.	40 randomized to either colestipol 10g/day alone or colestipol 5 g/day +pravastatin 10 mg/day	11 girls, 25 boys median age 14, range 9-18 BMI 22-25 kg/m2
Schwarz, 1980[253]	1. Hypercholesterolemic (values > 95th percentile for age) children aged 5 - 17 2. Plasma triglycerides normal 3. One or more 1st degree relative with type II hyperlipoproteinemia (1exception) 4. Secondary causes of elevated plasma concentrations eliminated 5. Cholesterol-lowering medications discontinued at least 3 months prior to study start 6. No supplemental vitamins or cholesterol drugs during study (except study drug)	23	Hypercholesterolemic children aged 5 to 17 years (mean 12.2) and 4 sibling controls 35% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
McCrindle, 2002[75]	colestipol 10g/day (10 tablets) alone vs. colestipol 5 g/day (5 tablets) plus pravastatin 10 mg/day (1 tablet) for first 18 week period, followed by 8 week wash-out period and then each group crossed over to the other treatment for the second 18 week period.	Symptoms reported at the end of the study in the final preference questionnaire showed that the majority of patients had no symptoms. 18% reported constipation with colestipol vs. 0% with the combination vs. 3% who had it with both, 12% reported bloating/gas with colestipol alone vs. 0% with combination (3% had it with both). 21% had stomach ache with colestipol alone vs. 0% with combination vs. 0% with both. 11% had headache with colestipol vs. 0% with combination vs. 3% with both regimens. 6% had muscle aches on colestipol along vs. 3% with combination vs. 0% with both regimens.
Schwarz, 1980[253]	Child and parents instructed in NIH type IIA diet, and adherence was reviewed at each visit by 24-hour dietary recall. Subjects had 2 - 8 months (average 3.6) of diet only therapy, after which those with cholesterol concentrations > 90th percentile for age were given colestipol 15 - 20 gm/day. Drug therapy up to 24 months in duration. Office visits every 2 months for diet and drug adherence checks and determination of total cholesterol and triglyceride levels in plasma. Blood work and physical exam performed twice during diet only period and at 6 monthly intervals during colestipol therapy. Measures: 1. 24 hour dietary recall 2. Package count of unused drug on > 3 separate visits 3. Detailed blood work: blood count, serum gluclose, urea nitrogen, glutaminic oxaloacetic transaminase, bilirubin, total and ionized calcium, phosphatase, parathormone, vitamin A, 25-hydroxycholecalciferol, prothrombin time, vitamin E, folic acid, and plasma lipid and lipoprotein quantification. 4. Complete urinalysis 5. Vitamin E analyzed by colorimetric assay in 1st part of study and microfluorometric assay in 2nd part. 6. Folic acid analyzed by Lactobacillus casei method in 1st part of study and later by radioimmunoassay. (Values converted)	No severe side effects reported. 1 patient developed Reynauld's phenomenon on 4 separate occasions during therapy but continued to take drug without recurrence of symptoms.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
McCrindle, 2002[75]	Compliance was 57-66% overall and was similar between treatment groups and dose groups. There was a decrease in compliance between the first 8-week and second (10-week) dispensing periods, this difference was not significant.	
Schwarz, 1980[253]	6 subjects complained of poor palatability of drug, and 4 withdrew for this reason. Only 7 patients completed 18 - 24 months of drug (30%); 3 controls completed this treatment segment	Many uncontrolled variables: 10 patients had been on low cholesterol diets 1 - 4 years prior to study start. Range of "diet alone" treatment was 2 to 8 months, with an average of 3.6 months. Drug compliance in the good adherence group (n=13) was 82% (range 100% - 63%), and was undetermined in the poor adherence group. Poor adherence group attended 66% of visits. Only 7 patients (30%) completed 18-24 months of drug. Both folic acid and vitamin E were analyzed by different lab methods in different parts of the study. Results section confusing. Design included 4 sibling controls with no resulting data analysis on this group. No separate analysis or adjustment for the 1 subject who did not have a 1st degree relative with hyperlipoproteinemia.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Tonstad, 1996[254]	Colestipol tablets in adolescents with familial hypercholesterolemia	Observational Oslo, Norway	To examine the palatability and side effects of colestipol tablets in adolescents with FH and report changes in lipid levels	6 months for colestipol; 2-10 (mean 6) years for diet
Tonstad, 1996[80]	"Low dose colestipol in adolescents with familial hypercholesterolemia"	DB RCT of colestipol 10g qd or 5g bid vs placebo 67 adolescents Norway	Effectiveness of colestipol in treating FH.	52 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Tonstad, 1996[254]	heFH attending a referral lipid clinic; none were siblings.	27 children	23 boys and 4 girls ages 10-16
Tonstad, 1996[80]	adolescents age 10-16 referred to lipid clinic; all had two or more TC >6.2mmol/l and TG<3.0 mmol/l.	74 targeted, 66 agreed to participate	37 boys (58%); 29 girls mean age 13.2 Tanner stage 2.6

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Tonstad, 1996[254]	All patients had previously been instructed to follow a diet restricted in saturated fat and cholesterol (<10% of caloric intake and <200 mg/day respectively). All had previously taken colestipol granules or cholestyramine or both; all but 4 had stopped taking granules, usually because of unpalatability. Colestipol was given as 2-12 g daily usually 6 g. Doses higher than 6gm/day were divided.	All showed normal growth and development according to standard height, weight and pubertal staging charts over the 2-10 years that they had been followed prior to this study (on diet alone). Two girls taking 4 tablets daily had difficulty swallowing the tablets. One boy taking 6 tablets had abdominal discomfort at bedtime 2-3 times/week - he was taken off the med. 1 subject had difficulty with flatulence and swallowing the tablets. 24/27 reported that they forgot tablets 1-2 times/week or less.
Tonstad, 1996[80]	All subjects instructed to follow a diet: 30% calories from fat; <10% from saturated fat and <200 mg cholesterol/day. Assessed with 4 day weighed food record. Subjects randomized to drug treatment got either colestipol 10g qd or 5g bid x 8 weeks. Open label trial after 8weeks in which placebo group started colestipol for 52 weeks; colestipol group continued on colestipol.	Total of 7 subjects dropped out 4 in colestipol; 3 in placebo. 5 pts dropped out because they refused to swallow the drug; 2 dropped out because they had unexpectedly low lipid concentrations at randomization. 8 girls did not agree to continue in the open phase. Of 51 in open phase, 42 completed 1 year. 8 subjects in colestipol group had GI side effects attributed to the drug: 2 had constipation that improved with temporary dose reduction; 1 had dyspepsia and 1 had flatulence throughout entire study; 2 had intermittent nausea, 1 had temporary decrease in appetite; 1 had abdominal pain improved with dose reduction. Linear growth velocity was within reference range for Norwegian adolescents. 1 pt lost >1 kg during the study (24.5 kg/m2 pre and 21.3 kg/m2 post). Lab values: Low-dose colestipol (10 g/day) reduced concentrations of serum folate after 8 weeks. Serum vitamin E and carotenoids decreased proportionally with decreases in cholesterol. Vitamin D did not change significantly, but decreased more in subjects who were more compliant after 1 year.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Tonstad, 1996[254]	All preferred the tablets to granules formulations of resins. 7 people did not complete 6 month labs (or at least are not reported). In SE table, 4 people noted to have stopped med prior to 6 months; reasons include unpalatable in all cases.	
Tonstad, 1996[80]	Compliance was 68% in colestipol group vs 76% in placebo group NS. Only one third of adolescents adhered to the drug regimen in the course of one year. Obstacles included vacations, special occasions, and unpalatability.	placebo group was older and more advanced tanner stage ($p<0.05$)

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Tonstad, 1996[81]	Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia	Random assignment to double-blind comparison Norway Boys aged 6 to 11 years and girls aged 6 to 10 years with familial hypercholesterolemia in a referral lipid clinic	To determine the efficacy and safety of cholestyramine therapy in young children with familial hypercholesterolemia	1 year
Tonstad, 1998[255] (See Tonstad 1996[81])	The C677T mutation in the methylenetetrahydrofolate reductase gene predisposes to hyperhomocysteinemia in children with familial hypercholesterolemia treated with cholestyramine	Placebo-controlled RCT; lipid clinic, Norway	To investigate whether the elevation of plasma total homocysteine observed during cholestyramine treatment was related to the methylenetetrahydrofolate reductase genotype in children with FH. Cholestyramine may increase tHcy by inhibiting the absorption of folate.	1 year
West, 1973[256]	Use of cholestyramine in the treatment of children with familial hypercholesterolemia	Descriptive study	To report the experience in the treatment of 19 children with HeFH using cholestyramine.	Up to 20 months

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Tonstad, 1996[81]	1. Familial hypercholesterolemia diagnosed if TC > 260 mg/dl and triglyceride levels < 200 dl, if 1 parent had baseline cholesterol > 300 mg/dl and triglyceride levels < 200 mg/dl, or tendon xanthoma, or if autosomal dominant inheritance present in other members. 2. Prepubertal girls aged 6 - 10, and prepubertal boys aged 6 - 11 who completed an initial medical evaluation and dietary session and had a parent who understood the diet. 4. Height velocity score standard deviation score > -2.0. 3. Those taking lipid-lowering drugs were required to discontinue doing so at least 4 weeks before study start 4. Secondary hyperlipidemia ruled out by clinical and lab examination.	96 randomized, 36 to drug 36 to placebo	Drug group Mean age: NR Female gender: 44% Race: NR Placebo group Mean age: NR Female gender: 33% Race: NR
Tonstad, 1998[255] (See Tonstad 1996[81])	Subjects were boys and girls aged 6 to 11 with FH who had participated in a 1-year open study of Step 1 diet.	96	Mean age 7.98 40% female
West, 1973[256]	Most children were referred because of a family history of early onset of ischemic heart disease. All were asymptomatic but one 13-year-old boy was detected because of skin xanthomata behind the knees, and one 9-year-old girl had corneal arcus. All patients had characteristic biochemical evidence of familial hypercholesterolemia (i.e. raised TC and normal fasting TG, with increased B-lipoprotein by electrophoresis and density gradient ultracentrifugation). Also, at least one of the parents had the same lipoprotein abnormality or had died of ischemic heart disease.	19 children from 11 families	38.7% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Tonstad, 1996[81]	After 1 year of a low-fat, low-cholesterol diet, children with LDL > 190 mg/dl or > 160 mg/dl in the presence of familial premature cardiovascular disease were randomly assigned to a double-blind comparison of 8 gm cholestyramine or placebo for 1 year. Dieticians reinforced the diet at each visit. Dietary composition assessed by a 7 day record, evaluated by FIBER. Assigned dose 8 gm/day, following 1 week build-up phase of 4 gm/day. Follow-up visits scheduled after 2, 5, 7, 9 and 12 months. Compliance assessed by counting leftover packages at each visit.	In the drug group, folate deficiency occurred in one subject, in whom the total homocysteine level increased concurrently. With the exception of modest decreases in levels of vitamin D during the winter, other nutritional deficiencies were not observed. No adverse effects on growth and bone age evident. No difference in mean height velocity standard deviation scores in those who hadn't started puberty. There was one case of intestinal obstruction caused by adhesions One on cholestyramine vomited after taking 2 packets, and withdrew. One on placebo reported vomiting for 3 weeks and withdrew. Another on cholestyramine reported more frequent headaches and withdrew.
Tonstad, 1998[255] (See Tonstad 1996[81])	Children were randomized to 8 g/day of cholestyramine or matching placebo granules for 1 year. Blood was collected at baseline and 1-year follow-up, and analyzed for plasma tHcy, serum folate, and MTFHR status. Serum folate was measured by radio assay.	During cholestyramine treatment, tHcy concentrated increased in subjects with the C677T mutation in one or both alleles but not in subjects with the CC genotype. In contrast, there was a reduction in serum folate in most subjects, regardless of genotype. In the placebo group, tHcy and folate showed no consistent changes.
West, 1973[256]	Cholestyramine twice daily in a total dosage of 8 to 24 g/day (0.3 to 1.1 g/kg body weight per day). In 11 patients cholestyramine therapy was combined with a diet low in saturated fat (<20 g daily) and containing some supplementary corn oil and corn oil products. 8 patients remained on a normal diet during cholestyramine therapy. In 4 patients a comparison of twice-daily therapy with 4-times daily was made, starting with a dose of 4 g 4 times daily before food, followed by 8 g twice daily (total dose unaltered).	Absorption of fat was impaired in some patients but has not been associated with diarrhea. Fecal fat was estimated in 9 patients receiving cholestyramine. 5 of 7 children on a normal fat intake had steatorrhea with mean fecal fat ranging from 5.3 to 10.5 g/day. Serum folate levels decreased in all patients, and 6 of 12 tested had subnormal red blood cell folate. There has been no evidence of malabsorption of other vitamins or of minerals. Growth rate has been normal in all children. In all patients, growth and height and weight continued along the pretreatment centiles, with no change in velocity. None developed anemia, and hemoglobin, prothrombin time, serum calcium, alkaline phosphatase, and serum vitamin A concentrations have remained unchanged.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Tonstad, 1996[81]	22 of 36 completed 1 year of cholestyramine, having taken 77% of all doses, and 26 of 36 on placebo completed 1 year, having taken 83% of all doses (ns). 12 of 14 withdrew on cholestyramine due to unpalatability within 2 months, as did 9 on placebo.	1. High attrition: only 22/36 (61%) in drug group and 26/36 (72%) in placebo completed the study. 2. Only about half the children were able to take cholestyramine in the amount prescribed, primarily because of unpalatability.
Tonstad, 1998[255] (See Tonstad 1996[81])	22 (61%) of 36 in the cholestyramine group, and 26 (72%) of 36 in the placebo group completed 1 year. Dropouts were usually due to unpalatability of the drug.	
West, 1973[256]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
West, 1975[257]	The effect of cholestyramine on intestinal absorption	Descriptive study UK	To monitor the effect of long-term treatment on the absorption of fat, vitamins, and some minerals among children with FH treated with cholestyramine.	1 to 2.5 years
West, 1975[258]	Treatment of children with familial hypercholesterolemia	Observational London	To report the results of three different treatment regimens used to control cholesterol in children with heterozygous familial hypercholesterolemia (familial type II hyperlipoproteinemia) over an 8 year period.	Varied, 2-8 years

