

# ***Evidence Synthesis***

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## **Number 141**

### **Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: A Systematic Evidence Review for the U.S. Preventive Services Task Force**

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## Structured Abstract

**Background:** Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism characterized by highly elevated total cholesterol (TC) concentrations early in life, independent of environmental influences. Around 1 in 200 to 1 in 500 persons in North America and Europe are estimated to have heterozygous FH. When untreated, FH is associated with a high incidence of premature clinical atherosclerotic cardiovascular disease.

**Purpose:** We conducted a systematic evidence review of the benefits and harms of screening children and adolescents for heterozygous FH. The purpose of this review is to assist the U.S. Preventive Services Task Force (USPSTF) in updating its previous recommendations on such screening.

**Data Sources:** We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and PubMed from 2006 through July 2014 to locate relevant trials for all key questions (KQs) published since the previous reviews in support of prior recommendations. We supplemented these searches with reference lists from relevant existing systematic reviews, cohort studies, suggestions from experts, and Clinicaltrials.gov to identify ongoing trials.

**Study Selection:** Investigators independently reviewed 6,752 abstracts and 375 articles against a set of a priori inclusion criteria. Investigators also independently critically appraised each study using design-specific quality criteria based on USPSTF methods. We included fair- or good-quality studies that met the a priori criteria for each KQ. We resolved discrepancies by consensus.

**Data Extraction and Analysis:** One investigator abstracted data from the 27 included articles into evidence tables and a second reviewer verified the accuracy of the abstracted data. We qualitatively summarized the evidence for screening and the effects of treatments on health outcomes. Lipid concentrations and measures of atherosclerosis were expressed as percent change from baseline or as differences from baseline. For KQ6, the number of included studies was sufficient to permit meta-analysis. For the randomized trials of statins that reported means and standard deviations for percent change ( $k=6$ ), we summarized the results using forest plots. We did not combine data across studies, given the variability in drug, dose, and intended duration in the included studies.

**Results:** We found no direct evidence for five KQs: the effectiveness of screening children and adolescents for FH in improving health outcomes (myocardial infarction [MI] or stroke) in adulthood (KQ1) or intermediate outcomes (lipid concentrations and atherosclerosis) in childhood (KQ2), the harms of screening for FH in children and adolescents (KQ4), the effectiveness of treating children and adolescents with FH on health outcomes (MI or stroke) in adulthood (KQ5), and the association between intermediate outcomes in childhood and adolescence and the future incidence or timing of MI and stroke in adulthood (KQ8). Studies met inclusion criteria for three KQs.

*KQ3. What is the diagnostic yield of appropriate screening tests for FH in children and adolescents?*

Two studies provided data allowing determination of the diagnostic yield of pediatric FH screening programs. A statewide universal screening program screened more than 80,000 10- to 11-year-olds in West Virginia schools and reported a diagnostic yield of about 1.3 cases per 1,000 screened. In this study, “probable FH” was defined as a low-density lipoprotein cholesterol (LDL-C) concentration greater than 155 mg/dL or TC concentration greater than 260 mg/dL plus DNA evidence of a low-density lipoprotein receptor (*LDLR*) mutation in a first- or second-degree relative. A Danish school-based study of more than 2,085 6- to 8-year-olds used the ApoB:ApoA-1 ratio and reported a diagnostic yield of 4.8 cases per 1,000 screened. We found no studies reporting diagnostic yield or effectiveness of selective screening for FH in youth (i.e., screening subjects with a family history or other targeting factor).

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

Eight good-quality randomized, controlled trials (RCTs) formed the evidence base for statin treatment of FH in youth. Studies of statins ranged from 6 weeks to 2 years long, with most shorter than 1 year. Treatment with statins lowered LDL-C and TC concentrations in the short term in children and adolescents with FH, with most studies reporting that statins lowered LDL-C by 20 to 40 percent compared to placebo. The greatest effect on LDL-C was in a trial of rosuvastatin. Participants who received the highest dose (20 mg/day) experienced a 50 percent decrease (least mean squares) in LDL-C from baseline compared to a 1 percent decrease among controls ( $p<0.001$ ).

Eight studies reported the effect of statins on TC, all showing decreases of about 20 to 30 percent from baseline (compared to no change with placebo). The effect on high-density lipoprotein cholesterol (HDL-C) was minimal or null. A single study assessed the effect on a measure of atherosclerosis and found that pravastatin reduced carotid intima-media thickness (CIMT) by 2.01 percent (compared to a 1.02% increase in the control group;  $p=0.02$ ). There were no consistent differences in treatment effect among different statins, but the number of studies for any one drug was limited. The two studies that compared different doses of statins reported a dose response with pravastatin and rosuvastatin. In the 2010 rosuvastatin trial, the only statin study reporting how many subjects attained the target LDL-C concentration, only 12 to 41 percent of participants reached a target LDL-C of less than 110 mg/dL, with greater effect at higher doses.

Six studies of statins provided the necessary data to create a forest plot of mean difference across statins between percent change from baseline of TC, LDL-C, and HDL-C. Treatment effects on TC and LDL-C were statistically significant for all five drugs in these six studies (atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin), with overlapping 95% confidence intervals across drugs.

Five fair- to good-quality RCTs evaluated nonstatin drugs in children and adolescents with FH. All trials reported decreases in LDL-C from baseline. Three RCTs studied bile-sequestering agents. A good-quality trial of colestipol found a mean reduction in LDL-C of 19.5 percent after 8 weeks of treatment compared to a 1 percent decrease in the control group. One fair-quality

RCT of cholestyramine found an 18.6 percent reduction in LDL-C after 1 year compared to a 1.5 percent increase in the control group. One good-quality 8-week RCT of colessevelam published after the 2007 USPSTF review found a least squares mean decrease in LDL-C of 10 percent (standard error [SE], 2.1%) at the higher of two doses compared to a least squares mean increase of 2.5 percent (SE, 2.0%). A lower dose provided a smaller, nonsignificant reduction. Two good-quality RCTs of ezetimibe were published after the 2007 USPSTF review. One reported that LDL-C decreased by a mean of 54.0 percent (SE, 1.4%) in participants who received a combination of ezetimibe and simvastatin, whereas the mean decrease was 38.1 percent (SE, 1.4%) in the simvastatin-only group at 33 weeks. The second found that, at 12 weeks, ezetimibe monotherapy decreased LDL-C by 28 percent (95% CI, -31 to -25) from baseline compared to a negligible change in the placebo group.

*KQ7. What are the harms of treatment of FH with medications in children and adolescents?*

There is a fair- to good-quality body of evidence about the short-term harms of pharmacologic treatment of children and adolescents with FH. Most studies were conducted outside the United States but were applicable to U.S. primary care setting. Most studies were of short duration (6 weeks to 2 years); the longest was 10 years. Statins were generally well-tolerated, although reversible elevations of liver enzymes and/or creatine kinase concentrations were noted in some studies. One study found lower dehydroepiandrosterone sulfate concentrations in men with FH treated with statins compared to unaffected siblings. Bile-acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-term harms are unknown.

**Limitations:** Direct evidence for the impact of screening on intermediate or health outcomes is lacking. One of the two studies assessing the diagnostic yield of screening for FH may not be generalizable to a U.S. population, and the other provides few details as to the screening and confirmatory testing for FH. Evidence on the effectiveness of pharmacotherapy lacks long-term studies assessing the effect of lipid-lowering medications on intermediate outcomes in childhood and adolescence or on health outcomes in adults. Participants in the eight statin trials were patients at tertiary care centers; none of the studies were conducted in screen-detected populations. Few studies were conducted in nonwhite populations. Three statin trials included children as young as age 8 years; however, the age distribution of the statin studies as a whole is skewed to early adolescence. We found no studies comparing outcomes between groups of children or adolescents who initiated treatment at different ages. Long-term studies of harms of pharmacotherapy in youth are lacking. Finally, this review was limited to FH alone; other atherogenic dyslipidemias are addressed in a separate review.

**Conclusions:** We found no direct evidence of the effect of screening on intermediate or health outcomes. The evidence describing the diagnostic yield of screening for FH in children is minimal. There is good evidence of the effectiveness of statins in reducing LDL-C and TC concentrations in studies up to 2 years long and limited evidence of a statin effect on measures of atherosclerosis. Statins were generally well-tolerated in the short term, although reversible elevations of liver enzymes and/or creatine kinase concentrations were noted in some studies and a decrease in dehydroepiandrosterone sulfate was noted in one study. Bile-acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-

term harms are unknown. Randomized trials of screening for FH in U.S. youth are needed, as are longer-term treatment trials evaluating the benefits and harms of medications in children and adolescents with FH.

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# Chapter 1. Introduction

## Scope and Purpose

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

As noted in the 2007 review, pediatric dyslipidemias are a heterogeneous set of conditions that include several monogenic disorders as well as dyslipidemias caused by a variety of factors, both genetic and environmental. Based on public comments on the draft research plan, the USPSTF decided to conduct separate systematic reviews on screening for familial hypercholesterolemia (FH) and screening for multifactorial dyslipidemia. This review focuses on FH. This review assesses the benefits and harms of screening for and treatment of FH in children and youth ages 0 to 20 years. The separate systematic review to update the 2007 USPSTF recommendation on multifactorial dyslipidemia will address screening children and adolescents for other dyslipidemias involving elevated low-density lipoprotein cholesterol (LDL-C) or total cholesterol (TC) that are not FH. These two concurrent systematic reviews will allow the USPSTF to simultaneously consider both bodies of evidence to evaluate the preventive health benefits of screening children and adolescents for dyslipidemias involving elevated LDL-C.

## Clinical Presentation and Diagnosis

FH is an inherited disorder of lipoprotein metabolism characterized by highly elevated TC concentrations early in life, independent of environmental influences. Tendon xanthomas (cutaneous deposits of cholesteryl ester-enriched foam cells in ligaments and tendons) may also be present, most commonly in the Achilles tendon.

Currently, no criteria for the diagnosis of FH are universally accepted. Studies of children with FH use several different diagnostic criteria, some of which are drawn from published definitions. The three most commonly cited diagnostic criteria are the Simon Broome criteria<sup>1</sup> from the United Kingdom, the Dutch Lipid Clinic Network criteria<sup>2</sup> from the Netherlands, and the MEDPED criteria<sup>3</sup> from the United States. All use a combination of elevated lipid concentrations, physical findings, family history, or genetic tests to establish the diagnosis. Further, combinations of diagnostic criteria are used to stratify diagnosis according to the probability of disease (i.e., definite, probable, or possible FH) (**Appendix D**). The use of genetic diagnosis alone is complicated by incomplete penetrance of the genes that cause FH and by varying expressivity of clinical symptoms, especially in childhood and adolescence.<sup>4, 5</sup>

## Etiology and Prevalence

FH is an autosomal-dominant disorder caused primarily by mutations in the low-density lipoprotein receptor (*LDLR*) gene.<sup>6, 7</sup> More than 80 percent of cases are attributed to 1 of 1,500

known deleterious mutations<sup>8</sup> in the *LDLR* gene.<sup>9</sup> The remainder of cases reflect mutations in other genes (*ApoB*, *PCKS9*) or unknown mutations.

The prevalence of heterozygous FH is estimated to be 1 in 200 to 1 in 500 persons in North America and Europe. It is higher (up to 1 in 100) for populations with known founder effects, including the Netherlands, South Africa's Afrikaner population, Quebec, and Lebanon.<sup>9</sup> Given population prevalence estimates, FH may be underdiagnosed, especially in children.<sup>10, 11</sup> Homozygous FH, a more severe condition than heterozygous FH, is far less common, with a prevalence of about 1 in 1,000,000 births.<sup>5</sup> This evidence review focuses exclusively on the heterozygous form of the disorder. In the remainder of this report, we refer to heterozygous FH simply as FH.

## Natural History

FH is normally asymptomatic in childhood and is rarely associated with cardiovascular illness in the first two decades of life. The burden of FH is caused largely by premature cardiovascular events in adulthood that are associated with long-term exposure to elevated, and in some cases severely elevated, serum cholesterol concentrations and the associated atherosclerotic burden. Lifelong elevation of plasma concentrations of LDL-C leads to cholesterol deposition in the arteries, where it forms an atherosclerotic plaque that can begin early in life. Early atherosclerotic lesions in children, adolescents, and young adults have been related to higher antecedent concentrations of TC and LDL-C<sup>12-15</sup> and mean carotid intima-media thickness (CIMT) values in young children (age <8 years) with FH, which may be greater than those of their unaffected siblings.<sup>16</sup>

Untreated, FH is associated with a high incidence of premature clinical atherosclerotic cardiovascular disease (CVD). Before statins were in common use, FH was associated with a 1-in-6 cumulative incidence of ischemic heart disease events in men and a 1-in-10 incidence in women by age 40 years.<sup>17</sup> By age 50 years, 25 percent of women and 50 percent of men with untreated FH will experience clinical CVD.<sup>18</sup> In adults with untreated FH, coronary artery disease (CAD) occurs in 50 percent of men by age 50 years and in 30 percent of women by age 60 years.<sup>19, 20</sup> CAD-associated mortality is increased in persons with FH younger than age 60 years. Among persons surviving to age 60 years, the risk of CAD approaches that in the general population.<sup>21</sup> Deposition of LDL-C in other body tissues can manifest as clinical findings, mainly tendon xanthomas and corneal arcus.

## Lipid Concentrations in Children and Adolescents

Lipid concentrations in healthy children vary with age, starting very low at birth, increasing slowly in the first 2 years of life, and then stabilizing until adolescence. TC and LDL-C concentrations subsequently decrease by 10 to 20 percent or more during adolescence, before rising again during late adolescence and young adulthood.<sup>22-25</sup> In children with FH, concentrations of TC and LDL-C in early childhood will be 2 to 3 times higher as those in unaffected children.

# Screening for FH

## Rationale for Screening

The rationale for screening for FH in childhood or adolescence is to identify presymptomatic children and to intervene with lipid-lowering agents before clinically significant atherosclerosis develops. Given the earlier onset and more severe clinical implications of FH compared to other dyslipidemias, the long preclinical disease course of atherosclerosis, and the availability of intervention for detected cases, FH may be a candidate for screening in primary care.

## Laboratory Studies

Because elevated LDL-C concentrations are the primary abnormality associated with FH, all FH diagnostic criteria are based in part on serum concentrations of TC, LDL-C, or both. LDL-C may be calculated with the Friedewald formula<sup>26</sup>:  $LDL-C = TC - (triglycerides/5) - \text{high-density lipoprotein cholesterol (HDL-C)}$ . Because the calculation depends on triglycerides, calculating LDL-C concentrations accurately requires blood to be drawn when the person is fasting. Direct LDL-C measurement does not require fasting.<sup>15</sup> Recent screening recommendations for childhood dyslipidemia have included guidelines for use of either LDL-C or non-high-density lipoprotein cholesterol (non-HDL-C).<sup>18, 27</sup>

## Screening Strategies

- *Screening by clinical examination.* Because only a few children have clinically detectable atherosclerotic deposits, such as xanthomas, by adolescence, detecting these deposits can aid in diagnosis but is not a useful screening marker for FH in children and adolescents.
- *Selective screening based on family history.* Targeted lipid screening of high-risk individuals ages 2 to 8 years has also been recommended, as well as screening in late adolescence and young adulthood (after lipid concentrations have once again risen).<sup>18</sup> Screening based on a family history of early CVD or hypercholesterolemia will identify only 30 to 60 percent of children with FH. The previous USPSTF review determined that having a parent or grandparent with CHD diagnosed before age 50 or 60 years or a cholesterol concentration greater than 240 mg/dL was only 46 to 74 percent sensitive for identifying TC concentrations greater than 170 mg/dL or LDL-C concentrations greater than 130 mg/dL. A family history of a parent or grandparent having early CHD alone was only 46 percent sensitive for LDL-C concentrations above the 95th percentile.<sup>15, 28-30</sup>
- *Universal screening.* In universal screening, all children in a population undergo blood lipid screening based on age alone, regardless of other risk factors. Recent recommendations from the National Heart, Lung, and Blood Institute (NHLBI) have suggested universal screening at ages 9 to 11 years and again at ages 17 to 21 years.<sup>18</sup> The National Lipid Association also recommends screening for FH at ages 9 to 11 years.<sup>27</sup>
- *Genetic screening.* Only one FH diagnostic guideline (the Dutch criteria) currently recommends assigning a diagnosis of FH based on mutation status alone (**Appendix D**).

Other schemes require other clinical or laboratory characteristics in addition to mutation status. In genetically homogeneous populations, population-based screening for genetic variants known to exist in the population may be a useful strategy. However, given the genetic heterogeneity of the U.S. population and the lack of validated genetic screening tests for this population, genetic screening is beyond the scope of this review.

- *Cascade screening.* Cascade screening involves case-finding among relatives with confirmed FH and often involves testing for genetic variants identified in the proband. Because implementing this approach in the United States would require new infrastructure, cascade screening is outside of the purview of U.S. primary care and beyond the scope of this review.

## Current Clinical Practice in the United States

Beginning in the 1990s, organizations have recommended selective screening for childhood dyslipidemia based on the presence of risk factors, such as a family history suggesting inherited dyslipidemia (e.g., early CVD, early myocardial infarction [MI] or sudden death, or early cerebrovascular disease) or a personal history of risk factors for CVD.<sup>6, 31</sup> A recent report from the NHLBI Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommended universal screening for children ages 9 to 11 years and 17 to 21 years, as well as targeted screening of high-risk younger children and adolescents.<sup>18</sup> These recommendations are controversial, in part because of concerns about the lack of data on long-term efficacy and the safety of lipid-lowering medications in children and adolescents.

## FH Screening in the United States

In the United States, there are no national screening programs, and FH identification falls to individual clinicians as a matter of differential diagnosis. At least one FH patient registry exists in the United States.<sup>32</sup>

## FH Screening in Other Countries

Cascade screening is the most common screening strategy in other countries. The Netherlands has a known founder population with a high rate of FH, a subsidized health care system, and an infrastructure that supports a disease registry, and so it has a successful cascade screening program. In this program, relatives of FH patients are identified and screened with clinical examinations, fasting lipid panels, and molecular testing for *LDLR* mutations. With a participation rate of more than 90 percent, it has been successful in detecting new cases, increasing coverage of lipid-lowering therapies, and is cost-effective in case-finding, although following up with children remains challenging.<sup>33-36</sup> These screening algorithms led to the Dutch Criteria described in this review. Norway and Wales have also implemented national cascade screening programs.<sup>37</sup> Several other countries have explored cascade screening programs or have begun implementation.<sup>21, 38-41</sup> U.K. public health authorities recommend cascade screening with identified FH patients using the clinically-focused Simon Broome criteria.<sup>42</sup> Regional implementation suggests that cascade screening is feasible but has mixed results in identifying

persons with FH.<sup>43-45</sup> Currently, the United States does not have the necessary health infrastructure to support cascade screening.

Italy promotes a selective screening strategy based on family history to guide lipid testing.<sup>36, 46</sup> We are aware of at least one universal screening program, in Slovenia, but its impact is not yet known.

## **Treatment of FH in Children**

Interventions for correcting lipid aberrations in children and adolescents include lifestyle modification and pharmacotherapy.

### **Lifestyle**

Current guidelines<sup>27</sup> recommend a low-fat, low-cholesterol diet and regular physical activity for children and adolescents with FH, although evidence for the effect of nonpharmacologic interventions in children with FH is limited. Some evidence indicates that low-fat, low-cholesterol diets are marginally effective in lowering lipid concentrations in children (age >2 years) with certain conditions (including FH). The 2007 USPSTF review noted some uncertainty about whether these improvements would be sustained.<sup>47</sup> Exercise is associated with minimal, if any, improvement in lipids in children with any sort of dyslipidemia. The 2007 USPSTF review found no studies that assessed the effect of physical activity interventions in children with FH.<sup>47</sup>

### **Pharmacotherapy**

Several lipid-lowering medications are used in children and adolescents with FH. Bile acid-binding resins have been available for decades. Several HMG-CoA reductase inhibitors (statins)<sup>48, 49</sup> are approved by the U.S. Food and Drug Administration for children with FH who are age 10 years and older and (if female) are postmenarchal; one statin is approved for children as young as age 8 years. A third class of lipid-lowering agents used in youth inhibits intestinal cholesterol absorption (e.g., ezetimibe).

Following the widespread adoption of statins to reduce LDL-C concentrations in adults with hypercholesterolemia (most of whom do not have FH), pediatric specialists have actively debated the appropriate age of statin initiation in youth with FH. Some experts in the field recommend waiting until after puberty—some suggesting as late as age 20 years<sup>50</sup>—to minimize potential adverse effects on growth and development. Others advocate starting statins in children with FH as young as age 8 or 10 years.<sup>27</sup>

## **Previous USPSTF Recommendation**

In 2007, the USPSTF found insufficient evidence to recommend for or against routine screening for lipid disorders in infants, children, or adolescents up to age 20 years (I statement).<sup>15, 47</sup> The 2007 recommendation referred to screening for all forms of childhood and adolescent

dyslipidemia, and no separate recommendation was made specifically regarding screening for FH. The 2007 evidence review found these evidence gaps relevant to screening children and adolescents for FH:

- Direct evidence on the impact of FH screening on intermediate and adult health outcomes
- The diagnostic yield of screening for FH
- The harms of screening
- The benefits and harms of long-term treatment of FH identified in childhood (noting that the long-term effectiveness of statins is a critical evidence gap)



# Chapter 2. Methods

## Overview

This systematic review was designed to complement the systematic review that supported the recommendation on screening for multifactorial dyslipidemia in children and adolescents. For this review, we adapted the analytic framework for lipid screening from the 2007 USPSTF review to address the benefits and harms of primary care–relevant screening and treatment of children and adolescents with FH.

## Key Questions and Analytic Framework

Using the USPSTF’s methods (detailed in **Appendix A**), we developed an analytic framework (**Figure 1**) and eight key questions (KQs).

### Screening KQs

1. Does screening for FH in asymptomatic children and adolescents delay or reduce the incidence of MI or stroke in adulthood?
  - a. Selective screening based on family history
  - b. Universal screening
2. Does screening for FH in asymptomatic children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?
  - a. Selective screening based on family history
  - b. Universal screening
3. What is the diagnostic yield of appropriate screening tests for FH in children and adolescents?
  - a. Selective screening based on family history
  - b. Universal screening
4. What are the harms of screening for FH in children and adolescents?

### Treatment KQs

5. Does treatment of FH with lifestyle modifications and/or lipid-lowering medications in children and adolescents delay or reduce the incidence of adult MI and stroke events?
6. Does treatment of FH with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?
7. What are the harms of treatment of FH with medications in children and adolescents?

## Outcomes KQ

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

In these KQs, intermediate outcomes include lipid concentrations (TC and LDL-C) and atherosclerosis markers (CIMT, calcium score, and pathological findings).

## Data Sources and Searches

We designed this review to extend the 2007 systematic review on screening in childhood lipids. In October 2013, we searched the following databases to identify systematic reviews on child lipid screening published since September 2005 (the date of the literature search for the previous USPSTF review on this topic): AHRQ, BMJ Clinical Evidence, Canadian Agency for Drugs and Technologies in Health, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment (Centre for Reviews and Dissemination), Institute for Clinical Systems Improvement, Institute of Medicine, MEDLINE and PubMed, and National Institute for Health and Care Excellence. We worked with a trained medical librarian to develop the appropriate search strategy for screening for childhood lipids (**Appendix A**). On February 12, 2014, we conducted our original search for this review, and the search was updated on June 13, 2014 and again on June 2, 2015.

For the published literature prior to September 2005, we searched all publications cited in the 2007 USPSTF review. Although that review did not specifically address diagnostic yield (KQ3 in this review), several of their KQs addressed various aspects of screening. We conducted a focused search of the studies cited in the 2007 USPSTF review to identify any that met our criteria for KQ3. Also, because the 2007 USPSTF review did not have a KQ on the association between screening and intermediate outcomes (KQ2 in this review) or on the association between intermediate outcomes in children and adolescents with FH and adult health outcomes (KQ8 in this review), we supplemented our search of the 2007 USPSTF citations with a search of the 2011 NHLBI expert panel report<sup>27</sup> and publications from large published cohort studies with longitudinal data (**Appendix E**). To ensure the comprehensiveness of our search strategy, we reviewed the reference lists of included studies and relevant systematic reviews and meta-analyses to identify relevant articles that were not identified in our literature searches. We also supplemented our database searches with suggestions from experts and searched Clinicaltrials.gov to identify relevant ongoing trials (**Appendix B**).

## Study Selection

Two investigators independently reviewed the title and abstracts of all identified articles to determine whether the study met the inclusion and exclusion criteria for design, population, screening, intervention, and outcomes (**Appendix A Table 2**). Two reviewers then independently evaluated 375 full-text articles against the complete inclusion and exclusion criteria (**Appendix A Table 1**). We resolved discrepancies through discussion and consultation

with a third reviewer. Excluded studies and their reason for exclusion are listed in **Appendix C**.

For screening studies (KQs 1–4), we included studies of asymptomatic children and adolescents ages 0 to 20 years at the time of screening. Acceptable screening interventions were defined as a lipid panel (fasting or nonfasting lipid measurement, TC or LDL-C alone or in combination with HDL-C) delivered in a universal or selective screening strategy. We excluded screening studies that focused on genetic screening alone or cascade screening because those screening approaches are not relevant to screening for FH in primary care. We excluded screening studies of populations with known dyslipidemia, a diagnosis associated with secondary dyslipidemia, or a documented family history of FH because these populations were not asymptomatic. Only screening studies that reported the number of children with probable or definite FH were included.

For treatment studies (KQs 5–7), we included interventions using lipid-lowering drugs or lifestyle interventions (including diet or exercise). We focused on interventions targeting persons ages 0 to 20 years who had a diagnosis of FH at the beginning of the intervention. We accepted any class of lipid-lowering drug, including, but not limited to, statins and bile-acid sequestrants. We excluded studies that focused on treating those with secondary dyslipidemia or monogenic dyslipidemia other than FH. We excluded treatment studies focusing on apheresis and revascularization, as those treatments are reserved for persons with homozygous FH. We included all reported clinical and laboratory harms associated with lipid-lowering drugs.

We included studies with mixed dyslipidemic populations when the outcome data for subjects with FH were presented separately. We included studies where the author specifically identified subjects with FH using any specified and accepted criteria (**Appendix D**). We limited studies of efficacy or effectiveness to fair- to good-quality randomized trials that were conducted in countries with a high Human Development Index (>0.9). Included intervention trials had to compare an intervention against a usual care or control group.

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

## Quality Assessment and Data Extraction

Two reviewers independently appraised all articles that met the inclusion criteria for this review. The appraisal criteria were adapted from the USPSTF's design-specific quality criteria<sup>51</sup> (**Appendix A Table 2**). Topic-specific quality criteria were designed with the assistance of clinical experts. The final quality rating recorded in the evidence tables was based on quality guidelines from the procedure manual for USPSTF reviews. We rated studies as good, fair, or poor quality. In general, a good-quality study met all criteria well. A fair-quality study did not meet, or it was unclear whether it met, at least one criterion but also had no known issue that would invalidate its results. A poor-quality study had important limitations that made inference

about a population difficult or unwarranted. We excluded poor-quality studies from this review. Poor-quality studies had severe limitations, including one or more of the following risk of biases: lack of randomization, possibly biased assignment, unclear diagnostic criteria, unclear classification procedures, or no reporting of baseline characteristics. Excluded articles are listed in a table with reasons for exclusion (**Appendix C**). One reviewer extracted data from all included fair- or good-quality studies into a standard evidence table. A second reviewer checked the data for accuracy. The reviewers abstracted study characteristics (e.g., population, purpose, exposure, and outcomes of the study), study design elements (e.g., recruitment procedures, eligibility criteria, duration of followup, and attrition), randomized trial characteristics (e.g., setting, blinding, methods of measurement for outcome and exposure, duration, and lipid concentrations), outcomes for screening studies (e.g., true positives, diagnostic yield, and positive predictive value), intermediate outcomes (e.g., lipid concentrations and CIMT) and health outcomes (e.g., MI and stroke), and harms.

## **Data Synthesis and Analysis**

The data are summarized in tables. Lipids and measures of atherosclerosis were expressed as the percent change from baseline or as the difference from baseline. One KQ, KQ6, had sufficient included studies to permit meta-analysis. The results of RCTs of statins that reported means and standard deviations (SDs) for percent change ( $k=6$ ) were summarized in forest plots. Intervention effects for each study are presented as the mean difference between groups with 95% confidence intervals (CIs). When trials reported standard errors (SEs) or CIs for the primary outcome, we used the reported results to compute SDs. For one trial with three groups randomly assigned to different doses of a statin,<sup>52</sup> we used weighted means and SDs to combine reported results into a single intervention effect for the study. Results are displayed in a forest plot. We did not combine data across studies, given the variability in drug, dosage, and intended duration of treatment.

## **Expert Review and Public Comment**

A draft research plan that included the analytic framework, KQs, and eligibility criteria was available for public comment from January 23 to February 19, 2014. This draft research plan was broadly focused on dyslipidemia in childhood and adolescence, not specifically FH. Because of public comment, we decided to conduct two complementary reviews: screening for FH and screening for multifactorial dyslipidemia in children and adolescents. A draft version of the current report was reviewed by three invited content experts, as well as by federal partners from the Centers for Disease Control and Prevention, the Centers for Medicare & Medicaid Services, the National Institutes of Health, the Veteran's Health Administration, and the Military Health Service. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and subsequently addressed, as appropriate, in the final version of this report. Additionally, a draft of the full report was posted on the USPSTF's Web site from December 22, 2015 to January 25, 2016. A few comments were received during this public comment period; there were no changes made to the report based on these comments.

## **USPSTF Involvement**

The authors worked with USPSTF liaisons at key points throughout the review process to refine the inclusion criteria, to address methodological decisions on applicable evidence, and to resolve issues around the scope of the final evidence review. AHRQ funded this research under a contract to support the work of the USPSTF. AHRQ staff oversaw the project and assisted in the external review of drafts of the evidence report. AHRQ was not involved in study selection, quality assessment, or synthesis.

## Chapter 3. Results

### Literature Search

We reviewed 6,753 unique abstracts and excluded 6,378. We reviewed 375 full-text articles and excluded 333 (**Appendix C**). An additional 15 articles were reviewed for contextual questions and not included for any KQs. The remaining set of 27 articles is the included body of evidence for this review. We included two screening studies, 13 studies of drug treatment, and 18 studies (24 publications) of treatment harms. We did not find any relevant studies on adult health outcomes, intermediate outcomes, or harms of FH screening.

### Results of Included Studies

#### **KQ1. Does Screening for FH in Asymptomatic Children and Adolescents Delay or Reduce the Incidence of MI or Stroke in Adulthood?**

No studies were identified.

#### **KQ2. Does Screening for FH in Asymptomatic Children and Adolescents Improve Intermediate Outcomes in Childhood and Adolescence?**

No studies were identified.

#### **KQ3. What Is the Diagnostic Yield of Appropriate Screening Tests for FH in Children and Adolescents?**

#### **Description of Included Studies**

We identified two fair-quality studies of universal screening for FH in school settings (**Table 1**). The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) study was a West Virginia screening program aimed at identifying the prevalence of obesity, dyslipidemia, hypertension, glucose intolerance, and other cardiac risk factors. While the program was not aimed at detection of FH, one publication from CARDIAC reports on children who met criteria for FH.<sup>53</sup> The second study was a Danish screening study, also based in a school setting, that measured apolipoproteins as a screening test for FH.<sup>54</sup> No studies on selective screening for FH were identified.

#### **Included Populations and Interventions**

The West Virginia study was a statewide screening program conducted in schools in all 55

counties between 1998 and 2012. All fifth-grade students (ages 10 to 11 years) were eligible for screening. Girls represented 53 percent of the children screened. The majority were white (93.2%), 2.9 percent were African American, and there were less than 1 percent in other race/ethnic categories. Fasting lipid panels were drawn during the school day and sent to local hospitals or commercial laboratories for analysis, along with other serum chemistries. Procedures for obtaining family history are not described. Children with LDL-C concentrations greater than 155 mg/dL or TC concentrations greater than 260 mg/dL plus DNA evidence of an *LDLR* mutation in a first- or second-degree relative were considered to have “probable FH.” Parents of children with probable FH were asked to take them to a health care provider for additional testing. Results of this testing are not shown; the procedures are not well described. The CARDIAC screening program was embedded in a series of cardiovascular risk reduction activities in the schools and the larger community.

The Danish study took place in a school setting in Copenhagen, targeting children ages 6 to 8 years who were starting first grade. Screening consisted of measuring apolipoproteins in capillary blood, with followup assessment of subjects and family members based on results. The initial questionnaire asked parents about the incidence and age of onset of chest pains or coronary occlusions in themselves or their relatives (parents, siblings, aunts, and uncles). A positive family history was defined as a report of angina pectoris or MI in men younger than age 50 years or in women younger than age 60 years. Questionnaire responses were not used to guide screening. All eligible children were offered screening, regardless of responses. The screening test consisted of a morning nonfasting capillary blood sample. The sample was dried at room temperature for 2 hours and transported to a laboratory within 6 hours.

Children with an Apo B:A-1 ratio greater than 0.83, which was value marking the 97.5th percentile for the sample, had their capillary apolipoprotein ratios rechecked. Children with an Apo B:A-1 ratio greater than 0.83 on repeat testing had their fasting TC, HDL-C, very-low-density lipoprotein cholesterol (VLDL-C), and triglyceride concentrations measured. Fasting lipid panels were obtained from this group of children and from all available first- and second-degree relatives. LDL-C was calculated as  $TC - (HDL-C + VLDL-C)$ . If LDL-C was greater than the 95th percentile for age, an additional lipid profile analysis was obtained after at least 3 weeks, and physical and laboratory studies were performed to rule out causes of secondary hyperlipidemia.

## **Quality**

The quality of the studies was fair. The West Virginia study provided inadequate information about family history screening, failed to report results of confirmatory testing, and lacked a control group. The Danish study gave a scant description of the recruitment and lipid screening of parents and data on nonparticipants, and lacked a control group.

## **Summary of Findings**

The statewide universal screening program in West Virginia schools reported a diagnostic yield of about 1.3 cases per 1,000 screened, with a high threshold for FH.<sup>53</sup> The Danish study identified 10 subjects with laboratory results and a family history consistent with FH from a

sample of 2,085, for a diagnostic yield of 4.8 cases per 1,000 screened.<sup>54</sup>

## Detailed Results

Detailed results are available in **Table 2**. The statewide universal screening program in West Virginia schools used fasting lipid profiles.<sup>53</sup> In this fair-quality study, 81,156 (42%) of 192,610 eligible fifth-grade students were screened between 1998 and 2012, and 12,204 (25.7% of the approximately 47,487 students with fasting lipid profiles) had at least one abnormal lipid value. The authors defined “probable FH” as having an LDL-C concentration greater than 155 mg/dL or TC concentration greater than 260 mg/dL plus DNA evidence of an *LDLR* mutation in a first- or second-degree relative. Results of confirmatory testing (second lipid panel and family history) are not shown. Based on the author’s definition of FH, even without confirmatory testing information, we may consider the 107 screen-positive children to be true positives. This results in a diagnostic yield of about 1.3 cases per 1,000 screened. This rate of 0.13 percent is considerably lower than published estimates.

In the Danish study, questionnaires were sent to 3,025 families; 2,675 were returned, and 2,166 parents consented to their children’s screening. Of these, successful blood testing and measurement of Apo B:A-1 ratio was obtained for 2,085 children. On initial screen, 47 children (2.2%) had an Apo B:A-1 ratio above 0.83; the ratio remained above 0.83 on repeat screening in 12 children (0.58%). Of the 12 children with a high ratio on the second screening, 11 had fasting lipid concentrations (TC and LDL-C) above the 95th percentile for age based on Danish norms. Almost all (10 of 12) showed biochemical evidence of familial involvement (both the child and one parent) consistent with FH. Diagnostic yield for universal screening was 4.8 cases per 1,000 screened, which was above the expected incidence of 2 to 3 cases per 1,000 screened. This result suggests either a higher proportion of FH in the Danish population or the existence of a broader set of inherited dyslipidemias beyond FH, because genetic mutation testing was not performed.

Lipid measurements in relatives of children with persistent Apo B:A-1 ratios above 0.83 identified 29 close relatives with previously undiagnosed hypercholesterolemia and were sufficient to establish an autosomal-dominant inheritance pattern of FH in 10 families. Physical examination and additional laboratory testing in subjects was unrevealing.

## KQ4. What Are the Harms of Screening for FH in Children and Adolescents?

No studies were identified.

## KQ5. Does Treatment of FH With Lifestyle Modifications and/or Lipid-Lowering Medications in Children and Adolescents Delay or Reduce the Incidence of Adult MI and Stroke Events?

No studies were identified.



## KQ6. Does Treatment of FH With Lifestyle Modifications and/or Lipid-Lowering Medications in Children and Adolescents Improve Intermediate Outcomes in Childhood and Adolescence?

### Description of Included Studies

Thirteen fair- to good-quality treatment trials in children with FH met our inclusion criteria (**Table 3**). All 13 trials evaluated lipid-lowering medications. Eight were trials of statins, three were trials of bile-sequestering agents,<sup>55-57</sup> and two were trials of ezetimibe, an inhibitor of intestinal cholesterol absorption.<sup>58, 59</sup> No studies meeting the inclusion criteria evaluated the effect of lifestyle modifications or dietary supplements on intermediate outcomes in children with FH.

### Included Populations

The 13 trials included 54 to 248 participants (**Table 3**). Trial participants' ages ranged from 6 to 18 years. In 11 of these trials, mean ages of participants ranged from 12 to 15 years; two trials had a mean age of 8 years.<sup>55, 59</sup> Both girls and boys were well represented in included trials, 11 of which included both sexes. One study included girls only<sup>60</sup> and one included boys only.<sup>61</sup> Half (k=7) of included trials were conducted in two or more countries in Europe, North America, or Asia.<sup>57-59, 61-65</sup> Four of these multicenter trials had centers in four or more countries and three included at least one country outside our inclusion criteria based on the Human Development Index.<sup>62, 63, 65</sup> The remaining trials were conducted in the Netherlands (k=2),<sup>52, 66</sup> Norway (k=2),<sup>55, 65</sup> Canada (k=1),<sup>67</sup> and the United States (k=1).<sup>60</sup> Only seven trials reported race, and in these, 80 to 94 percent of subjects were white.<sup>52, 57-59, 63, 64</sup> All participants were patients at specialty lipid clinics. None of the studies reported identifying screening-detected participants. Only one study required participants to be treatment-naïve.<sup>66</sup>

FH was defined by elevated fasting lipid concentrations in combination with family history using various standard criteria. Genetic mutations were among the possible inclusion criteria in five studies;<sup>55, 57, 58, 64, 66</sup> some studies specified mutations in *LDLR*<sup>56, 65</sup> and *apoB*<sup>65</sup> genes. In one study, *LDLR* mutation was a required criterion for the diagnosis of FH.<sup>65, 67</sup> One ezetimibe trial<sup>59</sup> included youth who did not meet criteria for FH but whose LDL-C concentrations were between 160 and 400 mg/dL; these children accounted for 9 percent of participants in that trial and were analyzed together with children with FH. Eleven trials used fasting LDL-C concentrations,<sup>52, 58-67</sup> and the other two used TC cut points.<sup>55, 56</sup> Fasting LDL-C or TC concentrations had to be elevated on at least two occasions in five trials.<sup>55, 56, 61, 66, 67</sup> Seven studies required that fasting LDL-C be elevated while the child or adolescent was on a low-fat diet, for a duration ranging from 4 weeks to 4 months.<sup>52, 58, 59, 61, 65-67</sup> LDL and TC cut points were based on age and were similar across studies.

Mean baseline TC ranged from 260 to 320 mg/dL. Mean baseline LDL-C ranged from 198 to 254 mg/dL. Mean baseline HDL-C ranged from 42 to 50 mg/dL. Mean baseline triglycerides ranged from 62 to 110 mg/dL.

Five studies required participants to be at least at Tanner stage II or greater<sup>58, 61-64</sup> or required

girls to be postmenarchal.<sup>58, 62, 64</sup> Three studies set a minimum weight or body mass index percentile for participation.<sup>58, 60, 67</sup>

For presumed safety reasons, four studies also excluded participants whose LDL-C was above a maximum cut point<sup>60-62, 67</sup> (400 mg/dL in two studies;<sup>60, 62</sup> 500 mg/dL in one study<sup>61</sup>). Individuals with elevated triglyceride concentrations were excluded from eight of these trials.<sup>56, 59, 60, 63, 65-67</sup> Most trials excluded participants with homozygous FH, secondary dyslipidemias, and use of medications that could affect lipid concentrations.

