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

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Structured Abstract

Background: Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism characterized by highly elevated low density lipoprotein cholesterol (LDL-C) levels early in life and is associated with substantial long-term cardiovascular risk. Multifactorial dyslipidemia includes dyslipidemias that are not FH that may be associated with environmental factors, with or without an inherited component. Lipid screening in childhood and adolescence can lead to early diagnosis of FH and non-FH multifactorial dyslipidemia. The long-term potential benefits of lipid screening and subsequent treatment are uncertain.

Purpose: To systematically review evidence for the effectiveness and harms of screening and treatment of pediatric dyslipidemia due to FH and multifactorial dyslipidemia.

Data Sources: We searched MEDLINE, and the Cochrane Central Register of Controlled Clinical Trials to identify literature that was published between January 2015 and May 16, 2022. Studies included in the 2016 review for the USPSTF were re-evaluated for potential inclusion. We supplemented our searches with reference lists from the previous review, relevant existing systematic reviews, suggestions from experts, and Clinicaltrials.gov to identify ongoing trials. We conducted ongoing surveillance for relevant literature through September 23, 2022.

Study Selection: Two investigators independently reviewed 7,058 abstracts and 272 full-text articles against prespecified inclusion criteria. We included English-language publications of studies conducted among children and adolescents 20 years of age or younger in countries categorized as “Very High” on the Human Development Index. For studies evaluating the benefits and harms of lipid screening, we included RCTs of universal or selective screening using a serum lipid panel compared to no screening or usual care that reported a health outcome (MI, ischemic stroke, CVD mortality, or all-cause mortality), intermediate outcome (serum lipid concentrations, atherosclerosis markers, BMI), intermediate behavioral outcome (physical activity, sedentary behavior, dietary intake), or harm. For studies evaluating the diagnostic yield of serum lipid screening, we included recent, large U.S. cohort studies that conducted universal or selective lipid screening and reported screen positivity for any stated threshold of abnormal lipids based on a single lipid test or the positive predictive value of a first elevated screening lipid result for a second confirmatory test. For studies evaluating the benefits and harms of treatment, we included RCTs of lipid-lowering medications, behavioral counseling interventions, and dietary supplements that had a comparator group of no treatment, placebo, or usual care and reported a health outcome, intermediate outcome, intermediate behavioral outcome, or harm. One investigator abstracted data into an evidence table and a second investigator checked these data.

Data Analysis: Random effects meta-analysis was used to evaluate the lipid-lowering efficacy of interventions with sufficient evidence to warrant pooled analyses. Other analyses for each key question were qualitative.

Results: 43 studies were eligible for inclusion (n=491,516). Twenty-six studies (n=437,000) were in children and adolescents with familial hypercholesterolemia (FH), 9 studies (n=143,265)

in children and adolescents with multifactorial dyslipidemia, and 9 studies (n=10,624) were among children and adolescents with FH or multifactorial dyslipidemia.

Familial Hypercholesterolemia:

Direct Screening Benefits and Harms (KQ 1, 3): There were no randomized screening trials directly addressing the effectiveness and harms of screening for FH in children and adolescents.

Screening Yield (KQ 2): No studies performed a confirmatory lipid or genetic test; thus, evidence is limited to screen-positivity (prevalence) rather than diagnostic yield of lipid screening for identifying FH. We included three fair-quality U.S. studies (n=395,465) reporting prevalence of FH of 0.2 to 0.4 percent (1:250 to 1:500) using diagnostic criteria exclusively based on lipid levels (LDL-C \geq 190 mg/dL or TC \geq 270 mg/dL). One study showed that targeted screening in those with a family history would miss many cases of children with LDL-C \geq 160 mg/dL (prevalence in those with family history: 1.2%, prevalence in those without family history: 1.7%).