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
West, 1975[257]	Children with the HeFH. IN the majority there was a history of premature ischemic heart disease in a near relative. None of the children had any evidence of heart disease, two had corneal arcus, and one had skin xanthomata and was also overweight.	18	Age 1-14 years
West, 1975[258]	45 children with diagnosis made as the result of a family study of serum lipoproteins carried out because of premature coronary heart disease in a near relative (often a parent); diagnosis confirmed by identification of the lipoprotein abnormality in a t least one other first degree relative.	45 children	23 boys, 22 girls ages 1-16

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
West, 1975[257]	Subjects were treated with Questran brand cholestyramine. For 16 children, treatment was given twice daily in a dose of 0.2 to 1.1 (mean 0.6) g/kg/day. Two children took an equivalent dose 3 times daily. Eight children remained on their normal diet, and 10 were initially given a diet low in saturated fats supplemented with corn oil and corn oil products. No patient received vitamin or mineral supplements. For most patients, hemoglobin, prothrombin time, plasma calcium, phosphorus, protein, and alkaline phosphatase, serum folate, iron, and vitamins B12, A, and E were estimated in the majority before treatment and at 3 month intervals thereafter. Red blood cell folate was not determined at baseline was later added to the investigations.	With prolonged treatment, folate deficiency occurred: mean serum folate decreased from 7.7 ng/ml pre-treatment to 4.4 ng/mL for patients on treatment for over 1 year; a corresponding lowering of red cell folate also occurred. Oral folic acid 5 mg daily overcame this depletion. Prothrombin time remained normal in all patients. There was a significant decrease in mean serum levels of vitamins A and E and of inorganic phosphorus over the first 2 years of treatment, although values remain within the normal range. In children on a normal intake of dietary fat, five of 7 tested had fecal fat >5g/day while on cholestyramine. No child developed diarrhea, and growth has been normal. Levels of serum iron, vitamin B12, plasma calcium, and protein did not change significantly.
West, 1975[258]	Three different regimens: 1. Diet modification alone (17 children): Diet consisted of a reduction in ordinary fat intake to about 18 g/day, and use of corn oil. 2. Dietary modification with clofibrate (9 children): clofibrate was administered 18-28 mg/kg/day; diet same as that above. All of these children failed diet alone before starting clofibrate. 3. Cholestyramine (36 children): given as Questran in a total daily dose of 0.3-1.1 g/kg/day given in two equal divide doses in most children. Initially, low saturated fat diet was given with cholestyramine but then changed to allow most children to consume a reasonably normal diet. Several children were managed sequentially be more than one regime.	Diet: lack of compliance Clofibrate: intolerance of drug No obvious short-term side effects were apparent with diet alone, or diet and clofibrate, but adherence to these regimens was poor. The growth rates of the 3 children maintained on diet alone have been normal. Cholestyramine: unpalatable in some. Side effects have included folate deficiency, steatorrhoea, and reduction in serum levels of vitamins A and E and of inorganic phosphorus although not to abnormally low values. (see withdrawals) Cholestyramine:

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
West, 1975[257]	NR	
West, 1975[258]	Diet: By the end of 18 months, only 20% of the group were either satisfactorily maintained (at a cholesterol 10% lower than baseline). Clofibrate: By 2-1/2 years, no child was still on the drug (stopped on their own, or stopped because of inadequate cholesterol lowering). Cholestyramine: A few children stopped the drug after a short period because they found in unpalatable. After 2 years of treatment 72% remained satisfactorily controlled and after 3 years this number was 57%.	Poor - can't tell really who got what, for how long, or which children switched regimens.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
West, 1980[259]	Long-term follow-up of children with familial hypercholesterolemia treated with cholestyramine	Observational London	To assess the impact of cholestyramine in children with FH.	1-8 years
Other drug therapies				
Baker, 1982[54]	Treatment of homozygous familial hypercholesterolemia with probucol	Open-label clinical study 10 HoFH patients aged 8-46, of whom 5 underwent portacaval shunt operation prior to probucol treatment.	To evaluate the effects of probucol in 10 HoFH patients	15-21 months

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
West, 1980[259]	children with FH as defined by 1) elevated plasma beta lipoprotein and cholesterol concentrations (cholesterol above 7 mmol/L or 270.7 mg/dL) in the patient, in the absence of other disease that could cause hyperlipidemia and with a first-degree relative who either had the same pioprotein disorder or who had died of IHD before age 45.	35 children	16 girls, 19 boys ages 1.3-17.4 years (mean 8.4) 8 sibling pairs.
Other drug therapies			
Baker, 1982[54]	Homozygous familial hypercholesterolemia based on presence of i) serum TC consistently > 14.3 mmol/l, ii) appearance of xanthomas in the first decade of life, and documentation in both parents of hypercholesterolemia or clinical signs indicative of the heterozygous state.	Included 7 children/adolescents aged 6, 8, 9, 11, 16, 18, 21 .	7 pediatric subjects: 2 males aged 8 and 16 5 females aged 6, 9, 11, 18, and 21

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
West, 1980[259]	For 8 children cholestyramine was started as initial therapy. For 27 patients initial treatment had been with a low saturated fat diet-- this either could not be tolerated long term or failed to lower the cholesterol levels below 6.5 mmol/L (251.3 mg/dL). Cholestyramine was started at 2 g or 4 g twice daily before meals, the dose gradually increased until either the plasma-cholesterol concentration was below 250 mg/dL or until the maximum tolerated dose was being taken. All patients were given 5 mg folic acid supplements daily.	Almost all children expressed some dislike of cholestryamine, and a few complained of transient gastric fullness after taking a dose. No patient had persistent constipation, loss of appetite or diarrhea. No other symptoms were reported. One girl (age 18.6 yrs) stopped medication after 79 months on cholestryamine because she developed nausea, dizziness and malaise.
Other drug therapies		
Baker, 1982[54]	All patients were kept on a low-cholesterol, low-saturated-fat diet supplemented with 30-60 ml maize oil daily for at least 3 months before starting probucol treatment. Two patients aged 8 and 9 were given probucol 250 mg bid, 8 patients were given 500 mg bid (one reduced to 375 mg dose because of nausea).	One patient developed nausea on 500 mg bid after 10 months, and the dose was reduced to 375 mg bid for 5 months; thereafter was given 500 mg/day without recurrence of nausea. No significant changes were noted in the results of endocrine, hepatic, or hematological investigations. In particular, The levels of total T1 and T4 and of free T1 and T4 did not alter. Otherwise probucol was well tolerated. "The probucol regimen was simple, convenient, well tolerated and did not interfere with growth and development in children or adolescents."

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
West, 1980[259]	2 children refused further medication after the first dose. 1 boy died of tercurrent infection 10 months after starting cholestryamine. Only 55% remained on treatment after 6 years; 48% after 8 years. Of the 25 children under age 10 who were started on cholestryamin, 14 or 67% remained on treatment at the end of the study period as compared with 1 of the 10 (13%) of the children over age 10 ($p<0.05$).	No intention-to-treat analysis.
Other drug therapies		
Baker, 1982[54]	Otherwise probucol was well tolerated. "The probucol regimen was simple, convenient, well tolerated and did not interfere with growth and development in children or adolescents."	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Becker, 1992[264]	Long-term treatment of severe familial hypercholesterolemia in children: effect of sitosterol and bezafibrate	Open-label clinical study Germany	To determine the effects of sitosterol and bezafibrate in sequence for 3-month periods, and a combination of both drugs at half-dose for 24 months, on serum lipid levels. Laboratory safety parameters, ultrasonography, and physical examination assessed side effects.	30 months exposure to drug: 3 month diet 3 month sitosterol 3 month bezafibrate 24 months sitosterol plus bezafibrate
Brun, 1980[265]	Effects of dextrothyroxine on the pituitary-thyroid axis in hypercholesterolemic children and goitrous adults	Descriptive Canada	To evaluate the effects of dextrothyroxine (D-T4) on the pituitary-thyroid axis, the study measured the secretion of TSH in response to TRH in six euthyroid children with FH. Since the effects of thyroid hormones appear to be mediated by specific nuclear receptors, the binding affinity of D-T4 was also studied.	12 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Becker, 1992[264]	1) family history of hypercholesterolemia and premature coronary heart disease in at least one first-degree family member 2) age 7 or older 3) total serum cholesterol >300 mg/dL and LDL >250 on at least 2 occasions with normal triglyceride levels after at least 3 months of strict dietary intervention 4) unsuccessful intervention with bile acid-binding resins 5) none of the children had phytosterolemia.	7 children with HeFH	Mean age 8.42 42.9% female
Brun, 1980[265]	FH criteria: one of the parents had tendinous xanthomas with increased levels of cholesterol in the LDL fraction. The children also had increased LDL. They were euthyroid and, due to their young age, had none of the clinical manifestations of FH except for hypercholesterolemia.	6	Aged 7-12 33% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Becker, 1992[264]	After 3-month diet that continued throughout the study, subjects received sitosterol pastils (3x2 g/d) for 3 months, followed by bezafibrate (2x200 mg/d) for 3 months, followed by sitosterol (3x1 g/d) combined with bezafibrate (200 mg/d) for 24 months. Safety was assessed by routine lab tests; abdominal sonography performed every 6 months.	After sitosterol: there was a slight but significant decrease in hemoglobin (-5%) and alkaline phosphatase activity (-19%). After bezafibrate: alkaline phosphatase remained lower and iron increased by 26%. After 24 months of combined drugs: transferrin increased 20%, reaching abnormal levels in 2 patients. All other lab values remained within normal range. Decrease in appetite for 2 weeks was reported by 2 patients at the beginning of sitosterol therapy. Physical exams and ultrasounds of gallbladder found no abnormalities during follow-up.
Brun, 1980[265]	All children were on a hypocholesterolemic diet at the time of the study. At the first visit, TRH stimulation (400 ug, iv) test was performed before and after 6 and 12 weeks of treatment with 6 mg D-T4 (choloxin). After 6 and weeks of therapy, the patient came back to the clinic for drug compliance assessment (via tablet counts), and measurements of serum T3 resin uptake and total T4 levels.	In the euthyroid hypercholesterolemic children before D-T4 treatment, the peak serum TSH response to TRH administration was normal. With D-T4 treatment, the secretion of both TSH and T3 in response to TRH was abolished. Also, an increase in the basal level of T3 was observed after treatment with D-T4. The high circulating levels of D-T4 and possibly of D-T3 after chronic administration of D-T4 may be responsible for the saturation of pituitary nuclear T3 receptors, resulting in the suppression of the TRH-induced TSH response.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Becker, 1992[264]	Children and parents reported a high degree of acceptance and compliance during all treatments.	
Brun, 1980[265]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Colletti, 1993[266]	Niacin treatment of hypercholesterolemia in children	Retrospective review of patients from 2 lipid clinics in Vermont (1986-1990) and Boston (1980-1991)	report of efficacy of niacin as single-drug treatment for hypercholesterolemia in children;	1-19 months, average 8.1 +5.3 months
Malloy, 1978[73]	Familial hypercholesterolemia in children: treatment with p-Aminosalicylic Acid	Single-blind random assignment pattern with cross-over at 6 months - drug USA in Children aged 5 to 21 years with severe familial hypercholesterolemia	To determine the effect of *p*-aminosalicylic (PAS) on serum cholesterol and triglycerides in 3 lipoprotein classes in children and adolescents with severe familial hypercholesterolemia.	1 year

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Colletti, 1993[266]	All children had been previously treated with diet and bile-acid sequestrants and had not reached NCEP goals; Niacin subsequently prescribed as sole treatment; this drug selected because of poor compliance (n=2) or anticipated poor compliance (n=11)with sequenstrant therapy, low HDL (n=6) and parent preference (n=2).	21 children ages 4-14 years	Baseline values (mean+s.d.): TC=7.84+1.13 mmol/L (303+44 mg/dL) LDL=6.28+1.16 mmol/L (243+45 mg/dL)
Malloy, 1978[73]	1. Severe familial hypercholesterolemia 2. Consistently elevated serum cholesterol while on $\geq$ 4 month diet restricted in cholesterol and saturated fats 3. No disorders known to contribute to secondary hyperlipidemia 4. No other serious disorder 5. No medications other than PAS 6. One parent with proven and one other in kindred with hypercholesterolemia.	20 enrolled	Median age: 12 years Female gender: 45%

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Colletti, 1993[266]	Niacin as sole treatment for hypercholesterolemia; maximum daily dose was 7-98 mg/kg of body weight.	one 7-year old girl developed a febrile influenza-like illness with elevated serum aminotransferase>400 IU/L two months after starting niacin treatment but before the first post-treatment lipid measurement. Pretreatment LFT's had been normal; Niacin at 1000mg/day sustained release was considered a possible cause of hepatitis and was discontinued. Dose reduced if nausea occurred. Flushing 71% itching 19% Abdominal pain 14% Nausea 14% headache 14% Constipation 5% Reversible serum aminotransferase elevations (dose related) in 6 patients; 4 with crystalline and 2 with sustained release form of niacin. 18 of 21 patients reported some adverse effect.
Malloy, 1978[73]	Dietary cholesterol and saturated fats restricted 4 months prior to and throughout the study. Subjects and their parents received monthly dietary counseling. Single-blind assignment to active drug (150 mg/kg/day, up to 8 gm/day) or placebo during first 6 months. Dose adjusted monthly for change in body weight. After 6 months, the alternate agent (placebo or active drug) was given for 6 months. Composite index of compliance for each subject based on interviews, tacit drug inventories, and tests for PAS metabolites. Monthly clinic visits including clinical exam.	No indicators of drug toxicity reported, other than mild gastric irritation that remitted with oral antacid treatment. No patient had occult blood in the stool at any time. No ophthamologic or hematologic abnormalities were observed. SGOT, SGPT, alkaline phosphatase, bilirubin, and glucose levels in fasting serum were consistently within normal limits in all subjects. There were no departures from expected growth curves during the administration of the active drug. Levels of TSH in serum were within normal range and showed no tendency to rise during treatment with PAS-C. Thyroxine levels were normal in all samples. Triiodothyronine levels were normal in all but two in active drug and 1 on placebo.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Colletti, 1993[266]	Drug discontinued in 1 pt for hepatitis; 1 for flushing; 1 for abdominal pain, 3 for vomiting; 2 for headache; 1 for elevation of serum aminotransferase, and 1 for poor compliance.	
Malloy, 1978[73]	Compliance was >50% for 11 subjects, <50% for 9 subjects.	Single-blind randomization No separate control group: patients served as own controls Only 11/20 subjects were > 50% compliant LDL change evaluated for 8 subjects only