## Included Interventions

Of 13 RCTs evaluating the effect of different lipid-lowering medications on dyslipidemia or atherosclerosis in children with FH (**Table 3**), statin medications were studied in eight trials (N=1,071): pravastatin (N=286),<sup>52, 66</sup> simvastatin (N=236),<sup>62, 67</sup> and lovastatin (N=186)<sup>60, 61</sup> were each evaluated in two studies, and atorvastatin (N=187)<sup>63</sup> and rosuvastatin (N=176)<sup>64</sup> were each evaluated once. Dose ranges for the different statins were: pravastatin, 5 to 40 mg;<sup>52, 66</sup> simvastatin, 20 to 40 mg;<sup>62, 67</sup> lovastatin, 40 mg;<sup>60, 61</sup> atorvastatin, 10 mg;<sup>63</sup> and rosuvastatin, 5 to 20 mg.<sup>64</sup> Duration of the blinded, randomized trials ranged from 6<sup>67</sup> to 104 weeks.<sup>66</sup>

The three trials of bile-sequestering agents<sup>55, 56, 65</sup> evaluated cholestyramine at a dose of 8 g/day for 1 year,<sup>55</sup> colestipol at a dose of 10 g/day for 8 weeks,<sup>56</sup> and colesevelam at two different doses (1.875 g and 3.75 g/day) for 8 weeks.<sup>65</sup> There were two trials of ezetimibe, an inhibitor of intestinal cholesterol absorption. One trial assessed ezetimibe monotherapy (10 mg/day) compared to placebo for 12 weeks.<sup>59</sup> Another studied ezetimibe (10 mg/day) in combination with simvastatin (up to 40 mg/day) for 33 weeks.<sup>58</sup>

Retention was greater than 90 percent in seven studies,<sup>52, 58-60, 63, 64, 66</sup> 80 to 90 percent in three studies,<sup>56, 61, 65</sup> 70 to 80 percent in two studies,<sup>62, 67</sup> and 67 percent in one study.<sup>55</sup>

## Quality

All trials were rated as fair- to good-quality. No trials were excluded for poor quality, although 32 studies were excluded for not being RCTs (**Appendix C**). We included 12 good-quality trials and one of fair quality.<sup>55</sup> The major limitation of the fair-quality study was low patient retention.

## Overall Results

### *Statins*

Eight trials reported on the effects of statins on lipid concentrations. All trials reported decreases in LDL-C from baseline, with mean decreases ranging from 23 to 57 mg/dL. Effect sizes were similar across different statins (**Figure 3**). Two trials compared a range of doses, and both showed a dose-response effect on lipid concentrations for pravastatin<sup>52</sup> and rosuvastatin.<sup>64</sup> Of the eight statin RCTs, three were longer than 6 months: two had 48 weeks of followup,<sup>61, 62</sup> and one had 104 weeks.<sup>66</sup> The greatest effect on LDL-C was in a trial of rosuvastatin.<sup>64</sup> Participants who received the highest dose (20 mg/day) experienced a 50 percent decrease (least mean squares) in

LDL-C from baseline compared to a 1 percent decrease among controls ( $p < 0.001$ ).

Eight studies reported the effect of statins on TC, all showing decreases of 20 to 30 percent from baseline (compared to no change with placebo). The effects of statins on HDL-C were mixed, with some studies reporting small but equivocal improvement and others reporting no important changes. Six studies could be summarized in a forest plot (**Figures 2–4**) of mean differences across statins by percent change from baseline of TC, LDL-C, and HDL-C. Significant treatment effects on TC and LDL-C, with overlapping 95% CIs, are seen for all five drugs in these studies: atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin. Mean differences for HDL-C include or come close to zero in all five studies. Because of differences across studies, the forest plots include a range of treatment durations, from 12 to 48 weeks.

A single trial assessed the effect of pravastatin on measures of atherosclerosis, reporting a 2.01 percent decrease in CIMT after 104 weeks compared with a 1.02 percent increase in the control group.<sup>66</sup> Mean change between groups differed significantly ( $p = 0.02$ ). No study assessed the effect of statins on calcium score or pathologic findings.

### *Nonstatin Medications*

Five fair- to good-quality RCTs of nonstatins in children and adolescents with FH met our inclusion criteria: three of bile-sequestering agents and two of ezetimibe. All trials reported decreases in LDL-C from baseline. There were three RCTs of bile-sequestering agents. A good-quality trial of colestipol found a mean reduction in LDL-C of 19.5 percent after 8 weeks of treatment compared to a 1 percent decrease in the control group.<sup>56</sup> One fair-quality RCT of cholestyramine found an 18.6 percent reduction in LDL-C after 1 year compared to a 1.5 percent increase in the control group.<sup>55</sup> One good-quality 8-week RCT of colesvelam<sup>65</sup> published after the 2007 USPSTF review found a decrease in mean LDL-C of 10 percent (SE, 2.1%) at the higher of two doses compared to a mean increase of 2.5 percent (SE, 2.0%) in the control group. A lower dose resulted in a smaller nonsignificant reduction. One good-quality RCT,<sup>58</sup> also published after the 2007 USPSTF review, reported that LDL-C decreased by a mean of 54.0 percent (SD, 1.4%) in participants who received ezetimibe and simvastatin compared to a decrease of 38.1 percent (SD, 1.4%) in the simvastatin-only group at 33 weeks. A good-quality RCT of ezetimibe monotherapy reported a 28 percent (95% CI, 25 to 31) reduction in LDL-C in the treatment group compared to negligible change in the placebo group.<sup>59</sup>

## **Detailed Results for Statins**

### *Effect on Lipid Concentrations*

Eight good-quality RCTs of statins in children and adolescents with FH were included (**Table 4**). Seven of these were included in the 2007 USPSTF review on this topic; one good-quality RCT<sup>64</sup> was published after that report. Details from these studies are discussed below.

**Pravastatin.** Two good-quality RCTs evaluated the effect of pravastatin on lipid concentrations in children with FH. The first<sup>52</sup> studied 72 children ages 8 to 16 years randomly assigned to one of four groups: a placebo group and three pravastatin groups receiving doses of 5, 10, or 20

mg/day. The authors do not report whether adherence was assessed. The intervention period lasted 12 weeks, at the end of which all three pravastatin arms had reductions in mean LDL-C relative to the control arm. There were greater reductions in TC and LDL-C concentrations in the group receiving 20 mg pravastatin compared to the groups receiving 5 or 10 mg of pravastatin. Changes in HDL-C and triglycerides were not statistically significant. Detailed results are provided in **Table 4a**.

The Dutch Pravastatin Trial, the longest of any statin trial in children,<sup>66</sup> followed 214 children ages 8 to 18 years for 2 years. Children younger than age 14 years received pravastatin 20 mg/day; those age 14 years and older received 40 mg/day. The authors do not report whether adherence was assessed. At the end of the intervention period, the pravastatin group had significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C and TG were minimal and not statistically significant. Detailed results are provided in **Table 4b**.

**Simvastatin.** Two RCTs evaluated the effect of simvastatin on lipid concentration in children with FH. The first was a good-quality trial<sup>67</sup> of 63 children ages 8 to 17 years randomly assigned in a 3:1 ratio to receive 20 mg/day of simvastatin or placebo for 6 weeks. Adherence was assessed by pill count but was not reported. At the end of the intervention period, the simvastatin group had significant reductions in TC and LDL-C relative to the control group. Detailed results are provided in **Table 4c**. Data for this RCT were extrapolated from a figure.

A multicenter, good-quality study<sup>62</sup> randomly assigned 173 children in a 3:2 ratio to receive simvastatin or placebo. Simvastatin was started at 10 mg/day for the first 8 weeks, increased to 20 mg/day for the second 8 weeks, and increased to 40 mg/day for the last 8 weeks of the 24-week trial. The authors do not report whether adherence was assessed. At the end of the intervention period, the simvastatin group had significant reductions in TC and LDL-C relative to the control group. HDL-C changes were minimal, and triglyceride changes were not statistically significant. Detailed results are provided in **Table 4d**.

**Lovastatin.** Two RCTs examined lovastatin<sup>60, 61</sup> with a combined sample size of 186, and both showed a decrease in LDL-C.

The first trial<sup>61</sup> compared lovastatin to placebo in 132 boys ages 10 to 17 years (mean, 13.2 years). This trial was rated good quality. Lovastatin was started at 10 mg/day and doubled every 8 weeks to a maximum dose of 40 mg/day. Adherence was assessed by pill count but was not reported. At the end of the 48-week intervention period, the lovastatin group had significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C and triglycerides were minimal and not statistically significant. The authors report that the U.S. Food and Drug Administration requested that subjects who had not reached Tanner stage II at entry discontinue the trial. This request resulted in the discontinuation of eight subjects, seven in the placebo group and one in the lovastatin group. Detailed results are provided in **Table 4e**.

The second lovastatin trial<sup>60</sup> enrolled 54 girls ages 11 to 18 years (mean, 15 years) and randomly assigned them to lovastatin or placebo. In this good-quality trial, lovastatin was administered at 20 mg for the first 4 weeks and then increased to 40 mg for the duration of the 24-week trial. Adherence was assessed by pill count but was not reported. At the end of the intervention period,

the lovastatin group had significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C and triglyceride concentrations were not statistically significant. Detailed results are provided in **Table 4f**.

**Atorvastatin.** One good-quality trial of atorvastatin randomly assigned 187 children ages 10 to 17 years (mean, 14.1 years) to receive 10 mg/day atorvastatin or placebo over 26 weeks.<sup>63</sup> The authors do not report whether adherence was assessed. At the end of the intervention period, the atorvastatin group had significant reductions in TC and LDL-C relative to the control group. There were small increases in HDL-C concentration and small decreases in triglyceride concentration; both were statistically significant. Detailed results are provided in **Table 4g**.

**Rosuvastatin.** The one RCT published after the 2007 USPSTF report, the PLUTO (Pediatric Lipid-reduction Trial of rOsuvastatin) study,<sup>64</sup> was a good-quality trial that randomly assigned 176 children and adolescents ages 10 to 17 years (mean, 14.5 years) to 5, 10, or 20 mg/day of rosuvastatin or placebo. Pill counts indicated that 90 percent of participants were at least 80 percent compliant with the protocol. At 12 weeks, all three intervention groups had marked decreases in mean LDL-C and TC. The 20-mg dose group had the greatest reduction in LDL-C among the eight statin trials reviewed here. Fewer than half the participants who received rosuvastatin reached the target LDL-C concentration of less than 110 mg/dL (12%, 41%, and 41% in the 5-mg, 10-mg, and 20-mg groups, respectively). No subject reached this target in the control group. HDL-C and triglyceride changes were neither clinically nor statistically different from the control group. Detailed results are provided in **Table 4h**.

#### *Effect on Atherosclerosis Markers*

Only the 2-year pravastatin trial<sup>66</sup> reported the effect of a statin (pravastatin) on a measure of atherosclerosis (CIMT) (**Table 5**). Study details are described above, along with the effect on lipid concentrations. One experienced sonographer, blinded to treatment status, measured CIMT on all B-mode ultrasonograms. After 2 years of treatment with 20 mg, then 40 mg of pravastatin daily, mean CIMT declined marginally in the pravastatin group (−0.010 mm [SD, 0.048 mm];  $p=0.049$ ) compared to a trend toward progression in the placebo group (+0.005 mm [SD, 0.044 mm];  $p=0.28$ ). Expressed as a percent change from baseline, CIMT decreased by 2.01 percent in the pravastatin group and increased by 1.02 percent in the control group (calculated). The mean change in CIMT between the two groups (0.014 mm [SD, 0.046 mm]) was significant ( $p=0.02$ ).

### **Detailed Results for Nonstatin Medications**

#### *Bile-Sequestering Agents*

A good-quality RCT evaluated colestipol (10 g/day) in 66 children and adolescents ages 10 to 16 years (mean age, 13.1 years) with FH.<sup>56</sup> Adherence was 68 percent in the colestipol group and 76 percent in the placebo group. After 8 weeks, the colestipol group had significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C were not significant. Detailed results are provided in **Table 4i**.

One fair-quality study examined the effect of cholestyramine in 72 children ages 6 to 11 years

(mean age, 8.4 years) with FH.<sup>55</sup> The intervention group received 8 g/day of cholestyramine for 1 year. Adherence was assessed but not reported. At the end of the 12-month intervention period, the cholestyramine group had significant reductions in TC and LDL-C relative to the control group. HDL-C did not change appreciably in either group. Detailed results are provided in **Table 4j**.

A single trial of bile-sequestering agents included in this review was published after the 2007 USPSTF review on child lipids. This good-quality, multisite RCT evaluated colesevelam in 194 children and adolescents ages 10 to 17 years (mean, 14.1 years).<sup>65</sup> Participants were randomly assigned to three groups: 1.875 g/day (low dose), 3.75 g/day (high dose), or placebo for 8 weeks. Adherence (assessed by pill count) was greater than 85 percent in all groups, and 89.2 percent of participants who were randomized completed the study. At the end of the 8-week intervention period, the colesevelam groups experienced greater reductions in LDL-C and TC than the placebo group, with more pronounced reductions in the high-dose group. The treatment goal of an LDL-C concentration less than 110 mg/dL was achieved by 3.2 percent (n=2) in the low-dose group and by 7.9 percent (n=5) in the high-dose group. Detailed results are provided in **Table 4k**.

### *Ezetimibe*

There were two studies of ezetimibe, an intestinal cholesterol absorption inhibitor. One good-quality RCT compared the effectiveness of ezetimibe plus simvastatin to simvastatin alone in 248 children and adolescents ages 10 to 17 years (mean, 14.2 years).<sup>58</sup> In this six-group trial, three received ezetimibe (10 mg/day) and three received placebo. All six groups received simvastatin, with three different doses for the first 6 weeks (10, 20, or 40 mg/day) but the same dose (40 mg/day) for the next 27 weeks. The last 20 weeks of the trial were open label (both medications). The six groups were combined into two groups for analysis: ezetimibe plus simvastatin and placebo plus simvastatin. The authors do not report whether adherence was assessed. At the end of the 33-week intervention period, the ezetimibe plus simvastatin group had significant reductions in TC and LDL-C relative to the placebo plus simvastatin group. Detailed results are provided in **Table 4l**.

One good-quality RCT compared the effectiveness of a 12-week course of ezetimibe to placebo in 138 children ages 6 to 10 years (mean, 8.3 years).<sup>59</sup> Children in this trial either met criteria for FH (n=125; 91%) or did not meet criteria but had LDL-C greater than or equal to 160 mg/dL. The study groups were analyzed together regardless of diagnosis status. Participants were randomized to receive ezetimibe (10 mg/day) or placebo in a 2:1 ratio. At the end of the 12-week intervention period, the ezetimibe group had significant reductions in TC and LDL-C relative to the placebo group. Maximum effect was achieved at 2 weeks. HDL-C changes were not significant. Detailed results are provided in **Table 4m**.

The number of studies of nonstatin medications was too small to explore heterogeneity or publication bias.

## KQ7. What Are the Harms of Treatment of FH With Medications in Children and Adolescents?

### Description of Included Studies

We identified 24 publications (18 trials) that met criteria for KQ7. Several of these publications have overlapping study populations (**Table 6**). Twelve RCTs (seven on statins and five on nonstatins) were included in both KQ6 and KQ7. Twelve articles were published before 2007 that fit our inclusion criteria: nine of statins,<sup>52, 60-63, 66, 68-70</sup> two of bile-sequestering agents,<sup>55, 56</sup> and one of a bile-sequestering agent coadministered with a statin.<sup>71</sup> We identified an additional 12 articles published since 2007 with relevant data on harms: nine of statins,<sup>64, 72-79</sup> one of a bile-sequestering agent,<sup>65</sup> and two of a selective inhibitor of intestinal cholesterol absorption (ezetimibe).<sup>58, 59</sup> Most studies were less than 2 years long. One study reported 10-year followup data of statin use.<sup>67</sup>

### Included Populations

The 18 included trials ranged in size from 6 to 248 children or adolescents with FH. Specific information on recruitment of subjects was not available for many studies; however, in most of those studies for which this was reported, subjects had already been diagnosed with FH and were often drawn from a specialty clinic population. Age at baseline ranged from 6 to 18 years; mean age ranged from 6 to 16 years. All but two studies included between 31 and 65 percent female subjects; the remaining two included exclusively female subjects<sup>60</sup> or male subjects.<sup>61</sup> Four studies (eight publications) were conducted in the Netherlands,<sup>52, 66, 70, 72, 74, 76-78</sup> two studies (two publications) were conducted in Norway,<sup>55, 56</sup> and one study each was conducted in the United States,<sup>60</sup> Canada,<sup>71</sup> Finland,<sup>68</sup> Austria,<sup>69</sup> and France.<sup>73</sup> Nine studies were conducted at multiple sites in two or more countries in North America, Europe, Africa, and/or Australia.<sup>58, 59, 61-65, 75, 79</sup> Identified countries involved in these studies include the United States (six studies), Canada (six), the Netherlands (four), Norway (four), Israel (two), South Africa (two), Australia, Austria, Belgium, Colombia, Costa Rica, the Czech Republic, France, Greece, Hungary, Italy, New Zealand, Slovakia, and Spain (one each). In these studies, the percentage of Caucasian subjects ranged from 80 to 100 percent. A case definition of FH was provided for all but one<sup>63</sup> study. Specific diagnostic criteria for FH varied from study to study but in all cases included either genetic testing or clinical criteria identical or similar to one of the three most-commonly cited diagnostic criteria (**Appendix D**).

### Included Interventions

Among the statin trials, there were five trials of pravastatin: two RCTs<sup>52, 66</sup> (six publications), two observational trials of pravastatin,<sup>68, 73</sup> and one randomized crossover trial of combination therapy with colestipol and pravastatin.<sup>71</sup> There were two RCTs of lovastatin<sup>60, 61</sup> and one RCT (two publications) of simvastatin.<sup>62, 70</sup> Two statins, atorvastatin<sup>63, 75</sup> and rosuvastatin,<sup>64, 79</sup> each had two trials, an RCT and an open-label trial. Finally, there was one observational cohort study of various statins.<sup>69</sup> The longest followup periods for statin studies were reported in a 48-week lovastatin RCT,<sup>61</sup> a 2-year open-label rosuvastatin trial,<sup>79</sup> and the Dutch Pravastatin Trial (a 2-year RCT with followup at 10 years).<sup>66</sup>

Studies evaluating harms of nonstatin medication included three RCTs of bile-sequestering medications: colestevlam,<sup>65</sup> cholestyramine,<sup>55</sup> and colestipol.<sup>56</sup> There were two trials of ezetimibe: one RCT of simvastatin coadministered with ezetimibe<sup>58</sup> and one RCT of ezetimibe monotherapy.<sup>59</sup> The longest of these nonstatin studies were two year-long RCTs: the cholestyramine trial and the trial of ezetimibe with simvastatin.

Two studies included for assessment of harms involved a statin and a nonstatin. The trial of pravastatin vs. placebo (in youth treated with colestipol)<sup>71</sup> is discussed in the section on statins. The trial of ezetimibe vs. placebo (in youth treated with simvastatin)<sup>58</sup> is discussed in the section on nonstatin medications.

## Quality

All included studies were fair- to good-quality. Among studies of statins, eight studies (13 publications) were good-quality and five studies (six publications) were fair-quality. The quality issues most often found in the fair-quality studies were lack of a control group, inadequate description of methods, and a followup of less than 90 percent. Four good-quality and one fair-quality studies assessed harms of nonstatin medication treatment. The primary concern with the fair-quality studies was a low rate of followup. The two studies of combination therapy with a statin and a nonstatin medication were both of good quality.

## Summary of Findings

The 18 studies included 2,210 children and adolescents, 2,197 of whom had FH.

### *Statins*

There were 13 studies (19 publications) on harms of statins, including 1,492 children and adolescents. The shortest intervention durations were 8 to 12 weeks (four studies) and the longest was 2 years (one RCT). Few studies conducted followup assessments beyond the intervention period. One study (the 2-year RCT) provided the longest followup data (10 years) for a group of whom almost all were treated with statins for much of the 10-year period. Dosage varied within and between studies, with some including an open-label phase with all subjects on active medication.

Most studies reported data on clinical adverse events (AEs) and laboratory abnormalities, and several studies of statins monitored growth and pubertal development. In many studies, reporting of harms assessment did not mention which harms were assessed, only those that were noted to have occurred. Statins were generally well-tolerated. There was no evidence of a consistent association between a particular subjective harm and statin use in general (**Tables 8 and 9**).

Serious AEs were rare. In controlled studies with a placebo group, the frequency of reported AEs usually did not differ significantly from those in placebo. The most common AEs were otorhinolaryngologic (mostly nasopharyngitis), gastrointestinal (predominantly abdominal pain, nausea/vomiting, and diarrhea), respiratory (mostly respiratory infection and influenza), and neurological (predominantly headache). Statins were well-tolerated, with 98.5 percent of young



adults still taking statin medications 10 years after beginning a clinical trial.<sup>78</sup> In this same study, adherence was good, with 78.7 percent reporting taking more than 80 percent of their medications. Most studies did not report on statistical significance of difference in rates for individual AEs between study groups. Those that did generally reported no significant associations. The most frequently reported AEs (**Table 9**) were generally not believed to be associated with medication use. Systemic, immunologic, and pain-related AEs were reported only sporadically in these studies (<10 reports per study).

In one small, uncontrolled study of statins in six professional athletes with FH (mean age, 16.8 years [SD, 2.6 years]), three subjects reported muscle pain on all five statins tried, and three reported muscle pain on three of the five statins tried.<sup>69</sup> However, musculoskeletal pain was infrequently reported in other studies, occurring in only 4.8 percent (56 of 1,018) of subjects taking statins in studies that reported these data. Musculoskeletal pain, myalgia, and muscle pain were reported as AEs in 10 statin studies. The incidence ranged between 0 and 10 percent for those on statins (and between 0% and 6.2% for those in the placebo groups). The incidence of musculoskeletal pain, myalgia, and muscle pain was not reported as being significantly different from control subjects in any studies for which this information was available.

All but two of the 13 statin studies assessed liver transaminase and creatine kinase (CK) concentrations as part of their safety assessment. Concentrations were checked at baseline and conclusion; many studies also included checks at scheduled intervals during treatment. Five of the 13 studies reported no abnormalities of either CK or transaminases. In the eight studies that did, the abnormalities were usually transient, with concentrations usually resolving either spontaneously or after temporary withdrawal of the medication (**Table 8**).

Ten statin studies also assessed the impact of treatment on growth and pubertal development in children or adolescents, either through physical examination and measurement, laboratory screening, or both.<sup>52, 60-64, 66, 72, 73, 76</sup> No studies suggested an important association between statin use and abnormalities in any of these outcomes.

Ten-year followup of the Dutch Pravastatin Trial measured sex hormones in young men and women (mean age, 24 years) with FH who had participated in the initial 2-year pravastatin trial, followed by continued use of pravastatin and other statins over the intervening years. Compared to their brothers without FH, the young men with FH in this study treated with statins had lower mean dehydroepiandrosterone sulfate (DHEAS) concentrations, although values were still within the normal range. These elevations are of unclear clinical significance.

### *Bile-Sequestering Agents*

Three RCTs evaluated the harms of monotherapy with three different bile-sequestering agents (colesevelam,<sup>65</sup> cholestyramine,<sup>55</sup> and colestipol<sup>56</sup>) in a total of 332 children and adolescents with FH. Two were 8-week trials and one lasted 1 year. The most common drug-related AEs were gastrointestinal. Abdominal pain, diarrhea, nausea, or vomiting were reported by 7 to 10 percent (calculated from reported data) of subjects in the two studies that reported data from the placebo-controlled period. However, these rates were similar to those reported in the placebo groups (4.6% to 5%, calculated).<sup>55, 65</sup> The studies on colestipol and cholestyramine both note that

unpalatability was a marked problem and caused 14 subjects to withdraw from the cholestyramine study. However, unpalatability was also often reported in the placebo group in the same study, in which 10 subjects withdrew.

The most notable laboratory abnormalities were decreased vitamin D concentrations in treated subjects (compared to placebo) in the cholestyramine study and, to a lesser extent, in the colestipol study. Folate concentrations were lower in subjects treated with colestipol than in those on placebo, and homocysteine was increased in subjects treated with cholestyramine, concentrations of which were negatively correlated with folate concentrations at baseline and at 1 year.<sup>55, 56</sup> No marked laboratory abnormalities were reported in the colesevelam trial, although it is not clear which safety factors were measured.

### *Ezetimibe*

Two RCTs evaluated harms of ezetimibe in 373 children and adolescents with FH. One was a 12-week trial of monotherapy and the other a 52-week trial of ezetimibe coadministered with simvastatin.<sup>58</sup> In the year-long study,<sup>58</sup> alanine aminotransferase (ALT) elevations occurred in 5 percent of participants in the simvastatin plus ezetimibe group and 2 percent of those in the simvastatin-only group. Laboratory values normalize with discontinuation of treatment. Most AEs and their rates were similar between groups: gastrointestinal symptoms, elevated transaminase concentrations (that resolved following interruption of therapy), and myalgia without associated CK elevation. The 12-week ezetimibe monotherapy trial<sup>59</sup> found no significant difference in AE distribution between study groups and no serious AEs in either group.

## **Detailed Results**

Studies are listed here by class and drug, then chronologically by date of the publication of the original study. All publications for a given study are considered together.

### *Statins*

**Pravastatin.** Four trials evaluated harms of pravastatin use in children with FH, including the Dutch Pravastatin Trial that produced five publications that addressed harms with up to 10 years followup. A fifth trial used a randomized crossover design to evaluate pravastatin in children treated with colestipol.<sup>71</sup>

In a 12-week good-quality RCT, 72 children ages 8 to 16 years with FH in the Netherlands were randomly assigned to placebo or to one of three pravastatin doses (5 mg, 10 mg, or 20 mg daily).<sup>52</sup> Physical examinations were performed at the beginning and end of the study, and fasting blood samples (hematology, ALT, aspartate aminotransferase [AST], CK, alkaline phosphatase, urinalysis, thyroid-stimulating hormone, cortisol, and adrenocorticotrophic hormone) were measured monthly. The incidence of laboratory abnormalities did not differ significantly between groups. The most common AEs were gastrointestinal symptoms and headache; both these and other sporadic complaints (rash, fatigue, epistaxis, and myalgia) were equally distributed between the placebo and treatment groups. None were believed to be medication-

related. (Note: This trial was conducted in the Netherlands; however, we use the shorthand term “Dutch Pravastatin Trial” to refer to a separate study by Wiegman and colleagues—described below—which was a larger trial with longer followup.)

In a good-quality randomized crossover trial of colestipol combined with pravastatin,<sup>71</sup> 36 youth ages 9 to 18 years received either colestipol alone (10 g/day) or low-dose colestipol (5 g/day) in combination with pravastatin (10 mg/day). This Canadian study consisted of an 8-week period without lipid-lowering medication followed by two 18-week treatment periods. Subjects crossed over to the alternate regimen after the first treatment period. Serum chemistries and blood counts were assessed at baseline and 2 weeks, 8 weeks, and 18 weeks into each treatment period. Alkaline phosphatase concentrations were significantly decreased in both treatment regimens at 2 and 8 weeks, but the decrease was significant only in the colestipol-only group at 18 weeks. The absolute reduction in ALT concentrations from baseline was significantly greater in the colestipol-only group than in the combination group at 8 and 18 weeks. No significant changes or differences between regimens were reported for CK, AST, other blood chemistries, or hematologic values. Increases in weight, height, and body mass index did not differ significantly between groups. Subject-reported AEs were more common in the higher-dose colestipol-only group than in the combination group: constipation occurred in 21 percent of subjects on colestipol only versus 3 percent of subjects on the combination regimen, bloating/gas in 15 versus 3 percent, stomach ache in 21 versus 0 percent, headache in 14 versus 3 percent, and muscle ache in 6 versus 3 percent, respectively.

One fair-quality, prospective observational study examined the pharmacokinetics and pharmacodynamics of pravastatin in Finnish children with FH.<sup>68</sup> Twenty children with FH ages 4 to 15 years received 10 mg pravastatin daily for 8 weeks. Subjects indicated AEs (gastrointestinal symptoms, headache, skin reactions, sleep disturbance, muscle/tendon tenderness, and pain) each day on a home questionnaire, and laboratory values (creatinine, ALT, and CK) were measured at baseline, 4 weeks, and 8 weeks. Laboratory values did not increase during the study. Other AEs were rare: four reports of headache, two reports of sleep disturbance, and one report each of abdominal pain, loose stool, muscle tenderness at rest, and muscle tenderness with activity.

The Dutch Pravastatin Trial was the largest RCT of a statin in youth with FH and also the single trial in this review with the longest followup (10 years). In this RCT, 214 children with FH ages 8 to 18 years were randomly assigned to receive either placebo or pravastatin (20 mg daily for children age <14 years, 40 mg daily for those age ≥14 years) for 2 years.<sup>66</sup> Subjects were evaluated by a physician every 6 months. Sex steroids, gonadotropins, and pituitary-adrenal axis markers were measured at baseline and at 1 and 2 years into the study; developmental and maturation indices were measured at the same times: growth (height, weight, body mass index, and body surface area), pubertal development (Tanner stage, menarche, and testicular volume), and academic progress (school records). Muscle and liver enzymes (ALT, AST, and CK) were measured at baseline, at 3 month intervals in year 1, and at 6 month intervals in year 2. CK concentrations were increased by more than a factor of 4 in four subjects in the intervention group and in three subjects in the placebo group; however, at the end of the trial, the groups had no relevant differences in CK or transaminase concentrations. Groups also did not differ in measures of endocrine function or in the aforementioned growth and maturation markers, and

academic performance was not affected.

At the end of 2 years, all participants in the Dutch Pravastatin Trial intervention and control groups were combined and all participants were treated with pravastatin (20 to 40 mg daily) and followed for varying periods (duration of statin therapy ranged from 2.1 to 7.4 years). Of the 186 subjects included in this fair-quality study,<sup>76</sup> 83 percent were still using pravastatin at the time of followup. No serious laboratory abnormalities were noted on followup. Two subjects had CK concentrations greater than 10 times normal. However, these elevations were considered to be associated with extreme fitness regimens, and they resolved without discontinuing treatment. Myalgia without CK elevation occurred in four subjects. Four subjects (three male, one female) had mildly elevated follicle-stimulating hormone concentrations, three had decreased DHEAS concentrations, and two had mildly elevated adrenocorticotrophic hormone concentrations. None of these changes were thought to be related to statin use.

The authors assessed Dutch Pravastatin Trial participants for harms at 10 years postrandomization and published findings in three articles.<sup>72, 77, 78</sup> In the main 10-year adherence and tolerability analysis, 205 patients were available for followup (mean age, 24 years).<sup>78</sup> Tolerability was 98.5 percent over the 10 years; three out of 205 subjects had discontinued medications due to side effects (gastrointestinal, muscle and joint pain, or headache). There were 55 side effects reported over 10 years by 40 subjects (19.5%), mainly consisting of muscle complaints and gastrointestinal symptoms. There were no reports of rhabdomyolysis or elevation of liver enzymes. By 10 years, 17 participants had had discontinued lipid-lowering medications due to pregnancy, lactation, and/or the advice of a physician, and 19 participants had chosen to discontinue the medication on their own. Among the 169 participants still taking lipid-lowering medications, 99 percent were on various statins and 36 percent were on ezetimibe. Most (78.7%) subjects reported adherence of greater than 80 percent in the previous month.

The last two articles from the Dutch Pravastatin Trial included the 214 patients with FH and 95 unaffected siblings who had been recruited at the conclusion of the 2-year RCT. One<sup>72</sup> of these two sibling comparison studies evaluated 194 participants (91% followup) and 83 siblings (87% followup) 10 years after randomization. All participants were ages 18 to 30 years at that time. In this study, 163 subjects were still using lipid-lowering medications at 10 years (31% pravastatin; 15% simvastatin; 27% rosuvastatin; 27% atorvastatin). Growth, maturation, level of education, history of AEs, liver transaminases, CK, glomerular filtration rate, and C-reactive protein were assessed. Subjects and unaffected siblings did not differ remarkably on any outcomes (except for extremely elevated CK concentrations in two unaffected siblings). Three subjects discontinued statin therapy because of unspecified AEs. No serious major AEs were reported.

Comparison with these siblings also formed the basis of a study<sup>77</sup> examining the possible effects of statins on sex hormones, including testosterone, estradiol, luteinizing hormone, follicle-stimulating hormone, and DHEAS concentrations after 10 years. There were 88 participants with FH and 62 siblings available for this analysis. The only significant difference between siblings and those with FH was for DHEAS, which was significantly lower in the males with FH (8.4  $\mu\text{mol/L}$  [SD, 3.0  $\mu\text{mol}$ ]) than in their brothers without FH (12.9  $\mu\text{mol/L}$  [SD, 4.9  $\mu\text{mol}$ ];  $p < 0.001$ ). The authors note that despite this difference, the mean DHEAS concentration in the FH group was still within the normal range.

The final pravastatin study was an observational analysis of the medical records of 185 French children age 18 years and younger with FH (mean age, 11 years) who were being treated with pravastatin at varying doses.<sup>73</sup> Subjects were followed for 3 months to 7 years. Of the 185 patients, 24 (13%) experienced AEs: four reported muscular pain that resolved after changing to a new statin; three others had muscle pain not apparently associated with treatment; and 12 had musculoskeletal pain (two with associated moderate CK elevation) that resolved spontaneously. Other AEs included asymptomatic CK elevation (eight subjects), transient headache (one), and gynecomastia with normal hormone concentrations (one). No subjects had elevated transaminase concentrations and no instances of growth problems, early maturation, or delayed puberty were observed.

**Lovastatin.** Two good-quality RCTs evaluated harms of lovastatin in children with FH. One trial, conducted in the United States and Finland, randomly assigned 132 boys ages 10 to 17 years with FH to either placebo or daily lovastatin (initially at a dose of 10 mg, titrated after 8 and 16 weeks to 20 mg and 40 mg, respectively, then maintained at 40 mg for the remaining 32 weeks of the study).<sup>61</sup> AEs were reported by 70.1 percent of subjects in the lovastatin group and by 73.8 percent in the placebo group. AEs reported in the lovastatin group included gynecomastia (1.5%); respiratory tract infection (47.8%); abdominal pain (10.4%); ear, nose, and throat infection (10.4%); skin disease (9.0%); gastroenteritis (7.5%); lymphadenopathy (3.0%); myalgia (4.5%); diarrhea (1.5%); and arthropathy (1.5%). The frequencies of these AEs did not differ significantly from those in the placebo group. Both the lovastatin and placebo groups had a statistically significant increase in ALT at 48 weeks; however, ALT concentrations did not differ significantly between the two groups. No sustained changes in AST or CK were noted in either group, although nonsustained CK elevations (>5 times the upper limit of normal) were noted in three subjects in the lovastatin group and in one subject in the placebo group. These elevations were reported to be associated with vigorous or unusual exercise. Participants reported no associated muscle pain. Indices of growth and development did not differ between groups.

In the other, a U.S. study, 54 postmenarchal girls (ages 11 to 18 years) were randomly assigned to receive placebo or lovastatin 20 mg or 40 mg daily for 24 weeks.<sup>60</sup> Just over two-thirds of the girls in both the lovastatin and placebo groups reported AEs; among these, the most common were upper respiratory infection (29% of girls on lovastatin, 47% of girls on placebo), headache (20% and 21%, respectively), and pharyngitis (17% and 11%, respectively); 11 percent of lovastatin subjects also reported an influenza-like disease. Three girls (9%) in the lovastatin group had AEs believed to be treatment-related: two girls (6%) with abdominal pain, one with diarrhea, one with nausea, and one with headache. All treatment-related AEs resolved spontaneously while patients continued on study medication. The only laboratory AE reported was a decrease in hemoglobin and hematocrit in one subject taking 40 mg of lovastatin. This AE was believed to be unrelated to treatment. Luteinizing hormone concentrations decreased in subjects on placebo but were unchanged in those on lovastatin. No significant between-group differences or changes from baseline were noted for other hormones (follicle-stimulating hormone, cortisol, estradiol, or DHEAS), AST, ALT, CK, height, weight, body mass index, or vital signs (except a small decrease in systolic blood pressure in the placebo group).

**Simvastatin.** One good-quality RCT (two publications) evaluated the safety of simvastatin for treating children with FH in the Netherlands. This trial randomly assigned 173 children ages 10

to 17 years with FH to receive simvastatin or placebo.<sup>62</sup> Simvastatin dose in the first phase was 10 mg/day for 8 weeks, with subsequent increase to 20 mg for 8 weeks and then to 40 mg for 8 weeks. Subjects then continued at a dose of 40 mg/day for an additional 24 weeks. Drug-related laboratory AEs occurred in two subjects on simvastatin and in one subject on placebo during the first phase of the trial, and in two simvastatin and one placebo subjects during the second phase. These AEs included two cases of transaminase elevations greater than 3 times the upper limit of normal (one of which improved after a 10-day interruption in therapy, the other of which occurred in a child with infectious mononucleosis) and three cases of elevated CK concentrations. One of these three children was on concurrent erythromycin therapy and had CK levels greater than 10 times the upper limit of normal, which resolved after completing antibiotic therapy. The other two children had CK levels greater than 5 times the upper limit of normal, which returned to normal on repeat testing. Clinical AEs reported during the study included headache (in four subjects on simvastatin), abdominal pain (three subjects on simvastatin), and myalgia (two subjects on simvastatin). Other AEs (one subject on simvastatin each) included chest pain, flatulence, weight gain, sleep disorder, and pruritus. Fewer subjects on placebo reported clinical AEs (five subjects) than did those on simvastatin (10 subjects); however, none of the differences between the placebo and simvastatin groups in either phase of the study was statistically significant. There were small but statistically significant between-group differences in the absolute change of DHEA concentrations in both boys and girls at 24 and 48 weeks, but no associated growth or pubertal development abnormalities (no significant differences between groups on growth, body mass index, cortisol and hormone concentrations, or pubertal development).

A fair-quality subanalysis of this simvastatin RCT assessed harms in 50 children with FH ages 9 to 18 years who received either placebo or simvastatin 10 mg/day for 8 weeks, then 20 mg/day for 8 weeks, and then 40 mg for 8 weeks.<sup>70</sup> Safety assessment included measuring AST, ALT, and CK and a physical examination. Laboratory values did not differ substantially between the simvastatin and placebo groups. The authors stated that no AEs were reported; no data were shown.

A different RCT<sup>58</sup> evaluated ezetimibe in children with FH being treated with simvastatin and is discussed in the section on ezetimibe below.

**Atorvastatin.** Two studies evaluated harms of atorvastatin used to treat FH in children. One good-quality RCT conducted in the United States, Canada, Europe, and South Africa randomly assigned 187 youth (ages 10 to 17 years with FH or severe hypercholesterolemia) to receive atorvastatin 10 mg/day or placebo daily for 26 weeks, followed by an additional 26 weeks during which all subjects received 10 mg atorvastatin daily.<sup>63</sup> During the RCT phase, the dose of atorvastatin could be titrated to 20 mg/day at week 4 for subjects not achieving target LDL-C levels. AEs occurred in 63 percent of the treatment group during the blinded phase and in 62 percent of the placebo group. Among subjects in the treatment group, AEs included infection (19%), accidental injury and headache (9% each), pharyngitis and flu syndrome (6% each), abdominal pain (4%), and fever (1%). All of these AEs occurred in the placebo group as well; the incidence did not differ significantly between groups. During the RCT phase, 7 percent of AEs in the atorvastatin group were judged to be treatment-related compared to 4 percent in the placebo group. AEs were mostly mild or moderate; one subject in the atorvastatin group

experienced increased depression that was thought to be possibly treatment-related, and this subject discontinued treatment. Marked laboratory abnormalities were noted in 29 percent of atorvastatin subjects and in 34 percent of placebo subjects during the RCT phase. Two subjects on atorvastatin had AST elevations (3 times the upper limit of normal), and one had an ALT elevation, none of which required treatment modifications. No such abnormalities occurred in the placebo group. Indices of growth and sexual development did not differ significantly between groups, nor did the incidence or severity of treatment-related AEs increase in the second phase of the study.