Treatment Benefits (KQ4): We included 22 fair- to good-quality trials (n=2,257) examining the effectiveness of various lipid-lowering treatments for FH including pharmacotherapy, behavioral counseling, and dietary supplements. Ten fair- to good-quality randomized, controlled trials (RCTs) (N=1,230) of statins comprised the largest body of evidence addressing FH treatment with followup up to 2 years. Pooled analyses demonstrated that statins were associated with an 81-82 mg/dL greater mean difference in total cholesterol (TC) and LDL-C compared to placebo at up to 2 years followup. Within-trial comparisons demonstrated that higher doses were generally associated with greater reductions in TC and LDL-C compared to lower doses, but confidence intervals overlapped. Pooled analysis showed no statistically significant difference in HDL-C. Individual trials showed mixed results for triglycerides (TG). We included one good- and two fair-quality bile acid sequestrant trials (n=332) trials demonstrating a significantly greater reduction in TC ranging from -22.1 to -40.6 mg/dL and LDL-C ranging from -13.2 to -45.9 mg/dL compared to placebo at 8 weeks. Bile acid sequestrants were not associated with statistically significant reductions in TG and results were mixed for HDL-C, with some variation in effect by dose. We included one good quality ezetimibe trial (n=138) showing a statistically significant 63.0 to 65.0 mg/dL mean reduction in TC and LDL-C, and non-HDL-C. Changes in HDL-C and TG were not significant. We included one very small fair-quality fibrate trial (N=14) reporting a statistically significant 84.9 mg/dL mean reduction in TC but no significant differences in HDL-C or TG at 13 weeks; however, this drug is not available in the U.S and not FDA-approved in children. One good quality PCSK9 inhibitor trial (n=158) demonstrated that evolocumab was associated with a statistically significant 38.3 percent reduction in LDL-C and absolute mean reduction of 68.6 mg/dL with 60.2 percent greater absolute difference in achievement of goal LDL-C <100 mg/dL compared to placebo at 24 weeks. One previously included trial of a statin and ezetimibe drug combination compared to a statin alone (n=248) showed that the two-drug intervention was associated with a 37.5 to 40.1 mg/dL greater reduction in TC, LDL-C, and non-HDL-C, and a 9.5 mg/dL median difference in percent change of TG compared to the single-drug intervention control group at 33 weeks.

We included one very small fair-quality behavioral counseling trial (n=21) in an FH population that reported no statistically significant improvement in lipid levels, overlapping confidence intervals for physical activity outcomes, and mixed results for dietary outcomes at 12 weeks.

We included four fair-quality randomized crossover supplement trials (n=116) in FH populations. The two trials of plant sterol food spreads demonstrated statistically significant reductions of 20.5 to 30.5 mg/dL in TC and 22.4 to 30.1 mg/dL in LDL-C at 4 to 8 weeks. The two trials of omega-3 fatty acids did not show a statistically significant difference in lipid level changes between the intervention and control groups.

Treatment Harms (KQ5): Harms reported in statin trials were similar in the intervention and control groups; however, most studies were relatively short term and small, with few events leading to imprecise estimates. Transaminitis (elevations in alanine transaminase [ALT] or aspartate transaminase [AST]) of three times or more the upper limit of normal occurred in 0 to 4.5 percent of participants in the intervention groups and 0 to 1.9 percent in control groups. The largest trial (n=214) with 2-year followup reported no cases in the statin group and only 2 cases of AST more than 3 times the upper limit of normal in the control group. In the 10-year observational followup of this trial, transaminitis at this threshold was similarly rare (ALT: 1 case of >3 times elevation in the statin group; AST: 1 case of >3 each in the statin and control group). Abnormal creatine kinase of 10 times or greater the upper limit of normal was reported as zero in two trials, up to 4.5 percent in the statin groups, and up to 1.7 percent in the control groups. One trial's 10-year observational followup reported no instances of elevated creatine kinase in participants on statins and in two non-FH siblings not taking statins. One fair-quality observational study evaluated the association of statins and new onset diabetes (n=9,393), showing no difference in new diabetes diagnoses over 9 years followup in those taking statins compared to controls. One fair-quality observational study (n=943) reported ALT more than 3 times the upper limit of normal with a frequency of 4.4 percent in the statin group and 1.5 percent in the control group over 3.5 years of observation. No significant differences between Tanner stages or other hormonal adverse events were reported in the RCTs or longer observational followup.