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
McDuffie, 2002[267]	Three-month tolerability of Orlistat in adolescents with obesity-related comorbid conditions	Observational study, US	To study the safety, tolerability, and potential efficacy of orlistat in adolescents with obesity and its comorbid conditions.	3 months
Stein, 1989[268]	Treatment of familial hypercholesterolemia with drugs in children	Cross-sectional study/chart review Lipid clinic, US	To assess plasma lipid levels in children and adolescents who were on various drug regimens and who were attending a specialized lipid treatment center.	N/A (cross-sectional study/chart review)

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
McDuffie, 2002[267]	Obese white and African-American adolescents (aged 12-17) were recruited through newspaper ads and letters to local physicians for participation in a weight-loss study. Inclusion criteria: BMI > NHANES I, 95th percentile for age, sex, and race; and the presence of one obesity-related comorbidity: hypertension, type 2 diabetes or glucose intolerance, hyperinsulinemia, hyperlipidemia, hepatic steatosis, or sleep apnea. Exclusions: a major pulmonary, hepatic, cardiac, or musculoskeletal disorder, history of substance abuse or other psychiatric disorder, use of a anorexiant in the past 6 months, or weight loss in the past 2 months.	20 adolescents	Mean age 14.6 50% female BMI 44.1 kg/m2
Stein, 1989[268]	Clinic charts from 30 HeFH children and adolescents who had been treated with medication at the Cholesterol Treatment Center for 1 to 9 years were reviewed.	30 HeFH children	Mean age 5.5, range 1-20

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
McDuffie, 2002[267]	A registered dietitian instructed subjects and at least one parent or guardian how to follow a 500-kcal-deficit diet containing no more than 30% of calories from fat. Subjects were given orlistat (120 mg, 3 times a day with meals) as well as a multivitamin supplement. Subjects returned medication at 4-week intervals to assess adherence. Subjects participated in a 12-week comprehensive behavioral program that reinforced dietary principles, encouraged physical activity, and provided psychosocial support. Subjects were queried weekly about AEs. At 3-month intervals, a clinical pharmacist interviewed subjects with a comprehensive questionnaire to identify expected and unexpected AEs.	All but one subject reported two adverse effects on at least one occasion. Five of the 12 AEs queried: increased defecation, soft stools, fatty or oily stools, oily spotting on clothes, and increased flatus were reported by >50% of subjects. AEs were generally mild, limited to gastrointestinal effects related to increased fat excretion , and resolved within the first 6 weeks of treatment. A small but significant drop in 25-hydroxy vitamin D levels was seen at 1 month. 3 subjects required additional vitamin D supplementation despite the prescription of a daily multivitamin containing vitamin D. TSH, free thyroxine, glycosylated hemoglobin, calcium, phosphorous, magnesium, zinc, measures of iron stores did not change significantly during the study.
Stein, 1989[268]	After stabilization and maximal lipid reduction by diet, drug therapy consisted of a BABR, either colestipol or cholestyramine. Niacin treatment was added only when LDL lowering with resin alone was insufficient to decrease values below the 90th percentile. Three children with HoFH were also treated with a variety of drug combinations, usually consisting of a BABR (colestipol 15 to 30 g/day or cholestyramine 8 to 16 g/day), niacin (1 to 3 g/day), and in some cases, clofibrate. Six subjects with severe HeFH, where resin and niacin were inadequate, were entered into formal studies with an HMG CoA reductase inhibitor (lovastatin 80 mg/day or simvastatin 40 mg/day).	The combination of resin and niacin produced elevated liver enzymes (AST and ALT) and clinical symptoms of hepatotoxicity in one subject. Niacin in this subject was associated with a significant rise in liver enzymes, suppression of albumin, and clinical symptoms of hepatotoxicity. No adverse clinical or biochemical side effects were noted on the HMG CoA reductase inhibitor.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
McDuffie, 2002[267]	Subjects who completed treatment (85%) reported taking 80% of prescribed medication. Only one subject (5%) cited intolerance of adverse effects as reason for withdrawal.	
Stein, 1989[268]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Steinmetz, 1981[269]	Biological variations in hyperlipidemic children and adolescents treated with fenofibrate	Descriptive study France	To learn how effective fenofibrate is in treating hyperlipoproteinemia and whether it has secondary effects on the biological parameters assessed in clinical laboratory tests.	18 months
Wheeler, 1985[82]	Double blind trial of bezafibrate in familial hypercholesterolemia	DB randomized cross-over trial	To evaluate the use of benafibrate for lower cholesterol in children.	6 month crossover; 3 months on bezafibrate
Low-fat diet				
Cetta, 1994[279]	Growth patterns of hyperlipidemic children enrolled in a preventive cardiovascular health clinic	Retrospective, descriptive study Cardiovascular health clinic, US	To assess growth patterns of hyperlipidemic children enrolled in a preventive cardiovascular health clinic, by retrospective chart review.	2 years of follow-up

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Steinmetz, 1981[269]	17 patients were followed in the Diabetes Service. Most patients had hyperlipoproteinemia Type Iia; four had mixed Type-Iib.	17	Aged 4-19
Wheeler, 1985[82]	Diagnosis of FH established by TC>6.7 mmol/l (269 mg/1000 ml), a type IIa pattern on lipoprotein electrophorsesis and normal fasting TG (<1.5mmol/l) in the pt; with either similar lipoprotein abnormalities in one of the parents or premature CHD death in a parent and a similar lipid abnormality in another close relative.	14 children; all had previously been treated with dietary measures (inadequate to control cholesterol), had been recommended cholestyramine but refused to take it.	Aged 4-15 (mean 10.9)
Low-fat diet			
Cetta, 1994[279]	Entrance criteria: 1) hyperlipidemia (LDL $\geq$110 mg/dL or TG >95th percentile with a normal LDL), 2) lack of any chronic disease, 3) a minimum of 2 years of clinic participation.	63	Mean age 7.8 (range 2 to 16) 47.6% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Steinmetz, 1981[269]	All were put on a low-lipid diet (cholesterol <300 mg/day). After 3 6 months of diet, fenofibrate was given at 200 mg/day, readjusting to 100 or 300 mg/day if needed. Fasting blood samples were collected before treatment and after 3 months, and after 6, 10, 12, 14, or 18 months in 10 patients. Reference values were obtained from a group of children of healthy families.	The study found a significant and major decrease in total alkaline phosphatase activities, uric acid, and bilirubin. 4 or 17 subjects had increases in ALT activity of at least 100%, and in AST activity of at least 80%. These increases persisted as long as the treatment was maintained. A decrease was observed only if the treatment was suspended. Uric acid decreased significantly (mean change -20%). Bilirubin decreased significantly (mean change -19%). Inorganic phosphates decreased slightly but significantly. Albumin was unchanged. Alkaline phosphatase decreased by 15% on average. GGT activity decreased slightly (by 1.5 U/l). ALT increased by 9 U/l. AST increased by 11 U/l.
Wheeler, 1985[82]	1. Children asked not to change their diets 2. 10-20 mg/kg/day given bid (in 100 mg tablets) given for 3 months	1. One child had high alk phosphatase at the end of 3 months of bezafibrate (had a slight intercurrent infection, and values returned to normal) 2. Another child had slight transient rise in alanine transaminase during first 2 months on bezafibrate but values were normal by end of 3rd month 3. growth was satisfactory throughout trial 4. no other reports of adverse effects
Low-fat diet		
Cetta, 1994[279]	All participants were counseled to eat an AHA Step-One Diet and exercise regularly. Weight and height were measured 12, 30, and 48 weeks after the initial visit, and every 3 months thereafter. Dietary counseling, including review of 3 to 5-day diaries, was performed every 6 weeks up to 1 year after the initial visit, and subsequently every 3 to 6 months.	All participants experienced normal height growth. Throughout the follow-up period, no deviations from attained height growth curves were observed. Two female patients experienced weight loss (at ages 10 and 17, respectively) that crossed below 2 major attained-weight percentiles during clinic participation. One child had anorexia nervosa. The other child entered the clinic eating a parent-instituted "vegetarian diet" that was more restrictive than the prescribed AHA-Step-One Diet.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Steinmetz, 1981[269]	NR	
Wheeler, 1985[82]	In all but one case bezafibrate was detected in the urine on all measurements during the active drug phase, and in none of the measurements while on placebo. All children declared a strong preference for this drug as compared with cholestyramine used previously.	Rated poor quality No results prior to cross-over. No wash out period between cross over periods.
Low-fat diet		
Cetta, 1994[279]	Compliance with recommended exercise activities was not evaluated. Estimates of dietary compliance were performed based on diaries collected periodically throughout the study.	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Copperman, 1995[270]	Nutrient quality of fat- and cholesterol-modified diets of children with hyperlipidemia	Cross-sectional case comparison tertiary care ambulatory pediatric atherosclerosis prevention center	To assess the nutritional adequacy of low-fat, low-saturated fat, low-cholesterol-modified diets of children with hyperlipidemia.	At least 1 year
DISC Collaborative Research Group, 1995[219]	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)	RCT 6 centers Prepubertal boys and girls recruited from public and private elementary schools, by mass mailings to members of an HMO, and from pediatric practices	To assess the efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol to decrease LDL-C levels in children	3 years
Feoli-Fonseca, 1998[282]	Familial lipoprotein lipase deficiency in infancy: clinical, biochemical, and molecular study	Retrospective, descriptive study, Quebec, Canada	To describe the clinical and biochemical features of familial LPL deficiency presenting in infancy, to evaluate the safety and efficacy of severe dietary fat restriction, and to define the LPL gene defects responsible for the disease.	23 years reviewed; mean duration of follow-up per patient was 6.76 years