One fair-quality, open-label, 8-week study assessed the tolerability of atorvastatin in 15 children ages 6 to 10 years (Tanner stage 1) and in 24 children ages 10 to 17 years (Tanner stage  $\geq 2$ ) with FH in Greece, Norway, and Canada.<sup>75</sup> Initial doses were 5 mg/day for younger children and 10 mg/day for older children. Doses were doubled after 4 weeks if the target LDL-C concentration was not achieved. Indices of safety and tolerability did not differ between the younger and older groups, and no serious AEs were observed. At least one AE was reported by nine of 15 subjects in the younger group and by 13 of 24 subjects in the older group. The only AEs reported by more than one subject were viral upper respiratory infection (three subjects in Tanner stage 1 group), nasopharyngitis (one subject in Tanner stage 1 group; two subjects in Tanner stage  $\geq 2$  group), headache (two subjects in Tanner stage 1 group, one in Tanner stage  $\geq 2$  group), and increased ALT (two subjects, both in Tanner stage  $\geq 2$  group). Only four subjects (two from each group) reported AEs that were believed to be treatment-related. These AEs included one instance each of headache, abdominal pain, nausea, and vomiting in the younger group, and the two aforementioned subjects with ALT elevations in the older group (at the end of the study, ALT concentrations returned to normal in one subject and were only slightly elevated in the other.) Data on vital signs, electrocardiography, urinalysis, hematology, and biochemistry tests (including CK) were obtained at baseline and 8 weeks. The only abnormality was a moderate but transient increase in CK that was not believed to be related to treatment in one 9-year-old child.

**Rosuvastatin.** Two good-quality trials (three publications) evaluated the safety of rosuvastatin for treating FH in children. Authors of the first of these also published a separate analysis of a subset of trial participants.<sup>74</sup> The PLUTO trial conducted in 20 centers in North America and Europe was a good-quality RCT that randomly assigned 176 participants with FH (ages 10 to 17 years) to receive placebo or rosuvastatin at a dose of 5 mg, 10 mg, or 20 mg daily for 12 weeks. This period was followed by a 40-week open-label phase in which dosing for all subjects was titrated to achieve target LDL-C concentrations (maximum dose, 20 mg/day).<sup>64</sup> Safety assessment included monitoring of growth, pubertal development, solicitation of AEs, and laboratory screening (consisting of complete blood count, albumin, total protein, liver enzymes, bilirubin, CK, blood urea nitrogen, creatinine, calcium, glucose, electrolytes, thyroid-stimulating hormone, HbA1c, and urinalysis). During the first phase of the study, AEs occurred in between 50 and 64 percent of subjects on rosuvastatin (varying by dose) and in 54 percent of subjects on placebo. The most common were headache (in six to nine subjects in rosuvastatin groups and in nine subjects on placebo), nasopharyngitis (three to seven in rosuvastatin groups, five on placebo), influenza (zero to two in rosuvastatin groups, four on placebo), myalgia (one to two in rosuvastatin groups, zero on placebo), and nausea (zero to two in rosuvastatin groups, two on placebo). Blurred vision occurred in one subject on placebo, and vesicular rash occurred in one subject on rosuvastatin during the open-label period. Overall changes in AST and ALT were

similar between groups, although transaminase concentrations were elevated (>3 times the upper limit of normal) in three rosuvastatin subjects on doses of 10 mg or 20 mg during the first phase and in one rosuvastatin subject in the second phase. Overall changes in CK were also similar between groups, although CK was elevated (>10 times upper limit of normal) in four rosuvastatin subjects on doses of 10 mg or 20 mg during the first phase and in four during the open-label phase. Myalgia was reported by four rosuvastatin subjects during the first phase and five during the second phase. In all subjects, transaminase concentrations, CK, and myalgia returned to normal during treatment or remained normal after treatment was restarted.

Another publication from the PLUTO trial addressed a potential harm of statins, hypothesized based on the role of HMG-CoA reductase in the synthesis of coenzyme Q10 (CoQ10). CoQ10 serves both as an electron carrier in adenosine triphosphate (ATP) synthesis and as an important cellular antioxidant. For this reason, inhibition of HMG-CoA reductase activity in the course of statin treatment could reduce endogenous CoQ10 synthesis, thus impairing mitochondrial energy metabolism and cellular antioxidant capacity. A substudy of PLUTO (conducted in the Netherlands) reports on CoQ10 concentrations in peripheral blood mononuclear cells (PBMCs) and plasma (at baseline and end of study) in 29 PLUTO participants and mitochondrial respiratory chain–driven ATP in PBMCs in 17 of these 29 subjects.<sup>74</sup> During rosuvastatin treatment, mean PBMC CoQ10 concentrations dropped, from 89 pmol/mg (SD, 59 pmol/mg) to 63 pmol/mg (21 pmol/mg). At the end of the study, CoQ10 concentrations (corrected for baseline concentrations) differed significantly between the 5-mg and 10-mg groups but not between other treatment groups, and no dose-related effect of rosuvastatin on PBMC CoQ10 concentration was found. Although the differences were statistically significant, they were of unclear clinical significance. Proportion of participants with CoQ10 concentrations below the reference range did not change with rosuvastatin treatment. PBMC ATP synthesis did not change. Mean plasma CoQ10 concentration also decreased significantly; however, although concentrations differed between the 10-mg and 20-mg groups, they did not differ between other treatment groups, and the rosuvastatin dose at the end of the study was not associated with plasma CoQ10 concentration. Ratios of plasma CoQ10/TC and CoQ10/LDL-C remained equal during treatment. The authors concluded that the observed 32% decrease in PBMC CoQ10 level did not perturb mitochondrial respiratory chain–driven ATP synthesis in these participants.

The second rosuvastatin trial was CHARON (hyperCholesterolaemia in cHildren and Adolescents taking Rosuvastatin OpeN label), a 2-year, single-arm, open-label trial conducted in several sites in Europe and North America. 198 children and adolescents ages 6 to 17 years (mean, 11.6 years [SD, 3.3 years]) received 10 or 20 mg daily of rosuvastatin (depending on age). Incidence and severity of AEs and serious AEs, rates of discontinuation due to AEs, and abnormal serum laboratory values were recorded. Laboratory assessments included AST, ALT, urine protein:creatinine ratio, and CK. Most participants (86% to 89% across age groups) reported at least one treatment-emergent AE during the study period. The most common AEs were nasopharyngitis, headache, influenza, and vomiting. There were 29 AEs that were considered to be possibly related to the study medication, including gastrointestinal disorders, myalgia, increased serum CK, and skin disorders. Myalgia was reported in none of the 6- to 9-year olds, 7 percent of the 10- to 13-year-olds, and 10 percent of the 14- to 17-year-olds. Arthralgias were reported in 3 percent of the 6- to 9-year-olds, 10 percent of the 10- to 13-year-olds, and 5 percent of the 14- to 17-year-olds. No serious treatment-related AEs were reported.



Three of 198 participants discontinued rosuvastatin due to AEs (nausea, migraine, and paresthesias).

**Various statins.** One Austrian study included youth treated with different statins. This fair-quality prospective clinical followup study of 22 professional adolescent and young adult athletes with FH investigated the possibility that the frequency of harms associated with statin use in athletes (muscle pain in particular) may be greater than in nonathletes with FH. Six of these subjects were age 20 years or younger, and FH had been diagnosed between 4 and 10 years earlier.<sup>69</sup> Safety outcomes included muscle pain, CK concentrations, and liver enzymes. The six subjects were started on the lowest available dose of either pravastatin or lovastatin and subsequently switched to an alternate statin if AEs developed or target values were not met. Three of the six subjects did not tolerate any of the five statins tried (pravastatin, lovastatin, simvastatin, fluvastatin, and atorvastatin), and muscle pain developed in all six subjects 2 to 18 days after the start of treatment with at least one of the medications. Two of the six subjects experienced CK elevations while on certain statins (one subject while on pravastatin and lovastatin, one while on pravastatin, simvastatin, and atorvastatin). Muscle pain developed in all six subjects while on pravastatin and simvastatin, in five while on lovastatin, in four while on atorvastatin, and in three while on fluvastatin. Concentrations of liver enzymes did not change in any patient. Symptoms disappeared in less than a week after drug withdrawal in most patients, and within 3 weeks in all patients.

#### *Nonstatin Medications*

**Bile-sequestering agents.** Three RCTs evaluated harms of bile-sequestering medications in children and adolescents with FH. A different study (a randomized crossover trial of combination pharmacologic therapy with colestipol and pravastatin) is described above in the section on statins.<sup>71</sup>

One good-quality RCT with a followup open-label period randomly assigned 66 adolescents with FH ages 10 to 16 years to receive colestipol 10 mg daily (10 mg once a day or 5 mg twice a day) or placebo for 8 weeks. Those in the placebo group then received colestipol 10 mg daily for 1 year, and the other groups continued at their originally assigned doses for 1 year total treatment.<sup>56</sup> Of the 42 subjects completing 1 year of colestipol treatment, eight reported AEs, including constipation (two subjects), intermittent nausea (two subjects), and one subject each for dyspepsia, flatulence, temporary reduction in appetite, and abdominal pain. Both constipation and abdominal pain improved with dose reduction. One subject lost 1 kg or more during the study, a boy with initial body mass index of 24.5 kg/m<sup>2</sup>. Folate concentrations decreased in the colestipol group (compared to the placebo group) during the initial 8-week phase and remained decreased after 1 year (although they were still above the laboratory's lower reference point in all but three subjects). The authors note that this decrease might be attributable to sexual maturation because the 1-year findings were not controlled. Vitamin E and carotenoid concentrations also decreased in the colestipol group during the initial 8-week phase; however, this decrease was proportionate to the decrease in cholesterol. Vitamin D concentrations did not change significantly during the initial 8 weeks, but after 1 year, vitamin D concentrations tended to be lower in the subset of subjects who took more than 80 percent of the prescribed colestipol dose than in others (p=0.07). Vitamin D, vitamin A, and vitamin-E-to-cholesterol ratio all

remained above the laboratory's lower reference point in all subjects after 1 year. As with cholestyramine, poor palatability was a frequent complaint for colestipol; only 21 percent "liked the taste" of the medication.

One fair-quality, double-blind RCT evaluated harms of cholestyramine treatment in children ages 6 to 11 years with FH.<sup>55</sup> The 96 children enrolled were instructed to follow a low-fat, low-cholesterol diet for 1 year. At that point, 72 subjects with elevated LDL-C concentrations and a family history of premature CVD who agreed to continue were randomly assigned to receive cholestyramine 8 g or placebo daily for 1 year. Of the 48 subjects completing the study, 22 were in the cholestyramine group and 26 were in the placebo group. Vitamin D concentration decreased from baseline by 30.9 percent (calculated) in the cholestyramine group and decreased by 20 percent (calculated) in the placebo group ( $p < 0.04$ ). None of the subjects whose vitamin D concentrations decreased below the reference range were taking daily multivitamins. Total homocysteine was increased in the cholestyramine group and was negatively correlated with folate concentrations at baseline and 1 year. One subject with an increased homocysteine concentration became folate-deficient. No differences in liver enzymes or hemoglobin were noted between groups. Height velocity and weight were not adversely affected, and no other nutritional deficiencies were observed. Carotenoid concentrations did decrease significantly (as expected with a decrease in cholesterol). Other AEs were enumerated but not statistically compared between groups. Those who completed the study reported sporadic gastrointestinal symptoms. Nausea, loose stool, or abdominal pain were reported by one to two subjects each on cholestyramine; one subject withdrew because of vomiting after taking two packets; one subject withdrew after 2 months because of headaches; and one subject who had undergone appendectomy 3 months before had an intestinal obstruction after two doses of cholestyramine. However, the frequency of AEs was similar to that in the placebo group. Three subjects on placebo reported intermittent abdominal pain. One withdrew due to vomiting for 3 weeks, and one developed appendicitis. Unpalatability (unpleasant enough to cause withdrawal from the study) was the most common report in the 14 cholestyramine subjects; however, 10 subjects in the placebo group also reported unpalatability.

One good-quality RCT evaluated harms of colesevelam treatment in children and adolescents with FH (including both statin-naïve subjects and those on a statin regimen).<sup>65</sup> This study measured changes in vital signs, physical examination findings, and laboratory values (blood chemistry, including lipids, hematology, selected hormone concentrations, vitamins A and E, clotting factors, and high sensitivity C-reactive protein and urine analysis) in 194 subjects (ages 10 to 17 years) who were randomly assigned to placebo, low-dose, or high-dose colesevelam treatment for 8 weeks, followed by open-label use for 18 weeks. AEs were reported by 34.5 percent of subjects during the initial 4-week period, during which all subjects received only placebo (plus their usual statin, if any). This increased to 42.8 percent during the blinded period (with a similar distribution in all three groups) and to 50.5 percent during the open-label period, when all subjects received colesevelam (again with their usual statin, if any). Drug-related AEs were reported by 9.3 percent of subjects in the blinded period (by 6.3% of those on high-dose colesevelam, 10.8% of those on low-dose colesevelam, and 10.8% of those on placebo), and medication was stopped in one subject on high-dose and in three subjects on low-dose therapy. The most common drug-related AEs were gastrointestinal (diarrhea, nausea, vomiting, and abdominal pain) and occurred in 7 percent of those on colesevelam and in 4.6 percent of those on

placebo. During the open-label period, 6.0 percent of subjects reported drug-related AEs; the most common again being gastrointestinal symptoms (occurring in 4.3%). The AEs most commonly reported during the open-label period were headache (7.6%), nasopharyngitis (5.4%), and upper respiratory infection (4.9%). Five patients reported serious treatment-emergent AEs, but none were believed to be drug-related. Clinically meaningful changes were not found in safety laboratory measurements, vital signs, or physical findings, and changes in heart rate, blood pressure, body weight, and height velocity were similar for both groups.

**Ezetimibe.** Two good-quality RCTs evaluated ezetimibe, one coadministered with simvastatin<sup>58</sup> and the other as monotherapy.<sup>59</sup> One good-quality RCT evaluated coadministration of ezetimibe with simvastatin in 248 subjects ages 10 to 17 years with FH.<sup>58</sup> Subjects were randomly assigned to receive varying doses of simvastatin plus either 10 mg/day ezetimibe or placebo for 6 weeks, followed by higher-dose (40 mg) simvastatin plus either 10 mg/day ezetimibe or placebo for 27 weeks, followed by an open-label regimen of lower-dose simvastatin (10 or 20 mg) plus 10 mg/day ezetimibe for 20 weeks. The study was not powered to detect differences between groups on safety endpoints. However, at the end of the second phase of the trial, 83 percent of the simvastatin-plus-ezetimibe group and 84 percent of the simvastatin-plus-placebo group reported AEs. The most frequent AEs were reported at the same rates (nasopharyngitis in 27 subjects in each group and headache in 16 subjects in each group). The only AEs that were noted in at least twice as many subjects in the ezetimibe group as in the placebo group occurred rarely: myalgia (7 vs. 1 subject), diarrhea (9 vs. 3 subjects), nausea (8 vs. 4 subjects), abdominal pain (6 vs. 3 subjects), pharyngolaryngeal pain (6 vs. 3 subjects), and ALT concentrations increased to 3 times the upper limit of normal on consecutive checks (6 vs. 3 subjects). Among the eight subjects with myalgia, CK concentrations were unremarkable. Persistently elevated transaminase concentrations returned to normal in all affected subjects after interrupting or discontinuing therapy. Three percent of participants discontinued treatment due to AEs. No clinically important AEs on growth, sexual maturation, or steroid hormones were reported.

The ezetimibe monotherapy RCT was conducted in 29 international sites and randomized 138 youth ages 6 to 10 years (mean, 8.3 years [SD, 1.6 years]) to 10 mg ezetimibe or placebo for 12 weeks. Clinical harms assessed included rhabdomyolysis, myopathy, hypersensitivity, cholecystitis, cholelithiasis, and pancreatitis. Laboratory harms assessed included consecutive increases in ALT or AST greater than 3 times the upper limit of normal, consecutive increases in creatine phosphokinase greater than 5 times the upper limit of normal with clinical muscle symptoms, or creatine phosphokinase greater than 10 times the upper limit of normal. There were no significant differences in AE distribution across the treatment groups. There were no serious drug-related AEs in either group. Three members of the ezetimibe group (3.3%) and none in the placebo group discontinued treatment because of AEs (two drug related, one serious): one elevated ACT, one prurigo, and one epileptic event.

## **KQ8. What Is the Association Between Intermediate Outcomes in Childhood and Adolescence and the Future Incidence or Timing of Adult MI and Stroke Events?**

No studies were identified.

# Chapter 4. Discussion

## Summary of Evidence

### Screening

Consensus in the current debate regarding screening for dyslipidemia in children and adolescents is that the primary benefit of screening is identifying children with FH.<sup>27, 80, 81</sup> Identifying children with mild or moderate elevations in LDL-C is cited as a secondary benefit of such screening, but experts disagree on its relative importance and even whether it represents a net benefit.<sup>17, 80-84</sup> Dyslipidemia screening to identify LDL-C elevations not caused by FH is addressed in a separate USPSTF evidence review.

Potential benefits of screening for FH include early identification of children and adolescents with FH; prompt initiation of treatment, including pharmacotherapy and low-fat, low-cholesterol diet; slowing the progression of atherosclerosis; and reducing the incidence or delaying the onset of CHD and stroke. In addition, identifying a child or adolescent with FH could accelerate identification of affected family members. Although most experts agree that the benefits of statin treatment likely outweigh the harms in persons with definite FH, the long-term benefits and harms of lipid-lowering medications in children and adolescents remain poorly understood.

In our review, we sought evidence about both universal and selective screening in studies published both before and since the 2007 USPSTF review. Consistent with that USPSTF review, we found no direct evidence that selective or universal screening programs improves intermediate or health outcomes in children or adolescents with FH. The few studies from which diagnostic yield could be determined for pediatric screening programs addressed only universal screening. The statewide universal screening program in West Virginia schools<sup>53</sup> found a diagnostic yield of 0.13 percent, a rate considerably lower than published estimates. The Danish study<sup>54</sup> of universal screening in first graders used a lipid screening approach (Apo B:A1 ratio), which to our knowledge is not commonly used. The authors reported a (calculated) diagnostic yield of 0.48 percent.

We found no studies reporting diagnostic yield or effectiveness of selective screening for FH in youth (i.e., screening focused on children with a family history of FH or other targeting factor). The 2007 review found 16 studies on the diagnostic accuracy of using family history to target screening for dyslipidemia in childhood. The quality of the overall body of evidence on this topic was rated as “good.” Studies include a range of family history definitions (e.g., whether grandparents or second-degree relatives were included) and definitions of risk (parental history of heart attack, other parental risk factors for dyslipidemia, and age of onset of early CHD). The evidence suggested that, across different family history definitions, using family history as a tool for targeting screening missed substantial numbers of children with elevated lipid concentrations—as many as 90 percent overall, but ranging from 30 to 60 percent in most studies. The 2007 USPSTF recommendation statement on this topic noted that for children with familial dyslipidemia, the group most likely to benefit from screening, use of family history in

screening may be inaccurate because of variability of definitions and unreliability of information.<sup>47</sup> It went on to point out that serum lipid levels are accurate screening tests for childhood dyslipidemia, although many children with multifactorial types of dyslipidemia would have normal lipid levels in adulthood.

A 2009 evidence report commissioned by AHRQ on the ability of family history to impact health outcomes (risk of stroke and CVD), although not focused exclusively on children, reached conclusions similar to those mentioned above.<sup>85</sup> The review also determined that across disease types, specificity (unaffected family members correctly reported) was consistently high, and sensitivity (affected family members correctly reported) was consistently much lower. No factors were clearly associated with reporting accuracy in relatives and affected individuals, including demographics, race, type of disease, insurance status, type of relative, and time since diagnosis. The studies had high risks for selection, verification, and masking biases that may have overestimated accuracy.<sup>85</sup>

Two recent reports also support the findings of the 2007 USPSTF report and the 2009 AHRQ report. In the Project Heartbeat! study, a longitudinal study tracking CVD risk factors in children in Texas, the accuracy of family history in predicting TC, LDL-C, and HDL-C concentrations was low. Sensitivity ranged from 38 to 43 percent, and specificity from 64 to 65 percent.<sup>86</sup> Similarly, the recent report from the CARDIAC school-based screening program in West Virginia<sup>87</sup> found that family history screening did not accurately predict either dyslipidemia warranting pharmacologic treatment (specificity, 63%; sensitivity, 20%) or the presence of any dyslipidemia (specificity, 30%; sensitivity, 63%).<sup>87</sup>

Thus, studies included in the previous USPSTF review, supplemented by several intervening systematic reviews and studies, consistently suggest that family history alone has low sensitivity for identifying children to be screened for FH. This approach should not be confused with “cascade screening” of all relatives (including children) of index cases with known FH, as has been recommended to improve early detection in several countries.<sup>11, 88</sup> The U.S. health system does not have the infrastructure to support cascade screening. Therefore, cascade screening was considered to be out of scope for this review.

We found no studies of the harms of screening children and adolescents for FH. The 2007 USPSTF review found that harms of screening for childhood dyslipidemia in general were poorly reported, but none of the studies in that review met our criteria because they were not focused on screening for FH in particular. There are some potential harms of screening for FH in children and adolescents. Screening asymptomatic populations for FH using TC or LDL-C norms carries the risk of false positives. As covered in the separate review on multifactorial dyslipidemia, at least some of these identified individuals may never experience clinically relevant lipid concentrations. Such “nondisease” can result in subtle harms, such as labeling a child as “sick” or causing parent or child anxiety, or unnecessary or even harmful treatment. In some cases, screening for FH may lead to unnecessary or even harmful treatment.

## **Treatment**

We found no direct evidence for the effectiveness of treating children and adolescents with FH

on health outcomes in adulthood; that is, reducing the incidence or delaying the onset of MI or stroke. However, the evidence is fair- to good-quality for the effectiveness of pharmacologic treatment of children and adolescents with FH on intermediate outcomes. Eight RCTs were of statins and five were of other drug classes. Studies of statins ranged from 8 weeks to 2 years in duration, with most being shorter than 1 year. Statins lowered LDL-C and TC concentrations in the short term, with most studies reporting that statins lowered LDL-C by 20 to 40 percent and as much as 50 percent compared to placebo. The greatest effect on LDL-C was in a trial of rosuvastatin;<sup>64</sup> participants who received the highest dose (20 mg/day) experienced a 50 percent decrease (least mean squares) in LDL-C from baseline compared to a 1 percent decrease among controls ( $p < 0.001$ ). The effect on HDL-C was minimal or none.

A single study found that pravastatin reduced CIMT by 2 percent in the treatment group, whereas CIMT increased by 1 percent in the control group. There were no consistent differences in treatment effects among different statins, but the number of studies for any one drug was limited. The two studies that compared different doses of statins reported a dose response with pravastatin<sup>52</sup> and rosuvastatin.<sup>64</sup> In the 2010 rosuvastatin trial,<sup>64, 65</sup> the only statin study in which attainment of LDL-C treatment targets was reported, only 12 to 41 percent of participants reached the target LDL-C concentration of less than 110 mg/dL, with greater effects at higher doses. Our findings are consistent with a recent systematic review<sup>48</sup> on the effectiveness of statins in children and adolescents with FH. Evidence is insufficient to allow comparison among different statins.

The three RCTs of bile-sequestering agents lasted from 8 weeks to 1 year. These drugs had more modest effects on LDL-C and TC than did statins. The study of colesevelam<sup>65</sup> showed a dose response. In the only nonstatin study reporting attainment of LDL-C treatment targets,<sup>65</sup> only 3.2 to 7.9 percent of participants reached a target LDL-C of 110 mg/dL or less, with a greater effect at the higher dose of colesevelam.

One additional drug, ezetimibe—an inhibitor of intestinal cholesterol absorption—was studied in two RCTs. In a trial of combination therapy with simvastatin, ezetimibe reduced LDL-C concentrations by 54 percent, 16 percent more than the 38 percent achieved by simvastatin alone.<sup>58</sup> In a 12-week RCT of ezetimibe monotherapy, LDL-C decreased by 28 percent from baseline compared to a negligible change in the placebo group.<sup>59</sup>

Most participants in whom lipid-lowering medications have been studied are children and adolescents with FH, as opposed to those with other, generally milder dyslipidemias. Most of these trials have been conducted in tertiary clinic populations, not screen-detected individuals. Therefore, subjects in these trials may not accurately represent the spectrum of children and adolescents that would be identified from a screening program.

The earlier USPSTF review found that dietary counseling and exercise (in the absence of medication) had limited effect in reducing LDL-C in children and adolescents with probable or definite FH. We found no new studies of lifestyle (diet or exercise) treatment for FH in youth. Neither did we find new studies of dietary supplements in children or adolescents with FH that met our inclusion and quality criteria. All medication trial protocols included a low-fat, low-cholesterol diet.

When the aim of pharmacologic treatment is reducing disease risk (rather than treating disease), only a low risk of harm is acceptable. The evidence about the short-term harms of pharmacologic treatment of children and adolescents with FH is fair- to good-quality. Most studies were conducted outside the United States but were applicable to U.S. primary care settings. Most studies were short, only 6 weeks to 2 years long. Statins were generally well-tolerated, although reversible elevations of liver enzymes and/or CK concentrations were noted in some studies. Ten-year followup of the Dutch Pravastatin Trial found lower DHEAS concentrations in individuals with FH treated with statins compared to unaffected siblings.<sup>77</sup> Clinical significance of this difference is unknown. No severe, permanent harms of statins were reported. Bile-acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-term harms are unknown. Ezetimibe, represented in only two studies, was well-tolerated in the short term. Reports of a small increase in cancer risk among adults treated with ezetimibe<sup>89</sup> emphasizes the importance of long-term followup studies when treatment is being initiated in children and adolescents.

## Outcomes

We found no evidence in individuals with FH to quantify the association between intermediate outcomes (such as lipid concentrations or measures of atherosclerosis) in children or adolescents and MI and stroke in adults. The previous USPSTF review did not examine the evidence related to health outcomes in adulthood.

The Simon Broome Register provides some of the first estimates of the increased mortality risk conferred by FH. This tertiary clinic-based U.K. registry found excess CHD mortality in individuals with FH compared to the general population, with markedly elevated standardized mortality ratios in the 20- to 39-year-old age group.<sup>1</sup> These data establish the severe natural history of FH among adults referred to lipid clinics; they do not allow direct estimation of the association between lipid concentrations or atherosclerosis in youth and CHD in adulthood.

Children and adolescents with severely elevated LDL-C have pathologic signs of atherosclerosis at earlier ages than do those with normal LDL-C concentrations of the same age,<sup>14, 90</sup> but these signs have not been directly related to the probability of CHD in adulthood. Elevated LDL-C in adults predicts MI and stroke.<sup>5, 20</sup> However, no direct evidence supports a link between lipid concentrations or measures of atherosclerosis in children and adolescents with FH and health outcomes in adulthood.

## Optimal Age of Statin Initiation (Contextual Question)

The rationale for screening for FH depends on the availability of safe and effective interventions that alter the course of disease for screen-identified cases compared to other methods of diagnosis.<sup>70</sup> One benefit of screening youth for FH would accrue if beginning statin treatment in childhood or adolescence improved health outcomes more than treatment for FH that is begun in young adulthood. Several lines of evidence have promoted interest in treatment at younger ages. An analysis of adults with FH in the Simon Broome Register compared standardized mortality rates in the prestatin and statin eras and found that the advent of statins coincided with a

reduction in fatal CHD in young adults, most of it ascribed to primary prevention.<sup>91</sup> This finding raises hopes that earlier statin initiation could reduce young adult mortality, although the authors note that addressing this possibility would require expansion of the cohort. The evidence in adults with elevated LDL-C concentrations (not FH) suggests that achieving lower LDL-C concentrations leads to more benefit.<sup>92-94</sup> Aggressive treatment in adults with FH suggests that it is possible to slow, and even reverse, the progression of atherosclerosis.<sup>95</sup>

Motivated by such evidence, experts have raised the question of what age to initiate statin therapy in youth with FH.<sup>50</sup> Answering this question would require a randomized trial in which statin treatment in children or adolescents would begin at different ages and that lasted long enough to measure cardiovascular events or intermediate outcomes in adulthood (such as LDL-C, CIMT, or calcium score). Such a trial has not been undertaken, and indeed, available trials of statin treatment in FH still have relatively short followup. Comparing the long-term incidence of MI or stroke in adults identified and successfully treated for FH from an earlier age with those identified in early or middle adulthood might also be informative. In 14 well-known cohort studies in children or adolescents (**Appendix E**), we found no such evidence.

The best evidence of statin exposure longer than 2 years in childhood comes from one study: the Dutch Pravastatin Trial.<sup>66, 72, 76</sup> Although the initial RCT<sup>66</sup> was included as primary evidence for efficacy of treatment (KQ6), the followup studies<sup>72, 76</sup> were designed as cohort studies and so were included only for harms (KQ7). As described above (see Results), this study began as a 2-year RCT of pravastatin compared to placebo (n=214; mean age, 13 years) and found a beneficial effect of pravastatin on LDL-C and CIMT.<sup>66</sup> Subsequently, the trial was converted to a cohort study, with all FH patients treated with pravastatin and a group of nonFH siblings enrolled as controls. Two publications from this later phase of the Dutch Pravastatin Trial<sup>72, 76</sup> provide observational data to inform this age of initiation question. The first followup of the Dutch Pravastatin Trial cohort was at a mean of 4.5 years after baseline.<sup>76</sup> Younger age at treatment initiation and longer duration of statin exposure independently predicted favorable CIMT values.<sup>76</sup> The other publication from the Dutch Pravastatin Trial that sheds light on age of statin initiation reports on CIMT in 91 percent of the original RCT population and 87 percent of the original sibling control group at 10-year followup.<sup>72</sup> The progression of CIMT was similar in both FH and sibling groups but began higher in the FH group at baseline and remained higher at followup. As in the other followup study, younger age at statin initiation was associated with thinner CIMT at 10 years.<sup>72</sup>

These observational findings from the Dutch Pravastatin Trial represent the best evidence to date on the benefits of earlier treatment of FH in youth. Thus, despite considerable trial and observational data in adults, and a biologically plausible pathway through which long-term statin treatment beginning in childhood could reduce or delay the occurrence of cardiovascular events in adulthood through the persistent reduction in atherosclerotic burden, the evidence to assess these benefits is limited. In the absence of RCT data comparing adult CHD outcomes in youth started on statins at different ages, the optimal age of statin initiation in children and adolescents with FH remains unclear.



## Limitations of the Review

One limitation of this review was by design: based on strong advice received during the public comment period, we restricted the KQs to FH alone and addressed other atherogenic dyslipidemias in a separate review. Thus, all findings here are limited to screening for and treatment of FH.

The literature has several limitations. No published studies met our inclusion criteria for several KQs in this review. Direct evidence for the impact of screening on intermediate or health outcomes is lacking. Evidence for the effectiveness of pharmacotherapy lacks data from long-term studies assessing the effect of lipid-lowering medications on intermediate outcomes in childhood and adolescence or on health outcomes in adulthood. Of the eight trials of statins that evaluated effects on lipid concentrations, only one (short-term) study of the effect of pravastatin on atherosclerosis (as measured by CIMT) met our inclusion criteria.<sup>66</sup> Participants in the eight statin trials were patients at tertiary care centers; none of the studies were conducted in screen-detected populations. Few studies were conducted in nonwhite populations.

Only two studies reported the percent of participants achieving target LDL-C. Two statin trials included children as young as age 8 years; however, the age distribution of the statin studies as a whole is skewed to early adolescence, with a mean age of 12 to 15 years. Thus, the bodies of evidence on screening (ages 6 to 8 years) and on statin treatment (largely adolescent subjects) are not aligned. We found no updated evidence on lifestyle interventions for FH or any trials comparing initiation of statins at different ages. The body of evidence on harms of pharmacotherapy also lacks long-term studies.

## Future Research Needs

Randomized trials are needed to assess the benefits and harms of FH screening programs in children and adolescents. Future studies should describe the screening programs in detail, including the followup and laboratory testing of children who screen positive and all screening and diagnostic criteria used to establish FH, as well as reporting the number of true positives. Standard genetic mutation testing of FH cases diagnosed by elevated lipid concentrations and family history alone could help confirm the utility of genetic tests in the multiethnic U.S. population. Reports of such studies should also describe efforts to educate parents about interpreting screening tests, because this knowledge is an important component of screening programs that can affect adherence (e.g., participation in screening and parental adherence to recommendations for followup of positive screens). Future studies of screening approaches should also describe any decision support for providers caring for children and adolescents who test positive for FH, because this information may be important for ensuring appropriate care.

Long-term trials of statin treatment are needed to assess harms as well as effectiveness in improving both intermediate outcomes (lipid concentrations and measures of atherosclerosis in youth) and, ideally, health outcomes in adulthood. More pharmacotherapy studies should be conducted in racially/ethnically diverse U.S. populations. Treatment studies in screen-detected FH cases are essential in the absence of RCTs of screening programs. Further consideration of

genetic mutation status in treatment response and outcomes for FH patients may provide important data for personalizing treatment. Studies examining benefits and harms of lipid-lowering medication are needed in children with FH younger than age 10 years. Long-term studies to assess harms are needed. Treatment studies should systematically report AEs of treatment.

Our understanding of outcomes in FH would be furthered by studies examining longitudinal data in persons with FH to better understand the association between intermediate outcomes in childhood and adolescence and MI and stroke in adulthood.

Some experts have advocated for the inclusion of Mendelian randomization studies in systematic evidence reviews of pediatric dyslipidemia. The Mendelian study takes advantage of the random assortment of alleles in reproduction and uses an observational design to infer causality. This study design has been used to examine the association between different loci (*LDLR*<sup>96, 97</sup> and apolipoprotein B mutations<sup>98-101</sup>) and CHD. Some studies provide evidence of an association between LDL-C concentration over long periods of time and CHD based on Mendelian randomization. However, experts have pointed out a number of limitations of this study design.<sup>102</sup> There is a need for a better understanding of the appraisal of Mendelian data and its integration into systematic reviews.

Past pediatric recommendations on screening for FH have generated controversy, much of which has centered on the advisability of accepting indirect evidence from relatively short-term trials that lack outcomes beyond lipid concentrations.<sup>80, 82-84, 103, 104</sup> Some experts have expressed skepticism that long-term RCTs of statins in children and adolescents with FH could be feasibly and ethically conducted,<sup>105</sup> while others have called for the conduct of RCTs as a public health priority.<sup>50, 106</sup> Reaching agreement on any acceptable surrogate endpoints, such as CIMT and other measures of atherosclerosis,<sup>106</sup> may increase the feasibility of such a trial, allowing a shorter time frame, provided such endpoints are predictive of CHD.

## Conclusions

We found no direct evidence of the effect of screening on intermediate or health outcomes. Evidence describing the diagnostic yield of screening for FH in children is minimal. Evidence of the effectiveness of statins to reduce LDL-C and TC concentrations is good in studies up to 2 years long. Evidence that statins affect measures of atherosclerosis in youth is limited. Statins were generally well-tolerated in the short term. Some studies reported reversible elevations of liver enzymes or CK concentrations and one study reported lower DHEAS concentrations at 10 years in men treated with statins starting in childhood or adolescence. Bile-acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-term harms are unknown. Randomized trials of screening for FH in U.S. youth are needed, as are longer-term treatment trials to evaluate benefits and harms of medications in children and adolescents with FH.

## References

1. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ*. 1991;303(6807):893-6. PMID: 1933004.
2. World Health Organization. Familial hypercholesterolemia—report of a second WHO Consultation. Geneva, Switzerland: World Health Organization; 1999.
3. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol*. 1993;72(2):171-6. PMID: 8328379.
4. Talmud PJ, Shah S, Whittall R, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. *Lancet*. 2013;381(9874):1293-301. PMID: 23433573.
5. Austin MA, Hutter CM, Zimmern RL, et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am J Epidemiol*. 2004;160(5):407-20. PMID: 15321837.
6. Kwiterovich PO, Jr. Recognition and management of dyslipidemia in children and adolescents. *J Clin Endocrinol Metab*. 2008;93(11):4200-9. PMID: 18697860.
7. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest*. 2003;111(12):1795-803. PMID: 12813012.
8. Do R, Stitzel NO, Won HH, et al. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature*. 2015;518(7537):102-6. PMID: 25487149.
9. Varghese MJ. Familial hypercholesterolemia: A review. *Ann Pediatr Cardiol*. 2014;7(2):107-17. PMID: 24987256.
10. Neil HA, Hammond T, Huxley R, et al. Extent of underdiagnosis of familial hypercholesterolaemia in routine practice: prospective registry study. *BMJ*. 2000;321(7254):148. PMID: 10894692.
11. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34(45):3478-90a. PMID: 23956253.
12. Kwiterovich PO, Gidding SS. Universal screening of cholesterol in children. *Clin Cardiol*. 2012;35(11):662-4. PMID: 22930527.
13. McGill HC, Jr., McMahan CA, Zieske AW, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol*. 2000;20(8):1998-2004. PMID: 10938023.
14. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338(23):1650-6. PMID: 9614255.
15. Haney EM, Huffman LH, Bougatsos C, et al. Screening for Lipid Disorders in Children and Adolescents. Rockville, MD: 2007.
16. Reiner Z. Impact of early evidence of atherosclerotic changes on early treatment in children with familial hypercholesterolemia. *Circ Res*. 2014;114(2):233-5. PMID: 24436424.

17. Gillman MW. Changing the conversation regarding pediatric cholesterol screening: the rare disease paradigm. *Arch Pediatr Adolesc Med.* 2012;166(12):1097-8. PMID: 23027526.
18. Expert Panel on Integrated Guidelines for Cardiovascular Health Risk Reduction in Children and Adolescents, National Heart Lung and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics.* 2011;128 Suppl 5:S213-56. PMID: 22084329.
19. Slack J. Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. *Lancet.* 1969;2(7635):1380-2. PMID: 4188273.
20. Stone NJ, Levy RI, Fredrickson DS, et al. Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation.* 1974;49(3):476-88. PMID: 4813182.
21. Setia N, Verma IC, Khan B, et al. Premature coronary artery disease and familial hypercholesterolemia: need for early diagnosis and cascade screening in the Indian population. *Cardiol Res Pract.* 2012;2012:658526. PMID: 22111029.
22. Kwiterovich PO. Clinical and laboratory assessment of cardiovascular risk in children: Guidelines for screening, evaluation, and treatment. *J Clin Lipidol.* 2008;2(4):248-66. PMID: 21291741.
23. Kwiterovich PO, Jr., Levy RI, Fredrickson DS. Neonatal diagnosis of familial type-II hyperlipoproteinaemia. *Lancet.* 1973;1(7795):118-21. PMID: 4118465.
24. Webber LS, Srinivasan SR, Wattigney WA, et al. Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. *Am J Epidemiol.* 1991;133(9):884-99. PMID: 2028978.
25. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ.* 2007;335(7620):599. PMID: 17855284.
26. Harris N, Neufeld EJ, Newburger JW, et al. Analytical performance and clinical utility of a direct LDL-cholesterol assay in a hyperlipidemic pediatric population. *Clin Chem.* 1996;42(8 Pt 1):1182-8. PMID: 8697574.
27. Daniels SR, Gidding SS, de Ferranti SD, et al. Pediatric aspects of familial hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol.* 2011;5(3 Suppl):S30-7. PMID: 21600527.
28. Griffin TC, Christoffel KK, Binns HJ, et al. Family history evaluation as a predictive screen for childhood hypercholesterolemia. Pediatric Practice Research Group. *Pediatrics.* 1989;84(2):365-73. PMID: 2748269.
29. Shea S, Basch CE, Irigoyen M, et al. Failure of family history to predict high blood cholesterol among hispanic preschool children. *Prev Med.* 1990;19(4):443-55. PMID: 2204914.
30. Diller PM, Huster GA, Leach AD, et al. Definition and application of the discretionary screening indicators according to the National Cholesterol Education Program for Children and Adolescents. *J Pediatr.* 1995;126(3):345-52. PMID: 7869190.
31. National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics.* 1992;89(3):495-501. PMID: 1741227.