Harms in the non-statin trials were similar in the intervention and control groups; however, for bile acid and fibrate trials, the trials were generally small with few events. The diet and physical activity counseling intervention did not mention harms and three supplement trials in FH reported that there were no adverse events.

Multifactorial Dyslipidemia:

Direct Screening Benefits and Harms (KQ 1, 3): There were no randomized screening trials directly addressing the effectiveness and harms of screening for multifactorial dyslipidemia in children and adolescents.

Screening Yield (KQ 2): No studies performed a confirmatory lipid test; thus, evidence is limited to screen-positivity (prevalence) rather than diagnostic yield of lipid screening for identifying multifactorial dyslipidemia. We included five fair-quality studies (n=142,257) reporting prevalence of multifactorial dyslipidemia showing that lipid abnormalities are common, being generally more common for the parameters of HDL-C and TG. Prevalence ranged from 7.1 to

9.4 percent for elevated TC (≥ 200 mg/dL), 6.4 to 7.4 percent for elevated LDL-C (≥ 130 mg/dL), 12.1 to 22.2 percent for low HDL-C (< 40 mg/dL), 8.0 to 17.3 percent for elevated TG (using various thresholds), and 6.4 to 13.0 percent for elevated non-HDL-C (≥ 145 mg/dL). Prevalence of any lipid abnormality in 6- to 19-year-olds was 19.2 percent based on NHANES data (2013-2016, n=4,381). Older age and higher BMI ($\geq 95^{\text{th}}$ percentile) were associated with higher prevalence of multifactorial dyslipidemia. Prevalence by sex was inconsistent across the cohorts and for different lipid measures.

Treatment Benefits (KQ4): We included four fair- to good-quality trials (n=1,008) examining the effectiveness of various lipid lowering treatments for multifactorial dyslipidemia. There were no included trials of drug interventions in child and adolescent populations with multifactorial dyslipidemia. We included two behavioral counseling trials (n=934), one fair-quality and one good-quality. These trials demonstrated statistically significant greater reductions in TC (3-6 mg/dL) and improvements in dietary intake outcomes in the intervention group compared to the control group in the short-term, but findings did not persist at longer follow-up.

We included two fair-quality supplement intervention trials (n=74) in populations with multifactorial dyslipidemia examining flaxseed and fish oil. These trials reported no statistically significant difference in TC or LDL-C, and flaxseed was associated with a statistically significant worsening of TG and HDL-C in the intervention group. There were no differences in BMI or total caloric intake.

Treatment Harms (KQ5): The two behavioral counseling trials in children with multifactorial dyslipidemia (n=934) reported no adverse effects in terms of growth and development, nutrient adequacy, and psychosocial outcomes in the dietary intervention group compared to the control group. The flaxseed trial (n=32) reported no adverse events; the fish oil trial (n=42) reported gastrointestinal symptoms, fishy taste, and frequent nose bleeds. Most trials reporting growth and development harms were limited by short duration.

Familial Hypercholesterolemia and Multifactorial Dyslipidemia:

Treatment Benefits (KQ4): We included seven fair- to good-quality supplement trials (n=288) which evaluated a wide range of supplement interventions in populations of children and adolescents with FH or multifactorial dyslipidemia. Only one trial, which evaluated the fiber glucomannan, showed a statistically significant improvement in TC, LDL-C and non-HDL-C (-10 to -11 mg/dL). Two other fiber trials, however, showed no statistically significant improvements in TC or LDL-C. One psyllium fiber trial showed a 60.2 mg/dL reduction in TG while other fiber trials showed no difference in TG. The trials of hempseed, probiotics, and hazelnuts showed no statistically significant reductions in any lipid parameter.

Treatment Harms (KQ5): Five of the seven supplement trials reported harms with two trials reporting no adverse events. The fiber trials reported various gastrointestinal side effects of 0 to 22.2 percent in intervention groups and 0 to 5.0 percent in control groups, and the probiotic trial reported three cases of abdominal pain (5.4% v 2.8%).