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Copperman, 1995[270]	All children in the study were from white middle-class families from suburban New York City area. Hyperlipidemic children were referred to the Schneider Children's Hospital Center for Atherosclerosis Prevention for evaluation and treatment. Controls consisted of 4th and 5th-grade children from a local elementary school recruited from 2 classes. These children were free of chronic illness and were consuming unrestricted diets.	54	Mean age 10.8 54% female
DISC Collaborative Research Group, 1995[219]	1. Girls aged 7 years, 10 months - 10 years 1 month; boys aged 8 years, 7 months - 10 years, 10 months 2. Average of 2 screening LDL-C values $\geq$ 80th and < 90th percentile for age and sex. 3. No medication or medical condition that could effect growth or blood cholesterol 4. No behavior problems in child or family likely to reduce adherence 5. Prepubertal 6. No plans to move within the 3 study years	663 (362 boys, 301 girls)	Mean age: boys 9.7 girls 9.0
Feoli-Fonseca, 1998[282]	Charts were reviewed for all patients with chylomicronemia who attended the lipid clinic of Hospital Sainte-Justine between 1972 and 1995. Inclusion criteria: presentation before 1 year of age, French-Canadian ancestry, and initial plasma TG > 10 mmol/L. 18 were selected; 16 were found to have LPL enzyme deficiency. To assess safety, the authors compiled available weight, height, and sex maturation stage data during the follow-up period, and hemoglobin levels and blood chemistry values of iron, alkaline phosphatase, total calcium, red blood cell folate, and albumin.	16	All patients were diagnosed at age <1 year. 62.5% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Copperman, 1995[270]	Subjects received individual nutrition counseling on a NCEP-Step 1 diet from a registered dietitian. Subjects and controls attended separate training sessions in which a registered dietitian instructed the children and/or families on the accurate completion of the food record and a food frequency questionnaire.	There was no significant difference in consumption of energy, minerals, or vitamins D and E between the groups. The children with hyperlipidemia consumed significantly more vitamin A ($p<0.005$).
DISC Collaborative Research Group, 1995[219]	Randomized to diet (334) or usual care (329). Diet: Behavioral intervention to promote adherence to a diet providing 28% of energy from total fat, less than 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75/mg (1000 kcal) per day of cholesterol (<150 mg/day). Family oriented, based on social learning and social action theory. 1st visit: eating pattern assessed and personalized program developed. In the 1st 6 months: 6 weekly and then 5 biweekly group sessions augmented by 2 individual visits of children with their family members. In the 2nd 6 months, 4 group and 2 individual sessions. Years 2 and 3: group individual and maintenance sessions held 4-6 x per year with monthly phone contacts between sessions. Usual care: Public educational publications on heart-healthy eating provided. Parents informed if child blood cholesterol high - no specific recommendations to see physician given. 3-year lipid results provided, with referral as clinically warranted.	No differences between groups in adjusted mean height, serum ferritin levels, or other safety measures. Serum ferritin decreased in both groups and the intervention group had slightly lower mean ferritin concentrations than did usual care at year 3 ($p=0.08$). In both groups, mean ferritin concentrations remained above the 75th percentile for age and sex. Risk of consuming less than 2/3 of the RDA was significant for vitamin E at all visits (baseline OR: 1.009; year 1 OR: 1.007; year 3 OR: 1.007; $p<0.0001$ for all visits); for zinc at all visits for boys (baseline OR: 1.004, $p<0.05$; year 1OR: 1.003, $p<0.02$, and year 3 OR: 1.004, $p<0.003$) and girls (baseline OR:1.007, $p<0.001$: year 1 OR: 1.008, $p< 0.0006$ and year 3 OR: 1.005, $p < 0.003$).
Feoli-Fonseca, 1998[282]	Dietary intervention was started in infancy at the hospital. Patients were first given an electrolyte solution intravenously or orally. Fats were progressively reintroduced to reach a level of 5% to 7% of energy as long-chain TG. Solid foods were added after 4 months. At 1 year of age the special formula was replaced by skim milk, and lean protein foods progressively added. Diet provided at most 10% of energy as long-chain TG.	2 children had abdominal pain requiring hospitalization, and another had a documented episode of acute pancreatitis 2 months after the introduction of an oral contraceptive agent. No persistent adverse effects on growth were seen. Abnormal values were observed for serum iron, alkaline phosphatase, and total calcium. All erythrocyte folate (15 measurements, 8 patients) and albumin (41 measurements, 11 patients) levels were within the normal range.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Copperman, 1995[270]	NR	
DISC Collaborative Research Group, 1995[219]	Attendance at intervention sessions averaged 96% during the first 6 months, 91% during the second 6 months, 91% during the second year, and 89% during the third year.	Rated good quality
Feoli-Fonseca, 1998[282]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Jacobson, 1998[280]	Normal growth in high-risk hyperlipidemic children and adolescents with dietary intervention	3-year longitudinal descriptive study	To assess the safety and efficacy of lowering dietary intake of total fat, saturated fat, and cholesterol in growing children and adolescents with severe hyperlipidemia.	3 years
Kaistha, 2001[285]	Overrestriction of dietary fat intake before formal nutritional counseling in children with hyperlipidemia	Cross-sectional study	To assess the nutritional adequacy of the diets of children with hyperlipidemia following medically unsupervised low-fat diets compared with children receiving unrestricted diets.	N/A: cross-section
Kuehl, 1993[227]	Effective control of hypercholesterolemia in children with dietary interventions based in pediatric practice.	RCT of parental and family education USA in children with TC $\geq$185 ages 2-15 (mean 7)	To identify and characterize a family-based group intervention to lower plasma cholesterol in children.	33 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Jacobson, 1998[280]	All children were diagnosed with hyperlipidemia and had been referred by their pediatricians. Patients who were older than age 15 at the first visit were excluded in order to minimize the effects of cessation of growth follow gin puberty. Subjects with secondary hyperlipidemia caused by hepatic, renal, or thyroid disease were also excluded. TC > 95th percentile for age, and had at least 3 visits over 3 years. Follow-up visits were at 3- to 6- month intervals.	138	Age range 2-15 46% female 84.1% white, 5.9% African-American, 8.7% Hispanic, 1.5% other race
Kaistha, 2001[285]	Children with hyperlipidemia were selected from patients referred Apr 1, 1996 to Dec. 31, 1997 to the Children's Cardiovascular Health Center (CCHC) at Columbia-Presbyterian Medical Center. 46 were found to be meeting current NCEP Step I diet recommendations for total fat (<=30% of calories). Exclusions: TG ?400 mg/dL or homozygous LDL-C receptor deficiency. Controls were recruited from local pediatric practices in the vicinity of the Medical Center. Controls were invited if their parents stated they were healthy, were free of chronic illness, and were not following a modified or restricted diet.	46 c/ hyperlipidemia 34 healthy controls	Mean age 9.7 47% female 57% Latino 43% white
Kuehl, 1993[227]	Children referred by physicians who participated in a seminar on the risk factors for atherosclerosis in children, identification and management of high cholesterol in children. 14 pediatric practices referred 295 children.	295 children randomized to either a single session intervention (SSI) or a multi-session intervention (MSI)	SSI group: mean age 6.6 gender: NR race: NR MSI group: mean age 7.6 gender NR race NR

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Jacobson, 1998[280]	Diet restricting total fat content to 30% of total calories, and saturated fat to 10% of total calories. Anthropometric measures, lipid profiles, and dietary assessment were obtained at each visit.	The participants grew as expected during the follow-up period. There was no significant change in height or weight percentile, expressed as Z score, from baseline to 3-year follow-up.
Kaistha, 2001[285]	At baseline, children and parents were given a 3-day food record with detailed instructions and training by a registered dietitian. Children were asked to complete 3 days of food records, including 2 weekdays and 1 weekend day. No dietary counseling or guidance was given to children or parents at the time of diet-monitoring instruction. Anthropometric data were obtained at baseline, and nutrient intakes were analyzed.	A significantly ($p<0.05$) greater proportion of children with hyperlipidemia consumed below 75% of the RDA/DRI for Vitamin E and calories, compared with controls. 90% of the decrease in caloric intake could be accounted for by a decrease in total fat intake. Many children in both groups also did not meet the RDA for folate and calcium, but between-group differences were not significant.
Kuehl, 1993[227]	1. SSI=one 90 minute nutrition education session for patient, siblings and parents (slides presentation, low fat food prep and tasting, distribution of fruit and cereal). "Returned for subsequent food sampling with nutritionist present" but no further formal education. 2. MSI= four 90 minute sessions with focus on food preparation for breakfast, snack, lunch and dinner. Received notebooks with nutrition information and recipes, incentives for attendance and completion of behavioral contracts (eating low fat meal) SS outcomes were measured at baseline, 8.5 weeks and 21 weeks MSI outcomes were measured at baseline, 9 weeks and 33 weeks	Both groups maintained iron intake at over 87% and calcium intake at over 81% of the RDA throughout the study. % RDA of iron reported baseline to visit 2: MSI 103+/-5 to 98+/-5 (pNS); SSI 87+/-4 to 90+/-4 (p=NS). All patients "grew linearly with a mean height increase of 2.0+/-0.3 inches in the MSI group and 2.0+/-0.1 in the SSI group. Both groups had a mean weight increase of 4.1 lbs. Growth parameters not significantly different between the two groups.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Jacobson, 1998[280]	NR	
Kaistha, 2001[285]	N/A: cross-section	Authors comment that the findings suggest that without formal nutritional counseling, parents of children with hypercholesterolemia may inadvertently overrestrict calories in their children's diet by attempting to eliminate obvious sources of dietary fat.
Kuehl, 1993[227]	"Compliance with providing food records was excellent during the intevervention."	Poor quality: Large and unequal drop out rates (35% for SSI and 16% for MSI) and analyses only use those who completed the second blood draw (215 of original 295); ie not intention to treat. No assessment of intervention fidelity. 18% of MSI and 20% of SSI had plasma TC values <170 and were excluded from the analyses because they didn't meet the initial referral criteria of TC $\geq$185.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Lavigne, 1999[281]	A cholesterol-lowering diet does not produce adverse psychological effects in children: three-year results from the dietary intervention study in children	RCT 6 centers Prepubertal boys and girls recruited from public and private elementary schools, by mass mailings to members of an HMO, and from pediatric practices	To describe the 3-year psychosocial safety results of the DISC study, in which a wide range of possible behavior and cognitive problems were assessed.	Mean length of follow-up 36.2 months
Lifshitz, 1989[278]	Growth failure - a complication of dietary treatment of hypercholesterolemia	Observational study, US	To describe 8 patients with growth failure among a group of 40 children who were advised by their pediatricians to eat a low-fat, low-cholesterol diet for the treatment of hypercholesterolemia. They consumed inappropriate diets with insufficient energy and micronutrients to sustain normal growth and weight gain.	Mean time from dx to nutritional consultation: 20.1 mos. for patients with growth failure; 3.9 mos. for patients without growth failure ($p<0.001$)

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Lavigne, 1999[281]	Children were eligible if the average of 2 LDL screening values was between 80-98th percentile, aged 8-10, and prepubescent (Tanner Stage 1). Exclusions were taking medication that affected growth or cholesterol; onset of puberty, non-English speaking; in a remedial special education class; high parental alcohol consumption; or total behavior problem score on CBCL >98th percentile.	663	Aged 8-10 47% female
Lifshitz, 1989[278]	40 children were referred in 1986-1987 to the Nutrition Center, Division of pediatric endocrinology, North Shore University Hospital in NY because of hypercholesterolemia. The children had no other medical abnormalities.	40	87.5% Tanner Stage I 10% Stage II 2.5% Stage III Mean age at diagnosis 7.7

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Lavigne, 1999[281]	A total of 663 8- to 10-year-old children with elevated LDL were randomly assigned to either an intervention or a usual-care group. Intervention included group and individual counseling sessions to assist participants in adopting a dietary pattern containing 28% or less of calories from total fat (<8% saturated fat, up to 9% polyunsaturated fat, and 11% as monounsaturated. fat) and dietary cholesterol intake of less than 75 mg/1000 kcal. Psychological measures included academic achievement (W-J), family cohesion or conflict (FES), total behavior problems (CBCL), diagnosed eating disorders and suicide threats, trait anxiety (STAIC), or depression (CDI).	3-year results showed no adverse effects of treatment in academic function, psychological symptoms, or family function. When statistically significant effects were observed, they generally indicated a beneficial effect from the dietary intervention. At 3 years, there were no significant treatment group differences in CBCL total behavior problem, externalizing, or internalizing scores. However, the intervention group scored significantly lower on CBCL Thought Problems and Social Competence subscales. Intervention-group girls had lower CBCL Anxious-Depressed subscale scores than usual-care-group girls (-0.029, p<0.05). There were no treatment group differences in CBCL Aggression or Conduct Problem subscale scores. Self-reports of anxiety showed no differences between groups, but self-reports of depression were significantly lower for the intervention group than for the usual-care group (-0.75, p<0.05)
Lifshitz, 1989[278]	The referring physician gave general advice to reduce levels of dietary fat and cholesterol at the time of diagnosis. The specific recommendations varied in each case, and implementation by the families was unsupervised. The patients' dietary intake and food patterns were evaluated the Nutrition Center 2 weeks to 4.5 years after diagnosis. Weight and height records throughout life were plotted on standard growth charts. Body composition was assessed by arm measurements as described by Frisancho.	8 (20%) of 40 patients had growth failure. Three of the 8 had nutritional dwarfing according to the anthropometric indexes of the Welcome Trust Classification, with no progression of puberty. The other 5 had a drop in body weight without linear growth alterations. Total dietary energy and zinc content of patients with growth failure were significantly less than those with normal growth. The diets of patients with growth failure provided an average of 66% of energy requirements and 40% of daily zinc requirements for their ideal body weight, age, and sex. Patients with normal growth consumed 84% of the energy requirements, and 58% of daily zinc requirements (p<0.05). Patients in both groups had similar fat intake: 25.4% with growth failure, 29.6% with normal growth; cholesterol and protein intake were also similar and appropriate (14.6% to 15.9%). The 3 patients with nutritional dwarfing had inadequate intake of vitamins and minerals: <50% RDA of vitamins B6, D, folacin, zinc, iron, calcium, and magnesium, and <66% of RDA for vitamins A and B12, niacin, and phosphorus. Only vitamins E and C were adequately consu

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Lavigne, 1999[281]	Compliance not reported. A total of 96% of the intervention and 92% of the usual-care participants returned for the 3-year follow-up visit.	
Lifshitz, 1989[278]	NA	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
McKenzie, 1996[274]	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	Prospective cohort study, Pennsylvania, US	To determine change in nutrient intakes, number of servings, and contributions of total fat from food groups in children who lowered their dietary fat intake.	3 months
Moreno, 1998[275]	Lymphocyte T Subset Counts in Children with hypercholesterolemia receiving dietary therapy	Descriptive study	To investigate the immunological effects of a step 1 diet from the NCEP in children and adolescents with hypercholesterolemia.	6 months

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
McKenzie, 1996[274]	The CHP was a prospective cohort study (1991-1994) with three groups of children aged 4-10 with hypercholesterolemia (LDL between 80th-98th percentiles) and one age- and gender-matched group of children with normal cholesterol. All children were recruited via their pediatricians' offices in suburbs north of Philadelphia.	300 children from suburbs north of Philadelphia, PA	aged 4-10
Moreno, 1998[275]	Hypercholesterolemic children were recruited from 3 groups: children whose parents presented dyslipoproteinemia; children whose parents suffered from early ischemic heart disease, and children with hypercholesterolemia detected by routine analyses. Excluded immunological diseases, use of corticosteroids or immunosuppressive drugs in previous month, hepatobiliary diseases and/or secondary dyslipoproteinemias.	42	Aged 7-15.9 years

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
McKenzie, 1996[274]	Participants were assigned randomly to one of four study groups. 2 groups of hypercholesterolemic children received different forms of nutrition education: One group of children and their caregivers received face-to-face counseling with a registered dietitian and had free telephone access to the dietitian during the study. The other group was provided with an at-home parenting autotutorial program (PCAT). Both programs promoted NCEP recommendations: total fat ≤30% of energy, ≤10% saturated fat; cholesterol ≤100 mg/1000 kcalories. The third group of hypercholesterolemic children and the control group received no formal nutrition education. Three 24-hour dietary recalls were collected by telephone interview at baseline and 3 months later, and measured for nutrient and food group intakes.	Regardless of study group, 74% of all the children failed to consume two thirds of the RDA for vitamin D. Children in this study had on average adequate intakes of all other nutrients, when they reduced their fat consumption.
Moreno, 1998[275]	Patients and at least one parent met with a pediatric nutritionist who established recommendations based on NCEP Step 1 diet (total fat 30%, saturated fat 10% of total energy). Detailed 24-hr dietary recalls were obtained at baseline, and 6 months after beginning therapy. Physical activity habits were not modified during the study. At baseline and 6 months, fasting blood was analyzed for lipoprotein profile, immunoproteins, and lymphocyte T subsets.	Lymphocyte T subset counts (CD3, CD4, and CD8) showed significant decreases after 6 months of dietary therapy. In all cases, lymphocyte T subset counts remained within normal ranges. Changes in CD3 and CD8 counts were significantly correlated with changes in triglyceride serum levels ($p<0.05$). The other immune indexes (immunoglobulins G, A, M, and complements C3, C4, and Factor B) did not change significantly.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
McKenzie, 1996[274]	NR	
Moreno, 1998[275]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Obarzanek, 2001[218]	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)	RCT Six clinical centers in the USA	To evaluate the long-term safety and efficacy of a cholesterol-lowering diet in children with elevated LDL	4 years
Rose, 1976[277]	Primary hyperlipoproteinemia in childhood and adolescence: identification and treatment of persons at risk for premature atherosclerosis	Descriptive study Toronto, Canada	To identify primary and familial hypercholesterolemia in children and adolescents; perform dietary treatment and continued assessment of effects and side effects of therapy.	16 patients followed for 1 year; 9 patients followed > 1 year