32. Chen LY, Tiong C, Tsai CH, et al. Early-life sleep deprivation persistently depresses melatonin production and bio-energetics of the pineal gland: potential implications for the development of metabolic deficiency. *Brain Struct Funct*. 2015;220(2):663-76. PMID: 24515890.
33. Avis HJ, Kusters DM, Vissers MN, et al. Follow-up of children diagnosed with familial hypercholesterolemia in a national genetic screening program. *J Pediatr*. 2012;161(1):99-103. PMID: 22284919.
34. Marang-van de Mheen PJ, ten Asbroek AH, Bonneux L, et al. Cost-effectiveness of a family and DNA based screening programme on familial hypercholesterolaemia in The Netherlands. *Eur Heart J*. 2002;23(24):1922-30. PMID: 12473254.
35. Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, et al. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet*. 2001;357(9251):165-8. PMID: 11213091.
36. Defesche JC. Defining the challenges of FH screening for familial hypercholesterolemia. *J Clin Lipidol*. 2010;4(5):338-41. PMID: 21122674.
37. Datta BN, McDowell IF, Rees A. Integrating provision of specialist lipid services with cascade testing for familial hypercholesterolaemia. *Curr Opin Lipidol*. 2010;21(4):366-71. PMID: 20613514.
38. Al-Sarraf A, Allard M, Martinka M, et al. Regional and national familial hypercholesterolemia registries: present international application, importance, and needs for Canada. *Can J Cardiol*. 2013;29(1):6-9. PMID: 22717249.
39. Delport R. Familial hypercholesterolaemia in South Africans: tracking findings and developments over time - with reference to : prevalence of hypercholesterolaemia in young Afrikaners with myocardial infarction. *Ischaemic heart disease risk factors. Cardiovasc J Afr*. 2009;20(1):18-22. PMID: 19287810.
40. O'Kane MJ, Menown IB, Graham I, et al. The detection of heterozygous familial hypercholesterolemia in Ireland. *Adv Ther*. 2012;29(5):456-63. PMID: 22610724.
41. Descamps OS, Tenoutasse S, Stephenne X, et al. Management of familial hypercholesterolemia in children and young adults: consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. *Atherosclerosis*. 2011;218(2):272-80. PMID: 21762914.
42. Daniels SR. Screening for familial hypercholesterolemia: what is the most effective strategy? *Nat Clin Pract Cardiovasc Med*. 2008;5(3):130-1. PMID: 18059381.
43. Hadfield SG, Horara S, Starr BJ, et al. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. *Ann Clin Biochem*. 2009;46(Pt 1):24-32. PMID: 19028807.
44. Marks D, Thorogood M, Neil SM, et al. Cascade screening for familial hypercholesterolaemia: implications of a pilot study for national screening programmes. *J Med Screen*. 2006;13(3):156-9. PMID: 17007658.
45. Gray J, Jaiyeola A, Whiting M, et al. Identifying patients with familial hypercholesterolaemia in primary care: an informatics-based approach in one primary care centre. *Heart*. 2008;94(6):754-8. PMID: 17575326.
46. Kusters DM, de Beaufort C, Widhalm K, et al. Paediatric screening for hypercholesterolaemia in Europe. *Arch Dis Child*. 2012;97(3):272-6. PMID: 21949015.

47. U. S. Preventive Services Task Force. Screening for lipid disorders in children: US Preventive Services Task Force recommendation statement. *Pediatrics*. 2007;120(1):e215-9. PMID: 17606545.
48. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2014;7:CD006401. PMID: 25054950.
49. Arambepola C, Farmer AJ, Perera R, et al. Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Atherosclerosis*. 2007;195(2):339-47. PMID: 17097660.
50. Stein EA. Statins and children: whom do we treat and when? *Circulation*. 2007;116(6):594-5. PMID: 17679628.
51. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3 Suppl):21-35. PMID: 11306229.
52. Knipscheer HC, Boelen CC, Kastelein JJ, et al. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. *Pediatr Res*. 1996;39(5):867-71. PMID: 8726243.
53. Cottrell L, John C, Murphy E, et al. Individual-, family-, community-, and policy-level impact of a school-based cardiovascular risk detection screening program for children in underserved, rural areas: the CARDIAC Project. *J Obes*. 2013;2013:732579. PMID: 23840946.
54. Skovby F, Micic S, Jepsen B, et al. Screening for familial hypercholesterolaemia by measurement of apolipoproteins in capillary blood. *Arch Dis Child*. 1991;66(7):844-7. PMID: 1863097.
55. Tonstad S, Knudtzon J, Sivertsen M, et al. Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia. *J Pediatr*. 1996;129(1):42-9. PMID: 8757561.
56. Tonstad S, Sivertsen M, Aksnes L, et al. Low dose colestipol in adolescents with familial hypercholesterolaemia. *Arch Dis Child*. 1996;74(2):157-60. PMID: 8660081.
57. Stein EA, Roth EM, Rhyne JM, et al. Safety and tolerability of dalcetrapib (RO4607381/JTT-705): results from a 48-week trial. *Eur Heart J*. 2010;31(4):480-8. PMID: 20097702.
58. van der Graaf A, Cuffie-Jackson C, Vissers MN, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. *J Am Coll Cardiol*. 2008;52(17):1421-9. PMID: 18940534.
59. Kusters DM, Caceres M, Coll M, et al. Efficacy and safety of ezetimibe monotherapy in children with heterozygous familial or nonfamilial hypercholesterolemia. *Journal of Pediatrics*. 2015;166(6):1377-84.e3. PMID: 25841542.
60. Clauss SB, Holmes KW, Hopkins P, et al. Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics*. 2005;116(3):682-8. PMID: 16140708.
61. Stein EA, Illingworth DR, Kwiterovich PO, Jr., et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 1999;281(2):137-44. PMID: 9917116.
62. de Jongh S, Ose L, Szamosi T, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. *Circulation*. 2002;106(17):2231-7. PMID: 12390953.

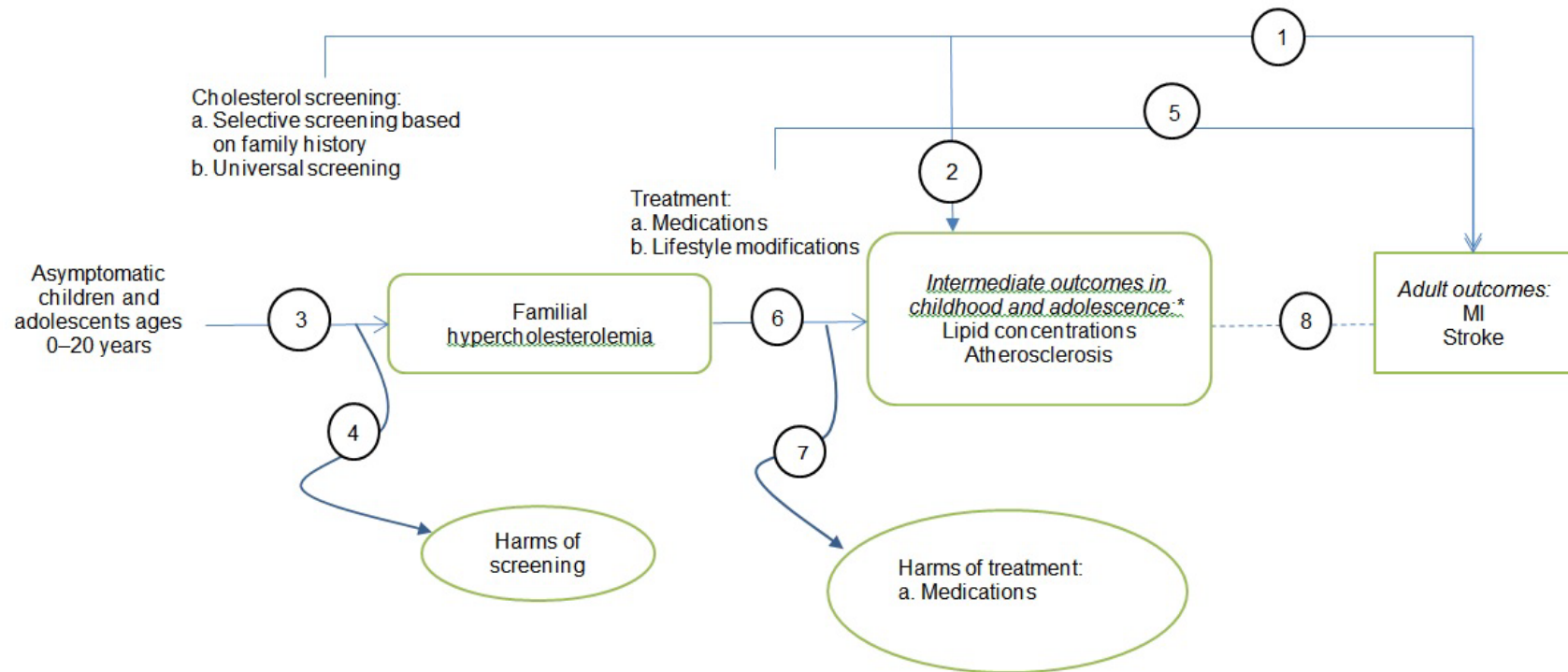
63. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. *J Pediatr*. 2003;143(1):74-80. PMID: 12915827.
64. Avis HJ, Hutten BA, Gagne C, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. *J Am Coll Cardiol*. 2010;55(11):1121-6. PMID: 20223367.
65. Stein EA, Marais AD, Szamosi T, et al. Colesevelam hydrochloride: efficacy and safety in pediatric subjects with heterozygous familial hypercholesterolemia. *J Pediatr*. 2010;156(2):231-6 e1-3. PMID: 19879596.
66. Wiegman A, Hutten BA, de Groot E, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. *JAMA*. 2004;292(3):331-7. PMID: 15265847.
67. Couture P, Brun LD, Szots F, et al. Association of specific LDL receptor gene mutations with differential plasma lipoprotein response to simvastatin in young French Canadians with heterozygous familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 1998;18(6):1007-12. PMID: 9633944.
68. Hedman M, Neuvonen PJ, Neuvonen M, et al. Pharmacokinetics and pharmacodynamics of pravastatin in children with familial hypercholesterolemia. *Clin Pharmacol Ther*. 2003;74(2):178-85. PMID: 12891228.
69. Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. *Br J Clin Pharmacol*. 2004;57(4):525-8. PMID: 15025753.
70. de Jongh S, Lilien MR, op't Roodt J, et al. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. *J Am Coll Cardiol*. 2002;40(12):2117-21. PMID: 12505222.
71. McCrindle BW, Helden E, Cullen-Dean G, et al. A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia. *Pediatr Res*. 2002;51(6):715-21. PMID: 12032266.
72. Kusters DM, Avis HJ, de Groot E, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. *JAMA*. 2014;312(10):1055-7. PMID: 25203086.
73. Carreau V, Girardet JP, Bruckert E. Long-term follow-up of statin treatment in a cohort of children with familial hypercholesterolemia: efficacy and tolerability. *Paediatr Drugs*. 2011;13(4):267-75. PMID: 21692550.
74. Avis HJ, Hargreaves IP, Ruiter JP, et al. Rosuvastatin lowers coenzyme Q10 levels, but not mitochondrial adenosine triphosphate synthesis, in children with familial hypercholesterolemia. *J Pediatr*. 2011;158(3):458-62. PMID: 20884007.
75. Gandelman K, Glue P, Laskey R, et al. An eight-week trial investigating the efficacy and tolerability of atorvastatin for children and adolescents with heterozygous familial hypercholesterolemia. *Pediatr Cardiol*. 2011;32(4):433-41. PMID: 21259004.
76. Rodenburg J, Vissers MN, Wiegman A, et al. Statin treatment in children with familial hypercholesterolemia: the younger, the better. *Circulation*. 2007;116(6):664-8. PMID: 17664376.
77. Braamskamp MJ, Kusters DM, Wiegman A, et al. Gonadal steroids, gonadotropins and DHEAS in young adults with familial hypercholesterolemia who had initiated statin therapy in childhood. *Atherosclerosis*. 2015;241(2):427-32. PMID: 26079405.

78. Braamskamp MJAM, Kusters DM, Avis HJ, et al. Long-term statin treatment in children with familial hypercholesterolemia: more insight into tolerability and adherence. *Paediatr Drugs*. 2015;17(2):159-66. PMID: 25644328.
79. Braamskamp MJ, Langslet G, McCrindle BW, et al. Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: Results from the CHARON study. *J Clin Lipidol*. 2015; In Press.
80. Psaty BM, Rivara FP. Universal screening and drug treatment of dyslipidemia in children and adolescents. *JAMA*. 2012;307(3):257-8. PMID: 22174386.
81. de Ferranti SD, Daniels SR, Gillman M, et al. NHLBI Integrated Guidelines on Cardiovascular Disease Risk Reduction: can we clarify the controversy about cholesterol screening and treatment in childhood? *Clin Chem*. 2012;58(12):1626-30. PMID: 22730451.
82. Kavey RE, McBride PE. Should family physicians routinely screen for hypercholesterolemia in children? Yes: the evidence supports universal screening. *Am Fam Physician*. 2012;86(8):1-2. PMID: 23062164.
83. Lefevre M. Should family physicians routinely screen for hypercholesterolemia in children? No: universal screening has uncertain benefits and a high risk of harms. *Am Fam Physician*. 2012;86(8):1-2. PMID: 23062165.
84. Newman TB, Pletcher MJ, Hulley SB. Overly aggressive new guidelines for lipid screening in children: evidence of a broken process. *Pediatrics*. 2012;130(2):349-52. PMID: 22826571.
85. Qureshi N, Wilson B, Santaguida P, et al. Family history and improving health. *Evid Rep Technol Assess (Full Rep)*. 2009(186):1-135. PMID: 19947667.
86. Eissa MA, Wen E, Mihalopoulos NL, et al. Evaluation of AAP guidelines for cholesterol screening in youth: Project HeartBeat! *Am J Prev Med*. 2009;37(1 Suppl):S71-7. PMID: 19524159.
87. Ritchie SK, Murphy EC, Ice C, et al. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. *Pediatrics*. 2010;126(2):260-5. PMID: 20624798.
88. National Clinical Guideline Centre. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Clinical Guideline Centre: National Institute for Health and Care Excellence; 2014.
89. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359(13):1343-56. PMID: 18765433.
90. Newman WP, 3rd, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. *N Engl J Med*. 1986;314(3):138-44. PMID: 3455748.
91. Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J*. 2008;29(21):2625-33. PMID: 18840879.
92. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med*. 1999;341(2):70-6. PMID: 10395630.
93. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352(14):1425-35. PMID: 15755765.



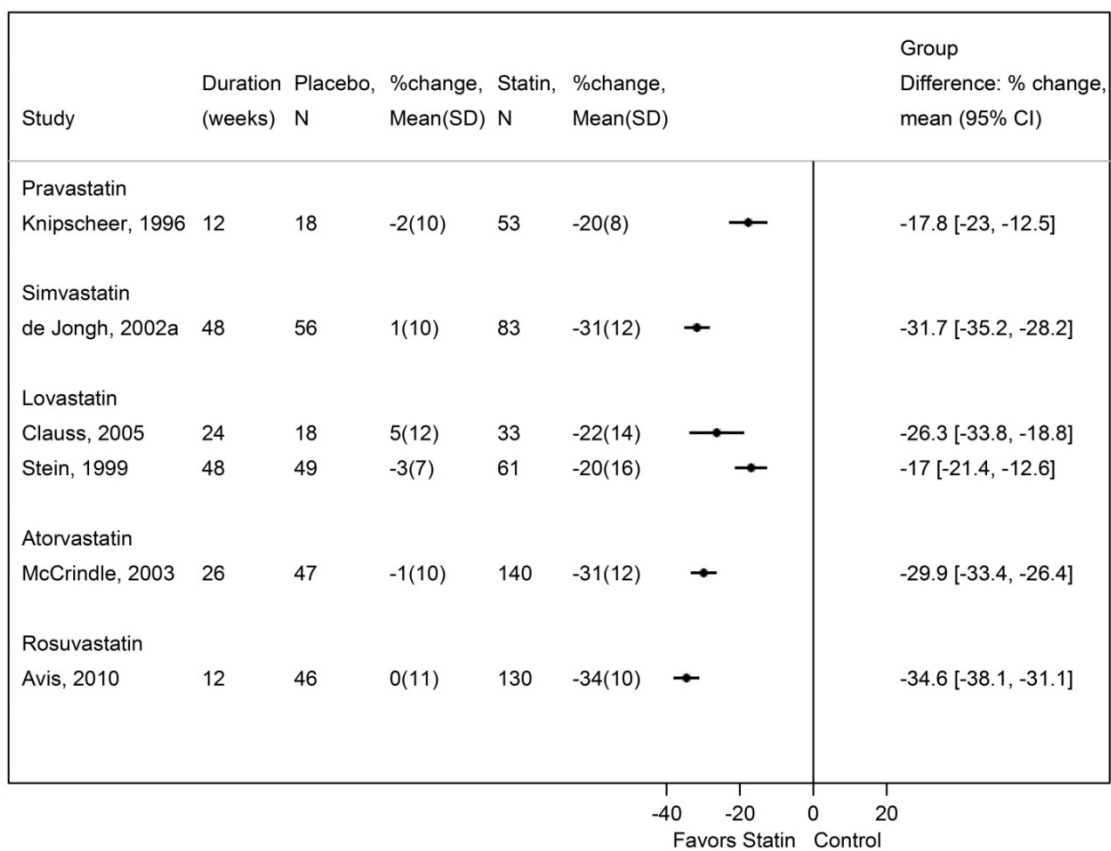
94. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294(19):2437-45. PMID: 16287954.
95. Smilde TJ, van Wissen S, Wollersheim H, et al. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet*. 2001;357(9256):577-81. PMID: 11558482.
96. Linsel-Nitschke P, Gotz A, Erdmann J, et al. Lifelong reduction of LDL-cholesterol related to a common variant in the LDL-receptor gene decreases the risk of coronary artery disease--a Mendelian Randomisation study. *PloS one*. 2008;3(8):e2986. PMID: 18714375.
97. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60(25):2631-9. PMID: 23083789.
98. Soria LF, Ludwig EH, Clarke HR, et al. Association between a specific apolipoprotein B mutation and familial defective apolipoprotein B-100. *Proc Natl Acad Sci U S A*. 1989;86(2):587-91. PMID: 2563166.
99. Tybjaerg-Hansen A, Humphries SE. Familial defective apolipoprotein B-100: a single mutation that causes hypercholesterolemia and premature coronary artery disease. *Atherosclerosis*. 1992;96(2-3):91-107. PMID: 1466657.
100. Myant NB. Familial defective apolipoprotein B-100: a review, including some comparisons with familial hypercholesterolaemia. *Atherosclerosis*. 1993;104(1-2):1-18. PMID: 8141833.
101. Tybjaerg-Hansen A, Steffensen R, Meinertz H, et al. Association of mutations in the apolipoprotein B gene with hypercholesterolemia and the risk of ischemic heart disease. *N Engl J Med*. 1998;338(22):1577-84. PMID: 9603795.
102. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *International journal of epidemiology*. 2004;33(1):30-42. PMID: 15075143.
103. Gillman MW, Daniels SR. Is universal pediatric lipid screening justified? *JAMA*. 2012;307(3):259-60. PMID: 22253390.
104. McCrindle BW, Kwiterovich PO, McBride PE, et al. Guidelines for lipid screening in children and adolescents: bringing evidence to the debate. *Pediatrics*. 2012;130(2):353-6. PMID: 22826573.
105. Daniels SR. Pediatric guidelines for dyslipidemia. *J Clin Lipidol*. 2015;9(5 Suppl):S5-S10. PMID: 26343212.
106. Vuorio A, Docherty KF, Humphries SE, et al. Statin treatment of children with familial hypercholesterolemia--trying to balance incomplete evidence of long-term safety and clinical accountability: are we approaching a consensus? *Atherosclerosis*. 2013;226(2):315-20. PMID: 23141908.

**Figure 1. Analytic Framework**



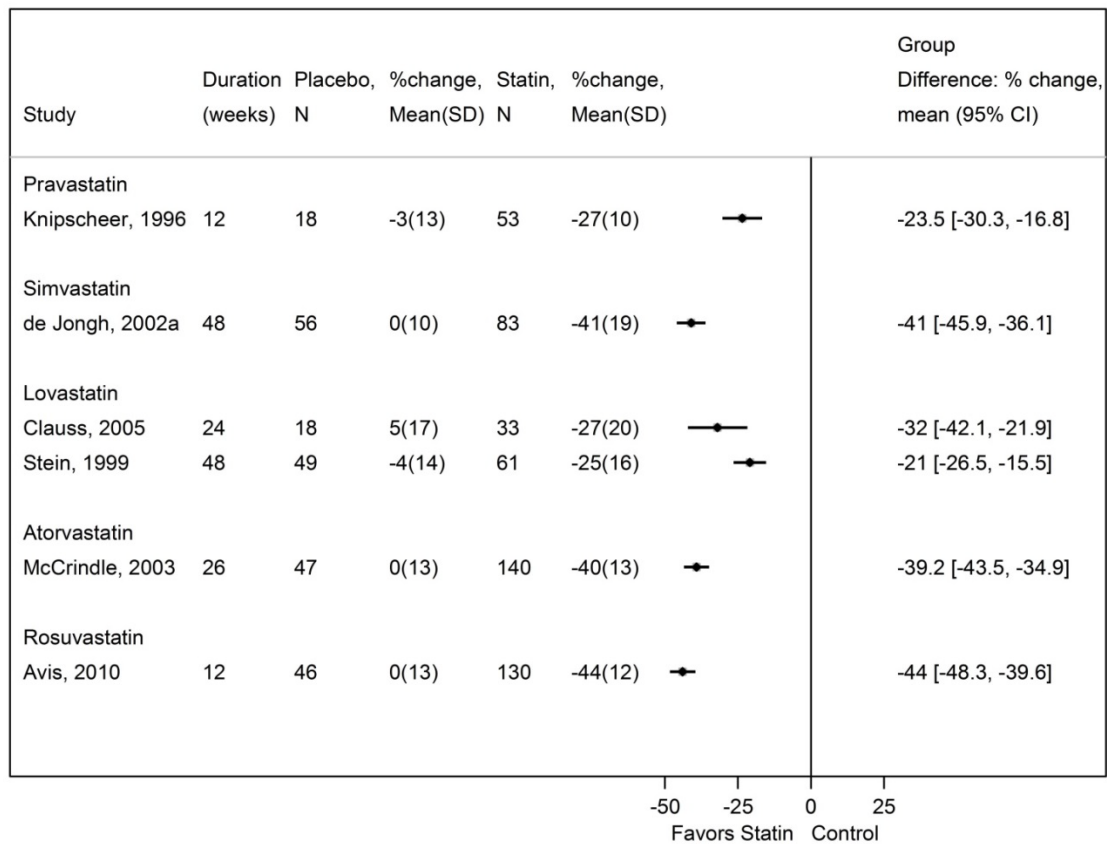
\*Intermediate outcomes include lipid concentrations (total and low-density lipoprotein cholesterol) and atherosclerosis markers (carotid intima-media thickness, calcium score, and pathological findings).

**Figure 3. Effect of Statins on Mean Percent Change of Low-Density Lipoprotein Cholesterol**



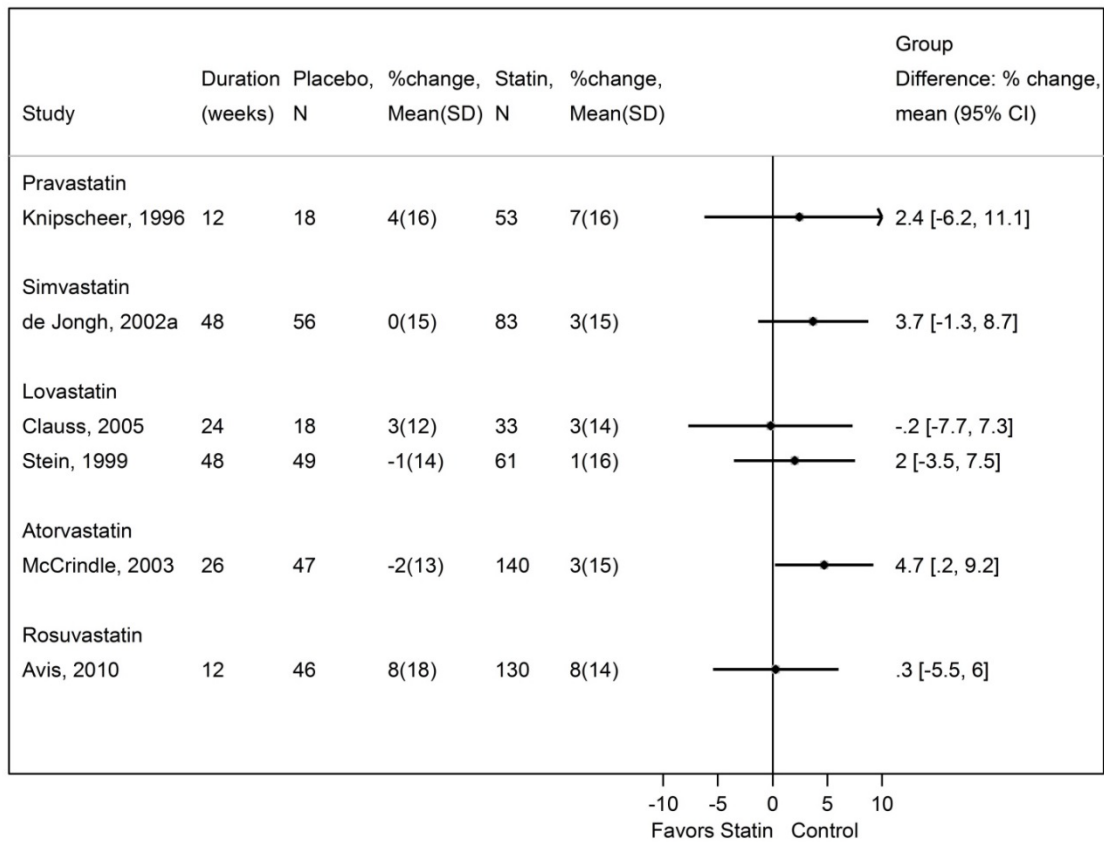
**Abbreviations:** SD=standard deviation, CI=confidence interval.

**Figure 3. Effect of Statins on Mean Percent Change of Low-Density Lipoprotein Cholesterol**



**Abbreviations:** SD=standard deviation, CI=confidence interval.

**Figure 4. Effect of Statins on Mean Percent Change of High-Density Lipoprotein Cholesterol**



**Abbreviations:** SD=standard deviation, CI=confidence interval.

**Table 1. Included Screening Studies**

Study, year Quality County	N	N with FH	Age, mean (SD), years	Age range, years	% Female	Race	Population	Years of data collection
Skovby, 1991 <sup>54</sup> Fair Denmark	2,085	10	NR	6 to 8	NR	NR	3,025 families with children ages 6 to 8 years in Copenhagen schools	1987
Cottrell, 2013 <sup>53</sup> Fair U.S.	81,156	107	NR	10 to 11*	53.0	93.2% White 2.9% African American 2.3% Bi-racial 0.4% Asian 0.7% Hispanic 0.5% Other	5th grade students in West Virginia at elementary schools screened annually	1998 to 2012

\*Study composed of 5th grade students; age range inferred from description.

**Abbreviations:** FH = familial hypercholesterolemia, SD=standard deviation, NR = not reported.

**Table 2. Diagnostic Yield of Screening for Familial Hypercholesterolemia**

Author	Context	FH diagnosis criteria	Number screened	Number with probable FH (screen-positives), n	True positives, n	False positives, n	Diagnostic yield, %*	PPV, %†
Skovby, 1991 <sup>54</sup> Fair Denmark	Copenhagen schools; all families with children starting 1st grade (ages 6 to 8 years) were offered to participate in the pilot screening program	Apolipoprotein B concentration above the 99th centile and Apo B:A-1 ratio >0.83	2,085	47	10	37	0.48	21.3
Cottrell, 2013 <sup>53</sup> Fair U.S.	CARDIAC project, school-based screening in 5th grade students in 53/55 West Virginia counties. All 5th graders eligible	TC >6.7mmol/L or LDL-C >4.0 mmol/L or <i>LDLR</i> gene mutation positive in FDR or SDR	81,156	NR	107‡	NR	0.13%	NR

\*Diagnostic yield is calculated as the number of true positives divided by the number of subjects screened.

†Positive predictive value is calculated as the number of true positives divided by the number of screen-positives.

‡Article describes 107 with probable FH, number of screen-positives not reported.

**Abbreviations:** FH=familial hypercholesterolemia, PPV=positive predictive value, Apo B=apolipoprotein B, CARDIAC=Coronary Artery Risk Detection in Appalachian Communities, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, LDLR=low-density lipoprotein receptor, FDR=first-degree relative, SDR=second-degree relative, NR=not reported.

**Table 3. Included Treatment and Harms of Treatment Studies (Ordered Chronologically by Statin Type and Nonstatin Type)**

Study, year Quality Country	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	% Female	Race	Population	Years of data collection
<b>Treatment</b> (KQ 6: 13 studies;12 report on harms and are included for KQ 7)										
<i>KQ 6 and KQ 7 statins</i>										
Knipscheer, 1996 <sup>52</sup> Good Netherlands	Pravastatin	12 weeks	72	72	12.0 (NR)	8 to 16	65.3	91.7% white 6.9% black 1.3% Asian	72 children with FH	NR
Wiegman, 2004 <sup>66</sup> Good Netherlands Dutch Pravastatin Trial	Pravastatin	104 weeks	214	214	13.0 (3)	8 to 18	53.3	NR	214 children with FH ages 8 to 18 years in the Netherlands	1997– 2001
Couture, 1998 <sup>67*</sup> Good Canada	Simvastatin	6 weeks	63	63	12.6 (2.3)	8 to 17	41.3	NR	63 FH patients enrolled at University Lipid Research Clinic with confirmed mutations in the <i>LDLR</i> gene	NR
De Jongh, 2002a <sup>62</sup> Good International multicenter	Simvastatin	RCT: 24 weeks Extension: 24 weeks	173	173	14.2 (2.1)	10 to 17	43.3	NR	173 children with FH	NR
Stein, 1999 <sup>61</sup> Good U.S; Finland	Lovastatin	48 weeks	132	132	13.2 (0.3)	10 to 17	0.0	NR	Boys ages 10 to 17 years with FH; 14 pediatric outpatient clinics in the U.S. and Finland	1990– 1994
Clauss, 2005 <sup>60</sup> Good USA	Lovastatin	24 weeks	54	54	15.0 (2)	11 to 18	100.0	80.0% white 20.0% not white	54 girls ages 10 to 18 years with FH and at least 1 year postmenarche	1999– 2000
McCrindle, 2003 <sup>63</sup> Good U.S., Canada, Europe, South Africa	Atorvastatin	RCT: 26 weeks Open label: 26 weeks	187	187	14.1 (2.1)	10 to 17	31.0	92% white 1.6% black 1.6% Asian 4.8% other	187 children with FH or severe hypercholesterolemia	NR



**Table 3. Included Treatment and Harms of Treatment Studies (Ordered Chronologically by Statin Type and Nonstatin Type)**

Study, year Quality Country	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	% Female	Race	Population	Years of data collection
Avis, 2010 <sup>64</sup> Good Europe and North America	Rosuvastatin	RCT: 12 weeks Open label: 40 weeks	176	176	14.5 (1.8)	10 to 17	45.0	93.8% Caucasian	Patients ages 10 to 17 years with FH recruited from 20 centers in Europe and North America	2006– 2008
<i>KQ 6 and KQ 7 nonstatins</i>										
Tonstad, 1996b <sup>56</sup> Good Norway	Colestipol	RCT: 8 weeks Open label: 52 weeks	66	66	13.1 (1.7)	10 to 16	43.5	NR	Adolescents previously referred to pediatric lipid clinic with elevated lipids	NR
Tonstad, 1996a <sup>55</sup> Fair Norway	Cholestyramine	52 weeks	72	72	8.4 (1.4) <sup>†</sup>	6 to 11	38.5	NR	Boys and girls ages 6 to 11 years with FH	NR
Stein, 2010 <sup>65</sup> Good International multicenter	Colesevelam	RCT: 8 weeks Open label: 18 weeks	194	194	14.1 (2.0)	10 to 17	36.6	87.1% Caucasian 3.1% black 4.1% Asian 5.2% multiple 0.5% other	Children ages 10 to 17 years with FH	2005– 2007
van der Graaf, 2008 <sup>58</sup> Good Netherlands, U.S., Canada	Ezetimibe and simvastatin	RCT: 33 weeks Open label: 20 weeks	248	248	14.2 (1.9)	10 to 17	42.7	81.9% Caucasian 3.6% Asian 1.6% black or African American 12.9% multiracial	Male and postmenarchal female adolescents ages 10 to 17 years with FH	2005– 2007
Kusters, 2015 <sup>59</sup> Good 9 countries	Ezetimibe	12 weeks	138	125	8.3 (1.6)	6 to 10	57%	80% white	138 children ages 6 to 10 years with diagnosed FH or LDL-C >160 mg/dL	2009– 2012

**Table 3. Included Treatment and Harms of Treatment Studies (Ordered Chronologically by Statin Type and Nonstatin Type)**

Study, year Quality Country	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	% Female	Race	Population	Years of data collection
<b>Harms of Treatment Only (KQ 7: 9 studies)</b>										
<i>KQ 7 only: statins</i>										
Hedman, 2003 <sup>68</sup> Fair Finland	Pravastatin	8 weeks	20	20	10.3 (2.9)	4.9 to 15.6	65.0	NR	20 patients verified by <i>LDLR</i> gene mutation analysis or by lymphocyte test	NR
Rodenburg, 2007 <sup>76</sup> Fair Netherlands  Dutch Pravastatin Trial	Pravastatin <sup>†</sup>	Mean duration of statin treatment: 4.5 years (range, 2.1 to 7.4 years)	186	186	13.7 (3.1)	NR	51.0	NR	Children and adolescents with FH in a study at the Academic Medical Center in Amsterdam	1997–2003
Kusters, 2014 <sup>72</sup> Good Netherlands Dutch Pravastatin Trial	Pravastatin <sup>†</sup>	10+ years	277	194	24.0 (95% CI, 23.6 to 24.5)	NR	53.6	NR	Children enrolled in the Dutch Pravastatin Trial; this followup describes outcomes for 194 members of the original cohort and 83 siblings	1997–2011
Braamskamp, 2015a <sup>78</sup> Good Netherlands Dutch Pravastatin Trial	Pravastatin	2 year (10-year followup)	Tolerability: 205  Adherence: 188	Tolerability: 205  Adherence: 188	At start of RCT: 13.0 (2.9) End of followup: 24.0 (3.2)	At start of RCT: 8 to 18 End of followup: 18 to 30	Tolerability (n=205): 54% Adherence (n=188): NR	NR	Children enrolled in the Dutch Pravastatin Trial between 1997 and 1999	1997–2009

**Table 3. Included Treatment and Harms of Treatment Studies (Ordered Chronologically by Statin Type and Nonstatin Type)**

Study, year Quality Country	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	% Female	Race	Population	Years of data collection
Braamskamp, 2015b <sup>77</sup> Good Netherlands  Dutch Pravastatin Trial	Pravastatin	2 year (10-year followup)	150	88	FH at baseline: 12.8 (3.1) FH at 10 years: 23.9 (3.2) Siblings at 10 years (n=62): 24.1 (3.0)	FH at baseline: 8 to 18 FH at 10 years: NR Siblings at 10 years: NR	24%	NR	Children enrolled in the Dutch Pravastatin Trial between 1997 and 1999 and their siblings	1997– 2009
Carreau, 2011 <sup>73</sup> Fair France	Pravastatin	Mean: 2 years and 2 months Range: 3 months and 7 years	185	185	11 (NR)	4 to 17	54.6	NR	Children identified from medical records at specialized French centers in Paris	2002– 2009
De Jongh, 2002b <sup>70</sup> Fair Netherlands	Simvastatin	28 weeks	69	50	14.6 (2.5) <sup>§</sup>	9 to 18	47.8 <sup>§</sup>	NR	50 heterozygous FH children plus 19 nonaffected controls. 28 in FH simvastatin group, 22 in FH placebo group, 19 nonFH controls.	NR
Gandelman, 2011 <sup>75</sup> Fair Greece, Norway, and Canada	Atorvastatin	8 weeks	39	39	11.6 (3.0)	6 to 17	48.8	100% white	Tanner stage 1 and stage 2 children with genetically verified FH	2008– 2009
Avis, 2011 <sup>74</sup> Good Netherlands	Rosuvastatin	RCT: 12 weeks Open label: 40 weeks	29	29	14.4 (1.9)	10 to 17	48.3	NR	Children ages 10 to 17 years with heterozygous FH participating in Avis 2010 (PLUTO) trial	2006– 2008

**Table 3. Included Treatment and Harms of Treatment Studies (Ordered Chronologically by Statin Type and Nonstatin Type)**

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	% Female	Race	Population	Years of data collection
Braamskamp, 2015 <sup>c79</sup> Good Netherlands, U.S., Canada, Belgium, Norway CHARON	Rosuvastatin	2 years	198	198	11.6 (3.3)	6 to 17	56%	NR	198 children with HeFH	2010– 2013
Sinzinger, 2004 <sup>69*</sup> Fair Austria	Various statins	8 years	22 (all subjects)  6 (in pediatric subgroup)	22 (all subjects)  6 (in pediatric subgroup)	16.8 (2.6) (all subjects)	13–35 (all subjects)  13-20 (pediatric subgroup)	40.0 (all subjects)	NR	Professional athletes with FH	NR
<i>KQ 7 only: nonstatins</i>										
McCrindle, 2002 <sup>†1</sup> Good Canada	Colestipol and pravastatin	18 weeks	36	36	Median: 14	9 to 18	30.6	NR	Children seen at the pediatric lipid disorder clinic at the Hospital for Sick Children (Toronto) and St. Joseph's Hospital (Hamilton)	NR

\*Couture 1998 only included for KQ 6.

†Mean age for 96 subjects who entered the yearlong dietary phase.

‡Pravastatin was original drug prescribed to study cohort.

§Data represent only those with FH.

\*\*This review focuses on the 6 athletes that met our inclusion criteria (study reported individual-level data).

**Abbreviations:** KQ=key question, FH=familial hypercholesterolemia, SD=standard deviation, NR=not reported, *LDLR*=low-density lipoprotein receptor, RCT=randomized, controlled trial, LDL-C=low-density lipoprotein cholesterol, PLUTO=Pediatric Lipid-redUction Trial of rOsuvastatin, HeFH=heterozygous familial hypercholesterolemia.