Limitations: No studies performed a confirmatory lipid or genetic test; thus, evidence is limited to screen-positivity (prevalence) rather than diagnostic yield of lipid screening for FH. FH

diagnostic criteria were limited to lipid levels alone, which is inconsistent with treatment trial criteria which also included genetic, family, or clinical history components in addition to lipid levels. Treatment trials were generally small with relatively short followup, with most trial durations of less than 6 months. Only one statin trial had a followup as long as 2 years. With the exception of statins evaluated in the FH population, the bodies of evidence for any specific intervention in either the FH or multifactorial dyslipidemia population were extremely sparse, often consisting of just one to three studies. Behavioral counseling and supplement trials were generally small, with short-term followup leading to uncertainty regarding long-term adherence and benefit persistence. Outcomes for treatment trials were limited to intermediate outcomes with insufficient followup periods to assess long-term health effects or harms.

Conclusions: There is no direct evidence from population-based screening trials addressing the benefits and harms of pediatric lipid screening for intermediate, behavioral, or health outcomes. Dyslipidemia is common in pediatric populations with a prevalence of 19.2 percent for any lipid abnormality and heterozygous FH prevalence estimated at 0.2 to 0.4 percent (1:250 to 1:500). The body of evidence on treatment benefit is strongest for statins in FH children and adolescents based on mostly small, short-term studies with the longest trial of 2 years showing beneficial effects on TC and LDL-C. Most of the evidence for statin harms is from small, short-term studies and limited longer-term evidence showing few withdrawals due to adverse events, slightly higher rates of liver and musculoskeletal lab elevations, and no significant differences in Tanner staging or hormonal adverse events between statin and placebo groups. The trials of bile acids, fibrates, and PCSK-9 inhibitors in FH populations show reductions in one or more lipid parameters and are generally associated with low withdrawals due to adverse events. There is scant evidence on behavioral counseling interventions and supplements in populations with FH; two small plant sterol supplement trials show improvement in TC and LDL-C at 4-8 weeks. The body of evidence on treatment of multifactorial dyslipidemia is sparse, being limited to two short-term behavioral counseling interventions showing modest short-term benefits in lipid levels that did not persist with longer followup and two supplement studies of flaxseed and fish oil showing no benefit in lipid levels. Supplement trials recruiting both FH and multifactorial dyslipidemia populations show mixed results for fiber supplements. Fiber supplements were commonly associated with gastrointestinal side effects; otherwise, four of the seven supplement trials in populations with FH or multifactorial dyslipidemia reported no adverse events, no serious adverse events, or no AEs leading to withdrawals.

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Chapter 1. Introduction

Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2016 recommendation on screening for lipid disorders in children and adolescents.¹ The 2016 recommendation was based on two separate systematic review reports: screening for familial hypercholesterolemia,² and screening for multifactorial dyslipidemia.³ This systematic review presents updated evidence in a single report with special attention to clearly delineating the evidence specific to familial hypercholesterolemia and multifactorial dyslipidemia.

Condition Background

Condition Definition

Familial hypercholesterolemia (FH) is an autosomal codominant genetic disorder of lipid metabolism associated with elevated levels of low-density lipoprotein-cholesterol (LDL-C) which causes premature atherosclerosis and early cardiovascular mortality and morbidity.⁴ There are both heterozygous and homozygous forms of FH, with the latter being characterized by much higher total and LDL-C levels.⁵ In addition to premature CVD experienced in homozygous and heterozygous FH patients, LDL-C deposits can cause tendon xanthomas and corneal arcus; these manifestations are more severe and occur earlier in homozygous FH compared to heterozygous FH.^{6,7} This report specifically addresses heterozygous FH as it is the most common monogenic cause of dyslipidemia.⁸