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Obarzanek, 2001[218]	1. Average of 2 LDL-C values in 80th - 98th sex-specific percentiles for 8 - 10 year old children in a fasting state 2. No medical conditions or medications that could effect growth or serum cholesterol, behavioral problems or onset of pubertal maturation.	663 randomized, 334 to intervention 329 to control	Intervention group Mean age: 9.5 (.74) Female gender: 46% Race: 86.5% of entire study sample white Control group Mean age: 9.5 (.70) Female gender: 44% Race: 86.5% of entire study sample white
Rose, 1976[277]	The populations screened were 936 patients at pediatricians' offices, 1232 inpatients without conditions likely to cause secondary hyperlipidemia, and 1845 patients with congenital heart disease attending the outpatient clinic or being investigated in the cardiac catherization lab. Betalipoprotein cholesterol was quantified in serum from subjects in whom the initial diagnosis was primary hypercholesterolemia and from children with borderline abnormal cholesterol values on repeat examination. Secondary causes of hypercholesterolemia such as diabetes, renal or liver disease, hypothyroidism and dysglobulinemia were excluded. Parents and siblings of affected individuals were screened to assess whether the primary lipid abnormality was familial.	4013 were screened; 16 cases of primary hyperbetalipoproteinemia were identified	Age range: 1 month to 20 years

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Obarzanek, 2001[218]	Randomized to dietary intervention or control group. Intervention: Dietary behavioral intervention that promoted adherence to a diet with 28% of energy from total fat,< 8% from saturated fat, up to 9% from polyunsaturated fat, and <75 mg/1000 kcal cholesterol per day. Control: Usual care - parents informed child's blood cholesterol high and were given educational materials on heart-healthy eating as available to the public. Annual examinations for study-wide measurements. Intervention: 1st six months: 6 weekly and then 5 biweekly group sessions led by nutritionists and behaviorists, and 2 individual sessions with nutritionist. 2nd six months: 4 group and 2 individual sessions. 2nd and 3rd years: group and individual maintenance sessions held 4 - 6 x/year, with monthly phone contacts between group sessions. 4th year: individualized approach with motivational interviewing and stage of change. 2 group events and 2 individual visits annually, with individual phone contacts "as appropriate".	No differences at any data collection point in height or serum ferritin or any differences in an adverse direction in red blood cell folate, serum retinol and zinc, sexual maturation or body mass index.
Rose, 1976[277]	A diet low in cholesterol and high in polyunsaturated fats was instituted.	Growth and development of these patients has progressed according to growth percentiles and no side effects of therapy have been detected.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Obarzanek, 2001[218]	Intervention attendance diminished from an average of 96% in the first 6 months to 89% during year 3, and 72% during year 5. After year 5, in the last 3 years of intervention, the percentage of intervention children having 2 or more visits per year decreased from 55% to 42% to 37%, and on average 1.8, 1.4, and 1.3 intervention contacts per participant per year were achieved.	
Rose, 1976[277]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Sanchez-Bayle, 1994[276]	Diet therapy for hypercholesterolemia in children and adolescents	Observational Spain	To evaluate the effectiveness and compliance of dietary restriction in a group of children and adolescents with hypercholesterolemia, and monitor growth velocity.	6-24 months (29 for 2 years; 160 for 1 year; 262 for 6 months).
Sanchez-Bayle, 2003[283]	Influence of dietary intervention on growth in children with hypercholesterolemia	Prospective descriptive study, Spain	To determine whether a moderately reduced fat diet affects longitudinal growth in children with hypercholesterolemia	Mean 7.42 years
Segall, 1970[272]	Effects of short-term high-carbohydrate feeding on serum triglyceride of children with familial hypercholesterolemia	Observational London	To described the effects of high carbohydrate diet on triglycerides in children with FH.	10 days

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Sanchez-Bayle, 1994[276]	507 children referred to Nino Jesus Children Hospital after school-based screening showed a total cholesterol value of 200 mg/dL or higher. More complete lipid study was performed after fasting, and those with cholesterol persisting above 200 mg/dL and LDL above 130 mg/dL were included. Of these 471 meeting criteria, 18 did not show up for 1st visit, 38 were unavailable for f/u.	451 children and adolescents 2-18 years	211 males (46.8%), 240 females (53.2%)
Sanchez-Bayle, 2003[283]	Children who had a TC > 200 mg/dL and LDL > 135 were included. Children with chronic disease were excluded.	144 children in Madrid, Spain	Age 2-13 y, mean age 5.53 at beginning of treatment 52% female
Segall, 1970[272]	Unclear	5 children with HeFH (6 total but results presented here without his data).	age range 6-15, 4 female and 1 male

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Sanchez-Bayle, 1994[276]	Dietary treatment was according to the AHA Step-One Diet proceeding to Step-Two Diet when TC persisted above 240 mg/dL after 5 months. Dietary counseling was given by one pediatrician to both parents and the child. Detailed written recommendations were given to each family. All subjects were advised as to the necessity of aerobic exercise and dangers of tobacco	Growth velocity was found to be normal in all subjects.
Sanchez-Bayle, 2003[283]	AHA Step-1 diet was implemented, proceeding to Step 2 if TC > 240 persisted after 5 months, as well as OMS 1985 and 10th RDA recommendations for caloric intake by age. Dietary counseling was given to both parents and children by the pediatrician. Compliance was assessed at 1 month, 6 months, and each year using a questionnaire. Patient weight and height were measured each year and compared with growth standards for Spanish children.	Change in Z-score for height was not affected by moderate dietary fat restriction (0.58 baseline to 0.45 endpoint). Subjects had a significant increase in weight ($p<0.001$), from Z xcore of 0.33 at the beginning of the study, to 0.58 at endpoint. The authors conclude that growth is not influenced by moderate fat restriction.
Segall, 1970[272]	10 day high carbohydrate diet: 75% of total calories from carbohydrate (of which 75% sucrose); 10% from fat and 15% from protein. Diet was given as normal foods and was isocaloric with home diet prior to intervention. Only 3 of the 5 children had blood levels measured after 10 days.	1 child lost 1.4 kg.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Sanchez-Bayle, 1994[276]	Follow-up was 100% at 6 months; 42% at 1 year and 6% at 2 years. Authors report 69% compliance with diet at 1 year, but data presented for 189 (42%) participants.	
Sanchez-Bayle, 2003[283]	Assessed but not reported	
Segall, 1970[272]	NR	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Tershakovec, 1998[284]	Growth of hypercholesterolemic children completing physician-initiated low-fat dietary intervention (PCAT)	RCT of dietary intervention USA	To evaluate the growth of hypercholesterolemic children completing a physician-initiated home-based nutrition education program or standard nutrition counseling to lower dietary fat intake.	12 months
Tonstad, 1996[271]	Psychosocial function during treatment for familial hypercholesterolemia	Cross-sectional study Norway	To determine whether children treated for FH have a greater psychosocial burden than their peers.	N/A (cross-sectional); children treated for 18 mo-=9 yrs prior to this study

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Tershakovec, 1998[284]	1. Mean fasting plasma LDL-C 107-164 mg/dl for boys and 112-164 mg/dl for girls 2. Free of secondary causes of dyslipidemia 3. At least 85% but not greater than 130% of ideal body weight	261 children with hypercholesterolemia recruited from 9 suburban pediatric practices, randomized to home-based education (PCAT) standard nutrition counseling or at-risk control group. Not-at-risk control group randomly selected from children whose TC was not elevated	Children aged 3.9 - 9.9 years recruited from 9 suburban pediatric practices PCAT group Mean age: 6.3 + 0.2 Female gender: 51% Counseling group Mean age: 6.2 + 0.2 Female gender: 50 At-risk control group Mean age: 6.4 + 0.2 Female gender: 48% Not-at-risk group Mean age: 6.4 + 0.2 Female gender: 51% Race of all participants stated as 84 - 99% white.
Tonstad, 1996[271]	FH diagnosis was made if the child had a TC >259 mg/dL, and if one or both parents and other relatives had TC >300 mg/dL or tendon xanthomas or if the LDL receptor mutation was identified (this was the case in 77%). 5 were excluded for familial combined hyperlipidemia, 3 for HoFH, 1 for a disabling chronic disease, and 1 for mental retardation.	185 children from 156 families	44.9% female Aged 7-16

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Tershakovec, 1998[284]	PCAT and counseling groups complied with recommendations of the National Cholesterol Education Program Expert Panel on Blood Cholesterol Levels in Children and Adolescents. PCAT: 10 talking books lessons and follow-up pencil/paper activities for children with manual for parents based on social cognitive theory. A story and activity completed each week for 10 weeks. Counseling: Child and at least 1 parent had 45-60 minute session with a pediatric registered dietitian. Controls: Not provided educational information or materials Measures evaluated at baseline, 3, 6 and 12 months	None noted. Outcomes included 1. Height 2. Weight 3. Skinfold measures 4. Dietary intake Percent calories from fat was associated with weight z-score ($p<0.01$), weight for height median ($p<0.005$), and sum of skinfolds ($p<0.05$). Caloric intake was positively associated with weight ($p<0.005$) and height ($p<0.005$) z-scores and weight for height median ($p<0.01$). After controlling for age, no significant time-related among-group differences were observed for the height or weight z-scores, weight-for-height median, caloric intake, or fat intake. Differences among groups in sum of skinfolds approached significance ($p=0.06$). Authors note results analysis shows these children could consume a relatively low-fat diet (down to 24.3% calories as fat in the lowest fat intake quintile group) and still maintain growth over the subsequent year.
Tonstad, 1996[271]	Mean years of treatment: 4 (range 1.5-9). Recommended diet was $\leq$30% total dietary energy from fat, <10% of total energy from saturated fat, and <100 mg cholesterol/1000 kcal. About 2/3 of children had been treated with BABRs at some point. Dietary compliance during the past year was assessed by food frequency questionnaire. Psychosocial assessments included the CBCL, the Teacher's Report Form, the Child Assessment Schedule, and the Children's Global Assessment Score. For a reference group, 2600 children aged 4-16 were sampled from the Norway Central Population Register and mailed the CBCL and TRF.	Overall behavioral and emotional scores of children with FH were similar to scores of a population-based sample. Mean CBCL scores and TRF scores for FH-children were similar to the reference group. YSR total and externalizing scores were lower in girls with FH than in the population. Total and content area CAS scores were similar for children with FH and the epidemiologic cohort, except for the scores for family, mood, and expression of anger, which were lower in the FH group. According to the CAS item, none of the children with FH had weight loss or gain indicating the presence of an eating disorder.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Tershakovec, 1998[284]	NR	Participants were from predominantly white and relatively affluent families; results may not generalize well. Diet evaluated by three 24-hour dietary recalls per assessment period
Tonstad, 1996[271]	Results of the FFQ indicated good compliance with the diet, except for a slight increase in saturated fat intake among girls with FH.	Assessments were made by parents and teachers.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Witschi, 1978[273]	Family cooperation and effectiveness in a cholesterol-lowering diet	Observational, uncontrolled study Boston, MA	To study the effect of a family dietary program for the purpose of lowering serum cholesterol	4 week baseline period followed by 3 week diet change period
Dietary supplements				
Amundsen, 2002[41]	Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia	Randomized, double-blind crossover Subjects recruited from patient register at Lipid Clinic of National Hospital in Oslo, Norway	To assess effect of SE-enriched spread on serum lipids, lipoproteins, carotenoids, fat-soluble vitamins, and physiologic variables in children with FH aged 7 - 12 years.	Study period: 25 weeks with run-ins and washouts 2 - 8 week treatment periods.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Witschi, 1978[273]	families recruited by notices in the academic community, telephone prescreening in the community and letters to volunteers for a prior study. Eligible if 1) an adult and at least one adolescent all living and eating most of their meals at home.	91 adolescents	55% female, age NR
Dietary supplements			
Amundsen, 2002[41]	Not specifically noted. Implied: 1. Parent with hypercholesterolemia 2. Diagnosed with "definite" or "possible" heterozygous FH 3. Healthy, with no clinical symptoms of hypercholesterolemia	38 2 non-study-related drop-outs; 1 drop out because the amount of spread required to be consumed was too large.	Mean age: 10.5 + 1.7 50% female Cholesterol (mmol/L) total: 7.01 + 1.26 LDL: 5.39 + 1.42 HDL: 1.37 + 0.32 Triacyglycerol (mmol/L) 0.56 + 0.22