**Table 4. Randomized, Controlled Trials of Medication in Children and Adolescents With Familial Hypercholesterolemia: Effect of Statins, Bile-Sequestering Agents, and Other Drugs on Lipid Concentrations**

Author, Year, Quality	N (IG/CG) % Female	Mean age (SD), years Range, years	Drug RCT duration	Measure of change from baseline	TC	LDL-C	HDL-C	Triglycerides
<b>Statins</b>								
Knipscheer, 1996 <sup>52</sup> Good Netherlands	72 (54/18) 65.3%	12.0 (NR) 8 to 16	Pravastatin 12 weeks	Mean (95% CI) % change	Mean % change 5 mg: -18.2 (-21.9 to -14.2) 10 mg: -17.2% (-21.1 to -13.1) 20 mg: -24.6% (-28.1 to -21.0) CG: -2.3% (-6.7 to 2.4)	Mean % change 5 mg: -23.3 (-27.9 to -18.4) 10 mg: -23.8 (-28.5 to -18.8) 20 mg: -32.9 (-37.0 to -28.6) CG: -3.2 (-9.0, to -3.0)	Mean % change 5 mg: +3.8 (-3.1 to 11.2) 10 mg: +5.5 (-1.7 to 13.2) 20 mg: +10.8 (3.4 to 18.8) CG: +4.3 (-2.7 to 11.8)	Mean % change 5 mg: -1.7 (-15.4 to 22.2) 10 mg: +6.6 (-12.0 to 29.0) 20 mg: +3.3 (-14.3 to 24.5) CG: -11.7 (-26.6 to 6.1)
Wiegman, 2004 <sup>66</sup> Good Netherlands	214 (106/108) 53.0%	13.0 (3) 8 to 18	Pravastatin 104 weeks	Mean (SD) difference	IG: -56.0 (43) CG: +2.0 (39)	IG: -57.0 (43) CG: 0.0 (36)	IG: +3.0 (10) CG: +1.0 (9)	IG: +12.0 (-35 to -16) CG: +1.0 (-20 to 22)
Couture, 1998 <sup>67*</sup> Good Canada	63 (47/16)	12.5 (2.4) 8 to 17	Simvastatin 6 weeks	Mean % change	IG: -29.5% CG: -5.8%	IG: -37.5% CG: -5.6%	NR by intervention group	NR by intervention group
De Jongh, 2002a <sup>62</sup> Good International multicenter	173 (106/69) 43.3%	14.2 (2.1) 10 to 17	Simvastatin 24 weeks	Mean (SD) % change	IG: -28.3% (13.4) CG: -0.7% (9.5)	IG: -38.4% (16.0) CG: -1.2% (11.0)	IG: +4.9% (13.5) CG: +0.3% (15.5)	IG: -7.9 (-74.1 to 92.5) CG: -3.2% (-56.2 to 179.5)
Stein, 1999 <sup>61</sup> Good U.S. and Finland	132 (67/65) 0.0%	13.2 (0.3) 10 to 17	Lovastatin 48 weeks	Mean (SE) % change	IG: -20.0% (2) CG: -3.0% (1)	IG: -25.0% (2) CG: -4.0% (2)	IG: +1.0% (2) CG: -1.0% (2)	IG: +6.0% (6) CG: +8% (7)
Clauss, 2005 <sup>60</sup> Good U.S.	54 (35/19) 100%	15.0 (2) 11 to 18	Lovastatin 24 weeks	LS mean % change (SE)	IG: -21.8% (2.5) CG: +4.5% (2.9)	IG: -26.8% (3.4) CG: +5.2% (3.9)	IG: +2.5% (2.5) CG: +2.7% (2.9)	IG: -22.7% (6.8) CG: -3.0% (9.6)
McCrindle, 2003 <sup>63</sup> Good U.S., Canada, Europe, South Africa	187 (140/47) 31.0%	14.1 (2.2) 10 to 17	Atorvastatin 26 weeks	Mean (SE) % change	Mean % change IG: -31.4% (1.0) CG: -1.5% (1.5)	Mean % change IG: -39.6% (1.1) CG: -0.4% (1.9)	Mean % change IG: +2.8% (1.3) CG: -1.9% (1.9)	Mean % change IG: -12.0% (2.9) CG: +1.0% (6.2)

**Table 4. Randomized, Controlled Trials of Medication in Children and Adolescents With Familial Hypercholesterolemia: Effect of Statins, Bile-Sequestering Agents, and Other Drugs on Lipid Concentrations**

Author, Year, Quality	N (IG/CG) % Female	Mean age (SD), years Range, years	Drug RCT duration	Measure of change from baseline	TC	LDL-C	HDL-C	Triglycerides
Avis, 2010 <sup>64</sup> Good Europe and North America	176 (130/46) 45.0%	14.5 (1.8) 10 to 17	Rosuvastatin 12 weeks	LS mean % change	5 mg: -30.0% 10 mg: -34.0% 20 mg: -39.0% CG: 0%	5 mg: -38.0% 10 mg: -45.0% 20 mg: -50.0% CG: -1.0%	5 mg: +4.0% 10 mg: +10.0% 20 mg: +9.0% CG: +7.0%	5 mg: -13.0% 10 mg: -15.0% 20 mg: -16.0% CG: -7.0%
Bile-sequestering agents								
Tonstad, 1996b <sup>56</sup> Good Norway	66 (33/33) 43.5%	13.1 (1.7) 10 to 16	Colestipol 8 weeks	Mean % change	IG: -14.0% CG: -1.0	IG: -19.5% CG: -1.0%	NR	NR
Tonstad, 1996a <sup>55</sup> Fair Norway	72 (36/36) 38.5%	8.4 (1.4) 6 to 11	Cholestyramine 52 weeks	Mean % change	IG: -11.5% CG: +3.0%	IG: -18.6% CG: +1.5%	IG: +13.4% CG: +8.8%	NR
Stein, 2010 <sup>65</sup> Good International multicenter	194 (129/65) 36.6%	14.1 (2.0) 10 to 17	Colesevelam 8 weeks	LS mean % change (SE)	3.75 g/d: -5.1% (1.58) 1.9 g/d: -0.9% (1.6) CG: +2.3% (1.6)	3.75 g/d: -10.0% (2.1) 1.9 g/d: -3.8% (2.1) CG: +2.5% (2.0)	3.75 g/d: +8.3 (1.6) 1.9 g/d: +4.5 (1.6) CG: +2.2% (1.6)	3.75 g/d: +17.4 (42.8) 1.875 g/d: +18.5 (34.9) CG: +12.3 (36.2)
				Treatment difference	3.75 g/d: -7.4% (2.23) (p<0.01) 1.9 g/d: -3.2% (2.23)	3.75 g/d: -12.5% (2.92) (p<0.001) 1.9 g/d: -6.3% (2.91) (p=0.031)	3.75 g/d: +6.1% (2.28) (p<0.01) 1.9 g/d: +2.4 % (2.3)	3.75 g/d: +5.1% (76.5) 1.875 g/d: +6.4% (70.7) (p=0.47)
Other drugs								
van der Graaf, 2008 <sup>58</sup> Good Netherlands, U.S., Canada	248 (126/122) 42.7%	14.2 (1.9) 10 to 17	Ezetimibe (ezetimibe + simvastatin vs. simvastatin) 33 weeks	Mean (SD) % change	IG: -42.5% (1.2) CG: -29.3% (1.2)	IG: -54.0% (1.4) CG: -38.1% (1.4)	IG: +4.67% (1.3) CG: +3.68% (1.3)	IG: -20.0% (23.8) CG: -13.0% (39.0)
Kusters, 2015 <sup>59</sup> Good 9 countries	138 <sup>†</sup> (93/45) 57%	8.3 (1.6) 6 to 10	Ezetimibe 12 weeks	Mean % change at 12 weeks (95% CI)	IG: -21 (-23 to -18) CG: 0.2 (-3 to 3)	IG: -28 (-31 to -25) CG: -0.95 (-4.9 to 3.0)	IG: 2 (-2 to 6) CG: 1 (-4 to 7)	IG: (geometric mean): -6 (-13 to 1) CG (geometric mean): 8 (-2 to 20)

\*For Couture 1998, data on TC and LDL-C were extrapolated from a figure.

†13 nonFH participants (9 in treatment group, 4 in placebo group) were not analyzed separately.

**Table 4. Randomized, Controlled Trials of Medication in Children and Adolescents With Familial Hypercholesterolemia: Effect of Statins, Bile-Sequestering Agents, and Other Drugs on Lipid Concentrations**

**Abbreviations:** FH=familial hypercholesterolemia, IG=intervention group, CG=control group, SD=standard deviation, RCT=randomized, controlled trial, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, NR=not reported, CI=confidence interval, LS=least square, SE=standard error, g/d=grams per day.

**Table 4a. Data From Knipscheer 1996 (Pravastatin Trial of 72 Children Ages 8 to 16 Years)**

Group	Baseline concentration, mean (range), mg/dL	Change from baseline concentration, mean % change (95% CI)	p-value*
<b>Placebo</b>			
TC	302 (216.0 to 516.8)	-2.3 (-6.7 to 2.4)	
LDL-C	247 (154.0 to 458.9)	-3.2 (-9.0 to 3.0)	
HDL-C	42 (30.9 to 54.0)	4.3 (-2.7 to 11.8)	
TG	71 (35.4 to 168.3)	-11.7 (-26.6 to 6.1)	
<b>Pravastatin 5 mg</b>			
TC	298 (227.6 to 397.3)	-18.2 (-21.9 to -14.2)	<0.05
LDL-C	240 (181.2 to 339.4)	-23.3 (-27.9 to -18.4)	<0.05
HDL-C	46 (34.7 to 65.6)	3.8 (-3.1 to 11.2)	
TG	62 (26.6 to 194.9)	1.7 (-15.4 to 22.2)	
<b>Pravastatin 10 mg</b>			
TC	294 (200.6 to 374.1)	-17.2 (-21.1 to -13.1)	<0.05
LDL-C	236 (138.9 to 304.7)	-23.8 (-28.5 to -18.8)	<0.05
HDL-C	42 (23.1 to 61.7)	5.5 (-1.7 to 13.2)	
TG	71 (35.4 to 186.0)	6.6 (-12.0 to 29.0)	
<b>Pravastatin 20 mg</b>			
TC	317.1 (216.0 to 513.0)	-24.6 (-28.1 to -21.0)	<0.05
LDL-C	259.1 (165.9 to 451.3)	-32.9 (-37.0 to -28.6)	<0.05
HDL-C	46.4 (30.9 to 69.4)	10.8 (3.4 to 18.8)	
TG	53.14 (26.6 to 115.1)	3.3 (-14.3 to 24.5)	

\*p-values apply to the difference in change from baseline between the treatment and control group.

**Abbreviations:** CI=confidence interval, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.



**Table 4b. Data From Wiegman 2004 (Pravastatin Trial of 214 Children Ages 8 to 18 Years)**

Group	Baseline concentration, mg/dL	Change from baseline concentration, mean (SD) difference, mg/dL	p-value*
<b>Placebo</b>			
TC	300 (47)	2 (39)	
LDL-C	237 (46)	0 (36)	
HDL-C	48 (11)	1 (9)	
TG	64 (46 to 90)	1 (-20 to 22)	
<b>Pravastatin<sup>†</sup></b>			
TC	302 (56)	-56 (43)	<0.001
LDL-C	239 (53)	-57 (40)	<0.001
HDL-C	47 (10)	3 (10)	0.09
TG	70 (50 to 112)	-12 (-35 to 16)	0.21

All values are given as mean (SD) except for TG values, which are given as median (interquartile range).

\*p-values apply to the difference in change from baseline between the treatment and control groups.

<sup>†</sup>Children age <14 years received 20 mg/day; those age ≥14 years received 40 mg/day.

**Abbreviations:** SD=standard deviation, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4c. Data From Couture 1998 (Simvastatin Trial of 63 Children Ages 8 to 17 Years)**

Group	Baseline concentration, mean (SE), mg/dL*	Change from baseline concentration, mean % change*†	p-value
<b>Placebo</b>			
TC	293 (13)	-5.8%	
LDL-C	228 (10)	-5.6%	
HDL-C	NR	NR	
TG	NR	NR	
<b>Simvastatin 20 mg</b>			
TC	286 (4)	-29.5%	NR
LDL-C	222 (4)	-37.5%	NR
HDL-C	NR	NR	NR
TG	NR	NR	NR

\*Data from baseline and followup (week 6) were extrapolated from a figure.

†Mean percent change from baseline was calculated from the extrapolated data.

**Abbreviations:** SE=standard error, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides, NR=not reported.

**Table 4d. Data From De Jongh 2002a (Simvastatin Trial of 173 Children Ages 10 to 17 Years)**

Group	Baseline concentration, mg/dL	Change from baseline concentration, mean or median % change	p-value*
<b>Placebo</b>			
TC	279 (52)	-0.7 (9.5)	
LDL-C	212 (49)	-1.2 (11.0)	
HDL-C	47 (12)	0.3 (15.5)	
TG	90 (39 to 326)	-3.2 (-56.2 to 179.5)	
<b>Simvastatin<sup>†</sup></b>			
TC	271 (44)	-28.3 (13.4)	<0.001
LDL-C	204 (42)	-38.4 (16.0)	<0.001
HDL-C	48 (9)	4.9 (13.5)	<0.05
TG	78 (42 to 279)	-7.9 (-74.1 to 92.5)	

All values are given as mean (SD) except for TG values, which are given as median (range).

\*p-values apply to the difference in change from baseline between the treatment and control groups.

†The treatment group received simvastatin at 10 mg/day for the first 8 weeks, 20 mg/day for the second 8 weeks, and 40 mg/day for last 8 weeks.

**Abbreviations:** SD=standard deviation, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4e. Data From Stein 1999 (Lovastatin Trial of 132 Male Children Ages 10 to 17 Years)**

Group	Baseline concentration, mean (SE), mg/dL	Change from baseline concentration, mean % change (SE)	p-value*
<b>Placebo</b>			
TC	315 (7)	-3 (1)	
LDL-C	250 (7)	-4 (2)	
HDL-C	44 (1)	-1 (2)	
TG	110 (6)	8 (7)	
<b>Lovastatin<sup>†</sup></b>			
TC	318 (6)	-20 (2)	<0.001
LDL-C	251 (6)	-25 (2)	<0.001
HDL-C	45 (1)	1 (2)	
TG	112 (7)	6 (6)	

\*p-values apply to the difference in change from baseline between the treatment and control groups.

†The treatment group received lovastatin starting at 10 mg/day, doubling every 8 weeks to a maximum dose of 40 mg/day.

**Abbreviations:** SE=standard error, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4f. Data From Clauss 2005 (Lovastatin Trial of 54 Female Children Ages 11 to 18 Years)**

Group	Baseline concentration, mean (SD), mg/dL	Least mean squares percent change (SE) from baseline concentration	p-value*
<b>Placebo</b>			
TC	269 (41)	4.5 (2.9)	
LDL-C	199 (40)	5.2 (3.9)	
HDL-C	45 (9)	2.7 (2.9)	
TG	103 (54) <sup>†</sup>	-3.0 (9.6)	
<b>Lovastatin<sup>‡</sup></b>			
TC	289 (50)	-21.8 (2.5)	<0.001
LDL-C	218 (48)	-26.8 (3.4)	<0.001
HDL-C	49 (12)	2.5 (2.5)	
TG	106 (54) <sup>†</sup>	-22.7 (6.8)	

\*p-values apply to the difference in change from baseline between the treatment and control groups.

<sup>†</sup>Values are given as median (SE).

<sup>‡</sup>The treatment group received lovastatin starting at 20 mg/day for the first 4 weeks, increasing to 40 mg/day for the duration of the trial.

**Abbreviations:** SD=standard deviation, SE=standard error, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4g. Data From McCrindle 2003 (Atorvastatin Trial of 187 Children Ages 10 to 17 Years)**

Group	Baseline concentration, mean (SEM) mg/dL	Change from baseline concentration, mean % change (SEM)	p-value*
<b>Placebo</b>			
TC	298 (8)	-1.5 (1.5)	
LDL-C	230 (7)	-0.4 (1.9)	
HDL-C	46 (2)	-1.9 (1.9)	
TG	106 (8)	1.0 (6.2)	
<b>Atorvastatin 10 mg</b>			
TC	285 (4)	-31.4 (1.0)	<0.001
LDL-C	219 (3.6)	-39.6 (1.1)	<0.001
HDL-C	46 (1)	2.8 (1.3)	0.02
TG	103 (5)	-12.0 (2.9)	0.03

\*p-values apply to the difference in change from baseline between the treatment and control groups.

**Abbreviations:** SEM=standard error of the mean, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4h. Data From Avis 2010 (Rosuvastatin Trial of 176 Children Ages 10 to 17 Years)**

Group	Baseline concentration, mean (SD), mg/dL	Least mean squares percent change from baseline concentration	p-value*
<b>Placebo</b>			
TC	293 (50)	0	
LDL-C	229 (43)	-1	
HDL-C	45 (11)	7	
TG	82 (57 to 124)	-7	
<b>Rosuvastatin 5 mg</b>			
TC	300 (60)	-30	<0.001
LDL-C	238 (55)	-38	<0.001
HDL-C	46 (12)	4	0.4
TG	80 (55 to 100)	-13	0.8
<b>Rosuvastatin 10 mg</b>			
TC	297 (49)	-34	<0.001
LDL-C	229 (45)	-45	<0.001
HDL-C	49 (10)	10	0.2
TG	81 (53 to 105)	-15	0.1
<b>Rosuvastatin 20 mg</b>			
TC	302 (49.9)	-39	<0.001
LDL-C	237 (47.9)	-50	<0.001
HDL-C	47.2 (13)	9	0.5
TG	81 (59 to 107)	-16	0.1

All values are given as mean (SD) except for TG values, which are given as median (interquartile range).

\*p-values apply to the difference in change from baseline between the treatment and control groups.

**Abbreviations:** SD=standard deviation, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4i. Data From Tonstad 1996b (Colestipol Trial of 66 Children Ages 10 to 16 Years)**

Group	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration, mean % change	p-value*
<b>Placebo</b>			
TC	297 (49)	-1.0	
LDL-C	237 (46)	-1.0	
HDL-C	43 (8)		
TG	85 (58)		
<b>Colestipol 10 g</b>			
TC	316 (57)	-14.0	p<0.01
LDL-C	254 (51)	-19.5	p<0.01
HDL-C	43 (10)		
TG	88 (54)		

\*p-values apply to the difference in change from baseline between the treatment and control groups.

**Abbreviations:** SD=standard deviation, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.



**Table 4j. Data From Tonstad 1996a (Cholestyramine Trial of 72 Children Ages 6 to 11 Years)**

Group	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration, mean % change	p-value*
<b>Placebo</b>			
TC	321 (47)	3.0	
LDL-C	NR	1.5	
HDL-C	44 (10)	8.8	
TG	84 (45)		
<b>Cholestyramine 8 g</b>			
TC	320 (51)	-11.5	<0.001
LDL-C	NR	-18.6	0.0001
HDL-C	49 (9)	13.4	
TG	69 (29)		

\*p-values apply to the difference in change from baseline between the treatment and control groups.

**Abbreviations:** SD=standard deviation, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4k. Data From Stein 2010 (Colesevelam Trial of 194 Children Ages 10 to 17 Years)**

Group	Baseline concentration, mean (SD), mg/dL	Treatment difference, mean % (SE)*	p-value†
<b>Placebo</b>			
TC	261 (47)		
LDL-C	197 (44)		
HDL-C	45 (9)		
TG	93 (40)‡		
<b>Colesevelam 1.875 g</b>			
TC	266 (45)	-3.2 (2.2)	
LDL-C	198 (44)	-6.3 (2.9)	<0.05
HDL-C	48 (12)	2.4 (2.3)	
TG	83 (46)‡	6.4 (70.7)	
<b>Colesevelam 3.75 g</b>			
TC	267 (51)	-7.4 (2.2)	<0.01
LDL-C	202 (50)	-12.5 (2.9)	<0.001
HDL-C	45 (10)	6.1 (2.3)	<0.01
TG	85 (55)‡	5.1 (76.5)	

\*Treatment difference is calculated versus placebo.

†p-values apply to the difference in change from baseline between the treatment and control groups.

‡TG values given as median (± interquartile range).

**Abbreviations:** SD=standard deviation, SE=standard error, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4I. Data From van der Graaf 2008 (Ezetimibe Trial of 248 Children Ages 10 to 17 Years)**

Group*	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration, mean % change (SD)	p-value <sup>†</sup>
<b>Placebo + Simvastatin</b>			
TC	286 (4.1)	-29.3 (1.2)	
LDL-C	219 (3.9)	-38.1 (1.4)	
HDL-C	46 (0.8)	3.7 (1.3)	
TG	88 (38.8) <sup>‡</sup>	-13.0 (39.0) <sup>‡</sup>	
<b>Ezetimibe + Simvastatin</b>			
TC	292 (4.0)	-42.5 (1.2)	<0.01
LDL-C	225 (3.8)	-54 (1.4)	<0.01
HDL-C	46 (0.8)	4.7 (1.3)	0.58
TG	89 (49.3) <sup>‡</sup>	-20.0 (23.8) <sup>‡</sup>	<0.01

\*In this six-group trial, three received ezetimibe (10 mg/day) and three received placebo. All six groups received simvastatin, with three different doses for the first 6 weeks (10, 20, or 40 mg/day) but the same dose (40 mg/day) for the last 27 weeks of the trial. The six groups were combined into two groups for analysis: ezetimibe plus simvastatin and placebo plus simvastatin.

<sup>†</sup>p-values apply to the difference in change from baseline between the ezetimibe plus simvastatin group and the placebo plus simvastatin group.

<sup>‡</sup>For triglycerides, median and standard deviation derived by (interquartile range)/1.075 are provided.

**Abbreviations:** SD=standard deviation, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, TG=triglycerides.

**Table 4m. Data From Kusters 2015 (Ezetimibe Trial of 138 Children Ages 6 to 10 Years)**

Group	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration at 12 weeks, mean % change (95% CI)	p-value*
<b>Placebo</b>			
TC	290 (44)	0.2 (-3, 3)	
LDL-C	222 (45)	-0.95 (-4.9, 3.0)	
HDL-C	50 (12)	1 (-4, 7)	
Non-HDL-C	240 (48)	0.3 (-4, 4)	
TG	92 (61)	8 (-2, 20) <sup>†</sup>	
<b>Ezetimibe 10 mg</b>			
TC	295 (48)	-21 (-23,-18)	<0.001
LDL-C	229 (46)	-28 (-31,-25)	<0.001
HDL-C	50 (9)	2 (-2, 6)	0.807
Non-HDL-C	245 (47)	-25 (-28, -22)	<0.001
TG	82 (30)	-6 (-13, 1) <sup>†</sup>	0.021

\*p-values apply to the difference in change from baseline between the treatment and control groups.

†For triglycerides, change from baseline presented as geometric mean.

**Abbreviations:** SD=standard deviation, CI=confidence interval, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, non-HDL-C=non-high-density lipoprotein cholesterol, TG=triglycerides.

**Table 5. Randomized, Controlled Trials of Medication in Children and Adolescents With Familial Hypercholesterolemia: Effect on Atherosclerosis**

Study, year Quality County	N	N with FH	Mean age (SD)	Age range	% Female	Race	Drug	CIMT* measurement at baseline (mm)	Change in CIMT measurement* from baseline (mm)
Wiegman, 2004 <sup>66</sup> Good Netherlands	214	214	13.0 (3)	8 to 18	53.3	NR	Pravastatin 20– 40 mg/day <sup>†</sup> vs. placebo for 104 weeks	IG: 0.497 (0.055) CG: 0.492 (0.045)	IG: -0.010 (0.048) CG: 0.005 (0.044)

\*Measures reported are mean (SD).

† 20 mg/day for those younger than age 14 years; 40 mg/day for those age 14 years and older.

**Abbreviations:** FH=familial hypercholesterolemia, SD=standard deviation, CIMT=carotid intima-media thickness, NR=not reported, IG=intervention group, CG=control group.

**Table 6. Overlapping Study Populations**

Study	Author, year Quality County	Drug name	N	N with FH	Mean (SD) age, years range	Female, %	Years of data collection	KQ	Description
PLUTO: Pediatric Lipid-redUction Trial of rOsuvastatin	Avis, 2010 <sup>64</sup> Good Europe and North America	Rosuvastatin	176	176	14.5 (1.8) 10 to 17	45.0	2006 to 2008	KQ 6, KQ 7	Parent study
	Avis, 2011 <sup>74</sup> Fair Netherlands	Rosuvastatin	29	29	14.4 (1.9) 10 to 17	48.3	2006 to 2008	KQ 7	Subset of PLUTO analyzing the effect of statin therapy on coenzyme Q10 and mitochondrial adenosine triphosphate synthesis
Dutch Pravastatin Trial	Wiegman, 2004 <sup>66</sup> Good Netherlands	Pravastatin	214	214	13.0 (3) 8 to 18	53.3	December 1997 to November 2001	KQ 6, KQ 7	Parent study
	Rodenburg, 2007 <sup>76</sup> Fair Netherlands	Pravastatin	186	186	24.0 (23.6 to 24.5)*	51.0	1997 to 2003	KQ 7	4- to 7-year followup of original RCT
	Kusters, 2014 <sup>72</sup> Good Netherlands	Pravastatin	277	194	12.9 (NR) 12.5 to 13.4	53.6	1997 to 2011	KQ 7	10-year followup of original RCT
	Braamskamp, 2015a <sup>78</sup> Good Netherlands	Pravastatin	Tolerability: 205 Adherence: 188	Tolerability: 205 Adherence: 188	Start of RCT: 13.0 (2.9) 8 to 18 End of followup: 24.0 (3.2) 18 to 30	Tolerability (n=205): 54% Adherence (n=88): NR	1997 to 2009	KQ 7	10-year followup of tolerability and adherence

**Table 6. Overlapping Study Populations**

Study	Author, year Quality County	Drug name	N	N with FH	Mean (SD) age, years range	Female, %	Years of data collection	KQ	Description
	Braamskamp, 2015b <sup>77</sup> Good Netherlands	Pravastatin	150 (includes 62 siblings)	88	FH at baseline: 12.8 (3.1) 8 to 18 FH at 10 years: 23.9 (3.2) NR Siblings at 10 years (n=62): 24.1 (3.0) NR	24%	1997 to 2009	KQ 7	10-year followup reporting hormone concentrations
Dutch simvastatin trial <sup>†</sup>	De Jongh, 2002a <sup>62</sup> Good Multicenter (n=9)	Simvastatin	173	173	14.2 (2.1) 10 to 17	43.3	NR	KQ 6, KQ 7	Parent study
	De Jongh, 2002b <sup>70</sup> Fair Netherlands	Simvastatin	69	50	14.6 (2.5) 9 to 18	47.8	NR	KQ7	Subset of De Jongh 2002a aiming to determine whether simvastatin improves endothelial function in children

\*95% confidence interval.

†De Jongh 2002b is a subset of De Jongh 2002a, and the two populations have different age ranges.

**Abbreviations:** FH=familial hypercholesterolemia, SD=standard deviation, KQ=key question, RCT=randomized, controlled trial, NR=not reported.

**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
<b>Statins</b>							
Knipscheer 1996 Good Netherlands	Pravastatin	72	8 to 16	12 weeks	Hematology, ALT, AST, CK, alkaline phosphatase, urinalysis, TSH, cortisol, ACTH	Clinical AEs equally distributed between treatment and placebo groups. Clinical AEs in treatment group included rash (n=1), nose bleeding (n=1), headache (n=3), nausea/vomiting (n=3), and abdominal pain (n=2)	No significant difference between treatment and placebo groups for lab AEs. CK level abnormal in placebo (n=8) and pravastatin 5 mg/d (n=6), 10 mg/d (n=11), and 20 mg/d groups (n=8); cortisol level abnormal in placebo (n=2) and pravastatin 5 mg/d (n=2), 10 mg/d (n=5), and 20 mg/d (n=3) groups. For other lab effects, <5 participants had abnormal values in placebo group, as well as in all pravastatin groups combined.
McCrindle 2002 Good Canada	Pravastatin + Colestipol (PC) vs. Colestipol only (CO)	36	9 to 18	18 weeks	Height, weight, blood pressure, serum chemistries, blood counts	Clinical AEs more prevalent in CO group. Clinical AEs included constipation (PC 3%, CO 21%), bloating/gas (PC 3%, CO 15%) stomach ache (PC 0%, CO 21%), headache (PC 3%, CO 14%), and muscle aches (PC 3%, CO 6%)	No effects on CK, AST, other blood chemistries, or hematologic values. Alkaline phosphatase levels decreased significantly from baseline for CO group at 18 weeks. Absolute reduction in ALT level from baseline was significantly greater in CO group than PC group at 8 and 18 weeks.
Hedman 2003 Fair Finland	Pravastatin	20	4 to 15	8 weeks	GI symptoms, headache, skin reactions, sleep disturbance, muscle/tendon tenderness, pain, creatinine, CK, ALT	Clinical AEs included abdominal pain (n=1), loose stools (n=1), headache (n=4), sleep disturbance (n=2), muscle tenderness or pain at rest (n=1), and muscle tenderness or pain associated with physical training (n=1)	No effects on serum ALT, CK, or creatinine levels
Wiegman 2004 Good Netherlands  Dutch Pravastatin Trial	Pravastatin	214	8 to 18	104 weeks	Sex steroids, gonadotropins, pituitary/adrenal axis markers, growth, sexual development, academic progress, AST, ALT, CK	No effects on growth, sexual development, or academic progress	No effects on muscle or liver enzyme levels (AST, ALT, CK) or on endocrine function



**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Rodenburg 2007 Fair Netherlands  Dutch Pravastatin Trial	Pravastatin	186	13.7 (mean age)	Mean duration of statin treatment: 4.5 years	Sex steroids, gonadotropins, pituitary adrenal axis markers, muscle and liver enzymes, growth, sexual development	Myalgia without CK elevation (n=4). No effects on growth or sexual development.	No serious lab AEs reported; no subjects discontinued treatment due to lab AEs. Lab AEs included elevated CK likely associated with extreme exercise (n=2), mildly elevated FSH (n=4), decreased DHEAS (n=3), and mildly elevated ACTH (n=2).
Kusters 2014 Good Netherlands  Dutch Pravastatin Trial	Pravastatin	194	24.0 (mean age)	10+ years	Growth, sexual development, AST, ALT, CK, glomerular filtration rate, C-reactive protein, level of education, reported AEs	No effects on growth, sexual development, or education level; no reports of rhabdomyolysis or other serious major AEs. 3 subjects discontinued treatment due to unspecified AEs.	No effects on AST, ALT, CK, glomerular filtration rate, or C- reactive protein. No differences between patients with FH and nonFH siblings for lab AEs.
Braamskamp 2015a Good Netherlands  Dutch Pravastatin Trial	Pravastatin	205*	8 to 18 (start of RCT) 18 to 30 (end of followup)	2 years (10 years followup)	AEs and reasons for discontinuation assessed by questionnaire. Physical exam and blood sample taken at 10 year followup	3 subjects discontinued treatment due to side effects (GI, muscle/joint pain, headache). Over 10 years, 55 side effects reported by 40 subjects (19.5%), including muscle complaints (n=19), GI symptoms (n=14), fatigue (n=9), headache (n=4), skin reaction (n=4), and other (n=5). <sup>§</sup> No reports of rhabdomyolysis.	No reports of elevated liver enzymes or other major lab Aes.
Braamskamp 2015b Good Netherlands  Dutch Pravastatin Trial	Pravastatin	88	8 to 18	2 years (10 years followup)	Testosterone, estradiol, LH, FSH, and DHEAS	No reports of irregular menstrual cycle, hyperandrogenism, or involuntary childlessness.	Compared with unaffected siblings, DHEAS was significantly lower in participants with FH (though still within normal range). No effects on testosterone, estradiol, LH, or FSH concentrations.

**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Carreau 2011 Fair France	Pravastatin	185	4 to 17	2 years + 2 months (mean duration)	Growth, sexual development, CK, AST, ALT. AEs assessed by review of medical files	24 subjects (13%) reported AEs, including muscle pain that resolved after changing statins (n=4), muscle pain not attributed to treatment (n=3), musculoskeletal pain (n=12), and headache that resolved spontaneously (n=1). No reports of alopecia or problems related to growth or sexual development.	Asymptomatic CK elevation (n=8) and pain with moderate CK elevation that resolved without changing treatment (n=2). No effects on AST or ALT.
Stein 1999 Good U.S., Finland	Lovastatin	132	10 to 17	48 weeks	Growth, sexual development, ALT, AST, CK, urinalysis, routine hematology, blood coagulation, thyroid function, blood nutrients, cortisol, DHEAS, FSH, LH, testosterone	No effect on growth or sexual development. AEs reported by 70.1% of subjects in treatment group and 73.8% in placebo group. Most common AEs in treatment group included respiratory tract infection (47.8%), abdominal pain (10.4%), ENT infection (10.4%), skin disease (9.0%), and gastroenteritis (7.5%). No significant difference between groups for any clinical AEs.	No effects on AST level; ALT level increased in placebo and treatment groups (no significant difference between groups); transient CK elevations in response to exercise (n=3 in lovastatin group, n=1 in placebo group); DHEAS increased (median increase 18% in treatment group, 5% in placebo group; p=0.03).
Clauss 2005 Good U.S.	Lovastatin	54 girls	11 to 18	24 weeks	ALT, AST, CK, creatinine, glucose, β-human chorionic gonadotrophin, hematology, urinalysis, sexual development, DHEAS, FSH, LH	No patients discontinued treatment due to AEs. No clinically meaningful differences between treatment groups in incidence of treatment-related AEs. Treatment-related AEs in lovastatin group included abdominal pain (n=2), diarrhea (n=1), nausea (n=1), and headache (n=1). Blood pressure significantly lower in placebo group (p<0.05). No effects on growth or menstrual cycle length. No reports of myopathy or rhabdomyolysis.	Transient decreased hematocrit and hemoglobin (n=1); LH levels slightly decreased in placebo group (p<0.05, difference not clinically meaningful). No effect on ALT, AST, CK, DHEAS, FSH, cortisol, or estradiol.

**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
de Jongh 2002a Good International multicenter	Simvastatin	173	10 to 17	RCT: 24 weeks Extension: 24 weeks	Growth, sexual development, ALT, AST, CK, cortisol, DHEAS, estradiol, testosterone, LH, FSH, human chorionic gonadatropin	No statistically significant differences between placebo and simvastatin groups in period 1 or 2. Clinical AEs in simvastatin group included: abdominal pain (n=3), chest pain (n=1), flatulence (n=1), myalgia (n=2), headache (n=4), sleep disorder (n=1), weight gain (n=1), and pruritus (n=1). No effect on growth or cortisol levels. No serious clinical AEs reported.	No statistically significant differences between placebo and simvastatin groups in period 1 or 2. Lab AEs in simvastatin group included: increased ALT (n=3), AST (n=3), and CK (n=1) levels. No serious lab AEs reported; no participants discontinued treatment due to AE. DHEAS levels decreased (period 1) or remained stable (period 2) in the simvastatin group compared to slight increases (periods 1 and 2) in placebo group.
de Jongh 2002b Fair Netherlands	Simvastatin	50	9 to 18	28 weeks	Growth, blood pressure, ALT, AST, CK	No effects on BMI and blood pressure. No clinical AEs reported.	No significant effects on ALT, AST, and CK levels.
McCrindle 2003 Good U.S., Canada, Europe, South Africa	Atorvastatin	187	10 to 17	RCT: 26 weeks Open label: 26 weeks	Blood pressure, physical exam, hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, AST, ALT, CK, alkaline phosphatase, blood urea nitrogen, creatinine, uric acid, albumin, total protein, glucose	No effect on sexual development. Most AEs were mild or moderate; no statistically significant differences between atorvastatin and placebo group for any clinical AEs. Clinical AEs in atorvastatin group included abdominal pain (n=6), accidental injury (n=13), fever (n=2), flu syndrome (n=9), headache (n=13), infection (n=27), and pharyngitis (n=9).	Increase in AST levels (n=2) and ALT levels (n=1) in atorvastatin group. No participants withdrew or stopped medications as a result of increased transaminase levels.

**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Gandelman 2011 Fair Greece, Norway, and Canada	Atorvastatin	39	6 to 17	8 weeks	Growth, sexual development, hematology, biochemical tests, AST, ALT, CK, urinalysis, ECG, blood pressure, and pulse	No difference in safety or tolerability between younger and older cohorts. No deaths, serious AEs, or premature discontinuations. Clinical AEs in both cohorts combined included nasopharyngitis (n=3), viral upper respiratory tract infection (n=3), headache (n=3), gastroenteritis (n=2), abdominal pain (n=1), nausea (n=1), toothache (n=1), vomiting (n=1), and other**	No difference in safety or tolerability between younger and older cohorts. Increased ALT (n=2), with one of the participants returning to normal ALT during study period. Increased blood creatinine (n=1) attributed to reduced water intake.
Avis 2010 Good Europe and North America	Rosuvastatin	176	10 to 17	RCT: 12 weeks Open label: 40 weeks	Growth, sexual development, AE reports, blood count, albumin, total protein, liver enzymes, bilirubin, CK, blood urea nitrogen, serum creatinine, calcium, fasting glucose, TSH, urinalysis, phosphorus, potassium sodium, glycosylated hemoglobin	No effect on growth or sexual development. During RCT period, clinical AEs in rosuvastatin groups included headache (n=22), nasopharyngitis (n=17), influenza (n=4), myalgia (n=4), and nausea (n=4). During open-label period, clinical AEs in rosuvastatin groups included vesicular rash that progressed to cellulitis (n=1) and myalgia (n=5). Overall, safety profile of rosuvastatin was similar to that of placebo.	During RCT period, lab AEs in rosuvastatin groups included transaminase (n=3) and CK elevation (n=4). Changes in ALT, AST, and CK were similar among groups. During open-label period, lab AEs in rosuvastatin groups included transaminase (n=1) and CK elevation (n=4). For all patients, transaminase and CK elevations normalized while continuing treatment or remained normal after resuming treatment. No clinically meaningful renal abnormalities observed.
Avis 2011 Good Netherlands	Rosuvastatin	29	10 to 17	RCT: 12 weeks Open label: 40 weeks	PBMC CoQ10, plasma CoQ10, ATP synthesis	Not reported	Subjects taking rosuvastatin experienced a significant decrease in both PBMC CoQ10 and plasma CoQ10 concentrations; however, the changes are of unclear clinical significance. No change in ATP synthesis.

**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Braamskamp 2015c Good Netherlands, Canada, Belgium, Norway, U.S.  CHARON	Rosuvastatin	198	6 to 17	2 years	Growth, sexual development, AE reports, AST, ALT, urine protein: creatine ratio, CK, ECG	No effect on growth or sexual development. Most commonly reported clinical AEs possibly related to treatment included GI disorders (8%), myalgia (2%), and skin disorders (1%). 3 patients experienced treatment-related AEs that led to discontinuation (nausea, migraine, paraesthesia). No cases of myopathy or rhabdomyolysis and no deaths. No abnormal ECG or vital signs.	No clinically important changes in hematology, clinical chemistry, or hepatic, skeletal muscle, and renal biochemistries. Lab AEs included elevated CK levels without associated muscle symptoms (n=3), elevated creatinine (n=1), and elevated urine protein:creatinine ratio (n=7, 5 of whom returned to normal levels by study completion). No patients had abnormal eGFR.
Sinzinger 2004 Fair Austria	Various statins	6 <sup>††</sup>	13 to 20 <sup>††</sup>	8 years	Blood samples for CK and liver enzymes (GGT, AST, ALT) drawn at monitoring intervals	On average, subjects reported muscle pain in 80% of periods of statin therapy (mean time of onset was 6.2 days) <sup>††</sup>	Elevated CK level in 2 subjects; no increase in liver enzyme levels. <sup>††</sup>
<b>Nonstatins</b>							
Tonstad 1996b Good Norway	Colestipol	66	10 to 16	RCT: 8 weeks Open label: 52 weeks	Physical exam, growth, sexual development, nutrient levels	No effects on growth or sexual development; in colestipol group, subjects reported GI side effects (n=8), including constipation, nausea, dyspepsia, flatulence, decreased appetite, and abdominal pain.	After 8 weeks, colestipol group experienced reduced serum folate, serum vitamin E, and carotenoid levels (significant compared with placebo). After 1 year, vitamin D levels decreased more in subjects who took ≥80% of dose compared with subjects taking <80% of dose.
Tonstad 1996a Fair Norway	Cholestyramine	72	6 to 11	52 weeks	Physical exam, growth, sexual development, nutrient levels, hemoglobin, AST, ALT, TSH, free thyroxine, ferritin, erythrocyte	No effects on growth or sexual development; clinical AEs reported in cholestyramine group include intestinal obstruction caused by adhesions (n=1), nausea (n=2), loose stools (n=2), and abdominal pain (n=2). Unpalatability, headaches, and vomiting were reasons for withdrawals.	No effects on hemoglobin or liver enzyme levels. Compared with placebo group, cholestyramine group experienced significant decrease in vitamin D (among subjects not taking multivitamin) and significant increase in total homocysteine (which was negatively correlated with serum folate at baseline and 1 year).

**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Stein 2010 Good International multicenter	Colesevelam	194	10 to 17	RCT: 8 weeks Open label: 18 weeks	Vital signs, physical exam, laboratory safety, chemistry, and hematologic studies, urinalysis, LH, TSH, FSH, testosterone, estradiol, fat- soluble vitamins, clotting factors, hsCRP	No effects on growth or sexual development. During RCT period, distribution of AEs was similar in all groups. Most common drug-related AE in colesevelam groups was GI symptoms (n=9) (including diarrhea, nausea, vomiting, and abdominal pain). During open-label period, reported AEs included headaches (n=14), nasopharyngitis (n=10), and upper respiratory infection (n=9).	No clinically meaningful changes in safety lab measurements, hormones, vitamins, or clotting factors.
van der Graaf 2008 Good Netherlands, U.S., Canada	Ezetimibe + simvastatin	248	10 to 17	RCT: 33 weeks Open label: 20 weeks	Physical exam, ECG, growth, sexual development, menstrual periods, AE reports, hormone assessments, thyroid function tests, blood chemistries, hematology, urinalysis	No effects on growth or sexual development. Clinical AEs in ezetimibe + simvastatin groups include nasopharyngitis (n=27), headaches (n=16), myalgia (n=7), diarrhea (n=9), nausea (n=8), abdominal pain (n=6), and pharyngolaryngeal pain (n=6). AEs leading to discontinuation were myalgia (n=2), nausea (n=1), and muscle spasms (n=1).	CK elevation 10 times or greater than upper limit of normal without associated muscle symptoms (n=2); transaminase elevations at least 3 times upper limit of normal (n=6); no effects on steroid hormones. AEs leading to discontinuation were increased ALT (n=2) and increased CK (n=2).
Kusters 2015 Good 9 countries	Ezetimibe	138 <sup>†</sup>	6 to 10	12 weeks	Physical exam, ECG, ALT, AST, CK, nutrient levels, abnormal liver function, rhabdomyolysis or myopathy, hypersensitivity, cholecystitis/ cholelithiasis, pancreatitis	No notable differences between ezetimibe and placebo groups for any AEs, drug-related AEs, serious AEs, or AEs leading to discontinuation. No serious drug-related AEs reported. Minor AEs in ezetimibe group include headache (n=1), proteinuria (n=1), prurigo (n=1), and rash (n=1).	No notable differences between ezetimibe and placebo groups for any hematology, blood chemistry, or urinalysis measures assessed. Lab AEs in ezetimibe group included elevated ALT more than 3 times the upper limit of normal (n=1).

\*N=205 participants included for tolerability analysis. N=188 included for adherence analysis.

<sup>†</sup>Age range of participants with FH at baseline. Age ranges for participants with FH and their siblings not reported at 10 years.

<sup>‡</sup>13 nonFH participants (9 in treatment group, 4 in placebo group) were not analyzed separately.

**Table 7. Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs**

§Other = frequent urination (x2), weight reduction, hair loss, and forgetfulness.

\*\*Other (n=1 each) includes pain, bronchopneumonia, ear infection, gastritis viral, influenza, lower respiratory tract bacterial infection, tonsillitis, viral rhinitis, hand fracture, arthralgia, musculoskeletal pain, pain in extremity, asthma, rhinitis allergic, and urticarial.