FH is genetically heterogeneous and is caused most frequently by pathogenic variants in the low-density lipoprotein receptor (*LDLR*), *APOB* or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes; there are additionally other pathogenic variants with very low frequency which manifest as a FH-like phenotype.⁹ However, the relationship between the FH genotype arising from these variants and the FH phenotype characterized by elevated LDL-C is not straightforward.¹⁰ For example, analyses in adults have shown that among those with LDL-C ≥ 190 mg/dL, less than 2 percent carried a FH mutation.¹¹ The rate of detection of pathogenic variants among those meeting clinical criteria for FH has been shown to be as low as 52 percent, suggesting deficiencies in genetic testing strategies or that there may be a more complex polygenic basis for the FH phenotype.¹⁰ Further, while a very high percentage of FH pathogenic variant carriers show elevated lipid levels, not all individuals with a confirmed genetic variation will have a severe dyslipidemia phenotype.¹²⁻¹⁴ For example, one analysis reported that the penetrance for 59 pathogenic/loss of function variants for *LDLR* ranged from 0 to 100 percent.¹⁵ This complex relationship between FH genotype and phenotype may give rise to controversy over whether clinical criteria or a molecular definition of FH is more appropriate. Some have suggested a new classification paradigm for FH whereby the presence or absence of the pathogenic variant and severe hypercholesterolemia are specified.¹⁶

There are no globally accepted diagnostic criteria for FH.^{7, 17} The US-based Make Early Diagnosis Prevent Early Death (MEDPED) criteria are genetically validated thresholds that use lipid levels in conjunction with age and family history of known FH.¹⁸ The UK-based Simon Broome criteria¹⁹ and the Dutch Lipid Clinic Network criteria (DLCNC)^{7, 20} involve personal and family history, physical signs, and DNA analysis in addition to lipid levels. These criteria are summarized in **Tables 1-3**.

For the purposes of this report, the term **multifactorial dyslipidemia** refers to dyslipidemias involving abnormal lipids that are not FH.³ Multifactorial dyslipidemia in children and adolescents may be associated with environmental factors, such as excessive intake of saturated fat, high carbohydrate diets containing principally simple sugars, and sedentary lifestyle, with or without an inherited component.^{3, 21-26} Even apart from a monogenic condition with high penetrance, such as FH where there is a major variant in one gene, there are a number of single nucleotide variants with smaller additive effects that contribute to multifactorial dyslipidemia.²⁷

Lipid disorders are defined according to population norms.^{28, 29} Cutpoints for abnormal lipid values defining multifactorial dyslipidemia correspond to approximately the 95th percentile from population-based cohorts.³⁰ **Table 4** shows thresholds for multifactorial dyslipidemia that are used in clinical guidelines and widely accepted in practice.^{30, 31} These thresholds have not been validated as predictors for CVD events and they are not age- and sex-specific.^{21, 32}

Secondary dyslipidemia can occur in children and adolescents with a variety of renal, infectious, hepatic, inflammatory and storage disorders, type 1 and 2 diabetes, and several other syndromes.³⁰ Secondary dyslipidemias will not be addressed in the review.

Prevalence and Burden

Prevalence of FH

FH is far more rare than multifactorial dyslipidemia. A 2020 systematic review by Hu and colleagues which included 42 studies representing 7,297,363 participants estimates that the international prevalence of FH in the general population is 0.32 percent (95% CI, 0.25 to 0.40) or 1:311 (95% CI, 1:250 to 1:397).³³ Stratified analyses by age suggest that FH prevalence point estimates were slightly lower in pediatric populations but with confidence intervals overlapping estimates in adults. In the review by Hu et al, the prevalence of FH in children was estimated to be 0.28 percent (95% CI, 0.11 to 0.51) compared to 0.33 percent (95% CI, 0.24 to 0.43) in adults.³³ Given that FH is a genetic condition, it might be assumed that prevalence would be constant across age. It has been postulated that rising LDL-C levels in older age may increase the likelihood that older individuals meet clinical criteria.³⁴ At the same time, prevalence estimates would be expected to decline in older ages because of CVD-related attrition, suggesting complex forces behind age-related prevalence trends. Investigators have found that underdiagnosis of FH is greatest among children and young adults.³⁵

Another 2022 meta-analysis pooled international prevalence data from over 1.1 million individuals demonstrating variation across racial and ethnic groups ranging from 0.25% to

0.52%.³⁶ Among US samples included in this analysis, the lowest point prevalence was in White populations (0.21%) and the highest point prevalence was in Black Americans (0.46%).