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Witschi, 1978[273]	A food record was kept by each participants for two weeks during 4-week baseline period. Each family was assigned a nutritionist who maintained contact throughout the study. The diet was based on AHA guidelines for decreasing dietary cholesterol and saturated fat. Weight and blood samples were taken at beginning and end of baseline period, and days 10 and 21 of the 3-week diet-change period. Samples were assayed for cholesterol analysis.	No significant changes in weight.
Dietary supplements		
Amundsen, 2002[41]	Exposure: In a double-blind crossover, with two 8-week interventions, 38 children with FH consumed 18.2 + 1.5 g SE spread/day, corresponding to 1.60 + 0.13 g SE, or a control spread. Blood samples were analyzed at the start and end of each diet period. Subjects consumed a recommended American Heart Association Step I diet during both intervention periods.	ALT increased in SE diet 16.8% (p = 0.04). No subjects had plasma concentration of ALT outside the reference concentration at any time. Starting concentration of ALT was significantly lower in the SE diet period compared to control. Serum levels of lycopene and B-carotene decreased with SE. After adjustment for lipid changes, differences in B-carotene disappeared; lycopene concentration was still 8.1% lower (p=0.015) in SE compared to control. Serum levels of retinol were higher in SE, and after lipid standardization: 15.6% (p<0.001) higher than control. After lipid standardization,) a tocopherol was 7.1% higher in SE than in control (p=0.027). Authors note results may be influenced by different starting concentrations in SE than control.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Witschi, 1978[273]	Compliance was better among females than males. More than 60% of the families attained an adherence rating of "excellent" or "good" during the diet test.	
Dietary supplements		
Amundsen, 2002[41]	Children consumed 90.9% of the control spread and 91.7% of the SE spread. 32% of subjects felt that the amount of spread was too large, but 68% were satisfied with the amounts. 46% of subjects could recognize a difference between the 2 spreads but could not identify which was SE, of whom 56% indicated that the SE spread tasted better than the control spread.	Small N Many children used supplements or vitamins during the study. These variables were not analyzed separately. FH was confirmed by mutation analysis in only 25/38 subjects. Some included children may not have had FH, as baseline total and LDL cholesterol concentrations were significantly higher in the confirmed FH group.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Amundsen, 2004[287]	Long-term compliance and changes in plasma lipids, plant sterols, and carotenoids in children and parents with FH consuming plant sterol ester-enriched spread	Open-label trial, following RCT above	To look at any sustained long-term effect of plasma lipids and level of compliance following an uncontrolled free intake of plant sterol ester-enriched spread; to measure changes in serum concentrations of non-cholesterol sterols, fat-soluble vitamins and carotenoids in children and their parents during the extended open-label period.	26 weeks
Becker, 1993 [288]	Treatment of severe familial hypercholesterolemia in childhood with sitosterol and sitostanol	Open-label clinical study Germany	To compare the ability of two plant sterols to reduce serum lipid levels and to compare their mechanism of action in children with severe HeFH.	10 months: 3 on sitosterol 7 on sitostanol

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Amundsen, 2004[287]	41 healthy children were recruited from the patient register at The Lipid Clinic at the National Hospital in Oslo. All subjects were diagnosed with 'definite' or 'possible' heterozygous FH. The diagnosis was documented by the presence of an FH mutation in 25 of the children. In the other 16 subjects, the responsible mutation was still unidentified. All children were healthy and none had clinical symptoms of hypercholesterolemia or used serum cholesterol-lowering drugs.	37	mean 9.6
Becker, 1993 [288]	1) family history of hypercholesterolemia and premature coronary artery disease in at least one first-degree family member, 2) serum cholesterol concentration (TC and LDL) that was on two occasions 1.5 times >95th percentile for age and gender after at least 3 months of strict diet, 3) exclusion of phytosterolemia, a rare inborn error of hyperabsorption of plant sterols.	9 children with HeFH	Mean age 11.96 33.3% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Amundsen, 2004[287]	37 children were advised to eat plant sterol ester spread (20 g of spread per day, corresponding to 1.76 g/day of plant sterol). Blood samples were taken at weeks 1 and 26. A total of 13 children took fish oil supplements (5 ml/day) and eight children took multivitamin supplements during the study.	lipid-adjusted lathosterol levels were stable; sitosterol levels were 77% higher compared to control period of RCT. Lipid-adjusted retinol levels were 11% higher at the end of the open label period as compared to control. No changes in lycopene or lutein. lipid-adjusted serum a-carotene increased in the open label period following a decrease in the trial period.
Becker, 1993 [288]	After a 3-month diet, subjects were given sitosterol pastils (3x2 g/d) for 3 months, followed by a 7-month course of sitostanol (3 x 0.5 g/d). Safety was assessed by routine lab tests, and abdominal sonography of the liver and gallbladder were performed every 3 months to check for possible gallstone formation.	After dietary intervention, alanine aminotransferase was decreased. Decreases in alkaline phosphatase and carotene concentration were noted with sitosterol, but with sitostanol these returned to initial values. After 7 months of sitostanol, there was a slight but significant increase in transferrin concentration, and the total bile acid concentration in serum was significantly reduced. These changes did not reach abnormal levels. All other lab values (hemoglobin, leukocyte count, platelet count, calcium, phosphate, lipase, iron, creatinine, and creatine kinase) showed no change. Weight and height percentiles of all children remained normal throughout the study. No changes in stool pattern were reported. No abnormalities in liver and gallbladder were found.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Amundsen, 2004[287]	Children consumed slightly less spread (14 g/day vs 18 g/day during trial).	
Becker, 1993[288]	All 9 subjects completed the study. Children and parents reported a high degree of acceptance and compliance during all treatments.	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Clarke, 1990[289]	Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil	Descriptive study Ontario, Canada	To evaluate the potentially beneficial effect of dietary fish oil supplementation on plasma lipid levels in a small group of adolescent patients with familial hyperlipoproteinemia type II, and to note possible undesirable side effects.	6 months
Dennison, 1993[223]	Randomized, double-blind placebo-controlled, two-period crossover clinical trial of psyllium fiber in children with hypercholesterolemia	randomized cross-over trial of psyllium in children ages 5-17 with LDL>110 mg/dL already being treated with diet, recruited from Pediatric Lipid Control Center and from private pediatricians in the vicinity.	To assess whether psyllium was effect at lowering TC and LDL values in children beyond the reduction achieved by diet alone	4-5 weeks each period with a 2 week wash-out period between

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Clarke, 1990[289]	Diagnosis of FHL type II was based on a positive family history, typical abnormalities of plasma lipid levels, and absence of evidence of any other condition to account for the lipid abnormalities. All subjects were maintained on their usual modified low cholesterol/low sat. fat diet throughout the study; two also received colestipol, 10 g/day.	11	Age 11-21, 63.6% female
Dennison, 1993[223]	Children with LDL>110 mg/dL after treatment with diet.	25 children began the study; 4 did not return for the final blood drawing (3 because of parental difficulties - timing, logistics; 1 boy because he refused to eat the cereal and have his blood redrawn); 1 second blood sample was lost.	11 males; 9 females age 11.1+3.8 years

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Clarke, 1990[289]	After 3 months of pretreatment observation, each subject was given a commercial fish oil supplement (containing 18% eicosapentaenoic acid, 12% other omega-3 fatty acids, and vitamin E) in a dosage started at 1 g/day, and increased by 1 g/day at monthly intervals to a total of 5 g/day for the 5th and 6th months of therapy.	3 of 11 subjects had prolongation of bleeding time during fish oil supplementation. 8 of the 11 subjects had a total of 9 episodes of epistaxis during 62 subject-months of fish oil treatment; no subject reported any nosebleeds during 43 subject-months of pretreatment and posttreatment observation ($p<0.02$). One subject experienced prolonged bleeding time (9 minutes; control, 3 to 5 minutes). The subject had been receiving 5 g/day of fish oil at the time of withdrawal. Two other subjects experienced epistaxis associated with modest prolongation of the bleeding time (7 minutes); one of these had a history of acetylsalicylic acid ingestion at the time. One subject had asymptomatic occult blood in the stool on one occasion; the bleeding time was normal. None of the subjects had any evidence of liver dysfunction; all prothrombin and partial thromboplastin times and platelet counts were normal.
Dennison, 1993[223]	Diet consisted of <30% calories as total fat, <10% as saturated fat and <200 mg dietary cholesterol/day. Total calories enough to ensure adequate growth. Subjects instructed to eat two 28gm servings (1 0z or 2/3 c each) of the control cereal (5 mg water-insoluble wheat fiber per serving) or the psyllium cereal (3 gm of water-insoluble fiber and 3 game water-soluble fiber per serving). Cereals were similar in appearance and provided by same manufacturer.	One child (a 17 year old girl reported a transient increase in loose stools (3 /day) with the control cereal with resolved with discontinuation and reappeared with a second challenge of the control cereal and resolved post discontinuation. No changes in subscapular or triceps skin-fold thicknesses. Height and weight increased equally during consumption of control and psyllium cereals. None of vitamin or mineral levels tested were lower after the psyllium cereal.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Clarke, 1990[289]	In two subjects, therapy was stopped as a result of epistaxis.	
Dennison, 1993[223]	Compliance was 82% for both cereals.	baseline lipid levels not different significantly for those (n=5) who did not complete the study. Most families were unaware of which cereal was in use (2/3 of children or parents incorrectly identified the psyllium containing cereal).

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Glassman, 1990[290]	Treatment of Type Iia hyperlipidemia in childhood by a simplified American Heart Association (AHA) diet and fiber supplementation	Descriptive study Lipid clinic, New York	To determine whether the AHA Step-One diet would effectively lower serum total and LDL cholesterol levels in children for prolonged periods.	8.1 (+- 2.4) months
Gulesserian, 2002[291]	Effect of a rapeseed oil substituting diet on serum lipids and lipoproteins in children and adolescents with familial hypercholesterolemia	Descriptive study Vienna, Austria	To investigate how adolescents and families with FH would respond to a lipid lowering diet enriched with rapeseed oil and what effects on serum lipids can be observed.	5 months
Gylling, 1995[39]	Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia	Randomized cross-over trial of diet 14 children with HeFH Helsinki, Finland	To assess the effect of sitosterol rape-seed margarine vs. rape-seed margarine without sitosterol	6 weeks each arm

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Glassman, 1990[290]	Children with primary type Iia cholesterolemia (evaluated TC with normal or elevated TG concentrations) who were treated at the Children's Nutrition Center of the New York Medical College, Valhalla, between January 1 1988 and December31 1988. These patients were identified during routine screening by their pediatricians and had the diagnosis confirmed by lipoprotein electrophoresis after a 14-hour fast. The children were otherwise in excellent health and were receiving no medications.	36	Age range 9-17, mean 9.74 38.9% female
Gulesserian, 2002[291]	HeFH patients were selected from a pediatric outpatient clinic with the following characteristics: plasma TC levels >200 mg/dL), LDL > 130 mg/dL, TG <250 mg/dL, BMI range 10% to 90% percentiles. Of 43 potential subjects, 26 were excluded because they were not able to adhere to the study protocol or did not provide an appropriate dietary protocol.	43 were enrolled, but analysis includes only 17	Age range 4-19, median 12.7 64.7% female
Gylling, 1995[39]	Diagnosis of FH established in children and in one parent mostly by DNA technique	14 children with HeFH and 1 child with HoFH (2 years old)	7 boys, 7 girls Mean age 9.1+1.1 (2-15)

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Glassman, 1990[290]	Patients were treated with a modified version of the AHA Step-One diet at the Children's Nutrition Center of the New York Medical College. The diet, in which a maximum of 10% of the energy intake was derived from saturated fat, did not specifically restrict cholesterol intake or the percentage of total energy ingested as fat. In addition, children under age 7 were required to consume 2.5 g of soluble fiber as psyllium mixed in water twice daily. Children older than 7 received 10 g of psyllium. Each patient was reassessed at 6-week intervals using a 24-hour dietary diary, a food-selection checklist, and a serum lipoprotein electrophoresis. Serum zinc and copper levels, as well as prothrombin and partial thromboplastin times, were measured in 10 patients over the course of therapy.	All patients tolerated both regimens well without developing abdominal distention or cramping, constipation, diarrhea, or excessive flatus production. There were no changes in serum zinc, copper, or hemoglobin concentrations; hematocrit; mean corpuscular volume; or prothrombin and partial thromboplastin times during the period of study.
Gulesserian, 2002[291]	Diet therapy had 2 approaches: 1) replacement of as many visible fats as possible by rapeseed oil (including use preparation of meals, as in frying, baking, and salad dressing) and 2) reduction of dietary cholesterol. High dietary fiber was achieved by prescribing a high quantity of fruits and vegetables. During the study patients met the dietician 7 times, and the pediatrician 6 times. Compliance to the diet was checked by routine 3-day protocols with children and parents.	NR
Gylling, 1995[39]	Children were randomized to replace 24 g of their normal daily fat intake by the same amount of a rapeseed oil-rich margarine with or without sitostanol ester (M vs MS) . All children had previously been advised to use a low animal fat-low cholesterol diet rich in monogenic fatty acids for years. Protocol results in daily consumption of 3 gm of free sitostanol in MS group.	Children noted no difference in taste between the two margarines. Report "good compliance," and "well tolerated."