††Sinzinger 2004 study included 22 participants ages 13 to 35 years. In this table, we report data from a pediatric subgroup of this population (n=6; age range, 13–20).

**Abbreviations:** FH=familial hypercholesterolemia, TSH= thyroid-stimulating hormone, ACTH=adrenocorticotrophic hormone, ALT=alanine transaminase, AST=aspartate transaminase, CK=creatine kinase, PC=pravastatin + colestipol group, CO=colestipol only group, AE=adverse effects, DHEAS=dehydroepiandrosterone sulfate, GI=gastrointestinal, FSH=follicle-stimulating hormone, LH=luteinizing hormone, ENT=ear, nose, and throat, GGT=gamma-glutamyl transpeptidase, hsCRP=high-sensitivity C-reactive protein, ECG=electrocardiography, eGFR=estimated glomerular filtration rate, CoQ10=coenzyme Q10, ATP=adenosine triphosphate.

**Table 8. Laboratory Harms Reported in Studies of Medication in Children and Adolescents With Familial Hypercholesterolemia (Statins, Bile-Sequestering Agents, and Other Drugs)**

Author, Year	Exposure	N	Abnormal CK	Transaminase elevation*	Abnormal ALT	Abnormal AST	Liver function labs	Endocrine reproductive labs	Miscellaneous labs
<b>Pravastatin</b>									
Knipscheer, 1996 <sup>68</sup>	Pravastatin	72	+	+	+	+	+	-	NR
McCrindle, 2002 <sup>71</sup>	Pravastatin + Colestipol	36	NR	NR	NR	NR	NR	NR	NR
Hedman, 2003 <sup>68</sup>	Pravastatin	20	-	NR	-	-	NR	NR	NR
Wiegman, 2004 <sup>66</sup>	Pravastatin	214	-	NR	-	-	NR	-	NR
Rodenburg, 2007 <sup>76</sup>	Pravastatin	186	+	NR	NR	NR	NR	+	NR
Kusters, 2014 <sup>72</sup>	Pravastatin	194	NR	NR	NR	NR	NR	NR	-
Braamskamp, 2015a <sup>78</sup>	Pravastatin	205†	-	-	-	-	-	NR	NR
Braamskamp, 2015b <sup>77</sup>	Pravastatin	88	NR	NR	NR	NR	NR	-	NR
Carreau, 2011 <sup>73</sup>	Pravastatin	185	+	NR	NR	NR	NR	NR	NR
<b>Lovastatin</b>									
Stein, 1999 <sup>61</sup>	Lovastatin	132	NR	NR	NR	NR	NR	NR	NR
Clauss, 2005 <sup>60</sup>	Lovastatin	54	-	NR	-	-	NR	-	-
<b>Simvastatin</b>									
De Jongh, 2002a <sup>62</sup>	Simvastatin	173	+	+	+	-	+	-	-
De Jongh, 2002b <sup>70</sup>	Simvastatin	50	-	NR	-	-	NR	NR	NR
<b>Atorvastatin</b>									
McCrindle, 2003 <sup>63</sup>	Atorvastatin	187	NR	+	NR	+	+	NR	NR
Gandelman, 2011 <sup>75</sup>	Atorvastatin	39	NR	+	+	NR	+	NR	NR
<b>Rosuvastatin</b>									
Avis, 2010 <sup>64</sup>	Rosuvastatin	176	+	+	NR	NR	+	NR	NR
Avis, 2011 <sup>74</sup>	Rosuvastatin	29	NR	NR	NR	NR	NR	NR	+
Braamskamp, 2015c <sup>79</sup>	Rosuvastatin	198	+	-	-	-	-	-	+
<b>Various statins</b>									
Sinzinger, 2004 <sup>69</sup>	Various statins	6‡	+	NR	NR	NR	-	NR	NR
<b>Bile-Sequestering Agents</b>									
Tonstad, 1996b <sup>56</sup>	Colestipol	66	NR	NR	NR	NR	NR	NR	NR
Tonstad, 1996a <sup>55</sup>	Cholestyramine	72	NR	NR	NR	NR	NR	-	-
Stein, 2010 <sup>65</sup>	Colesevelam	194	+	NR	NR	NR	NR	NR	NR
<b>Other</b>									
van der Graaf, 2008 <sup>58</sup>	Ezetimibe + simvastatin	248	+	+	+	NR	+	NR	NR
Kusters, 2015 <sup>59</sup>	Ezetimibe	138	-	NR	+	-	+	NR	-

\*Transaminase elevation was considered reported if the author specifically mentioned transaminase elevation.

†N=205 participants included in tolerability analysis. N=188 participants included in adherence analysis.

‡Sinzinger 2004 study included 22 participants ages 13–35. In this table, we report data from a pediatric subgroup of this population (n=6; age range, 13–20).

**Abbreviations:** FH=familial hypercholesterolemia, CK=creatinine kinase, ALT=alanine transaminase, AST= aspartate transaminase, NR=not reported.



**Table 9. Clinical Harms Reported in Studies of Medications in Children and Adolescents With Familial Hypercholesterolemia (Statins, Bile-Sequestering Agents, and Other Drugs)**

Author, Year	N	Loose stool/ diarrhea	GI	Neuro- psychiatric	ENT	Respiratory	Dermatologic	Musculo- skeletal	Endocrine	Immunologic	Systemic	Infection NOS	Pain NOS	Misc
<b>Pravastatin</b>														
Knipscheer, 1996 <sup>52</sup>	72	NR	+	+	+	NR	+	NR	NR	NR	NR	NR	NR	NR
McCrindle, 2002 <sup>71*</sup>	36	NR	+	+	NR	NR	NR	+	-	NR	NR	NR	NR	NR
Hedman, 2003 <sup>68</sup>	20	+	NR	+	NR	NR	NR	+	NR	NR	NR	NR	+	NR
Wiegman, 2004 <sup>66</sup>	214	NR	NR	-	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
Rodenburg, 2007 <sup>76</sup>	186	NR	NR	NR	NR	NR	NR	+	-	NR	NR	NR	NR	NR
Kusters, 2014 <sup>72</sup>	194	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Braamskamp, 2015a <sup>78</sup>	205 <sup>†</sup>	NR	+	+	NR	NR	+	+	NR	NR	NR	NR	NR	+
Braamskamp, 2015b <sup>77</sup>	88	NR	NR	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
Carreau, 2011 <sup>73</sup>	185	NR	NR	+	NR	NR	NR	+	-	NR	NR	NR	+	NR
<b>Lovastatin</b>														
Stein, 1999 <sup>61</sup>	132	+	+	NR	+	+	+	+	-	+	NR	NR	NR	NR
Clauss, 2005 <sup>60</sup>	54	+	+	+	+	+	NR	NR	-	NR	NR	NR	NR	NR
<b>Simvastatin</b>														
De Jongh, 2002a <sup>62</sup>	173	NR	+	+	NR	NR	+	+	-	NR	+	NR	+	NR
De Jongh, 2002b <sup>70</sup>	50	NR	NR	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
<b>Atorvastatin</b>														
McCrindle, 2003 <sup>63</sup>	187	NR	NR	+	+	+	NR	NR	-	NR	+	+	NR	+
Gandelman, 2011 <sup>75</sup>	39	NR	+	+	+	+	NR	NR	NR	NR	NR	NR	NR	NR
<b>Rosuvastatin</b>														
Avis, 2010 <sup>64</sup>	176	NR	+	+	+	+	+	+	-	NR	NR	NR	NR	NR
Avis, 2011 <sup>74</sup>	29	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Braamskamp, 2015c <sup>79</sup>	198	NR	+	+	+	+	+	+	-	NR	+	+	NR	NR
<b>Various statins</b>														
Sinzinger, 2004 <sup>69</sup>	6 <sup>§</sup>	NR	NR	NR	NR	NR	NR	+	NR	NR	NR	NR	NR	NR

**Table 9. Clinical Harms Reported in Studies of Medications in Children and Adolescents With Familial Hypercholesterolemia (Statins, Bile-Sequestering Agents, and Other Drugs)**

Author, Year	N	Loose stool/ diarrhea	GI	Neuro- psychiatric	ENT	Respiratory	Dermatologic	Musculo- skeletal	Endocrine	Immunologic	Systemic	Infection NOS	Pain NOS	Misc
<b>BSA (colestipol)</b>														
Tonstad, 1996b <sup>56</sup>	66	+	+	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
<b>BSA (cholestyramine)</b>														
Tonstad, 1996a <sup>55</sup>	72	+	+	+	NR	NR	NR	NR	-	NR	NR	NR	+	NR
<b>BSA (colesevelam)</b>														
Stein, 2010 <sup>65</sup>	194	+	+	+	+	+	NR	NR	-	NR	+	NR	NR	NR
<b>Ezetimibe</b>														
van der Graaf, 2008 <sup>58‡</sup>	248	+	+	+	+	+	+	+	-	NR	NR	NR	NR	-
Kusters, 2015 <sup>59</sup>	138	+	+	+	+	+	+	-	NR	+	+	+	NR	NR

\*Study assessed pravastatin + colestipol vs. colestipol only.

†N=205 participants included in tolerability analysis. N=188 participants included in adherence analysis.

‡Study assessed ezetimibe + simvastatin vs. placebo + simvastatin.

§Sinzinger 2004 study included 22 participants ages 13–35. In this table, we report data from a pediatric subgroup of this population (n=6; age range, 13–20).

**Abbreviations:** FH=familial hypercholesterolemia, BSAs=bile-sequestering agents, GI=gastrointestinal, ENT=ear, nose, and throat, NOS=not otherwise specified, Misc=miscellaneous.

**Table 10. Overall Summary of Evidence by Key Question**

Key Question	Studies (k) Participants (n)	Overall quality	Consistency	Applicability	Summary of findings
<b>Screening</b>					
KQ1. Health outcomes in adulthood KQ2. Intermediate outcomes	0	-	-	-	No evidence on the impact of either selective or universal screening for FH on adult health outcomes or intermediate outcomes in childhood and adolescence.
KQ3. Diagnostic yield of screening for FH	k=2 n=83,241	Fair	N/A (different screening tests, different populations [U.S. and Denmark])	School-based setting is relevant to primary care. Limited applicability of findings from non-US population.	Using two different tests, the diagnostic yield of screening for FH ranged from 0.13% to 0.48%.
KQ4. Adverse effects of screening	0	-	-	-	No evidence on harms of screening.
<b>Treatment</b>					
KQ5. Treatment and adult health outcomes	0	-	-	-	No evidence on effect of treatment in childhood or adolescence on adult health outcomes.
KQ6. Effect of treatment on intermediate outcomes	Statins: k=8 n=1,071  Nonstatins: k=5 n=718	Good/fair: 3 studies had <80% retention.	Consistent treatment effects on LDL-C and TC across 5 different statins. Nonstatins (3 bile-sequestering agents and a cholesterol absorption inhibitor) had more modest effects.	Studies applicable to youth with FH cared for in U.S. primary care settings. Participants were recruited from tertiary clinics and were not screen-identified.	Statins: All trials reported statistically significant LDL-C decreases, with most effect sizes ranging from 20% to 40%, compared to negligible changes with placebo. Dose response was seen in 2 studies. All 8 studies that evaluated effect on TC found decreases that were smaller than for LDL-C and consistent across studies. 1 trial reported decrease in CIMT. Nonstatins: All 5 trials (including bile-sequestering agents and ezetimibe) reported decreases in LDL-C ranging from 10% to 27%.
KQ7. Harms of treatment	k=18 n=2,210*	Fair: Most studies were <2 years duration.	Consistent findings of harms within class: statins and bile-sequestering agents	Good. Most studies were applicable to U.S. primary care setting.	Statins were generally well-tolerated; adverse effects were transient. There was no reported impact on growth or maturation. 1 trial showed lower DHEAS in children with FH treated with pravastatin compared to unaffected siblings. Bile-sequestering agents were commonly associated with gastrointestinal symptoms and poor palatability.
<b>Outcomes</b>					
KQ8. Association of intermediate outcomes and adult health outcomes	0	-	-	-	No evidence on the association between intermediate outcomes in childhood or adolescence and adult health outcomes in persons with FH.

\*Studies included for KQ7 involved 2,210 patients, 2,197 of whom had FH.

**Abbreviations:** KQ=key question, FH=familial hypercholesterolemia, N/A=not applicable, TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, CIMT=carotid intima-media thickness, DHEAS=dehydroepiandrosterone sulfate.

## Search Strategy

### Sources searched:

Cochrane Central Register of Controlled Clinical Trials, via Wiley

Medline, via Ovid

PubMed, publisher-supplied

### Key:

/ = MeSH subject heading

\$ = truncation

ti = word in title

ab = word in abstract

adj# = adjacent within x number of words

pt = publication type

\* = truncation

ae = adverse effects

ci = chemically induced

de=drug effects

mo=mortality

nm = name of substance

### Cochrane Central Register of Controlled Clinical Trials

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

## Appendix A. Detailed Methods

### MEDLINE

#### Dyslipidemia screening, screening harms

Database: Ovid MEDLINE(R) without Revisions <1996 to June Week 1 2015>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <June 2, 2015>, Ovid MEDLINE(R)

Daily Update <June 2, 2015>

Search Strategy:

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

## Appendix A. Detailed Methods

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

### Dx yield/accuracy

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

### Search Strategy:

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

## Appendix A. Detailed Methods

24 or/1-23  
25 Cholesterol/bl  
26 Triglycerides/bl  
27 Lipoproteins/bl  
28 Cholesterol, HDL/  
29 Cholesterol, LDL/  
30 Apolipoprotein B-100/  
31 Apolipoprotein B 100.ti,ab.  
32 apob 100.ti,ab.  
33 apo b 100.ti,ab.  
34 ((high or elevated or abnormal or aberr\$) adj3 (cholesterol or lipid\$ or LDL\$)).ti,ab.  
35 ((low or decrease\$ or deficien\$ or abnormal or aberr\$) adj3 HDL\$).ti,ab.  
36 ((cholesterol or lipid\$ or lipoprotein\$ or LDL\$ or HDL\$) adj3 (detect\$ or measur\$ or check\$ or assess\$ or analyz\$ or analys\$ or test\$ or panel\$ or profile\$)).ti,ab.  
37 (fasting adj (lipid\$ or lipoprotein\$ or cholesterol)).ti,ab.  
38 (non-fasting adj (lipid\$ or lipoprotein\$ or cholesterol)).ti,ab.  
39 or/25-38  
40 "Sensitivity and Specificity"/  
41 "Predictive Value of Tests"/  
42 ROC Curve/  
43 False Negative Reactions/  
44 False Positive Reactions/  
45 Diagnostic Errors/  
46 "Reproducibility of Results"/  
47 Reference Values/  
48 Reference Standards/  
49 Observer Variation/  
50 Receiver operat\$.ti,ab.  
51 ROC curve\$.ti,ab.  
52 sensitivit\$.ti,ab.  
53 specificit\$.ti,ab.  
54 predictive value.ti,ab.  
55 accuracy.ti,ab.  
56 false positive\$.ti,ab.  
57 false negative\$.ti,ab.  
58 miss rate\$.ti,ab.  
59 error rate\$.ti,ab.  
60 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or  
56 or 57 or 58 or 59  
61 (24 or 39) and 60  
62 adolescent/ or child/ or young adult/  
63 61 and 62  
64 (child\$ or teen or teens or teenage\$ or adolescen\$ or youth or youths or young people or  
pediatric\$ or paediatric\$).ti,ab.  
65 61 and 64  
66 limit 65 to ("in data review" or in process or "pubmed not medline")

## Appendix A. Detailed Methods

67 63 or 66

68 limit 67 to (english language and yr="2007 -Current")

69 remove duplicates from 68

### Drug Tx Harms

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

Search Strategy:

- 
- 1 Hyperlipidemias/
  - 2 Dyslipidemias/
  - 3 Hypercholesterolemia/
  - 4 Lipid Metabolism Disorders/
  - 5 Hyperlipoproteinemias/
  - 6 Hypertriglyceridemia/
  - 7 Hyperlipoproteinemia Type II/
  - 8 Hyperlipidemia, Familial Combined/
  - 9 Hypobetalipoproteinemias/
  - 10 Abetalipoproteinemia/
  - 11 hyperlipid?emia\$.ti,ab.
  - 12 dyslipid?emia\$.ti,ab.
  - 13 hypercholesterol?emia\$.ti,ab.
  - 14 hyperlipoprotein?emia\$.ti,ab.
  - 15 hypertriglycerid?emia\$.ti,ab.
  - 16 dysbetalipoprotein?emia\$.ti,ab.
  - 17 familial hypercholesterol\$emi\*.ti,ab.
  - 18 familial hyperlipid?emi\*.ti,ab.
  - 19 essential hypercholesterol?emi\*.ti,ab.
  - 20 (familial adj3 apolipoprotein).ti,ab.
  - 21 heterozygous fh.ti,ab.
  - 22 homozygous fh.ti,ab.
  - 23 lipid disorder\$.ti,ab.
  - 24 ((high or elevated or abnormal or aberr\$) adj3 (cholesterol or lipid\$ or LDL\$)).ti,ab.
  - 25 ((low or decrease\$ or deficien\$ or abnormal or aberr\$) adj3 HDL\$).ti,ab.
  - 26 or/1-25
  - 27 hypolipidemic agents/ or bezafibrate/ or buroxamine/ or clofenapate/ or clofibrate/ or clofibric acid/ or colestipol/ or fenofibrate/ or gemfibrozil/ or halofenate/ or meglutol/ or nafenopin/ or niacin/ or niceritrol/ or pyridinolcarbamate/ or simvastatin/ or triparanol/
  - 28 anticholesteremic agents/ or azacosterol/ or chitosan/ or cholestyramine resin/ or clofibrate/ or clofibric acid/ or lovastatin/ or meglutol/ or pravastatin/ or probucol/ or simvastatin/ or "trans-1,4-bis(2-chlorobenzaminomethyl)cyclohexane dihydrochloride"/
  - 29 hydroxymethylglutaryl-coa reductase inhibitors/ or lovastatin/
  - 30 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor\$.ti,ab.
  - 31 hydroxymethylglutaryl coa reductase inhibitor\$.ti,ab.
  - 32 hydroxymethylglutaryl coa inhibitor\$.ti,ab.



## Appendix A. Detailed Methods

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

## Appendix A. Detailed Methods

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

### Drug and lifestyle treatment efficacy

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

Search Strategy:

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

## Appendix A. Detailed Methods

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

## Appendix A. Detailed Methods

59 portion size/  
60 Food habits/  
61 Diet Therapy/  
62 Soybean Proteins/  
63 Fatty Acids, Omega-3/  
64 Phytosterols/  
65 Dietary Fiber/  
66 Dietary Protein/  
67 Dietary Carbohydrates/  
68 Dietary Fats/  
69 diet\$.ti,ab.  
70 ((reduce\$ or reduction\$ or manipulat\$ or restrict\$) adj3 (fat\$ or carbohydrate\$ or cholesterol)).ti,ab.  
71 low fat.ti,ab.  
72 lowfat.ti,ab.  
73 fiber.ti,ab.  
74 omega 3 fatty acid\$.ti,ab.  
75 n 3 polyunsaturated fatty acid\$.ti,ab.  
76 n 3 fatty acid\$.ti,ab.  
77 n 3 pufa.ti,ab.  
78 soy\$ protein\$.ti,ab.  
79 plant stanol\$.ti,ab.  
80 esters.ti,ab.  
81 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80  
82 Exercise/  
83 Exercise therapy/  
84 Motor activity/  
85 Physical fitness/  
86 Plyometric Exercise/  
87 Physical Conditioning, Human/  
88 Running/  
89 Jogging/  
90 Swimming/  
91 Walking/  
92 Resistance training/  
93 (exercise or exercising or exercises).ti,ab.  
94 physical fitness.ti,ab.  
95 physical conditioning.ti,ab.  
96 (running or jog\$ or swim\$ or walk\$).ti,ab.  
97 (lifestyle\$ or life style\$).ti,ab.  
98 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97  
99 26 and (50 or 81 or 98)  
100 Hyperlipidemias/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention and Control, Therapy]  
101 Dyslipidemias/dh, dt, pc, th

## Appendix A. Detailed Methods

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

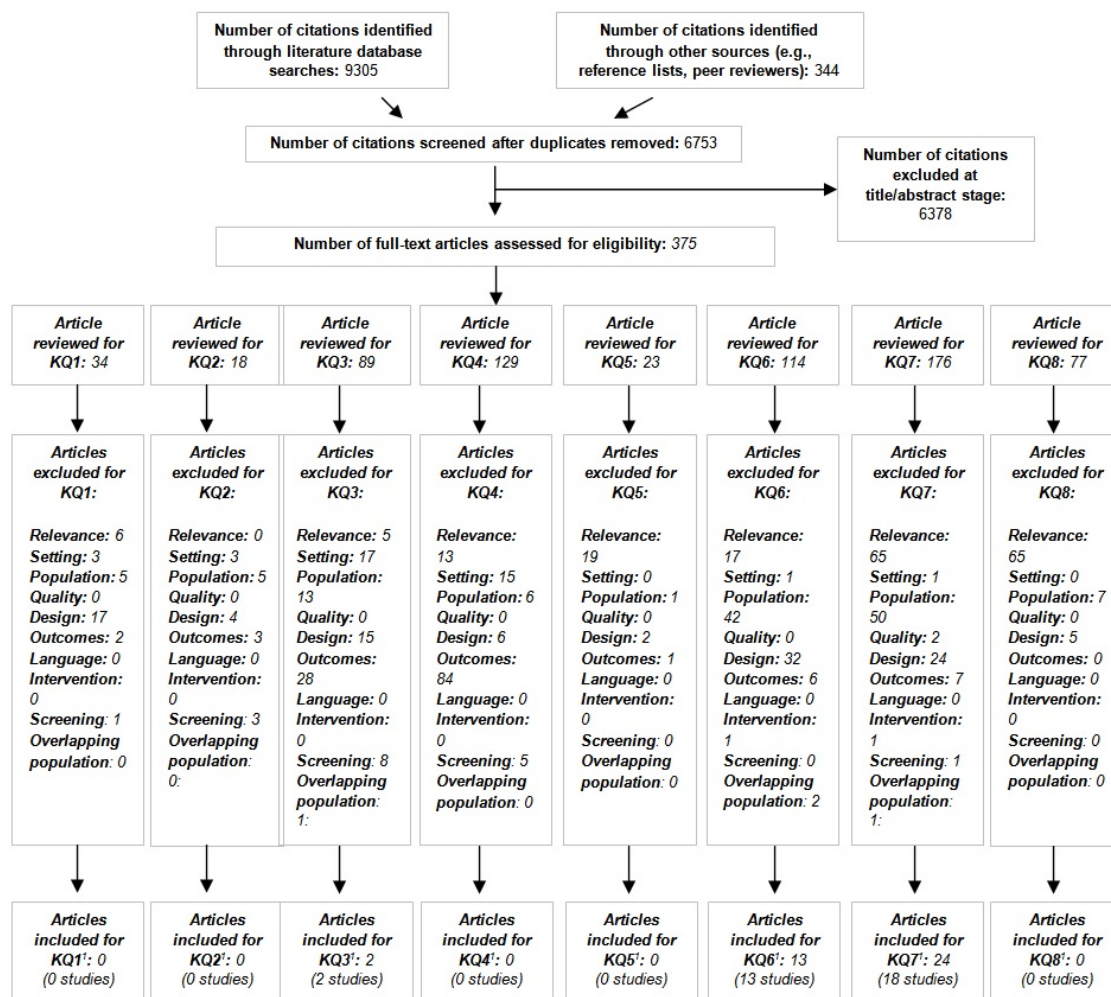
**PubMed** search strategy [publisher-supplied references only]

Search	Query
<u>#11</u>	Search #10 AND publisher[sb] Filters: Publication date from 2007/01/01 to 2015/06/02; English
<u>#10</u>	Search #8 AND #9
<u>#9</u>	Search child*[tiab] OR teen[tiab] OR teens[tiab] OR teenage*[tiab] OR adolescen*[tiab] OR youth[tiab] OR youths[tiab] OR "young people"[tiab] OR pediatric*[tiab] OR paediatric*[tiab]
<u>#8</u>	Search #1 or #2 or #3 or #4 or #5 or #6 or #7
<u>#7</u>	Search (fasting[tiab] or non fasting[tiab] OR nonfasting[tiab]) AND (lipid*[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab])
<u>#6</u>	Search (lipid[tiab] OR lipids[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab])

## Appendix A. Detailed Methods

Search	Query
	OR LDL*[tiab] OR HDL*[tiab]) AND (detect*[tiab] OR measur*[tiab] OR check*[tiab] OR assess*[tiab] OR analyz*[tiab] OR analys*[tiab] OR test*[tiab] OR panel*[tiab] OR profile*[tiab])
<u>#5</u>	Search (lipid[tiab] OR lipids[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab] OR LDL*[tiab] OR HDL*[tiab]) AND (low[tiab] OR high[tiab] OR elevated[tiab] OR abnormal[tiab] OR aberr*[tiab])
<u>#4</u>	Search lipid disorder*[tiab] OR lipid dysfunction*[tiab]
<u>#3</u>	Search familial[tiab] AND apolipoprotein[tiab]
<u>#2</u>	Search familial hypercholesterolemia*[tiab] OR familial hypercholesterolaemia*[tiab] OR familial hyperlipidemi*[tiab] OR familial hyperlipidaemi*[tiab] OR essential hypercholesterolemi*[tiab] OR essential hypercholesterolaemi*[tiab] OR heterozygous fh[tiab] OR homozygous fh[tiab]
<u>#1</u>	Search (hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR dyslipidemia*[tiab] OR dyslipidaemia*[tiab] OR hypercholesterolemia*[tiab] OR hypercholesterolaemia*[tiab] OR hyperlipoproteinemia*[tiab] OR hyperlipoproteinaemia*[tiab] OR hypertriglyceridemia*[tiab] OR hypertriglyceridaemia*[tiab] OR dysbetalipoproteinemia*[tiab] OR dysbetalipoproteinaemia*[tiab])

## Appendix A Figure 1. Literature Flow Diagram



<sup>1</sup> Number of articles that were not included in prior review: KQ1=0; KQ2=0; KQ3=2; KQ6=4; KQ7=12; KQ8=0

**Abbreviation:** KQ=key question.

**Appendix A Table 1. Inclusion and Exclusion Criteria**

	Included	Excluded
<b>Population</b>	<p><b>KQs 1–4:</b> Asymptomatic children and adolescents ages 0 to 20 years at time of screening</p> <p><b>KQs 5–7:</b> Children and adolescents ages 0 to 20 years at time of treatment initiation with a diagnosis of FH</p> <p><b>KQ 8:</b> Children and adolescents ages 0 to 20 years at beginning of study period with a diagnosis of FH</p>	<p><b>KQs 1–4:</b> Children and adolescents with any of the following:</p> <ul style="list-style-type: none"> <li>• Known dyslipidemia</li> <li>• Diagnosis associated with secondary dyslipidemia*</li> <li>• Established family history of FH</li> </ul> <p><b>KQs 5–7:</b> Children and adolescents with dyslipidemia not due to FH</p>
<b>Diseases</b>	<b>KQs 5–7:</b> FH	<p><b>KQs 5–7:</b></p> <ul style="list-style-type: none"> <li>• Monogenic dyslipidemia other than FH</li> <li>• Secondary dyslipidemia*</li> <li>• Multifactorial dyslipidemia</li> </ul>
<b>Screening interventions</b>	<p><b>KQs 1–4:</b></p> <ul style="list-style-type: none"> <li>• Lipid panel (fasting or nonfasting lipid measurement, total or LDL cholesterol alone or in combination with HDL cholesterol)</li> <li>• Comparison with no screening or usual care</li> <li>• Universal or selective screening strategy</li> </ul>	<p><b>KQs 1–4:</b></p> <ul style="list-style-type: none"> <li>• Genetic screening alone</li> <li>• Cascade screening</li> </ul>
<b>Treatments</b>	<p><b>KQs 5–7:</b></p> <ul style="list-style-type: none"> <li>• Lipid-lowering medications</li> <li>• Lifestyle modifications, including diet or exercise</li> </ul>	<p><b>KQs 5–7:</b></p> <ul style="list-style-type: none"> <li>• Apheresis</li> <li>• Revascularization</li> </ul>
<b>Outcomes</b>	<p><b>KQs 1, 5, 8:</b></p> <ul style="list-style-type: none"> <li>• MI</li> <li>• Ischemic stroke</li> </ul> <p><b>KQs 2, 6:</b></p> <ul style="list-style-type: none"> <li>• Lipid concentrations (total and LDL cholesterol)</li> <li>• Atherosclerosis markers (carotid intima-media thickness, calcium score, pathological findings)</li> </ul> <p><b>KQ 3:</b></p> <ul style="list-style-type: none"> <li>• Diagnostic yield (true positives/number screened)</li> <li>• Positive predictive value (true positives/true positives + false positives)</li> </ul> <p><b>KQ 4:</b> All harms (e.g., false-positive or false-negative results, psychosocial effects, overdiagnosis)</p> <p><b>KQ 7:</b> All harms from lipid-lowering medications (e.g., AEs, long-term safety, overtreatment)</p>	<p><b>KQs 1, 5, 8:</b></p> <ul style="list-style-type: none"> <li>• Diabetes</li> <li>• Metabolic syndrome</li> <li>• Hypothyroidism</li> <li>• Renal failure</li> <li>• Obstructive liver disease</li> <li>• Nephrotic syndrome</li> <li>• Lipodystrophy</li> </ul>
<b>Study design</b>	<p><b>KQs 1–3:</b> RCTs, CCTs, cohort studies, systematic reviews</p> <p><b>KQs 4, 7:</b> RCTs, CCTs, cohort studies, systematic reviews, observational studies, systematically selected case series</p> <p><b>KQs 5, 6:</b> RCTs, systematic reviews</p> <p><b>KQ 8:</b> RCTs, CCTs, cohort studies, systematic reviews, registry studies, long-term trial followup, high-quality case-control studies</p>	<p><b>All KQs:</b> Studies rated as poor quality</p> <p><b>KQs 1–3, 5, 6, 8:</b> Qualitative studies, case reports, cost-effectiveness studies</p> <p><b>KQs 4, 7:</b> None</p> <p><b>KQs 5, 6:</b> Cohort studies, plus all study designs excluded for KQ 1</p> <p><b>KQ 8:</b> All study designs excluded for KQ 1</p>
<b>Settings</b>	<ul style="list-style-type: none"> <li>• Publication date of 2007 to present</li> <li>• Conducted in countries with a Human Development Index score of <math>\geq 0.9</math>, as defined by the United Nations</li> </ul>	Settings not generalizable to primary care

**Abbreviations:** KQ=key question, LDL=low-density lipoprotein, HDL=high-density lipoprotein, MI=myocardial infarction, AE=adverse effects, RCT=randomized, controlled trial, CCT=controlled clinical trial; FH=familial hypercholesterolemia.



## Appendix A Table 1. Inclusion and Exclusion Criteria

**Additional definitions:** Secondary dyslipidemias: Renal (chronic renal disease, hemolytic uremic syndrome, nephrotic syndrome); Infectious (acute viral or bacterial infections, HIV, hepatitis); hepatic (obstructive liver disease, cholestasis, biliary cirrhosis, Alagille syndrome); inflammatory (systemic lupus erythematosus, juvenile rheumatoid arthritis); storage (glycogen storage disease, Gaucher's disease, cystine storage disease, Tay-Sachs, Niemann-Pick); other (Kawasaki disease, anorexia nervosa, cancer, previous solid organ transplantation, progeria, idiopathic hypercalcemia, Klinefelter, Werner's syndrome).

## Appendix A Table 2. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized, controlled trials (adapted from the USPSTF methods)*	<ul style="list-style-type: none"> <li>• Valid random assignment?</li> <li>• Was allocation concealed?</li> <li>• Was eligibility criteria specified?</li> <li>• Were groups similar at baseline?</li> <li>• Were measurements equal, valid and reliable?</li> <li>• Was there intervention fidelity?</li> <li>• Was there adequate adherence to the intervention?</li> <li>• Were outcome assessors blinded?</li> <li>• Was there acceptable followup?</li> <li>• Were the statistical methods acceptable?</li> <li>• Was the handling of missing data appropriate?</li> <li>• Was there evidence of selective reporting of outcomes?</li> <li>• Was the device calibration and/or maintenance reported?</li> </ul>

\*Source: U.S. Preventive Services Task Force Procedure Manual.

## Appendix B. Ongoing Studies

We identified one potentially relevant ongoing or recently completed RCT through four registries: ClinicalTrials.gov (<http://clinicaltrials.gov>), Current Controlled Trials (<http://www.controlled-trials.com>), Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>) and the World Health Organization's International Clinical Trials Registry Platform (<http://www.who.int/ictpr>). We restricted our searches to (heterozygous) familial hypercholesterolemia in children.

One RCT studied rapeseed oil and sunflower oil as treatments for FH in children. This study, "Effect of a Diet With Rapeseed Oil /Sunflower Oil on Lipoprotein in Children and Adolescents With Familial Hypercholesterolemia," was last updated on clinicaltrials.gov in June of 2009 (NCT00924274).<sup>1</sup> It is a randomized double-blind trial for the purpose of treatment. One group received rapeseed oil as a dietary supplement, and the active comparator group received sunflower oil. The current recruitment status of the study is unknown.

We identified one patient registry study currently recruiting participants as of February 27, 2015. This study is based in Montreal and is establishing an FH patient registry of children, adults, and seniors with FH. The primary outcome measure is the number of patients with FH. The secondary outcome measure is the prevalence of FH. The study began in November 2013. The estimated study completion date is November 2020.<sup>2</sup>

We identified a Russian cohort and registry of FH begun in January 2014 that has an estimated completion date of December 2026, and a primary outcome measure completion date of December 2016.<sup>3</sup>

One randomized double crossover study of a Mediterranean diet in children with FH or familial combined hyperlipidemia has completed. Results are not yet available.<sup>4</sup>

## References

1. Effect of a Diet With Rapeseed Oil/Sunflower Oil on Lipoprotein in Children and Adolescents With Familial Hypercholesterolemia. Bethesda (MD): National Library of Medicine (US) [2015 March 3]. <https://clinicaltrials.gov/ct2/show/NCT00924274>.
2. Familial Hypercholesterolemia Canada / Hypercholesterolemie Familiale Canada. Bethesda (MD): National Library of Medicine (US) [2015 March 3]. <https://clinicaltrials.gov/ct2/show/NCT02009345>.
3. Prospective Russian Study Evaluating the Extent of Underdiagnosed and Undertreated of Familial Hypercholesterolaemia in the Population. National Library of Medicine (US) [2015 March 3]. <https://clinicaltrials.gov/ct2/show/NCT02208869>.
4. Endothelial Assessment of Risk From Lipids in Youth: Mediterranean Diet. Bethesda (MD): National Library of Medicine (US) [2015 March 3]. <https://clinicaltrials.gov/ct2/show/NCT01308710>.

## Appendix C. Excluded Studies

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

\*The exclusion code E3 was not used.

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

- Two controversial recommendations: screening (and treating) children for cholesterol. *Child Health Alert*. 2008;26:1-2. PMID: 18953695. **KQ1E2**.
- American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89(3 Pt 2):525-84. PMID: 1538956. **KQ4E6**.
- American Academy of Pediatrics Committee on Nutrition American Academy of Pediatrics. Committee on Nutrition. Cholesterol in childhood. *Pediatrics*. 1998;101(1 Pt 1):141-7. PMID: 11345978. **KQ4E6**.
- Andersen GE, Brokhattingen K, Lous P. Familial hypobetalipoproteinemia in 9 children diagnosed as the result of cord blood screening for hypolipoproteinemia in 10,000 Danish newborns. *Arch Dis Child*. 1979;54(9): 691-4. PMID: 229774. **KQ4E6**.
- Andersen GE, Lous P, Friis-Hansen B. Screening for hyperlipoproteinemia in 10,000 Danish newborns. Follow-up studies in 522 children with elevated cord serum VLDL-LDL-cholesterol. *Acta Paediatr Scand*. 1979;68(4): 541-5. PMID: 223372. **KQ4E6**.
- Andersen GE, Nielsen HG. Neonatal screening for hyperlipoproteinemia. Methods for direct estimation of cord serum VLDL + LDL. *Clin Chim Acta*. 1976;66(1): 29-41. PMID: 177231. **KQ4E6**.
- Arambepola C, Farmer AJ, Perera R et al. Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Atherosclerosis*. 2007;195(2): 339-47. PMID: 17097660. **KQ6E13, KQ7E13**.
- Asgary S, Kelishadi R, Rafieian-Kopaei M et al. Investigation of the lipid-modifying and antiinflammatory effects of Cornus mas L. supplementation on dyslipidemic children and adolescents. *Pediatr Cardiol*. 2013;34(7): 1729-35. PMID: 23625305. **KQ6E5, KQ7E5**.
- AstraZeneca. A phase IIIb, efficacy, and safety study of rosuvastatin in children and adolescents 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH): a 12-week, double-blind, randomized, multicenter, placebo-controlled study with a 40-week, open-label, followup. 2011. NCT00355615. **KQ6E2, KQ7E2**.
- Averna M, Zaninelli A, Le Grazie C et al. Ezetimibe/simvastatin 10/20 mg versus simvastatin 40 mg in coronary heart disease patients. *J Clin Lipidol*. 2010;4(4): 272-8. PMID: 21122660. **KQ6E5, KQ7E5**.
- Avis HJ, Hargreaves IP, Ruiters JP et al. Rosuvastatin lowers coenzyme Q10 levels, but not mitochondrial adenosine triphosphate synthesis, in children with familial hypercholesterolemia. *J Pediatr*. 2011;158(3): 458-62. PMID: 20884007. **KQ5E13, KQ6E9, KQ7E6**.
- Avis HJ, Vissers MN, Stein EA et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2007;27(8): 1803-10. PMID: 17569881. **KQ6E13, KQ7E13**.
- Bachman RP, Schoen EJ, Stembridge A et al. Compliance with childhood cholesterol screening among members of a prepaid health plan. *Am J Dis Child*. 1993;147(4): 382-5. PMID: 8456792. **KQ4E6**.