Prevalence of Multifactorial Dyslipidemia

Abnormal lipid levels are highly prevalent worldwide. The latest estimates from the World Health Organization (2008) estimate a global prevalence of elevated total cholesterol (TC) among adults of 39 percent.³⁷ Work to update these prevalence estimates is currently underway.³⁸ In 2017, high LDL-C was reported to be the fifth-leading cause of risk-attributable deaths, responsible for 4.3 million deaths worldwide in 2017.³⁹

Recent prevalence estimates for FH and multifactorial dyslipidemia specific to pediatric populations in the U.S. are systematically reviewed in this report and presented in the results.

Prognosis

Prognosis of FH

FH is associated with very high cardiovascular risk and accelerated vascular aging.⁴ Subclinical atherosclerotic changes appear early in children with FH, with evidence suggesting statistically significant differences in carotid intima-media thickness (cIMT) between children with and without FH as early as 8 years of age with FH children experiencing a far more rapid progression of cIMT.^{40, 41} By adulthood, atherosclerotic burden in individuals with FH has increased substantially because of cumulative exposure to high LDL-C.

There is robust evidence showing the association of the FH phenotype in adulthood with substantially increased risk for cardiovascular events in adulthood. An individual patient data (IPD) meta-analysis of 68,565 adults from six U.S. cohorts found that the FH phenotype, defined by LDL-C ≥ 190 mg/dL, was associated with an adjusted hazard ratio of 4.1 (95% CI, 1.2 to 13.4) for CVD events over 30 years of followup, compared to a reference group defined by LDL-C < 130 mg/dL.⁴² Results were similar when using alternate FH phenotype definitions. These investigators found that the FH phenotype accelerated coronary heart disease (CHD) risk by 10 to 20 years in men, and 20 to 30 years in women. However, these data were primarily collected before the widespread use of statins, with enrollment periods ranging from 1968 to 1990. Observational studies in adults with FH recruited from lipid clinics suggest that the prognosis of FH has improved substantially with the advent of statin treatment.^{43, 44}

Prognostic data for FH as determined by genotype is more scant. Data in adults from the Myocardial Infarction Genetic Consortium Studies shows that carriers of FH variants are at increased risk for coronary artery disease at any level of LDL-C.¹¹ For example, the odds ratio for coronary artery disease was 5.2 (95% CI, 4.4 to 6.2) for an individual with LDL-C ≥ 190 -220 mg/dL but without a genetic variant (compared to an individual with LDL-C < 130 mg/dL and no genetic variant) but the odds ratio for CAD was 17.0 (95% CI, 5.3 to 77.9) among individuals with this level of LDL-C in the presence of an FH genetic variant.¹¹

Prognosis of Multifactorial Dyslipidemia

Multifactorial dyslipidemia in adulthood is widely established as a risk factor for CVD based on robust evidence from IPD meta-analyses showing strong associations between cholesterol levels in adulthood and ischemic heart disease mortality.⁴⁵ Total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) are risk factors included in the Pooled Cohort Equations which are the standard of care risk calculator currently used to estimate 10-year CVD risk in adults and guide initiation of preventive therapies.⁴⁶⁻⁴⁸

To establish linkages between elevated lipids in childhood and adolescence with later CVD events, extremely long followup from prospective cohort studies beginning in childhood is required. A 2022 publication from the International Childhood Cardiovascular Cohorts (i3C) Consortium does suggest that elevated lipid levels in childhood (ages 3 to 19 years) are associated with fatal cardiovascular events in adulthood with 35 years of followup; however, the evidence is complicated by the role of adult lipid levels and lack of control for other risk factors.⁴⁹ This evidence is explored more fully in the Discussion.

Risk Factors

Familial hypercholesterolemia is an inherited genetic condition that can be passed down from one or both parents. Heterozygous FH occurs when a child inherits the gene from one parent. The more severe form of FH (homozygous FH) occurs when a child inherits the gene from both parents.