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Glassman, 1990[290]	All patients tolerated both regimens well.	
Gulesserian, 2002[291]	The diet was well accepted; no patient canceled the study due to dislike of the oil.	26 enrolled patients were not able to adhere to the study protocol or did not provide an appropriate dietary protocol. The report of compliance only includes the patients who adhered to the protocol.
Gylling, 1995[39]	Report "good compliance," and "well tolerated."	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Laurin, 1991[294]	Effects of a soy-protein beverage on plasma lipoproteins in children with familial hypercholesterolemia	RCT, crossover study Quebec City	To examine the effects of a beverage based on isolated soy protein in the diet on plasma lipid, lipoprotein-fraction cholesterol, and apolipoprotein concentrations in HeFH children.	4 weektreatment/4 week washout/4 week crossover treatment
McCrindle, 1998[235]	Garlic Extract Therapy in Children with Hypercholesterolemia	DB RCT: placebo-controlled trial of garlic extract 30 patients	To determine tolerance, compliance, safety, and efficacy of therapy with a commercially available garlic extract in lowering cholesterol in pediatric patients with hypercholesterolemia	8 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Laurin, 1991[294]	Hypercholesterolemic children from the Quebec City area where the heterozygote frequency of FH is ~2.5-fold higher than in most populations elsewhere. Baseline fasting concentrations of TC and LDL > 95th percentile adjusted for age and sex. Other criteria: detection of hypercholesterolemia in at least 2 first-degree relatives; the presence of tendinous xanthomas or type II· A lipoprotein pattern in 3 generations of relatives, or with compatible autosomal dominant transmission; exclusion of secondary forms of hypercholesterolemia. No subjects had fasting hyperchylomicronemia or type III hyperlipoproteinemia, recent weight loss (within 6 months), acute disease or major surgery in the past 3 months, and allergy to or dislike for milk.	10	Mean age 7.9 40% female
McCrindle, 1998[235]	Included patients age 8-18, a positive family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease in first-degree relatives, a minimum fasting TC > 4.8 mmol/L (>185 mg/dL), participation in a dietary counseling program, and compliance with a NCEP Step II diet for at least 6 months. Excluded secondary causes of hyperlipidemia or a history of major surgery or serious illness within 3 months prior to enrollment.	30 patients age 8-18	Mean age 14 53% male

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Laurin, 1991[294]	5 subjects per group were randomly assigned to receive either the cow-milk or the soy-beverage diet, with subsequent switch to the other diet in a crossover design, each diet and washout lasting 4 week. During the washout, subjects consumed their regular diet. The soy beverage was formulated to provide similar amounts of protein, carbohydrate, fat, calcium, and phosphorus as 2%-fat cow milk as well as a minimum of 20% of the US RDA of 16 other vitamins and minerals. The nutrient composition of the two experimental diets was comparable with their regular regimen, and the same menus were used for the two experimental periods.	All participants had adequate growth and development as verified by the tracking of each subject against physical-growth charts.
McCrindle, 1998[235]	Patients were instructed to stop taking lipid-lowering medications for ≥8 weeks prior to the study. Participants were instructed to take 1 capsule (containing 300 mg garlic extract or identical placebo) t.i.d. for 8 weeks. A random number generated list was supplied to an independent pharmacist who assigned patients consecutively when they were enrolled. Logbooks and questionnaires were used.	1 patient on garlic experienced unpleasant body odor, but had been working concomitantly on a garlic farm during the study period. The most commonly reported AEs were headache and upset stomach, but reporting of AEs was similar between garlic and placebo groups. There were no significant differences between groups in height, weight, blood pressure. The only significant differences in laboratory parameters were in serum albumin level (+2.0 g/L, p=0.002) and hemoglobin (+5.2 g/L, p=0.02) with garlic. 1 patient was unable to swallow the capsules and withdrew. Compliance was similar between garlic and placebo groups.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Laurin, 1991[294]	Authors report that good control over mean dietary intake was achieved, as indicated by similar percentages of protein energy consumed as a dairy source in the two experimental diets.	
McCrindle, 1998[235]	1 patient was unable to swallow the capsules and withdrew. Compliance was similar between garlic and placebo groups. 86% vs 93%, (p=0.34).	

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Mietus-Snyder, 1998[292]	Endothelial dysfunction occurs in children with two genetic hyperlipidemias: Improvement with antioxidant vitamin therapy	Non-randomized controlled trial 33 of 45 subjects were members of families followed in a lipid clinic. Control Group: Unaffected siblings or children with normal lipid profiles	To confirm the previously-reported finding of impaired endothelium-dependent vascular relaxation in children with FH, to extend these observations to other hyperlipidemic phenotypes and to assess the efficacy of antioxidant vitamin therapy in reducing endothelial dysfunction.	6 weeks
Sanchez-Bayle, 2001[293]	The effect of fiber supplementation on lipid profile in children with hypercholesterolemia	Observational study, Spain	To assess the effects of fiber supplements on lipid levels in children with dyslipidemia who were following a dietary treatment.	3 months
Schlierf, 1978[295]	Sitosterol in juvenile type II hyperlipoproteinemia	Randomized cross-over trial comparing verum (sitosterol) to placebo; 3 months each treatment. West Germany	To determine the effect of verum to placebo	6 months, 3 on sitosterol

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Mietus-Snyder, 1998[292]	1. Good health and diagnosed with heterozygous FH (LDL > 95th percentile, normal triglycerides, affected parent) or familial combined hyperlipoproteinemia (LDL or fasting triglycerides > 95th percentile, parent with 1 of 3 phenotypic presentations of FCH).	45 11 received treatment No withdrawals reported 18 subjects with FH 15 subjects with FCH 12 controls	Mean age: 12.5 56% female
Sanchez-Bayle, 2001[293]	Children with persistently elevated LDL (>135 mg/dL) after a minimum of 6 months dietary treatment (<30% calories as total fat, <10% as sat. fat, and <300 mg dietary cholesterol per day) were recruited from Hospital Nino Jesus in Madrid from 1989 to 1990. As a control group, 33 children with persistently elevated LDL were recruited from 1992 to 1993.	53 children in Madrid, Spain	Mean age 7.3 (range 4-18)
Schlierf, 1978[295]	NR	15 children and adolescents, randomized to receive either sitosterol (n=7)or placebo first (n=8).	Age 8-20

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Mietus-Snyder, 1998[292]	Exposures: Combined regimen of partial difference-alpha tocopherol (400 IU twice a day) and vitamin C (500 mg twice a day) for 6 weeks. At follow-up the protocol was repeated except for nitroglycerin administration. Brief medical history, physical exam, and nutritional counseling including American Heart Association diet guidelines. Vascular reactivity in brachial artery measured with high-resolution two-dimensional ultrasonography. Primary outcome was change in brachial artery diameter in response to either hyperemia or sublingual administration of nitroglycerin	No adverse effects of antioxidant vitamin therapy reported.
Sanchez-Bayle, 2001[293]	In addition to dietary restriction, children were given fiber supplements for 3 months in tablets that contained 50% wheat bran and 50% pectin and were given 2 to 3 times per day at doses of 50 mg/kg/day. Compliance with diet and fiber supplementation was confirmed by interview. Diet was assessed by a food frequency questionnaire and a 24-hour recall. Control families were instructed to maintain their current dietary restriction and subjects were re-evaluated 3 months later.	Two children reported abdominal discomfort and soft stools and refused to continue the study.
Schlierf, 1978[295]	Treatment: 12g of B-sitosterol granulate with 20g NaBr Placebo: 20g of NaBr with 12 g cellulose. Each taken in 3 portions of 4g, 30 minutes before meals.	3 patients terminated the study before completion, unclear reasons; in the other 12 plasma bromide levels, drug intake sheets and used med packs indicated good compliance. Sitosterol levels 0.88$\pm$0.24 in placebo group vs 1.48$\pm$0.62 in sitosterol group.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Mietus-Snyder, 1998[292]	"All subjects tolerated the study well, although approximately 1/3 complained of a transient, mild headache after nitroglycerin administration, coincident with a 10 to 20 mm Hg decrease in systolic pressure."	Small sample size Short follow-up
Sanchez-Bayle, 2001[293]	Fiber supplements were generally well tolerated except for two children who withdrew due to abdominal discomfort.	
Schlierf, 1978[295]	3 of the 15 patients withdrew before completion. In the remaining 12 patients, plasma bromide levels, drug intake control sheets, and the returned packs of unused medication indicated good adherence to the study protocol.	Poor quality results lumped after 6 months (no pre-cross over data). No wash-out period. Authors comment that this not probably recommended for use in children because of increases in HDL and sitosterol levels.

Evidence Table 5. Adverse Effects of Interventions

Author, year	Title	Type of Study/Setting	Aims	Duration of Study
Zavoral, 1983[296]	The hypolipidemic effect of locust bean gum food products in familial hypercholesterolemic adults and children	Non-randomized, crossover study	To assess the hypolipidemic effect of locust bean gum food products.	8 weeks
Exercise				
Kavey, 1997[298]	Valvular and pediatric congenital heart disease - exaggerated blood pressure response to exercise in children with increased low-density lipoprotein cholesterol	Cross-sectional study, US	To compare the blood pressure response to exercise in a group of children with increased LDL with the response in a group of normal control subjects.	0 (cross-sectional study)
Tolfrey, 1998[297]	Exercise training induced alterations in prepubertal children's lipid-lipoprotein profile	Observational pre-test/post-test Recruitment from primary schools England February - July 1995 (ET) February - July 1996 (Control)	Examine effect of exercise training on prepubertal children's lipid-lipoprotein profile	12 weeks

Evidence Table 5. Adverse Effects of Interventions

Author, year	Main Eligibility Criteria	Enrolled	Demographics
Zavoral, 1983[296]	Normal and familial hypercholesterolemia patients were selected from the Hennepin County Medical Center's Hyperlipidemia Clinic. All of the families had one parent and child and at least one additional first degree relative with FHC.	11 children	Aged 10-18
Exercise			
Kavey, 1997[298]	The study group consisted of boys aged >10 with LDL ≥160 mg/dL who had been referred to the Pediatric Preventive Cardiology clinic over a 2-year period. Higher SBP on termination of exercise in these children was evaluated by using a retrospective control group consisting of boys 10-18 with normal results on cardiac examination who had undergone elective treadmill exercise testing during the same period. Children with relative weight >120% were excluded from both groups. A prospective evaluation was also undertaken: 10 hypercholesterolemic boys with LDL >160 mg/dL and 10 age-matched control subjects age 10-17 were examined by the same protocol.	15 hypercholesterolemic children; 32 control children	Age 10-17, mean 12.7 0% female
Tolfrey, 1998[297]	1. Volunteered for study after attending school-based presentation and visiting university exercise physiology lab. 2. Determined by medical screening to be healthy and asymptomatic. 3. No medication known to effect lipid profile.	48 enrolled ET group: 28 Control group: 20	Mean age: 10.6 (0.7) 50% female

Evidence Table 5. Adverse Effects of Interventions

Author, year	Interventions/Exposures	Adverse Effects
Zavoral, 1983[296]	Identical food products with and without locust bean gum (LBG) were consumed by two groups of arbitrarily assigned patients using a cross-over design. The food products contained 8 to 10% LBG by dry weight. Each portion contained between 1.7 and 2.0 g of LBG. LBG in the food products was prescribe to the subjects on the basis of body size. Families were seen at 2-week intervals, and dieticians collected 3-day diet histories and 2week dietary records for the food products. Safety assessments included WBC counts, calcium, and SGOT before and after feedbing LBG food products.	There was no change observed in the white blood cell counts, serum calcium, or SGOT determinations. Subjects reported increased rectal gas while on the LBG-containing products, but decreased and at 1-2 weeks the amount of gas reported was usually not a problem. No one had diarrhea, and stool size increased slightly. One patient had significant constipation that remitted after discontiuing the diet for 3 days. This subject was able to resume the diet without further problems.
Exercise		
Kavey, 1997[298]	Treadmill exercise tests were performed on a cardioexercise treadmill, using published protocol and pediatric normal data for maximum predicted heart rate and endurance time. Blood pressures were measured in the right arm at rest before beginning exercise, immediately after termination of exercise, and then every 2 minutes during recovery.	Combined results for retrospective and prospective comparisons: Children with severely increased LDL cholesterol had an exaggerated blood pressure response to exercise when compared with normolipidemic control subjects. Children with increased LDL had significantly higher systolic and diastolic blood pressures before treadmill exercise (S 120 vs 113 mmHG, p<0.03; D 68 vs 63 mmHg, p<0.01). Among children with high LDL, blood pressures were significantly higher after exercise (S 182 vs 160 mmHg, p<0.0003; D 77 vs 72 mmHg, p<0.03), and systolic blood pressures remained significantly higher at the end of recovery (120 vs 112 mmHg, p<0.005.
Tolfrey, 1998[297]	Exercise Training Group (ET): Supervised stationary cycling for 30 minutes, 3x/week for 12 weeks at 79.3% (+ 1.2) peak heart rate Control group: Maintained their usual lifestyle pattern	NR

Evidence Table 5. Adverse Effects of Interventions

Author, year	Compliance/Tolerance	Comment
Zavoral, 1983[296]	Children ate the prescribed amount of LBG food products. Author states "LBG food acceptance was good, and there were no significant side effects."	
Exercise		
Kavey, 1997[298]	NR	
Tolfrey, 1998[297]	100% adherence to training program reported	

Table 18. Summary of Systematic Evidence Review

Arrow	Key question	Level and Type of Evidence	Quality of Evidence	Conclusions
9	What are the adverse effects of drug, diet, exercise, and combination therapy in children/adolescents?	I, II-1, II-2	Fair	Controlled and non-controlled studies of treatment reported adverse effects of drug, diet, exercise, and combination therapy in children and adolescents. Statin drugs were associated primarily with elevations in LFTs and CK. Bile-acid binding resins were associated with GI side effects and decreased levels of serum vitamins and minerals. Low fat diet has been associated with growth retardation and nurtional dwarfing in 3 children who were placed on low-fat diets without formal advice and monitoring. Most studies show normal growth and development in children over 2 years old on monitored low-fat diets. Few side effects other than elevated blood pressure were noted with exercise. The duration of follow-up in these studies ranged from 10 days to 8 years. Studies were generally not of sufficient duration to determine long-term effects of either short or extended use.
10	Does improving dyslipidemia in childhood reduce the risk of dyslipidemia in adulthood?	None		
11	What are the cost issues involved in screening for dyslipidemia in asymptomatic children?	None		

Abbreviations

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

Appendix 1. Abbreviations

AAP:	American Academy of Pediatrics
AE:	Adverse Event
BL:	Baseline
BMI:	Body Mass Index [kg/m^2]
CAD:	Coronary Artery Disease
CHD:	Coronary Heart Disease
CVD:	Cardiovascular Disease
DB:	Double Blind
EDRF/NO:	Endothelium-derived Relaxing Factor/Nitric Oxide
ET:	Treatment Group
FCH:	Familial Combined Hyperlipidemia
FCHL:	Familial Combined Hyperlipoproteinemia
FH:	Familial Hypercholesterolemia
FHTG:	Familial Triglyceridemia
FMD:	Flow Mediated Dilation
HC:	Hypercholesterolemia
HDL:	High Density Lipoprotein
HDL-C:	High Density Lipoprotein Cholesterol
HeFH:	Heterozygous Familial Hypercholesterolemia
HoF:	Homozygous Familial Hypercholesterolemia
HR:	Heart Rate
HTN:	Hypertension
IMT:	Intimal-medial Thickness
LDL:	Low-density Lipoprotein
LDL-C:	Low-density Lipoprotein Cholesterol
LRC:	Lipid Research Clinic
MI:	Myocardial Infarction
NA:	Not Applicable
NCEP:	National Cholesterol Education Program
NIH:	National Institute of Health
NR:	Not Reported
NS:	Not Significant
OCP:	Oral Contraceptive Pills
RCT:	Randomized Controlled Trial
RF:	Risk Factor
RR:	Risk Ratio
SEM:	Standard Error of Measure
SSF:	Sum of Skinfolds
TC:	Total Cholesterol
TG:	Triglycerides
VLDL:	Very Low-density Lipoprotein

Appendix 2. Units of Measure Conversion Formulas

Conversion for TC (total cholesterol), HDL (high density lipoprotein) and LDL (low density lipoprotein)* †:

To get from SI units (mmol/L) to mg/dL multiply by 38.67.