## Appendix C. Excluded Studies

14. Backes JM, Gibson CA, Ruisinger JF et al. The high-dose rosuvastatin once weekly study (the HD-ROWS). *J Clin Lipidol*. 2012;6(4): 362-7. PMID: 22836073. **KQ6E5, KQ7E5.**
15. Baker SG, Joffe BI, Mendelsohn D et al. Treatment of homozygous familial hypercholesterolaemia with probucol. *S Afr Med J*. 1982;62(1): 7-11.. PMID: 7089781. **KQ7E13, KQ8E13.**
16. Ballantyne C, Gleim G, Liu N et al. Effects of coadministered extended-release niacin/laropiprant and simvastatin on lipoprotein subclasses in patients with dyslipidemia. *J Clin Lipidol*. 2012;6(3): 235-43. PMID: 22658147. **KQ6E5, KQ7E5.**
17. Bang OY, Saver JL, Liebeskind DS et al. Association of serum lipid indices with large artery atherosclerotic stroke. *Neurology*. 2008;70(11): 841-7. PMID: 18160673. **KQ8E5.**
18. Bangert SK, Eldridge PH, Peters TJ. Neonatal screening for familial hypercholesterolaemia by immunoturbidimetric assay of apolipoprotein B in dried blood spots. *Clin Chim Acta*. 1992;213(1-3):95-101. PMID: 1477991. **KQ4E6.**
19. Barra S, Cuomo V, Silvestri N et al. Lipoprotein(a) concentration does not differ between sexes in healthy offspring of patients with premature myocardial infarction. *J Cardiovasc Med (Hagerstown)*. 2011;12(7): 482-6. PMID: 21519277. **KQ2E7.**
20. Barter PJ, Ballantyne CM, Carmena R et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259(3): 247-58. PMID: 16476102. **KQ4E6.**
21. Bastida S, Sanchez-Muniz FJ, Cuena R et al. High density lipoprotein-cholesterol changes in children with high cholesterol levels at birth. *Eur J Pediatr*. 2002;161(2): 94-8. PMID: 11954759. **KQ4E6.**
22. Baumer JH, Shield JP. Hypercholesterolaemia in children guidelines review. *Arch Dis Child Educ Pract Ed*. 2009;94(3): 84-6. PMID: 19460897. **KQ8E2.**
23. Bazzano LA, Thompson AM, Tees MT et al. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2011;21(2): 94-103. PMID: 19939654. **KQ6E5, KQ7E5.**
24. Becker DJ, French B, Morris PB et al. Phytosterols, red yeast rice, and lifestyle changes instead of statins: a randomized, double-blinded, placebo-controlled trial. *Am Heart J*. 2013;166(1): 187-96. PMID: 23816039. **KQ6E5, KQ7E5.**
25. Becker DJ, Gordon RY, Morris PB et al. Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial. *Mayo Clin Proc*. 2008;83(7): 758-64. PMID: 18613992. **KQ6E5, KQ7E5.**
26. Becker M, Staab D, Von Bergman K. Long-term treatment of severe familial hypercholesterolemia in children: effect of sitosterol and bezafibrate. *Pediatrics*. 1992;89(1): 138-142. PMID: 1727999. **KQ7E13, KQ8E13.**
27. Beeso J, Wong N, Ayling R et al. Screening for hypercholesterolaemia in 10,000 neonates in a multi-ethnic population. *Eur J Pediatr*. 1999;158(10): 833-7. PMID: 10486088. **KQ4E6.**
28. Bell DA, Hooper AJ, Edwards G et al. Detecting familial hypercholesterolaemia in the community: impact of a telephone call from a chemical pathologist to the requesting general practitioner. *Atherosclerosis*. 2014;234(2): 469-72. PMID: 24814411. **KQ1E5, KQ3E5.**
29. Bell MM, Joseph S. Screening 1140 fifth graders for hypercholesterolemia: family history inadequate to predict results. *J Am Board Fam Pract*. 1990;3(4): 259-63. PMID: 2248092. **KQ4E6.**
30. Benlian P, Turquet A, Carrat F et al. Diagnosis scoring for clinical identification of children with heterozygous familial hypercholesterolemia. *J Pediatr Gastroenterol Nutr*. 2009;48(4): 456-63. PMID: 19330934. **KQ3E7, KQ4E7.**
31. Bergmann ML, Bergmann GG, Halpern R et al. Associated factors to total cholesterol: school based study in southern Brazil. *Arq Bras Cardiol*. 2011;97(1): 17-25. PMID: 21625818. **KQ3E4.**
32. Bistritzer T, Rosenzweig L, Barr J et al. Lipid profile with paternal history of coronary heart disease before age 40. *Arch Dis Child*. 1995;73(1): 62-5. PMID: 7639553. **KQ4E6.**
33. Blades BL, Dudman NP, Wilcken DE. Screening for familial hypercholesterolemia in 5000 neonates: a recall study. *Pediatr Res*. 1988;23(5): 500-4. PMID: 3387172. **KQ4E6.**

## Appendix C. Excluded Studies

34. Blazek M, Blaha M, Pecka M et al. Primary hemostasis in patients treated with LDL-apheresis for severe familial hypercholesterolemia: A prospective pilot trial using PFA-100 analysis to rationalize therapeutic LDL-apheresis procedure. *Hematology*. 2007;12(6): 571-6. PMID: 17852459. **KQ6E8, KQ7E8.**
35. Boulton TJ. The validity of screening for hypercholesterolaemia at different ages from 2 to 17 years. *Aust N Z J Med*. 1979;9(5): 542-6. PMID: 231425. **KQ4E6.**
36. Braamskamp MJ, Hutten BA, Wiegman A. Early initiation of statin treatment in children with familial hypercholesterolaemia. *Curr Opin Lipidol*. 2015;26(3): 236-9. PMID: 25943840. **KQ6E2, KQ7E2.**
37. Braamskamp MJ, Tsimikas S, Wiegman A et al. Statin therapy and secretory phospholipase A2 in children with heterozygous familial hypercholesterolemia. *Atherosclerosis*. 2013;229(2): 404-7. PMID: 23880195. **KQ6E9, KQ7E6.**
38. Braga MF, Grace MG, Lenis J et al. Efficacy and safety of ursodeoxycholic acid in primary, type IIa or IIb hypercholesterolemia: a multicenter, randomized, double-blind clinical trial. *Atherosclerosis*. 2009;203(2): 479-82. PMID: 18801487. **KQ6E5, KQ7E5.**
39. Brandao MP, Pimentel FL, Cardoso MF. Impact of academic exposure on health status of university students. *Rev Saude Publica*. 2011;45(1): 49-58. PMID: 21203695. **KQ3E5.**
40. Brewster TG, Waite DJ, Hudson GA. Quantitation of beta-lipoprotein in cord serum by rate nephelometric immunoassay: a potential screening test for familial hypercholesterolemia. *Clin Chem*. 1982;28(5): 1192-6. PMID: 7074903. **KQ4E6.**
41. Broekhuizen K, van Poppel MN, Koppes LL et al. A tailored lifestyle intervention to reduce the cardiovascular disease risk of individuals with Familial Hypercholesterolemia (FH): design of the PRO-FIT randomised controlled trial. *BMC Public Health*. 2010;10:69. PMID: 20156339. **KQ6E2, KQ7E2.**
42. Browne B, Vasquez S. Pediatric dyslipidemias: Prescription medication efficacy and safety. *J Clin Lipidol*. 2008;2(3): 189-201. PMID: 21291737. **KQ6E2, KQ5E13, KQ7E2.**
43. Brun LD, Gagne C, Coulombe P et al. Effects of dextrothyroxine on the pituitary-thyroid axis in hypercholesterolemic children and goitrous adults. *J Clin Endocrinol Metab*. 1980;51(6):1306-1310. PMID: 6777394. **KQ7E13, KQ8E13.**
44. Calonge N, Guirguis-Blake J. Screening for familial hypercholesterolaemia. *BMJ*. 2007;335(7620):573-4. PMID: 17884865. **KQ2E2, KQ1E2, KQ4E13, KQ3E2.**
45. Campagna F, Martino F, Bifulco M et al. Detection of familial hypercholesterolemia in a cohort of children with hypercholesterolemia: results of a family and DNA-based screening. *Atherosclerosis*. 2008;196(1): 356-64. PMID: 17196209. **KQ2E7.**
46. Cannioto Z, Tamburlini G, Marchetti F. Statins for children? A word of caution. *Eur J Clin Pharmacol*. 2009;65(2): 217-8. PMID: 18987851. **KQ8E2.**
47. Civeira F, Ros E, Jarauta E et al. Comparison of genetic versus clinical diagnosis in familial hypercholesterolemia. *Am J Cardiol*. 1193;102(9): 1187-93, 1193 e1. PMID: 18940289. **KQ3E5, KQ4E5.**
48. Clauss S, Wai KM, Kavey RE et al. Ezetimibe treatment of pediatric patients with hypercholesterolemia. *J Pediatr*. 2009;154(6): 869-72. PMID: 19230898. **KQ6E9, KQ7E9.**
49. Codoner-Franch P, Lopez-Jaen AB, Muniz P et al. Mandarin juice improves the antioxidant status of hypercholesterolemic children. *J Pediatr Gastroenterol Nutr*. 2008;47(3): 349-55. PMID: 18728533. **KQ6E9, KQ7E9.**
50. Colletti RB, Neufeld EJ, Roff NK et al. Niacin treatment of hypercholesterolemia in children. *Pediatrics*. 1993;92(1):78-82. PMID: 8516088. **KQ7E13, KQ8E13.**
51. Coskun A. Preanalytical factors for non-HDL cholesterol measurements/ Serum lipid profiles including non-high density lipoprotein cholesterol levels in Turkish school-children. *Anadolu Kardiyol Derg*. 2008;8(1): 84-5; author reply 85-6. PMID: 18258549. **KQ2E2, KQ1E2, KQ3E2, KQ4E13, KQ5E13.**
52. Croyle RT, Sun YC, Louie DH. Psychological minimization of cholesterol test results: moderators of appraisal in college students and community residents. *Health Psychol*. 1993;12(6): 503-7. PMID: 8293735. **KQ7E13, KQ8E13.**

## Appendix C. Excluded Studies

53. Curtis DM, Driscoll DJ, Goldman DH et al. Loss of dental enamel in a patient taking cholestyramine. *Mayo Clin Proc.* 1991;66(11):1131. PMID: 1943246. **KQ7E13, KQ8E13.**
54. da Luz Giroldo M, Villela Baroncini LA, Champoski AF et al. Household cardiovascular screening in adolescents from high-risk families. *Atherosclerosis.* 2013;226(1): 286-90. PMID: 23195519. **KQ2E4, KQ3E4, KQ1E4, KQ4E4.**
55. Daniels SR. Management of hyperlipidemia in pediatrics. *Curr Opin Cardiol.* 2012;27(2): 92-7. PMID: 22233976. **KQ6E2, KQ7E2.**
56. Daniels SR. Screening and treatment of dyslipidemias in children and adolescents. *Horm Res Paediatr.* 2011;76 Suppl 1:47-51. PMID: 21778749. **KQ1E2.**
57. Daniels SR. Screening for familial hypercholesterolemia: what is the most effective strategy? *Nat Clin Pract Cardiovasc Med.* 2008;5(3): 130-1. PMID: 18059381. **KQ3E13, KQ4E13.**
58. Daniels SR, Gidding SS, de Ferranti SD et al. Pediatric aspects of familial hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol.* 2011;5(3 Suppl):S30-7. PMID: 21600527. **KQ3E13, KQ4E13, KQ6E13.**
59. Daniels SR, Greer FR, Committee on Nutrition Lipid screening and cardiovascular health in childhood. *Pediatrics.* 2008;122(1): 198-208. PMID: 18596007. **KQ3E2, KQ4E2.**
60. Darmady JM, Fosbrooke AS, Lloyd JK. Prospective study of serum cholesterol levels during first year of life. *Br Med J.* 1972;2(5815):685-8. PMID: 5067674. **KQ4E6.**
61. Das B, Daga MK, Gupta SK. Lipid Pentad Index: A novel bioindex for evaluation of lipid risk factors for atherosclerosis in young adolescents and children of premature coronary artery disease patients in India. *Clin Biochem.* 2007;40(1-2):18-24. PMID: 17052698. **KQ3E4, KQ4E4.**
62. Davidson DM, Bradley BJ, Landry SM et al. School-based blood cholesterol screening. *J Pediatr Health Care.* 1989;3(1): 8-Mar. PMID: 2492600. **KQ4E6.**
63. Davidson DM, Van Camp J, Iftner CA et al. Family history fails to detect the majority of children with high capillary blood total cholesterol. *J Sch Health.* 1991;61(2): 75-80. PMID: 2016863. **KQ4E6.**
64. Davidson MH. A systematic review of bile acid sequestrant therapy in children with familial hypercholesterolemia. *J Clin Lipidol.* 2011;5(2): 76-81. PMID: 21392720. **KQ6E13, KQ7E13.**
65. Davidson M. The efficacy of colessevelam HCl in the treatment of heterozygous familial hypercholesterolemia in pediatric and adult patients. *Clin Ther.* 2013;35(8): 1247-52. PMID: 23916045. **KQ6E13, KQ7E13.**
66. de Ferranti S, Shapiro D, Markowitz R et al. Nonfasting low-density lipoprotein testing: utility for cholesterol screening in pediatric primary care. *Clin Pediatr (Phila).* 2007;46(5): 441-5. PMID: 17556742. **KQ3E6, KQ4E6.**
67. de Jongh S, Kerckhoffs MC, Grootenhuys MA et al. Quality of life, anxiety and concerns among statin-treated children with familial hypercholesterolaemia and their parents. *Acta Paediatr.* 2003;92(9): 1096-101.. PMID: 14599077. **KQ7E13, KQ8E13.**
68. Defesche JC. Defining the challenges of FH screening for familial hypercholesterolemia. *J Clin Lipidol.* 2010;4(5): 338-41. PMID: 21122674. **KQ5E13.**
69. Demerath E, Muratova V, Spangler E et al. School-based obesity screening in rural Appalachia. *Prev Med.* 2003;37(6 Pt 1 ):553-60. PMID: 14636788. **KQ4E6.**
70. Dennison BA, Jenkins PL, Pearson TA. Challenges to implementing the current pediatric cholesterol screening guidelines into practice. *Pediatrics.* 1994;94(3): 296-302. PMID: 8065853. **KQ4E6.**
71. Dennison BA, Kikuchi DA, Srinivasan SR et al. Parental history of cardiovascular disease as an indication for screening for lipoprotein abnormalities in children. *J Pediatr.* 1989;115(2): 186-94. PMID: 2754548. **KQ4E6.**
72. Derinoz O, Tumer L, Hasanoglu A et al. Cholesterol screening in school children: is family history reliable to choose the ones to screen? *Acta Paediatr.* 2007;96(12): 1794-8. PMID: 17971187. **KQ3E4, KQ4E4.**
73. Derks M, Abt M, Mwangi A et al. Lack of effect of dalcetrapib on QT interval in healthy subjects following multiple dosing. *Eur J Clin Pharmacol.* 2010;66(8): 775-83. PMID: 20521033. **KQ7E5.**
74. Derks M, Abt M, Phelan M. Lack of clinically relevant drug-drug interactions when dalcetrapib is co-administered with ezetimibe. *Br J Clin Pharmacol.* 2010;70(6): 825-33. PMID: 21175438. **KQ7E5.**

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75. Derks M, Anzures-Cabrera J, Turnbull L et al. Safety, tolerability and pharmacokinetics of dalcetrapib following single and multiple ascending doses in healthy subjects: a randomized, double-blind, placebo-controlled, phase I study. *Clin Drug Investig.* 2011;31(5): 325-35. PMID: 21366361. **KQ7E5.**
76. Derks M, Fowler S, Kuhlmann O. A single-center, open-label, one-sequence study of dalcetrapib coadministered with ketoconazole, and an in vitro study of the S-methyl metabolite of dalcetrapib. *Clin Ther.* 2009;31(3): 586-99. PMID: 19393849. **KQ7E5.**
77. Descamps OS, Tenoutasse S, Stephenne X et al. Management of familial hypercholesterolemia in children and young adults: consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. *Atherosclerosis.* 2011;218(2): 272-80. PMID: 21762914. **KQ6E2, KQ7E2.**
78. Diller PM, Huster GA, Leach AD et al. Definition and application of the discretionary screening indicators according to the National Cholesterol Education Program for Children and Adolescents. *J Pediatr.* 1995;126(3): 345-52. PMID: 7869190. **KQ4E6.**
79. Dirisamer A, Hachemian N, Bucek RA et al. The effect of low-dose simvastatin in children with familial hypercholesterolaemia: a 1-year observation. *Eur J Pediatr.* 2003;162(6): 421-5. Epub 2003 Mar 15.. PMID: 12756561. **KQ7E13, KQ8E13.**
80. Doll H, Shine B, Kay J et al. The rise of cholesterol testing: how much is unnecessary. *Br J Gen Pract.* 2011;61(583):e81-8. PMID: 21276328. **KQ4E5.**
81. Doshi N, Perrin EM, Lazorick S et al. Short-term change in body mass index in overweight adolescents following cholesterol screening. *Arch Pediatr Adolesc Med.* 2009;163(9): 812-7. PMID: 19736334. **KQ3E6, KQ4E6.**
82. Douglas MB, Birrer RB, Medidi S et al. Obese children should be screened for hypercholesterolemia. *J Health Care Poor Underserved.* 1996;7(1): 24-35. PMID: 8645782. **KQ4E6.**
83. Drogari E, Ragia G, Mollaki V et al. POR\*28 SNP is associated with lipid response to atorvastatin in children and adolescents with familial hypercholesterolemia. *Pharmacogenomics.* 2014;15(16):1963-72. PMID: 25521355. **KQ7E13, KQ8E13.**
84. Ducobu J, Brasseur D, Chaudron JM et al. Simvastatin use in children. *Lancet.* 1992;339(8807):1488. PMID: 1351171. **KQ7E13, KQ8E13.**
85. Dulay D, LaHaye SA, Lahey KA et al. Efficacy of alternate day versus daily dosing of rosuvastatin. *Can J Cardiol.* 2009;25(2): e28-31. PMID: 19214297. **KQ6E5, KQ7E5.**
86. Duncan CJ, Rowland R, Lillie PJ et al. Incidental diagnosis in healthy clinical trial subjects. *Clin Transl Sci.* 2012;5(4): 348-50. PMID: 22883613. **KQ2E5, KQ1E5, KQ3E5.**
87. Eiland LS, Luttrell PK. Use of statins for dyslipidemia in the pediatric population. *J Pediatr Pharmacol Ther.* 2010;15(3): 160-72. PMID: 22477808. **KQ6E9, KQ7E9.**
88. Eissa MA, Wen E, Mihalopoulos NL et al. Evaluation of AAP guidelines for cholesterol screening in youth: Project HeartBeat! *Am J Prev Med.* 2009;37:S71-7. PMID: 19524159. **KQ3E6, KQ4E6.**
89. Elis A, Zhou R, Stein EA. Treatment of familial hypercholesterolaemia in children and adolescents in the last three decades. *Cardiol Young.* 2013;24(3): 437-41. PMID: 23659280. **KQ5E13, KQ6E9, KQ7E10.**
90. Espinheira Mdo C, Vasconcelos C, Medeiros AM et al. Hypercholesterolemia--a disease with expression from childhood. *Rev Port Cardiol.* 2013;32(5): 379-86. PMID: 23669405. **KQ6E9, KQ7E10.**
91. Estevez-Gonzalez MD, Saavedra-Santana P, Lopez-Rios L et al. HDL cholesterol levels in children with mild hypercholesterolemia: effect of consuming skim milk enriched with olive oil and modulation by the TAQ 1B polymorphism in the CETP gene. *Ann Nutr Metab.* 2010;56(4): 288-93. PMID: 20413969. **KQ6E5, KQ7E5.**
92. Eyre H, Kahn R, Robertson RM et al. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation.* 2004;109(25):3244-55. PMID: 15198946. **KQ4E6.**



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93. Faigel HC. Screening college students for hypercholesterolemia. *J Am Coll Health*. 1992;40(6): 272-5. PMID: 1602094. **KQ4E6**.
94. Farah JR, Kwiterovich PO Jr, Neill CA et al. Dose-effect relation of cholestyramine in children and young adults with familial hypercholesterolaemia. *Lancet*. 1977;1(8002):59-63. PMID: 63709. **KQ7E13, KQ8E13**.
95. Farah JR, Kwiterovich PO, Neill CA. A study of the dose-effect relationship of cholestyramine in children with familial hypercholesterolemia. *Adv Exp Med Biol*. 1977;82:212-215. PMID: 200092. **KQ7E13, KQ8E13**.
96. Farrokhi F, Moohebati M, Aghdaei HR et al. Effects of statin therapy on serum trace element status in dyslipidemic patients: results of a randomized placebo-controlled cross-over trial. *Clin Lab*. 2012;58(9-10):1005-15. PMID: 23163117. **KQ7E5**.
97. Fazio S, Guyton JR, Polis AB et al. Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia. *Am J Cardiol*. 2010;105(4): 487-94. PMID: 20152243. **KQ6E5, KQ7E5**.
98. Feliciano-Alfonso JE, Mendivil CO, Ariza ID et al. Cardiovascular risk factors and metabolic syndrome in a population of young students from the National University of Colombia. *Rev Assoc Med Bras*. 2010;56(3): 293-8. PMID: 20676535. **KQ3E4, KQ4E4**.
99. Fisher-Hoch SP, Vatcheva KP, Laing ST et al. Missed opportunities for diagnosis and treatment of diabetes, hypertension, and hypercholesterolemia in a Mexican American population, Cameron County Hispanic Cohort, 2003-2008. *Prev Chronic Dis*. 2012;9:110298. PMID: 22863308. **KQ3E5, KQ4E5**.
100. Flechtner-Mors M, Wiegand S, Gellhaus I et al. Screening for co-morbidity in 65,397 obese pediatric patients from Germany, Austria and Switzerland: adherence to guidelines improved from the year 2000 to 2010. *Obes Facts*. 2013;6(4): 360-8. PMID: 23970145. **KQ3E6, KQ4E6**.
101. Flouris AD, Bouziotas C, Christodoulos AD et al. Longitudinal preventive-screening cutoffs for metabolic syndrome in adolescents. *Int J Obes (Lond)*. 2008;32(10): 1506-12. PMID: 18698315. **KQ3E6, KQ2E6**.
102. Frich JC, Malterud K, Fugelli P. Experiences of guilt and shame in patients with familial hypercholesterolemia: a qualitative interview study. *Patient Educ Couns*. 2007;69(1-3):108-13. PMID: 17889493. **KQ7E13, KQ4E7**.
103. Frontini MS, Srinivasan SR, Xu J, et al. Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the Bogalusa Heart Study. *Pediatrics*. 2008;121(5): 924-9. PMID: 18450895. **KQ2E5, KQ8E13, KQ3E13**.
104. Fujita Y, Kouda K, Nakamura H et al. Height-specific serum cholesterol levels in pubertal children: data from population-based Japanese school screening. *J Epidemiol*. 2011;21(2): 102-7. PMID: 21212578. **KQ3E6, KQ4E6**.
105. Futema M, Shah S, Cooper JA et al. Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. *Clin Chem*. 2015;61(1): 231-8. PMID: 25414277. **KQ4E13**.
106. Gaeta G, Cuomo S, Capozzi G et al. Lipoprotein(a) levels are increased in healthy young subjects with parental history of premature myocardial infarction. *Nutr Metab Cardiovasc Dis*. 2008;18(7): 492-6. PMID: 17962002. **KQ3E6, KQ4E6**.
107. Gagliano NJ, Emans SJ, Woods ER. Cholesterol screening in the adolescent. *J Adolesc Health*. 1993;14(2): 104-8. PMID: 8476872. **KQ4E6**.
108. Gagne C, Kusters M, Caceres M et al. Efficacy and safety of ezetimibe monotherapy in 6-10 year old children with heterozygous familial or nonfamilial hypercholesterolemia. *J Clin Lipidol*. 2013. **KQ7E13, KQ8E13**.
109. Garaiova I, Muchova J, Nagyova Z et al. Effect of a plant sterol, fish oil and B vitamin combination on cardiovascular risk factors in hypercholesterolemic children and adolescents: a pilot study. *Nutr J*. 2013;12:7. PMID: 23297818. **KQ7E4, KQ6E4**.
110. Garcia RE, Moodie DS. Routine cholesterol surveillance in childhood. *Pediatrics*. 1989;84(5): 751-5. PMID: 2640549. **KQ4E6**.

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111. Gauer R. Hyperlipidemia treatment in children: the younger, the better. *Am Fam Physician*. 2010;82(5): 460. PMID: 20822078. **KQ6E2, KQ7E2.**
112. Giannini C, D'Esse L, D'Adamo E et al. Influence of the Mediterranean diet on carotid intima-media thickness in hypercholesterolaemic children: A 12-month intervention study. *Nutr Metab Cardiovasc Dis*. 2013;24(1): 75-82. PMID: 23809150. **KQ6E5, KQ7E5.**
113. Gidding SS, Prospero C, Hossain J et al. A double-blind randomized trial of fish oil to lower triglycerides and improve cardiometabolic risk in adolescents. *J Pediatr*. 2014;165(3): 497-503 e2. PMID: 25008950. **KQ7E13, KQ8E13.**
114. Gillman MW, Cupples LA, Moore LL et al. Impact of within-person variability on identifying children with hypercholesterolemia: Framingham Children's Study. *J Pediatr*. 1992;121(3): 342-7. PMID: 1517906. **KQ4E6.**
115. Giugliano RP, Desai NR, Kohli P et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet*. 2012;380-(9858):2007-17. PMID: 23141813. **KQ6E5, KQ7E5.**
116. Glassman MS, Schwarz SM. Cholesterol screening in children: should obesity be a risk factor? *J Am Coll Nutr*. 1993;12(3): 270-3. PMID: 8409081. **KQ4E6.**
117. Glueck CJ, Fallat R, Tsang R. Pediatric familial type II hyperlipoproteinemia: therapy with diet and cholestyramine resin. *Pediatrics*. 1973;52(5):669-679. PMID: 4355362. **KQ7E13, KQ8E13.**
118. Glueck CJ, Mellies MJ, Dine M et al. Safety and efficacy of long-term diet and diet plus bile acid-binding resin cholesterol-lowering therapy in 73 children heterozygous for familial hypercholesterolemia. *Pediatrics*. 1986;78(2):338-348. PMID: 3526270. **KQ7E13, KQ8E13.**
119. Glueck CJ, Tsang RC, Fallat RW et al. Therapy of familial hypercholesterolemia in childhood: diet and cholestyramine resin for 24 to 36 months. *Pediatrics*. 1977;59(3):433-441. PMID: 840563. **KQ7E13, KQ8E13.**
120. Glueck CJ, Tsang RC, Fallat RW et al. Plasma vitamin A and E levels in children with familial type II hyperlipoproteinemia during therapy with diet and cholestyramine resin. *Pediatrics*. 1974;54(1):51-55. PMID: 4365953. **KQ7E13, KQ8E13.**
121. Goff DC Jr, Donker GA et al. Cholesterol screening in pediatric practice. *Pediatrics*. 1991;88(2): 250-8. PMID: 1861922. **KQ4E6.**
122. Goldstein JL, Albers JJ, Schrott HG et al. Plasma lipid levels and coronary heart disease in adult relatives of newborns with normal and elevated cord blood lipids. *Am J Hum Genet*. 1974;26(6): 727-35. PMID: 4440681. **KQ4E6.**
123. Gong CD, Wu QL, Chen Z et al. Glycolipid metabolic status of overweight/obese adolescents aged 9- to 15-year-old and the BMI-SDS/BMI cut-off value of predicting dyslipidemia in boys, Shanghai, China: a cross-sectional study. *Lipids Health Dis*. 2013;12:129. PMID: 23984682. **KQ3E6, KQ4E6.**
124. Graves L, Garnett SP, Cowell CT et al. Waist-to-height ratio and cardiometabolic risk factors in adolescence: findings from a prospective birth cohort. *Pediatr Obes*. 2013;9(5): 327-38. PMID: 23894119. **KQ3E6, KQ4E6.**
125. Groot PH, Dijkhuis-Stoffelsma R, Grose WF et al. The effects of colestipol hydrochloride on serum lipoprotein lipid and apolipoprotein B and A-I concentrations in children heterozygous for familial hypercholesterolemia. *Acta Paediatr Scand*. 1983;72(1):81-85. PMID: 6407278. **KQ7E13, KQ8E13.**
126. Guardamagna O, Abello F, Anfossi G et al. Lipoprotein(a) and family history of cardiovascular disease in children with familial dyslipidemias. *J Pediatr*. 2011;159(2): 314-9. PMID: 21392785. **KQ3E7, KQ4E7.**
127. Guardamagna O, Abello F, Baracco V et al. The treatment of hypercholesterolemic children: efficacy and safety of a combination of red yeast rice extract and policosanols. *Nutr Metab Cardiovasc Dis*. 2011;21(6): 424-9. PMID: 20153154. **KQ6E5, KQ7E5.**
128. Guardamagna O, Abello F, Cagliero P et al. Could dyslipidemic children benefit from glucomannan intake? *Nutrition*. 2013;29(7-8):1060-5. PMID: 23759268. **KQ6E6, KQ7E6.**

## Appendix C. Excluded Studies

129. Guardamagna O, Cagliero P, Abello F. Management of inherited atherogenic dyslipidemias in children. *Ther Apher Dial.* 2013;17(2): 150-61. PMID: 23551671. **KQ6E9, KQ7E9.**
130. Guyton JR, Brown BG, Fazio S et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in patients with type IIa or type IIb hyperlipidemia. *J Am Coll Cardiol.* 2008;51(16):1564-72. PMID: 18420099. **KQ6E5, KQ7E5.**
131. Guyton JR, Fazio S, Adewale AJ et al. Effect of extended-release niacin on new-onset diabetes among hyperlipidemic patients treated with ezetimibe/simvastatin in a randomized controlled trial. *Diabetes Care.* 2012;35(4): 857-60. PMID: 22338103. **KQ7E5.**
132. Gylling H, Hallikainen M, Nissinen MJ et al. The effect of a very high daily plant stanol ester intake on serum lipids, carotenoids, and fat-soluble vitamins. *Clin Nutr.* 2010;29(1): 112-8. PMID: 19709787. **KQ6E5, KQ7E5.**
133. Gylling H, Plat J, Turley S et al. Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. *Atherosclerosis.* 2014;232(2): 346-60. PMID: 24468148. **KQ6E2, KQ5E2, KQ7E2, KQ8E2.**
134. Hadfield SG, Horara S, Starr BJ et al. Family tracing to identify patients with familial hypercholesterolaemia: the second audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. *Ann Clin Biochem.* 2009;46:24-32. PMID: 19028807. **KQ2E6, KQ1E6, KQ3E7, KQ4E7.**
135. Hajat C, Harrison O, Al Siksek Z. Weqaya: a population-wide cardiovascular screening program in Abu Dhabi, United Arab Emirates. *Am J Public Health.* 2012;102(5): 909-14. PMID: 21940918. **KQ3E6, KQ4E6.**
136. Hammond J, Chinn S, Richardson H et al. Response to venepuncture for monitoring in primary schools. *Arch Dis Child.* 1994;70(5): 367-9; discussion 369-72. PMID: 8017955. **KQ4E6.**
137. Hanlin ER, Hendricks B, Jenkins K et al. Cardiovascular risk profile: comparison between white and Southeast Asian youth in Wausau SCHOOL Project. *WMJ.* 2009;108(4): 189-93. PMID: 19753824. **KQ2E6, KQ3E6, KQ1E6, KQ4E6.**
138. Hanna KJ, Ewart CK, Kwiterovich PO et al. Child problem solving competence, behavioral adjustment and adherence to lipid-lowering diet. *Patient Educ Couns.* 1990;16(2): 119-31. PMID: 2290766. **KQ7E13, KQ8E13.**
139. Hansen D, Michaelsen KF, Skovby F. Growth during treatment of familial hypercholesterolemia. *Acta Paediatr.* 1992;81(12):1023-1025. PMID: 1290846. **KQ7E13, KQ8E13.**
140. Harada-Shiba M, Arai H, Oikawa S et al. Guidelines for the management of familial hypercholesterolemia. *J Atheroscler Thromb.* 2012;19(12): 1043-60. PMID: 23095242. **KQ6E9, KQ7E9.**
141. Harris N, Neufeld EJ, Newburger JW et al. Analytical performance and clinical utility of a direct LDL-cholesterol assay in a hyperlipidemic pediatric population. *Clin Chem.* 1996;42(8 Pt 1):1182-8. PMID: 8697574. **KQ4E6.**
142. Harvengt C, Desager JP. Colestipol in familial type II hyperlipoproteinemia: a three-year trial. *Clin Pharmacol Ther.* 1976;20(3):310-314. PMID: 182429. **KQ7E13, KQ8E13.**
143. Haymond S, Mohanty N. Pediatric lipid screening rates in the us are low: what can labs do to help? *Clin Chem.* 2015. PMID: 25724661. **KQ6E6.**
144. Haymond S, Mohanty N. Insulin-like growth factor-1, insulin-like growth factor binding protein-3, and cardiovascular disease risk factors in young black men and white men: the CARDIA Male Hormone Study. *Clin Chem.* 2004;61(8): 1019-21. PMID: 25724661. **KQ4E13.**
145. Hernandez-Mijares A, Banuls C, Rocha M et al. Effects of phytosterol ester-enriched low-fat milk on serum lipoprotein profile in mildly hypercholesterolaemic patients are not related to dietary cholesterol or saturated fat intake. *Br J Nutr.* 2010;104(7): 1018-25. PMID: 20456813. **KQ6E5, KQ7E5.**
146. Heyden S, Schneider KA, Roberts KF. Effectiveness of education-screening on cholesterol levels of students. *Ann Nutr Metab.* 1991;35(2): 71-6. PMID: 1872595. **KQ4E6.**
147. Hirschler V, Maccallini G, Aranda C et al. Dyslipidemia without obesity in indigenous Argentinean children living at high altitude. *J Pediatr.* 2012;161(4): 646-51 e1. PMID: 22658786. **KQ3E4, KQ4E4.**

## Appendix C. Excluded Studies

148. Hirschler V, Molinari C, Maccallini G et al. Comparison of different anthropometric indices for identifying dyslipidemia in school children. *Clin Biochem.* 2011;44-42225:659-64. PMID: 21349259. **KQ3E4, KQ4E4.**
149. Hopcroft KA. Familial hypercholesterolaemia: Child-parent screening may have adverse psychological effects. *BMJ.* 2007;335-7622:683. PMID: 17916819. **KQ3E2, KQ4E2.**
150. Hu C, Tao F, Wan Y et al. Normal reference values for serum lipid levels in Chinese adolescents between 12 and 18 years of age. *J Trop Pediatr.* 2010;56(1): 13-8. PMID: 19506026. **KQ3E6, KQ4E6.**
151. Hui Y, Jie M, Ying L et al. Profiles of levels of lipids and dyslipidaemia in children from Beijing, China. *Cardiol Young.* 2009;19(5): 456-64. PMID: 19674498. **KQ3E6, KQ4E6.**
152. Huijgen R, Abbink EJ, Bruckert E et al. Colesevelam added to combination therapy with a statin and ezetimibe in patients with familial hypercholesterolemia: a 12-week, multicenter, randomized, double-blind, controlled trial. *Clin Ther.* 2010;32(4): 615-25. PMID: 20435231. **KQ6E5, KQ7E5.**
153. Huijgen R, Homsma SJ, Hutten BA et al. Improved access to life insurance after genetic diagnosis of familial hypercholesterolaemia: cross-sectional postal questionnaire study. *Eur J Hum Genet.* 2012;20(7): 722-8. PMID: 22293687. **KQ4E5.**
154. Huijgen R, Kindt I, Verhoeven SB et al. Two years after molecular diagnosis of familial hypercholesterolemia: majority on cholesterol-lowering treatment but a minority reaches treatment goal. *PLoS One.* 2010;5(2): e9220. PMID: 20169164. **KQ6E5, KQ7E5.**
155. Hussein O, Minasian L, Itzkovich Y et al. Ezetimibe's effect on platelet aggregation and LDL tendency to peroxidation in hypercholesterolaemia as monotherapy or in addition to simvastatin. *Br J Clin Pharmacol.* 2008;65(5): 637-45. PMID: 18241285. **KQ7E5, KQ8E13, KQ6E5.**
156. Ice CL, Cottrell L, Neal WA. Body mass index as a surrogate measure of cardiovascular risk factor clustering in fifth-grade children: results from the coronary artery risk detection in the Appalachian Communities Project. *Int J Pediatr Obes.* 2009;4(4): 316-24. PMID: 19922047. **KQ3E6, KQ4E6.**
157. Ice CL, Murphy E, Cottrell L et al. Morbidly obese diagnosis as an indicator of cardiovascular disease risk in children: results from the CARDIAC Project. *Int J Pediatr Obes.* 2011;6(2): 113-9. PMID: 20545480. **KQ3E6, KQ4E6, KQ5E9.**
158. Igase M, Kohara K, Katagi R et al. Predictive value of the low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio for the prevention of stroke recurrence in Japanese patients treated with rosuvastatin. *Clin Drug Investig.* 2012;32(8): 513-21. PMID: 22741749. **KQ1E5, KQ2E5, KQ3E5.**
159. Im JA, Lee JW, Shim JY et al. Association between brachial-ankle pulse wave velocity and cardiovascular risk factors in healthy adolescents. *J Pediatr.* 2007;150(3): 247-51. PMID: 17307539. **KQ3E6, KQ4E6.**
160. Izzo R, de Simone G, Giudice R et al. Effects of nutraceuticals on prevalence of metabolic syndrome and on calculated Framingham Risk Score in individuals with dyslipidemia. *J Hypertens.* 2010;28(7): 1482-7. PMID: 20498621. **KQ6E5, KQ7E5.**
161. Jacobson TA, Wertz DA, Kuznik A et al. Cardiovascular event rates in atorvastatin patients versus patients switching from atorvastatin to simvastatin. *Curr Med Res Opin.* 2013;29(7): 773-81. PMID: 23647370. **KQ1E13.**
162. Jago R, Drews KL, McMurray RG et al. Fatness, fitness, and cardiometabolic risk factors among sixth-grade youth. *Med Sci Sports Exerc.* 2010;42(8): 1502-10. PMID: 20139783. **KQ3E6, KQ4E6.**
163. Jahagirdar R, Hemchand KP, Chiplonkar SA et al. Relationship between body mass index, fat distribution and cardiometabolic risk factors in Indian children and adolescents. *Pediatr Obes.* 2012;7(4): E37-41. PMID: 22585579. **KQ3E4, KQ4E4.**
164. Jehlicka P, Stozicky F, Mayer O et al. Asymmetric dimethylarginine and the effect of folate substitution in children with familial hypercholesterolemia and diabetes mellitus type 1. *Physiol Res.* 2009;58(2): 179-84. PMID: 18380539. **KQ6E6, KQ7E6, KQ8E13.**
165. Jenssen BP, Jacobson MS. Screening adolescents for lipid disorders: what is the best approach? *Adolesc Med State Art Rev.* 2008;19(3): 507-20, x. PMID: 19227389. **KQ1E13, KQ3E13.**

## Appendix C. Excluded Studies

166. John C, Neal W. Screening children for hyperlipidemia by primary care physicians in West Virginia. *W V Med J*. 2012;108(3): 30-5. PMID: 22792653. **KQ3E6, KQ4E6.**
167. Jones ML, Martoni CJ, Prakash S. Oral supplementation with probiotic *L. reuteri* NCIMB 30242 increases mean circulating 25-hydroxyvitamin D: a post hoc analysis of a randomized controlled trial. *J Clin Endocrinol Metab*. 2013;98(7): 2944-51. PMID: 23609838. **KQ6E13, KQ7E13.**
168. Juonala M, Viikari JS, Kahonen M et al. Childhood levels of serum apolipoproteins B and A-I predict carotid intima-media thickness and brachial endothelial function in adulthood: the cardiovascular risk in young Finns study. *J Am Coll Cardiol*. 2008;52(4): 293-9. PMID: 18634985. **KQ1E13, KQ8E5.**
169. Kamerow D. Should we screen for and treat childhood dyslipidaemia? *BMJ*. 2008;337:a886. PMID: 18650230. **KQ1E13.**
170. Kaneshi T, Yoshida T, Ohshiro T et al. Birthweight and risk factors for cardiovascular diseases in Japanese schoolchildren. *Pediatr Int*. 2007;49(2): 138-43. PMID: 17445028. **KQ3E6.**
171. Kang WM, Zhang JS, Liu XX et al. Prevalence of abnormality of blood lipid and associated factors in health examination population in Beijing. *Chin Med Sci J*. 2009;24(3): 142-6. PMID: 19848313. **KQ3E4, KQ4E4.**
172. Kapur NK. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. *Expert Rev Cardiovasc Ther*. 2007;5(2): 161-75. PMID: 17338662. **KQ6E2, KQ7E2.**
173. Kastelein JJP, Kusters M, Caceres M et al. Efficacy and safety of ezetimibe monotherapy in children six to ten years of age with heterozygous familial or non-familial hypercholesterolemia. *J Am Coll Cardiol*. 2013. **KQ7E13, KQ8E13.**
174. Kaur S, Kapil U. Dyslipidemia amongst obese children in national capital territory (NCT) of Delhi. *Indian J Pediatr*. 2011;78(1): 55-7. PMID: 20936509. **KQ3E4, KQ4E4.**
175. Kavey RE, Allada V, Daniels SR et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *J Cardiovasc Nurs*. 2007;22(3): 218-53. PMID: 17545824. **KQ1E2, KQ8E2, KQ6E2, KQ7E2.**
176. Kavey RE, McBride PE. Should family physicians routinely screen for hypercholesterolemia in children? Yes: the evidence supports universal screening. *Am Fam Physician*. 2012;86(8): 2-Jan. PMID: 23062164. **KQ2E2, KQ1E2, KQ3E2, KQ4E2, KQ5E13.**
177. Kelishadi R, Cook SR, Motlagh ME et al. Metabolically obese normal weight and phenotypically obese metabolically normal youths: the CASPIAN Study. *J Am Diet Assoc*. 2008;108(1): 82-90. PMID: 18155992. **KQ2E4, KQ1E4, KQ3E4, KQ4E4, KQ5E13.**
178. Kelishadi R, Sabri M, Motamedi N et al. Factor analysis of markers of inflammation and oxidation and echocardiographic findings in children with a positive family history of premature coronary heart disease. *Pediatr Cardiol*. 2009;30(4): 477-81. PMID: 19322601. **KQ3E4, KQ4E4.**
179. Kenny D, Ward OC, Mulhern B et al. Failure of cord serum cholesterol and betalipoprotein as screening tests for familial hyperlipoproteinaemia. *Ir J Med Sci*. 1984;153(3): 100-5. PMID: 6724853. **KQ4E6.**
180. Kessler DA, Ortiz C, Grima K et al. Cardiovascular disease risk assessment and prevention in blood donors. *Transfusion*. 2012;52(10): 2174-82. PMID: 22320854. **KQ3E5.**
181. Khalil A, Aggarwal A, Arora S et al. Lipoprotein (a)--lipid profile and apolipoprotein B in children of young parents with coronary artery disease. *Indian Heart J*. 2011;63(5): 450-3. PMID: 23550425. **KQ3E4, KQ4E4.**
182. Kim J, Bhattacharjee R, Kheirandish-Gozal L et al. Insulin sensitivity, serum lipids, and systemic inflammatory markers in school-aged obese and nonobese children. *Int J Pediatr*. 2010;2010:846098. PMID: 21274450. **KQ3E6, KQ4E13.**
183. Kit BK, Carroll MD, Lacher DA et al. Trends in serum lipids among U.S. youths aged 6 to 19 years, 1988-2010. *JAMA*. 2012;308(6): 591-600. PMID: 22871871. **KQ3E6.**