Multifactorial dyslipidemia in children and adolescents may be associated with environmental factors, such as lifestyle, with or without a genetic component.³⁰ Abnormal lipid levels have consistently been shown to be associated with various measures of adiposity.⁵⁰⁻⁵⁶ Data from the National Health and Nutrition Examination Survey (NHANES) show that while higher BMI ($\geq 85^{\text{th}}$ percentile) roughly doubles the risk for elevated TC, that a substantial proportion of those with elevated TC have a BMI $< 85^{\text{th}}$ percentile (42% to 63%).⁵⁷ Evidence in children and adolescents suggests that higher rates of physical activity and lower rates of sedentary time are associated with more favorable lipid profiles.²²⁻²⁵

A family history of dyslipidemia or premature cardiovascular disease is a risk factor for childhood dyslipidemia.⁵⁸ Even apart from a monogenic condition with high penetrance, such as FH where there is a major variant in one gene, there are a number of single nucleotide variants with smaller additive effects that contribute to multifactorial dyslipidemia.²⁷

Rationale for Screening

FH is normally asymptomatic in childhood⁴ and is rarely associated with cardiovascular illness in the first two decades of life.^{44, 59} However, early identification of elevated lipid levels, particularly in populations with FH whereby lipid levels are much higher than in multifactorial dyslipidemia, could aid in identifying populations for initiation of lipid control to reduce lifelong exposure to elevated lipids, and in turn reduce cardiovascular risk in adulthood. Some experts

suggest that the primary purpose of lipid screening in pediatric populations is to identify those with FH (rather than those with multifactorial dyslipidemia).⁶⁰

FH is underdiagnosed and undertreated. The extent of underdiagnosis is not known but likely varies by country. In countries with robust screening programs like the Netherlands, it is estimated that as many as 71% of cases are identified.⁶¹ Investigators in the UK have further found that underdiagnosis of FH is greatest among children and young adults.³⁵ In the US, analyses of the CASCADE FH registry have found that FH patients tend to be diagnosed and treated late in life, with median treatment initiation of 39 years and median age of diagnosis of 47 years.⁶² Given that subclinical atherosclerotic changes appear early in children with FH and that CVD risk is increased by cumulative exposure to elevated lipid levels, missed diagnoses at earlier ages likely increase the burden of atherosclerotic CVD. However, the burden of atherosclerotic CVD associated with undiagnosed or undertreated FH in the general U.S. population has not been quantified.⁴²

Screening Strategies

Targeted vs. Universal Screening

Targeted and universal screening have been proposed as possible screening strategies for both FH and multifactorial dyslipidemia in children and adolescents (**Table 5**). There are some differences in current screening guidelines in the US. In 2016, the USPSTF issued an I Statement, stating that current evidence was insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents aged 20 years or younger.¹ In comparison, the American Academy of Pediatrics endorsed and adopted the 2012 recommendations from the National Heart, Lung, and Blood Institute (NHLBI) which have a positive recommendation to selectively screen children 2 to 8 years of age with family history of CVD or dyslipidemia, or in the presence of other risk factors, and universally screen children between 9 and 11 years and again between 17 and 21 years.^{30, 63}

FH

Several models for FH screening have been studied and/or implemented internationally including cascade screening, universal screening, and precision screening.⁶⁴⁻⁶⁷ Several guidelines have suggested targeted serum lipid screening in children who have a positive family history of premature CVD or relatives with known familial hyperlipidemia. However, studies have shown that patient reports of family history have poor accuracy,⁶⁸ potentially limiting the usefulness of this strategy. A large ongoing population-based screening study of children in one U.S. state has found that use of family history alone is not a strong indicator of LDL-C values warranting pharmacological treatment.⁶⁹ Targeted screening for FH based on other risk factors like elevated BMI is also not ideal because the mechanisms of FH are independent of obesity. Estimates of FH in U.S. youth by obesity status are not available, but estimates are available in adults. While adults with obesity are more likely to meet FH criteria, there are a nontrivial number of nonobese individuals with FH (0.58% [1:172] in adults with obesity compared to 0.31% [1:325] in adults without obesity).⁷⁰