To get from mg/dL to SI (in mmol/L) multiply by 0.02586.

Conversion for TG (triglycerides)* †:

To get from SI units (mmol/L) to mg/dL multiply by 88.57.

To get from mg/dL to SI units, multiply by 0.01129.

*References:
www.ulb.ac.be/eraseme/edu/gastrocd/convers.htm
www.fatfreekitchen.com/cholesterol/cholesterol_units.html
www.unc.edu/~rowlett/units/scales/clinical_data.html
www.globalrph.com/conv_si.htm
www.nephron.com/cgi-bin/SI.cgi (conversion calculator)

These accessed December 15, 2004

†Note: for both TC and TG conversions, some people use rounded conversion factors to get from mg/dL to SI units (i.e. 0.0259 and 0.0113).

Appendix 3. Search Strategies for Child and Adolescent Dyslipidemia

Adverse Effects
Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:
---
1 exp Hyperlipidemia/
2 ((adverse$ adj effect$) or harm$ or stigma$ or prejudice$ or discriminate$). mp. or exp stress, psychological/et or exp life change events/ or exp prejudice/ or exp stereotyping/ or exp self concept/
3 exp "Wounds and Injuries"/et [Etiology]
4 exp hyperlipidemia/dt
5 exp Antilipemic Agents/ae, ct, to
6 1 and (2 or 3)
7 4 and 5
8 6 or 7
9 limit 8 to English language
10 8 not 9
11 limit 10 to abstracts
12 9 or 11
13 limit 12 to "all child (0 to 18 years)"

Cost
Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:
---
1 exp HYPERLIPIDEMIA/
2 exp lipoproteins/bl
3 1 or 2
4 Mass Screening/
5 exp hyperlipidemia/di
6 3 and 4
7 5 or 6
8 exp "Costs and Cost Analysis"/
9 7 and 8
10 exp HYPERLIPIDEMIA/ec [Economics]
11 9 or 10
12 limit 11 to all children <0 to 18 years>
13 limit 12 to English language

Diet
Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:

Appendix 3. Search Strategies for Child and Adolescent Dyslipidemia

1 exp HYPERLIPIDEMIA/dh [Diet Therapy]
2 exp HYPERLIPIDEMIA/
3 exp Diet/
4 exp Diet Therapy/
5 3 or 4
6 2 and 5
7 1 or 6
8 limit 7 to human
9 limit 8 to all children <0 to 18 years>
10 limit 9 to English language
11 9 not 10
12 limit 11 to abstracts
13 10 or 12

Drug
Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:
---
1 exp HYPERLIPIDEMIA/dt [Drug Therapy]
2 exp Antilipemic Agents/ad, ae, ct, tu, to [Administration & Dosage, Adverse Effects, Contraindications, Therapeutic Use, Toxicity]
3 exp HYPERLIPIDEMIA/
4 2 and 3
5 1 or 4
6 limit 5 to all children <0 to 18 years>
7 limit 6 to English language
8 6 not 7
9 limit 8 to abstracts
10 7 or 9

Exercise
Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:
---
1 exp HYPERLIPIDEMIA/
2 exp lipoproteins/bl
3 1 or 2
4 exp Exercise Movement Techniques/
5 exercis$.mp.
6 (physical$ adj3 active$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7 (physical$ adj (fit or fitness)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8 4 or 5 or 6 or 7

9 3 and 8
10 limit 9 to all child <0 to 18 years>
11 limit 10 to English language
12 10 not 11
13 limit 12 to abstracts
14 11 or 13

Family History
Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:
---
1 exp HYPERLIPIDEMIA/ge [Genetics]
2 exp HYPERLIPIDEMIA/
3 exp lipoproteins/bl
4 2 or 3
5 exp Disease Susceptibility/
6 4 and 5
7 1 or 6
8 exp RISK/
9 7 and 8
10 limit 9 to all child <0 to 18 years>
11 (family$ adj3 histor$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
12 4 and 11
13 limit 12 to all child <0 to 18 years>
14 13 and 8
15 10 or 14
16 limit 15 to English language
17 15 not 16
18 limit 17 to abstracts
19 16 or 18

Outcomes
Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:
---
1 exp Hyperlipidemia/co, dh, dt, th
2 exp Cerebrovascular Disorders/mo, pc, ep, et [Mortality, Prevention & Control, Epidemiology, Etiology]
3 exp Myocardial Ischemia/mo, pc, ep, et [Mortality, Prevention & Control, Epidemiology, Etiology]
4 1 and 2
5 1 and 3
6 4 or 5

7 exp "OUTCOME AND PROCESS ASSESSMENT (HEALTH CARE)"/
8 exp prognosis/
9 7 or 8
10 1 and 9
11 6 or 10
12 limit 11 to all child <0 to 18 years>
13 limit 12 to English language
14 12 not 13
15 limit 14 to abstracts
16 13 or 15

Screening

Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:

---

1 exp HYPERLIPIDEMIA/
2 exp Lipoproteins/bl [Blood]
3 Cholesterol/bl [Blood]
4 Triglycerides/bl [Blood]
5 2 or 3 or 4
6 exp Mass Screening/
7 5 and 6
8 1 and 6
9 7 or 8
10 limit 9 to all child <0 to 18 years>
11 limit 10 to English language
12 10 not 11
13 limit 12 to abstracts
14 11 or 13

Sensitivity

Database: Ovid MEDLINE(R) <1966 to September 2005>
Search Strategy:

---

1 exp HYPERLIPIDEMIA/
2 exp Lipoproteins/bl [Blood]
3 Cholesterol/bl [Blood]
4 Triglycerides/bl [Blood]
5 2 or 3 or 4
6 1 or 5
7 exp "Sensitivity and Specificity"/
8 exp Diagnostic Errors/
9 7 or 8
10 6 and 9

Appendix 3. Search Strategies for Child and Adolescent Dyslipidemia

11 limit 10 to all child <0 to 18 years>
12 limit 11 to English language
13 11 not 12
14 limit 13 to abstracts
15 12 or 14

Appendix 4. Inclusion/Exclusion Criteria and Results of Searches

Key Questions	Applicable Searches	Abstract Level Inclusion / Exclusion Criteria	Paper Level Inclusion / Exclusion Criteria	Number of Abstracts Screened with Eligibility Criteria*†	Number of Articles Reviewed from Abstracts and other Sources*†‡	Number of Articles Included in Evidence Synthesis*†
Screening						
2	screening family history sensitivity	Include: RCTs, observational studies, cross-sectional studies, practice guidelines, meta analyses, or other reviews; Examines screening for dyslipidemia in children or adolescents, specifically risk factors, adverse effects of screening, tests or test performance; Information on background or cost Exclude: Wrong publication type, or population; Not relevant to topic, non-U.S./Western culture, or non-English language; Examines metabolic syndrome, triglyceride specific outcomes, screening in secondary dyslipidemia	Include: RCTs, observational studies, cross-sectional studies, practice guidelines, meta analyses, or other reviews; Examines screening for dyslipidemia in children and adolescents, specifically family history, biological (obesity, insulin level, etc) and lifestyle (physical activity, diet, etc) risk factors, measurement of serum lipids (TC, HDL, LDL, TG), tests or test performance (sensitivity, specificity), other screening measurements, adverse effects of screening; Information on background or cost; *For prevalence, normal values papers:* include non-U.S.-based if n>100 *For neonatal screening and testing papers:* include only if has mutation analysis Exclude: Wrong publication type, or population; Not relevant to topic, non-U.S./Western culture, or non-English language; Examines metabolic syndrome, triglyceride specific outcomes, screening in secondary dyslipidemia	780	369	160

Appendix 4. Inclusion/Exclusion Criteria and Results of Searches

Key Questions	Applicable Searches	Abstract Level Inclusion / Exclusion Criteria	Paper Level Inclusion / Exclusion Criteria	Number of Abstracts Screened with Eligibility Criteria*†	Number of Articles Reviewed from Abstracts and other Sources*†‡	Number of Articles Included in Evidence Synthesis*†
Interventions						
4-8, 10	diet exercise drug outcomes	Include: Treatment trials, longitudinal studies, natural history studies, cross sectional studies, practice guidelines, meta analyses, or other reviews; Examines interventions for dyslipidemia in children or adolescents, specifically drugs, diets, exercise or combinations, family history, risk factors, adverse effects of interventions, tests or test performance; Information on background or cost; *For natural history papers:* include non-Western culture Exclude: Wrong publication type or population; Not relevant to topic, non-U.S./Western culture (except natural history papers), or non-English language; Examines metabolic syndrome, triglyceride specific outcomes, screening in secondary dyslipidemia	Include: RCTS, clinical controlled trials, non-controlled trials, observational studies, cross sectional studies, practice guidelines, meta analyses, or other reviews; Examines interventions for dyslipidemia in children and adolescents, specifically drugs, diets, exercise, or combinations, lipid outcomes, other outcomes (intimal thickness, medial dilation, etc), adverse effects of interventions, tests and test performance; Information on background or cost; *For natural history papers:* include non-Western culture Exclude: Wrong population type, or population (< 50% child/adolescent or no separate analysis for child/adolescent); Not relevant to topic, non-U.S./Western culture (except natural history papers), or non-English language; Examines metabolic syndrome, triglyceride specific outcomes, screening in secondary dyslipidemia	1668	707	68

Appendix 4. Inclusion/Exclusion Criteria and Results of Searches

Key Questions	Applicable Searches	Abstract Level Inclusion / Exclusion Criteria	Paper Level Inclusion / Exclusion Criteria	Number of Abstracts Screened with Eligibility Criteria*†	Number of Articles Reviewed from Abstracts and other Sources*†‡	Number of Articles Included in Evidence Synthesis*†
Adverse Effects of Screening						
3	adverse effects	same as KQ 2	same as KQ 2	163	84	8
Adverse Effects of Interventions						
9	adverse effects	same as KQ 1, 4-8, 10	<u>Include:</u> Treatment trials, longitudinal studies, natural history studies, meta analyses, or other reviews Examines adverse effects of dyslipidemia in children and adolescents, specifically from drugs, diets, exercise, or combinations; Information on background or cost <u>Exclude:</u> Wrong publication type, or population; Not relevant to topic, non-U.S./Western culture, or non-English language	same as KQ 3	same as KQ 3	81

Appendix 4. Inclusion/Exclusion Criteria and Results of Searches

Key Questions	Applicable Searches	Abstract Level Inclusion / Exclusion Criteria	Paper Level Inclusion / Exclusion Criteria	Number of Abstracts Screened with Eligibility Criteria*†	Number of Articles Reviewed from Abstracts and other Sources*†‡	Number of Articles Included in Evidence Synthesis*†
Cost						
11	cost	Include: Study of cost of screening and/or treatment for elevated cholesterol in children; Information on background Exclude: Genetic screening or tracking study based on identified FH individual; Wrong population; Not relevant to topic, non-U.S./Western culture , or non-English language	same as cost abstract criteria	26	15	7

*All abstracts were reviewed for applicability to other key questions.

†Duplicates may exist between key questions.

‡Other sources include reference lists, experts, etc.

Appendix 5. U.S. Preventive Services Task Force Quality Rating Criteria*

Diagnostic Accuracy Studies

Criteria

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

Definition of ratings based on above criteria

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

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

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

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria

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

Appendix 5. U.S. Preventive Services Task Force Quality Rating Criteria

Definition of ratings based on above criteria

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

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

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

Case Control Studies

Criteria

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

Definition of ratings based on criteria above

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

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

Appendix 5. U.S. Preventive Services Task Force Quality Rating Criteria

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

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

Appendix 6. Statistical Methods Used for Meta Analysis

Steps to get mean percentage change:

1. Use reported mean change.
2. If not reported, calculated using mean lipid level changes from endpoint to baseline of the treatment and control group.

Steps to get standard error (SE) for mean percentage change:

1. Use reported SE.
2. If SE is not reported and standard deviation (SD) is reported, calculated from SD.
3. If both SE and SD not reported, calculated from 95% CI if reported.
4. If none of above is reported, calculated from the reported mean lipid level change and the associated variance (or SD). Let $\bar{x}$ and $\bar{y}$ denote the mean lipid level change from endpoint to baseline of the control and treatment group, respectively, the variance of mean percentage change is given by

$$Var(\frac{\bar{y}-\bar{x}}{\bar{x}}) = Var(\frac{\bar{y}}{\bar{x}}) = \left(\frac{\bar{y}}{\bar{x}}\right)^2 \left(\frac{Var(\bar{x})}{\bar{x}^2} + \frac{Var(\bar{y})}{\bar{y}^2}\right)$$

using delta method.

Let $z = \frac{y-x}{x}$, where x and y denote the individual lipid level change from endpoint to baseline, then mean percentage change is given by the mean z, $\bar{z}$. It could be shown that $Var(\frac{\bar{y}}{\bar{x}})$ could be approximated by $Var(\bar{z})$ using delta-method.

5. If SD for endpoint is not available, use estimates of SD from baseline (or maximum estimates for HDL) to get a conservative estimate of SE for mean percent change.