## Appendix C. Excluded Studies

184. Kleiser C, Schienkiewitz A, Schaffrath Rosario A et al. Indicators of overweight and cardiovascular disease risk factors among 11- to 17-year-old boys and girls in Germany. *Obes Facts*. 2011;4(5): 379-85. PMID: 22166758. **KQ3E7.**
185. Klos K, Hamon A, Clark A et al. APOA5 polymorphisms influence plasma triglycerides in young, healthy African Americans and whites of the CARDIA Study. *J Lipid Res*. 2005;46(3): 564-571. PMID: M400437. **KQ4E13.**
186. Knebel W, Gastonguay MR, Malhotra B et al. Population pharmacokinetics of atorvastatin and its active metabolites in children and adolescents with heterozygous familial hypercholesterolemia: selective use of informative prior distributions from adults. *J Clin Pharmacol*. 2013;53(5): 505-16. PMID: 23381936. **KQ6E6, KQ7E6.**
187. Koletzko B, Kupke I, Wendel U. Treatment of hypercholesterolemia in children and adolescents. *Acta Paediatr*. 1992;81-1421908:682-685. PMID: 1421908. **KQ7E13, KQ8E13.**
188. Kones R. Primary prevention of coronary heart disease: integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey. *Drug Des Devel Ther*. 2011;5:325-80. PMID: 21792295. **KQ1E9.**
189. Koren MJ, Scott R, Kim JB et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet*. 2012;380-9858:1995-2006. PMID: 23141812. **KQ7E5, KQ8E13, KQ6E5.**
190. Koskinen J, Kahonen M, Viikari JS et al. Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in young Finns study. *Circulation*. 2009;120(3): 229-36. PMID: 19581494. **KQ2E5, KQ1E13, KQ3E6.**
191. Kouda K, Nakamura H, Nishio N et al. Trends in body mass index, blood pressure, and serum lipids in Japanese children: Iwata population-based annual screening (1993-2008). *J Epidemiol*. 2010;20(3): 212-8. PMID: 20208399. **KQ3E6.**
192. Krysiak R, Zmuda W, Okopien B. The effect of ezetimibe and simvastatin on hemostasis in patients with isolated hypercholesterolemia. *Fundam Clin Pharmacol*. 2012;26(3): 424-31. PMID: 21392096. **KQ6E5, KQ7E5.**
193. Kuba VM, Leone C, Damiani D. Is waist-to-height ratio a useful indicator of cardio-metabolic risk in 6-10-year-old children? *BMC Pediatr*. 2013;13:91. PMID: 23758779. **KQ3E4.**
194. Kumar SS, Lahey KA, Day A et al. Comparison of the efficacy of administering a combination of ezetimibe plus fenofibrate versus atorvastatin monotherapy in the treatment of dyslipidemia. *Lipids Health Dis*. 2009;8:56. PMID: 20017910. **KQ7E5, KQ8E13, KQ6E5.**
195. Kusters DM, de Beaufort C, Widhalm K et al. Paediatric screening for hypercholesterolaemia in Europe. *Arch Dis Child*. 2012;97(3): 272-6. PMID: 21949015. **KQ3E2.**
196. Kwiterovich PO Jr, Barton BA et al. Effects of diet and sexual maturation on low-density lipoprotein cholesterol during puberty: the Dietary Intervention Study in Children (DISC). *Circulation*. 1997;96(8): 2526-33. PMID: 9355889. **KQ4E6.**
197. Kwiterovich PO Jr, Heiss G et al. Assessment of plasma total cholesterol as a test to detect elevated low density (beta) lipoprotein cholesterol levels (type IIa hyperlipoproteinemia) in young subjects from a population-based sample. *Am J Epidemiol*. 1982;115(2): 192-204. PMID: 7058778. **KQ4E6.**
198. Lamaida N, Capuano E, Pinto L et al. The safety of statins in children. *Acta Paediatr*. 2013;102(9): 857-62. PMID: 23631461. **KQ6E13, KQ7E13, KQ8E13.**
199. Lamb MM, Ogden CL, Carroll MD et al. Association of body fat percentage with lipid concentrations in children and adolescents: United States, 1999-2004. *Am J Clin Nutr*. 2011;94(3): 877-83. PMID: 21775565. **KQ3E6.**
200. Lambert M, Lupien PJ, Gagne C et al. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. Canadian Lovastatin in Children Study Group. *Pediatrics*. 1996;97(5): 619-28. PMID: 8628597. **KQ7E13, KQ8E13.**

## Appendix C. Excluded Studies

201. Langslet G, Ose L. Screening methods in the diagnosis and assessment of children and adolescents with familial hypercholesterolemia. *Expert Rev Cardiovasc Ther.* 2013;11(8): 1061-6. PMID: 23984929. **KQ2E2, KQ3E2, KQ1E2.**
202. Lannon CM, Earp J. Parents' behavior and attitudes toward screening children for high serum cholesterol levels. *Pediatrics.* 1992;89:1159-63. PMID: 1594369. **KQ7E13, KQ8E13.**
203. Lapinleimu J, Lapinleimu H, Nuotio IO et al. Expression of common familial dyslipidemias in early childhood. *Atherosclerosis.* 2009;204(2): 573-9. PMID: 19026413. **KQ3E7, KQ4E6.**
204. Larsson B, Vaara I. Cholesterol screening of seven-year-old children. How to identify children at risk. *Acta Paediatr.* 1992;81(4): 315-8. PMID: 1606391. **KQ4E6.**
205. Lebenthal Y, Horvath A, Dziechciarz P et al. Are treatment targets for hypercholesterolemia evidence based? Systematic review and meta-analysis of randomised controlled trials. *Arch Dis Child.* 2010;95(9): 673-80. PMID: 20515970. **KQ6E13, KQ7E13, KQ8E13, KQ5E6.**
206. Leone L, Malamisura M, Matteo A et al. Efficacy of a new symbiotic formulation containing lactobacillus paracasei B21060 in children with familial hypercholesterolemia. *Digestive and liver disease.* 2013. PMID: CN-01024785. **KQ7E13, KQ8E13.**
207. Liacouras CA, Coates PM, Gallagher PR et al. Use of cholestyramine in the treatment of children with familial combined hyperlipidemia. *J Pediatr.* 1993;122-8441109:477-482. PMID: 8441109. **KQ7E13, KQ8E13.**
208. Lilley JS, Linton MF, Fazio S. Dyslipidemias in children. *Pediatr Ann.* 2012;41(2): e1-7. PMID: 22299622. **KQ1E2.**
209. Lindman AS, Veierod MB, Tverdal A et al. Nonfasting triglycerides and risk of cardiovascular death in men and women from the Norwegian Counties Study. *Eur J Epidemiol.* 2010;25(11): 789-98. PMID: 20890636. **KQ8E5.**
210. Lipshultz SE, Schaechter J, Carrillo A et al. Can the consequences of universal cholesterol screening during childhood prevent cardiovascular disease and thus reduce long-term health care costs? *Pediatr Endocrinol Rev.* 2012;9(4): 698-705. PMID: 23304806. **KQ4E2, KQ3E2.**
211. Lipska K, Sylaja PN, Sarma PS et al. Risk factors for acute ischaemic stroke in young adults in South India. *J Neurol Neurosurg Psychiatry.* 2007;78(9): 959-63. PMID: 17220290. **KQ2E4, KQ1E4, KQ3E4, KQ4E4, KQ5E13.**
212. Magnussen CG, Raitakari OT, Thomson R et al. Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. *Circulation.* 2008;117(1): 32-42. PMID: 18071074. **KQ3E6, KQ4E13, KQ8E5.**
213. Magnussen CG, Venn A, Thomson R et al. The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the cardiovascular risk in Young Finns study, the Boga. *J Am Coll Cardiol.* 2009;53(10): 860-9. PMID: 19264243. **KQ3E13, KQ4E13, KQ8E5.**
214. Malhotra A, Shafiq N, Arora A et al. Dietary interventions (plant sterols, stanols, omega-3 fatty acids, soy protein and dietary fibers) for familial hypercholesterolaemia. *Cochrane Database Syst Rev.* 2014;6:CD001918. PMID: 24913720. **KQ1E9, KQ6E13.**
215. Malloy MJ, Kane JP, Rowe JS. Familial hypercholesterolemia in children: treatment with p-aminosalicylic acid. *Pediatrics.* 1978;61(3): 365-72.. PMID: 205828. **KQ7E13, KQ8E13.**
216. Manchester RA, McDuffie C, Diamond E. Screening for hypercholesterolemia in college students. *J Am Coll Health.* 1989;37(4): 149-53. PMID: 2926025. **KQ4E6.**
217. Mar Bibiloni M, Martinez E, Llull R et al. Metabolic syndrome in adolescents in the Balearic Islands, a Mediterranean region. *Nutr Metab Cardiovasc Dis.* 2011;21(6): 446-54. PMID: 20211550. **KQ3E6, KQ4E6.**
218. Marais AD, Raal FJ, Stein EA et al. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. *Atherosclerosis.* 2008;197(1): 400-6. PMID: 17727860. **KQ6E5, KQ7E5.**

## Appendix C. Excluded Studies

219. Martin AC, Coakley J, Forbes DA et al. Familial hypercholesterolaemia in children and adolescents: a new paediatric model of care. *J Paediatr Child Health*. 2013;49(4): E263-72. PMID: 23252991. **KQ1E2, KQ6E2, KQ8E13, KQ7E2.**
220. Martin SS, Blaha MJ, Elshazly MB et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310-19:2061-8. PMID: 24240933. **KQ3E6.**
221. Martin SS, Blaha MJ, Toth PP et al. Very large database of lipids: rationale and design. *Clin Cardiol*. 2013;36(11): 641-8. PMID: 24122913. **KQ2E7, KQ1E7, KQ3E7.**
222. Mata N, Alonso R, Badimon L et al. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). *Lipids Health Dis*. 2011;10:94. PMID: 21663647. **KQ6E5, KQ3E5, KQ2E5.**
223. Matsuyama T, Shoji K, Takase H et al. Effects of phytosterols in diacylglycerol as part of diet therapy on hyperlipidemia in children. *Asia Pac J Clin Nutr*. 2007;16:40-48. PMID: 17215179. **KQ6E9, KQ8E13, KQ7E9.**
224. McCrindle BW, O'Neill MB, Cullen-Dean G et al. Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children: a randomized, crossover trial. *J Pediatr*. 1997;130(2): 266-73. PMID: 9042130. **KQ7E13, KQ8E13.**
225. McDuffie JR, Calis KA, Uwaifo GI et al. Three-month tolerability of orlistat in adolescents with obesity-related comorbid conditions. *Obes Res*. 2002;10(7):642-650. PMID: 12105286. **KQ7E13, KQ8E13.**
226. McHale SM, Tershakovec AM, Corneal DA et al. Psychosocial factors in nutrition education for hypercholesterolemic children. *Ann Behav Med*. 1998;20(3): 233-40. PMID: 9989332. **KQ7E13, KQ8E13.**
227. Meulenkamp TM, Tibben A, Mollema ED et al. Predictive genetic testing for cardiovascular diseases: impact on carrier children. *Am J Med Genet A*. 2008;146A(24):3136-46. PMID: 19012345. **KQ4E7.**
228. Mitka M. Screening misses high LDL in many youths. *JAMA*. 2010;304(9): 952-3. PMID: 20810367. **KQ3E2, KQ4E2.**
229. Mohaupt MG, Karas RH, Babiychuk EB et al. Association between statin-associated myopathy and skeletal muscle damage. *CMAJ*. 2009;181(1-2):E11-8. PMID: 19581603. **KQ7E5.**
230. Moodie D. Cholesterol screening in children. *Congenit Heart Dis*. 2012;7(1): 2-Jan. PMID: 22276662. **KQ3E2.**
231. Muir LA, George PM, Whitehead L. Using the experiences of people with familial hypercholesterolaemia to help reduce the risk of cardiovascular disease: a qualitative systematic review. *J Adv Nurs*. 2012;68(9): 1920-32. PMID: 22348692. **KQ4E13, KQ3E2.**
232. Nader PR, Yang M, Luepker RV et al. Parent and physician response to children's cholesterol values of 200 mg/dL or greater: the Child and Adolescent Trial for Cardiovascular Health Experiment. *Pediatrics*. 1997;99(5): E5. PMID: 9113962. **KQ7E13, KQ8E13.**
233. Negele L, Schneider B, Ristl R et al. Effect of a low-fat diet enriched either with rapeseed oil or sunflower oil on plasma lipoproteins in children and adolescents with familial hypercholesterolaemia. Results of a pilot study. *Eur J Clin Nutr*. 2015;69(3): 337-43. PMID: 25424602. **KQ6E9.**
234. Neil A, Cooper J, Betteridge J et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J*. 2008;29-21:2625-33. PMID: 18840879. **KQ5E13, KQ8E5.**
235. Noto D, Cefalu AB, Barraco G et al. Plasma non-cholesterol sterols: a useful diagnostic tool in pediatric hypercholesterolemia. *Pediatr Res*. 2010;67(2): 200-4. PMID: 20091938. **KQ3E6.**
236. O'Gorman CS, Higgins MF, O'Neill MB. Systematic review and metaanalysis of statins for heterozygous familial hypercholesterolemia in children: evaluation of cholesterol changes and side effects. *Pediatr Cardiol*. 2009;30(4): 482-9. PMID: 19189168. **KQ5E13, KQ6E13, KQ7E13.**
237. O'Gorman CS, O'Neill MB, Conwell LS. Considering statins for cholesterol-reduction in children if lifestyle and diet changes do not improve their health: a review of the risks and benefits. *Vasc Health Risk Manag*. 2011;7:14-Jan. PMID: 21339908. **KQ5E13, KQ6E2, KQ7E2.**



## Appendix C. Excluded Studies

238. O'Grady MJ, Brown AM, O'Neill MB. Cholesterol screening in an at-risk pediatric population. *Pediatr Cardiol.* 2008;29(3): 609-13. PMID: 18094916. **KQ3E7, KQ4E6.**
239. Ohta T, Nakamura R, Ikeda Y et al. Follow up study on children with dyslipidaemia detected by mass screening at 18 months of age: effect of 12 months dietary treatment. *Eur J Pediatr.* 1993;152(11): 939-43. PMID: 8276030. **KQ7E13, KQ8E13.**
240. O'Loughlin J, Lauzon B, Paradis G et al. Usefulness of the American Academy of Pediatrics recommendations for identifying youths with hypercholesterolemia. *Pediatrics.* 2004;113(6): 1723-7. PMID: 15173497. **KQ4E6.**
241. Pasquali SK, Li JS. Prevention of future cardiovascular disease in high-risk pediatric patients: a role for lipid lowering therapy? *Circ Cardiovasc Qual Outcomes.* 2008;1(2): 131-3. PMID: 20031800. **KQ1E2.**
242. Perry CM. Colesevelam: in pediatric patients with heterozygous familial hypercholesterolemia. *Paediatr Drugs.* 2010;12(2): 133-40. PMID: 20218749. **KQ6E11, KQ7E11.**
243. Plana N, Nicolle C, Ferre R et al. Plant sterol-enriched fermented milk enhances the attainment of LDL-cholesterol goal in hypercholesterolemic subjects. *Eur J Nutr.* 2008;47(1): 32-9. PMID: 18193377. **KQ6E5, KQ7E5.**
244. Pletcher MJ, Bibbins-Domingo K, Liu K et al. Nonoptimal lipids commonly present in young adults and coronary calcium later in life: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Ann Intern Med.* 2010;153(3): 137-46. PMID: 20679558. **KQ5E13.**
245. Polonsky SM, Bellet PS, Sprecher DL. Primary hyperlipidemia in a pediatric population: classification and effect of dietary treatment. *Pediatrics.* 1993;91(1): 92-6. PMID: 8416512. **KQ4E6.**
246. Porkka KV, Viikari JS, Taimela S et al. Tracking and predictiveness of serum lipid and lipoprotein measurements in childhood: a 12-year follow-up. The Cardiovascular Risk in Young Finns study. *Am J Epidemiol.* 1994;140(12): 1096-110. PMID: 7998592. **KQ4E6.**
247. Primrose ED, Savage JM, Boreham CA et al. Cholesterol screening and family history of vascular disease. *Arch Dis Child.* 1994;71(3): 239-42. PMID: 7979498. **KQ4E6.**
248. Raal FJ, Stein EA, Dufour R et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;385(9965):331-40. PMID: 25282519. **KQ1E5, KQ3E5.**
249. Resnicow K, Cross D, Lacosse J et al. Evaluation of a school-site cardiovascular risk factor screening intervention. *Prev Med.* 1993;22(6): 838-56. PMID: 8115342. **KQ4E6.**
250. Resnicow K, Futterman R, Vaughan RD. Body mass index as a predictor of systolic blood pressure in a multiracial sample of U.S. schoolchildren. *Ethn Dis.* 1993;3(4): 351-61. PMID: 7888986. **KQ4E6.**
251. Richard Hobbs FD, Gensini G, John Mancini GB et al. International open-label studies to assess the efficacy and safety of single-pill amlodipine/atorvastatin in attaining blood pressure and lipid targets recommended by country-specific guidelines: the JEWEL programme. *Eur J Cardiovasc Prev Rehabil.* 2009;16(4): 472-80. PMID: 19407658. **KQ6E5, KQ7E5, KQ5E5.**
252. Rifai N, Neufeld E, Ahlstrom P et al. Failure of current guidelines for cholesterol screening in urban African-American adolescents. *Pediatrics.* 1996;98(3 Pt 1):383-8. PMID: 8784361. **KQ4E6.**
253. Ritchie SK, Murphy EC, Ice C et al. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. *Pediatrics.* 2010;126(2): 260-5. PMID: 20624798. **KQ3E11, KQ4E6.**
254. Rohatgi A. Cholesterol screening in children: makes sense but what is the impact? *Future Cardiology.* 2010;6(3): 275-280. PMID: 20462333. **KQ1E2.**
255. Rosenberg E, Lamping DL, Joseph L et al. Cholesterol screening of children at high risk: behavioural and psychological effects. *CMAJ.* 1997;156(4): 489-96. PMID: 9054818. **KQ7E13, KQ8E13.**
256. Roseneu M, Van Biervliet JP. Screening and follow-up of infants with dyslipoproteinemia. *Prog Clin Biol Res.* 1985;188:79-86. PMID: 3933016. **KQ4E6.**
257. Rosenthal SL, Knauer-Black S, Stahl MP et al. The psychological functioning of children with hypercholesterolemia and their families. A preliminary investigation. *Clin Pediatr (Phila).* 1993;32(3): 135-41. PMID: 8453828. **KQ7E13, KQ8E13.**

## Appendix C. Excluded Studies

258. Rowan C, Brinker AD, Nourjah P et al. Rhabdomyolysis reports show interaction between simvastatin and CYP3A4 inhibitors. *Pharmacoepidemiol Drug Saf.* 2009;18(4): 301-9. PMID: 19206087. **KQ7E5.**
259. Russo MW, Scobey M, Bonkovsky HL. Drug-induced liver injury associated with statins. *Semin Liver Dis.* 2009;29(4): 412-22. PMID: 19826975. **KQ7E5.**
260. Ryu SK, Hutten BA, Vissers MN et al. Lipoprotein-associated phospholipase A2 mass and activity in children with heterozygous familial hypercholesterolemia and unaffected siblings: effect of pravastatin. *J Clin Lipidol.* 2011;5(1): 50-6. PMID: 21262507. **KQ6E11, KQ7E6.**
261. Sabzghabae AM, Ataei E, Kelishadi R et al. Effect of hibiscus sabdariffa calices on dyslipidemia in obese adolescents: a triple-masked randomized controlled trial. *Mater Sociomed.* 2013;25(2): 76-9. PMID: 24082826. **KQ6E5, KQ7E5.**
262. Sabzghabae AM, Khayam I, Kelishadi R et al. Effect of Zizyphus jujuba fruits on dyslipidemia in obese adolescents: a triple-masked randomized controlled clinical trial. *Med Arch.* 2013;67(3): 156-9. PMID: 23848030. **KQ6E5, KQ7E5.**
263. Saenger AK. Universal lipid screening in children and adolescents: a baby step toward primordial prevention? *Clin Chem.* 2012;58(8): 1179-81. PMID: 22510399. **KQ1E2.**
264. Sanchez Bayle M, Gonzalez Vergaz A, Garcia Cuartero B et al. Is a parental history of coronary arterial disease in children as discriminating as their lipoprotein profile? Nino Jesus Group. *Int J Cardiol.* 1992;36(3): 267-71. PMID: 1428260. **KQ4E6.**
265. Schwarz KB, Goldstein PD, Witztum JL et al. Fat-soluble vitamin concentrations in hypercholesterolemic children treated with colestipol. *Pediatrics.* 1980;65-7354970:243-250. PMID: 7354970. **KQ7E13, KQ8E13.**
266. Shafiq N, Bhasin B, Pattanaik S et al. A meta-analysis to evaluate the efficacy of statins in children with familial hypercholesterolemia. *Int J Clin Pharmacol Ther.* 2007;45(10): 548-55. PMID: 17966840. **KQ6E13, KQ7E13.**
267. Shafiq N, Singh M, Kaur S et al. Dietary treatment for familial hypercholesterolaemia. *Cochrane Database Syst Rev.* 2010;(1): CD001918. PMID: 20091526. **KQ6E13, KQ7E13.**
268. Shah S, Ceska R, Gil-Extremiera B et al. Efficacy and safety of extended-release niacin/laropirant plus statin vs. doubling the dose of statin in patients with primary hypercholesterolaemia or mixed dyslipidaemia. *Int J Clin Pract.* 2010;64(6): 727-38. PMID: 20518948. **KQ6E5, KQ7E5.**
269. Shamir R, Feig JE, Fisher EA. Therapeutic approach to childhood hypercholesterolemia. *Pediatr Endocrinol Rev.* 2007;5(2): 649-55. PMID: 18084159. **KQ3E2, KQ4E2.**
270. Shannon BM, Tershakovec AM, Martel JK et al. Reduction of elevated LDL-cholesterol levels of 4- to 10-year-old children through home-based dietary education. *Pediatrics.* 1994;94(6 Pt 1):923-7. PMID: 7971012. **KQ4E6.**
271. Sharma P, Boyers D, Boachie C et al. Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: a systematic review and economic evaluation. *Health Technol Assess.* 2012;16-17:1-266. PMID: 22469073. **KQ3E5.**
272. Shea S, Basch CE, Irigoyen M et al. Failure of family history to predict high blood cholesterol among Hispanic preschool children. *Prev Med.* 1990;19(4): 443-55. PMID: 2204914. **KQ4E6.**
273. Shepherd J, Vidt DG, Miller E et al. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. *Cardiology.* 2007;107(4): 433-43. PMID: 17363845. **KQ7E5.**
274. Shulman ST. Screening all children for lipid disorders. *Pediatr Ann.* 2012;41(7): 260-1. PMID: 22765033. **KQ1E2.**
275. Sonnett T, Robinson J, Milani P et al. Role of colesvelam in managing heterozygous familial hypercholesterolemia in adolescents and children. *Adolesc Health Med Ther.* 2010;1:53-60. PMID: 24600261. **KQ6E2, KQ7E2.**
276. Starc TJ, Belamarich PF, Shea S et al. Family history fails to identify many children with severe hypercholesterolemia. *Am J Dis Child.* 1991;145(1): 61-4. PMID: 1985431. **KQ4E13, KQ5E13.**
277. Stefanutti C, Lucani G, Vivenzio A et al. Diet only and diet plus simvastatin in the treatment of heterozygous familial hypercholesterolemia in childhood. *Drugs Exp Clin Res.* 1999;25(1): 23-8. PMID: 10337501. **KQ7E13, KQ8E13.**

## Appendix C. Excluded Studies

278. Stein EA. Treatment of familial hypercholesterolemia with drugs in children. *Arteriosclerosis*. 1989;9(1 Suppl):145-151. PMID: 2912428. **KQ7E13, KQ8E13.**
279. Stein EA. Statins and children: whom do we treat and when? *Circulation*. 2007;116(6): 594-5. PMID: 17679628. **KQ6E2, KQ7E2.**
280. Stein EA, Honarpour N, Wasserman SM et al. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation*. 2013;128-(19):2113-20. PMID: 24014831. **KQ6E5, KQ7E5.**
281. Steiner NJ, Neinstein LS, Pennbridge J. Hypercholesterolemia in adolescents: effectiveness of screening strategies based on selected risk factors. *Pediatrics*. 1991;88(2): 269-75. PMID: 1861925. **KQ4E6.**
282. Steinmetz J, Morin C, Panek E et al. Biological variations in hyperlipidemic children and adolescents treated with fenofibrate. *Clin Chim Acta*. 1981;112(1):43-43. PMID: 6113065. **KQ7E13, KQ8E13.**
283. Sultan SM, Schupf N, Dowling MM et al. Review of lipid and lipoprotein(a) abnormalities in childhood arterial ischemic stroke. *Int J Stroke*. 2014;9(1): 79-87. PMID: 24148253. **KQ1E13, KQ8E9.**
284. Superko HR, Garrett BC, King SB et al. Effect of combination nicotinic acid and gemfibrozil treatment on intermediate density lipoprotein, and subclasses of low density lipoprotein and high density lipoprotein in patients with combined hyperlipidemia. *Am J Cardiol*. 2009;103(3): 387-92. PMID: 19166694. **KQ6E5, KQ7E5.**
285. Tan AT, Low LP, Lim CH et al. Effects of rosuvastatin on low-density lipoprotein cholesterol and plasma lipids in Asian patients with hypercholesterolemia. *J Atheroscler Thromb*. 2009;16(4): 509-16. PMID: 19729865. **KQ6E13, KQ7E13.**
286. Tandon N, Garg MK, Singh Y et al. Prevalence of metabolic syndrome among urban Indian adolescents and its relation with insulin resistance (HOMA-IR). *J Pediatr Endocrinol Metab*. 2013;26-42320:1123-30. PMID: 23751385. **KQ3E4, KQ4E4.**
287. Task Force for the management of dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society, Catapano AL, Reiner Z, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis*. 2011:S1-44. PMID: 21723445. **KQ6E2, KQ7E2.**
288. Teber S, Deda G, Akar N et al. Lipoprotein (a) levels in childhood arterial ischemic stroke. *Clin Appl Thromb Hemost*. 2010;16(2): 214-7. PMID: 19752039. **KQ8E5.**
289. Terai N, Spoerl E, Fischer S et al. Statins affect ocular microcirculation in patients with hypercholesterolaemia. *Acta Ophthalmol*. 2011;89(6): e500-4. PMID: 21457486. **KQ6E5, KQ7E5.**
290. Teramoto T, Ohashi Y, Nakaya N et al. Practical risk prediction tools for coronary heart disease in mild to moderate hypercholesterolemia in Japan: originated from the MEGA study data. *Circ J*. 2008;72(10): 1569-75. PMID: 18762707. **KQ1E5, KQ3E5, KQ4E5.**
291. Teramoto T, Shirakawa M, Kikuchi M et al. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib in Japanese patients with dyslipidemia. *Atherosclerosis*. 2013;230(1): 52-60. PMID: 23958252. **KQ6E6, KQ7E7.**
292. Ticho BS, Neufeld EJ, Newburger JW et al. Utility of direct measurement of low-density lipoprotein cholesterol in dyslipidemic pediatric patients. *Arch Pediatr Adolesc Med*. 1998;152(8): 787-91. PMID: 9701139. **KQ4E6.**
293. Tonstad S. Familial hypercholesterolaemia: a pilot study of parents' and children's concerns. *Acta Paediatr*. 1996;85(11): 1307-13. PMID: 8955457. **KQ7E13, KQ8E13.**
294. Tonstad S, Novik TS, Vandvik IH. Psychosocial function during treatment for familial hypercholesterolemia. *Pediatrics*. 1996;98(2 Pt 1):249-55. PMID: 8692626. **KQ4E6.**
295. Tonstad S, Ose L. Colestipol tablets in adolescents with familial hypercholesterolaemia. *Acta Paediatr*. 1996;85(9): 1080-1082. PMID: 8888922. **KQ7E13, KQ8E13.**
296. Tonstad S, Refsum H, Ose L et al. The C677T mutation in the methylenetetrahydrofolate reductase gene predisposes to hyperhomocysteinemia in children with familial hypercholesterolemia treated with cholestyramine. *J Pediatr*. 1998;132-9506661:365-368. PMID: 9506661. **KQ7E13, KQ8E13.**

## Appendix C. Excluded Studies

297. Toth PP, Ballantyne CM, Davidson MH et al. Changes in prescription patterns before and after reporting of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression trial (ENHANCE) results and expected effects on low-density lipoprotein-cholesterol reduction. *J Clin Lipidol*. 2012;6(2): 180-91. PMID: 22385552. **KQ6E5, KQ7E5.**
298. Troxler RG, Park MK, Miller MA et al. Predictive value of family history in detecting hypercholesterolemia in predominantly Hispanic adolescents. *Tex Med*. 1991;87(11): 75-9. PMID: 1759247. **KQ4E6.**
299. Van Biervliet JP, Vercaemst R, De Keersgieter W et al. Evolution of lipoprotein patterns in newborns. *Acta Paediatr Scand*. 1980;69(5): 593-6. PMID: 7234379. **KQ4E6.**
300. Van Biervliet JP, Vinaimont N, Caster H et al. A screening procedure for dyslipoproteinemia in the newborn. Apoprotein quantitation on dried blood spots. *Clin Chim Acta*. 1982;120(2): 191-200. PMID: 7067144. **KQ4E6.**
301. van der Graaf A, Cuffie-Jackson C, Vissers MN et al. Online appendix to 'Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia.' *J Am Coll Cardiol*. 2008;52-17:1421-9. PMID: 18940534. **KQ6E13, KQ7E13.**
302. van der Graaf A, Kastelein JJ, Wiegman A. Heterozygous familial hypercholesterolaemia in childhood: cardiovascular risk prevention. *J Inherit Metab Dis*. 2009;32(6): 699-705. PMID: 19898954. **KQ6E2, KQ7E2.**
303. van der Graaf A, Rodenburg J, Vissers MN et al. Atherogenic lipoprotein particle size and concentrations and the effect of pravastatin in children with familial hypercholesterolemia. *J Pediatr*. 2008;152(6): 873-8. PMID: 18492534. **KQ7E6, KQ6E6.**
304. Verduci E, Agostoni C, Radaelli G et al. Blood lipids profile in hyperlipidemic children undergoing different dietary long chain polyunsaturated supplementations: a preliminary clinical trial. *Int J Food Sci Nutr*. 2013;65(3): 375-9. PMID: 24228803. **KQ6E5, KQ7E5.**
305. Viigimaa M, Vaverkova H, Farnier M et al. Ezetimibe/simvastatin 10/20 mg versus rosuvastatin 10 mg in high-risk hypercholesterolemic patients stratified by prior statin treatment potency. *Lipids Health Dis*. 2010;9:127. PMID: 21050476. **KQ6E5, KQ7E5.**
306. Vladutiu GD, Glueck CJ, Schultz MT et al. beta-Lipoprotein quantitation in cord blood spotted on filter paper: a screening test. *Clin Chem*. 1980;26(9): 1285-90. PMID: 7398043. **KQ4E6.**
307. Vobecky JS, David P, Vobecky J. Dietary habits in relation to tracking of cholesterol level in young adolescents: a nine-year follow-up. *Ann Nutr Metab*. 1988;32(42130):312-23. PMID: 3254688. **KQ4E6.**
308. Vuorio A, Docherty KF, Humphries SE et al. Statin treatment of children with familial hypercholesterolemia--trying to balance incomplete evidence of long-term safety and clinical accountability: are we approaching a consensus? *Atherosclerosis*. 2013;226(2): 315-20. PMID: 23141908. **KQ5E13, KQ6E2, KQ7E2.**
309. Vuorio A, Kuoppala J, Kovanen PT et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2010;(7): CD006401. PMID: 20614444. **KQ5E13, KQ6E13, KQ7E13.**
310. Vuorio A, Kuoppala J, Kovanen PT et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. 2014;7:CD006401. PMID: 25054950. **KQ6E13, KQ7E13, KQ8E13.**
311. Wadowski SJ, Karp RJ, Murray-Bachmann R et al. Family history of coronary artery disease and cholesterol: screening children in a disadvantaged inner-city population. *Pediatrics*. 1994;93(1): 109-13. PMID: 8265303. **KQ4E6.**
312. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *BMJ*. 2007;335(7620):599. PMID: 17855284. **KQ3E9.**
313. Warner M. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. *Ann Clin Biochem*. 2008;45:114. PMID: 18275690. **KQ3E2, KQ8E13.**

## Appendix C. Excluded Studies

314. Weghuber D, Widhalm K. Effect of 3-month treatment of children and adolescents with familial and polygenic hypercholesterolaemia with a soya-substituted diet. *Br J Nutr*. 2008;99(2): 281-6. PMID: 17697400. **KQ6E13, KQ7E13.**
315. Weiner K, Durrington PN. Patients' understandings and experiences of familial hypercholesterolemia. *Community Genet*. 2008;11(5): 273-82. PMID: 18493125. **KQ4E5.**
316. West RJ, Fosbrooke AS, Lloyd JK. Treatment of children with familial hypercholesterolaemia. *Postgrad Med J*. 1975;51(8): suppl 82-87. PMID: 768952. **KQ7E13, KQ8E13.**
317. West RJ, Lloyd JK. Use of cholestyramine in treatment of children with familial hypercholesterolaemia. *Arch Dis Child*. 1973;48(5):370-374. PMID: 4703066. **KQ7E13, KQ8E13.**
318. West RJ, Lloyd JK. The effect of cholestyramine on intestinal absorption. *Gut*. 1975;16(2):93-98. PMID: 1168607. **KQ7E13, KQ8E13.**
319. West RJ, Lloyd JK, Leonard JV. Long-term follow-up of children with familial hypercholesterolaemia treated with cholestyramine. *Lancet*. 1980;2(8200):873-875. PMID: 6107543. **KQ7E13, KQ8E13.**
320. Wheeler KA, West RJ, Lloyd JK et al. Double blind trial of bezafibrate in familial hypercholesterolaemia. *Arch Dis Child*. 1985;60(1): 34-7.. PMID: 3882058. **KQ7E13, KQ8E13.**
321. Widhalm K, Dirisamer A, Lindemayr A et al. Diagnosis of families with familial hypercholesterolaemia and/or Apo B-100 defect by means of DNA analysis of LDL-receptor gene mutations. *J Inherit Metab Dis*. 2007;30(2): 239-47. PMID: 17347910. **KQ3E7.**
322. Wierzbicki AS, Viljoen A. Hyperlipidaemia in paediatric patients: the role of lipid-lowering therapy in clinical practice. *Drug Saf*. 2010;33(2): 115-25. PMID: 20082538. **KQ7E2.**
323. Wilcken DE, Blades BL, Dudman NP. A neonatal screening approach to the detection of familial hypercholesterolaemia and family-based coronary prevention. *J Inherit Metab Dis*. 1988;11 Suppl 1:87-90. PMID: 3141689. **KQ4E6.**
324. Williams RR, Hunt SC, Barlow GK et al. Prevention of familial cardiovascular disease by screening for family history and lipids in youths. *Clin Chem*. 1992;38(8B Pt 2):1555-60. PMID: 1643739. **KQ4E6.**
325. Wilson DP, Gidding SS. Learning More about Dyslipidemia in Childhood. *J Pediatr*. 2013;164(3): 442-4. PMID: 24373576. **KQ1E2.**
326. Wineinger NE, Harper A, Libiger O et al. Genomic risk models improve prediction of longitudinal lipid levels in children and young adults. *Front Genet*. 2013;4:86. PMID: 23734161. **KQ3E5, KQ6E5, KQ7E5.**
327. Wong H, Chahal N, Manlhiot C et al. Flaxseed in pediatric hyperlipidemia: a placebo-controlled, blinded, randomized clinical trial of dietary flaxseed supplementation for children and adolescents with hypercholesterolemia. *JAMA Pediatr*. 2013;167(8): 708-13. PMID: 23733031. **KQ6E5, KQ7E5.**
328. Wong ND, Hei TK, Qaqundah PY et al. Television viewing and pediatric hypercholesterolemia. *Pediatrics*. 1992;90(1 Pt 1):75-9. PMID: 1614784. **KQ4E6.**
329. Wu BU, Pandol SJ, Liu IL. Simvastatin is associated with reduced risk of acute pancreatitis: findings from a regional integrated healthcare system. *Gut*. 2015;64(1): 133-8. PMID: 24742713. **KQ8E13.**
330. Xu H, Li Y, Liu A et al. Prevalence of the metabolic syndrome among children from six cities of China. *BMC Public Health*. 2012;12:13. PMID: 22225617. **KQ3E4, KQ4E4.**
331. Zachariah JP, Johnson PK. Pediatric lipid management: an earlier approach. *Endocrinol Metab Clin North Am*. 2014;43(4): 981-92. PMID: 25432392. **KQ1E2, KQ3E2.**
332. Zakim D, Fritz C, Braun N et al. Computerized history-taking as a tool to manage dyslipidemia. *Vasc Health Risk Manag*. 2010;6:1039-46. PMID: 21127700. **KQ3E5, KQ6E5, KQ7E5.**
333. Zung A, Shachar S, Zadik Z et al. Soy-derived isoflavones treatment in children with hypercholesterolemia: a pilot study. *J Pediatr Endocrinol Metab*. 2010;23-42006:133-41. PMID: 20432816. **KQ6E5, KQ7E5.**

## Appendix D. Diagnostic Criteria for Familial Hypercholesterolemia

**Table 1. MEDPED Criteria (United States)<sup>\*1</sup>**

Age	Total Cholesterol (LDL-C) concentrations, mg/dL			
	First-degree relative	Second-degree relative	Third-degree relative	General population
<18	220 (155)	230 (165)	240 (170)	270 (200)
20	240 (170)	250 (180)	260 (185)	290 (220)
30	270 (190)	280 (200)	290 (210)	340 (240)
40 +	290 (205)	300 (215)	310 (225)	360 (260)

\*Cutoffs for 98% specificity and 54% to 88% sensitivity.

**Abbreviation:** LDL-C=low-density lipoprotein cholesterol.

**Table 2. Simon Broome Criteria (United Kingdom)<sup>2</sup>**

Total cholesterol (LDL-C) of 290 mg/dL (190 mg/dL) in adults or 260 mg/dL (155 mg/dL) in pediatrics (age <16 years) <b>AND</b>	
1. DNA mutation	Definite FH
2. Tendon xanthomas in the patient or in a first- or second-degree relative	Probable FH
3. Family history of MI at age <50 years in second-degree relative or at age <60 years in first-degree relative	Possible FH
<b>OR</b>	
Family history of total cholesterol >290 mg/dL in first- or second-degree relative	

**Abbreviations:** LDL-C=low-density lipoprotein cholesterol, MI=myocardial infarction, FH=familial hypercholesterolemia.

**Table 3. Dutch Criteria (The Netherlands)<sup>3</sup>**

1 point	First-degree relative with premature cardiovascular disease or LDL-C >95 <sup>th</sup> percentile, or personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 and 189 mg/dL
2 points	First-degree relative with tendinous xanthoma or corneal arcus, or first-degree relative child (<18 years) with LDL-C >95 <sup>th</sup> percentile, or personal history of coronary artery disease
3 points	LDL-C between 190 and 249 mg/dL
4 points	Presence of corneal arcus in patient age <45 years
5 points	LDL-C between 250 and 329 mg/dL
6 points	Presence of a tendon xanthoma
8 points	LDL-C >330 mg/dL or functional mutation in the <i>LDLR</i> gene

**Abbreviations:** LDL-C=low-density lipoprotein cholesterol, LDLR=low-density lipoprotein receptor, FH=familial hypercholesterolemia.

Definite FH (≥8 points); probable FH (6–7 points); possible FH (3–5 points).

## References

1. Williams RR, Hunt SC, Schumacher MC, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardiol.* 1993;72(2):171-6. PMID: 8328379.
2. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ.* 1991;303(6807):893-6. PMID: 1933004.
3. World Health Organization. Familial hypercholesterolemia—report of a second WHO Consultation. Geneva, Switzerland: World Health Organization; 1999.

## Appendix E. Cohort Studies

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