Universal serum lipid testing would lead to greater identification of FH but would also lead to more testing compared to targeted screening. Identification of youth with FH may also offer the additional benefit of identifying adults in the family through reverse cascade screening.^{71, 72}

Multifactorial Dyslipidemia

Targeted serum lipid screening for those identified as overweight or obese has been proposed based on the high prevalence of multifactorial dyslipidemia in overweight and obese youth. Epidemiologic data confirms higher prevalence of abnormal lipids in higher BMI populations,⁵² however, screening guided by weight status alone would miss a nontrivial number of individuals with multifactorial dyslipidemia who are not in overweight or obese BMI categories.

Serum Lipid Components for Screening

Clinical questions arise about which components of the lipid panel are needed for screening in all ages. In children, data are limited regarding which components of the lipid panel are predictive of CVD events and mortality later in life. Analyses from the i3C Consortium show that both TC and TG are associated with mortality in adulthood, but data for LDL-C and HDL-C are not reported.⁴⁹ Some evidence suggests that non-HDL-C in childhood is equivalent to LDL-C for predicting adult cIMT.⁷³ Thus, non-HDL-C may have clinical utility for nonfasting samples or in those with TG >400 mg/dL. Data in adults are somewhat conflicting about the lipid component with the best predictive power for CVD events, with conclusions being limited by the fact that not all lipid components are available in each analysis. In 2019, the Multinational Cardiovascular Risk Consortium reported that non-HDL-C and LDL-C have comparable prognostic relevance for atherosclerotic CVD.⁷⁴ The Pooled Cohort Equations, currently used for multivariate CVD risk assessment in adults, use TC and HDL-C.⁷⁵

Fasting vs. Nonfasting Tests

There are dynamic effects of eating on some lipid components, particularly TG.⁷⁶ Because LDL-C is often estimated using the Friedewald formula ($LDL-C = [TC - HDL-C] - [TG/5]$),⁷⁷ this calculated LDL-C value is also affected by fasting status. Other methods of calculating LDL-C, however, have been validated in nonfasting samples.⁷⁸

Nonfasting tests are recommended as a method for improving the feasibility and acceptability of screening, where fasting may be particularly burdensome for pediatric populations.^{30, 76} Nonfasting tests are accepted as a first screening step in youth ages 9 to 11 years in prominent U.S. guidelines.³⁰ However, it is recommended that initially abnormal lipid levels be confirmed by an additional test in the fasting state. Nonfasting lipid tests have become standard in some European countries for screening in adults.⁷⁶ Large analyses in both children and adults have shown that differences in lipid values between fasting and nonfasting samples may be small and may not be clinically important.⁷⁹

Treatment Approaches

The treatment pathway is different in FH and multifactorial dyslipidemia because of the substantially higher lipid levels seen in FH (**Appendix A Table 3**). Various treatment modalities have been recommended for lipid-lowering, including lifestyle modification (**Appendix A Table 4**), pharmacotherapy, and dietary supplements. Several drugs are approved by the FDA for use in pediatric populations with heterozygous FH (**Appendix A Table 5**).⁸⁰⁻⁸³ Seven statins are approved in pediatric populations with heterozygous FH in ages as young as 8 years old. Other agents, including bile acid sequestrants, ezetimibe, and PCSK9 inhibitors are FDA-approved in pediatric populations with heterozygous FH in ages as young as 10 years old.

FH

Youth with heterozygous FH are considered “moderate risk” in the AHA Scientific Statement on CVD Risk Reduction in High-Risk Pediatric Patients.⁴ Treatment algorithms in this guidance differ based on risk stratification. For “moderate risk” youth, therapeutic lifestyle change is recommended for 3 months, with the addition of a statin if LDL-C remains above goal (LDL-C <130 mg/dL). General lifestyle advice is a diet high in fiber from fruits and vegetables, whole grains, high in polyunsaturated and monounsaturated fats, low in saturated fat, and devoid of trans fats; five or more hours of moderate to vigorous physical activity per week; and consideration of phytosterol supplements.

Multifactorial Dyslipidemia

Youth with multifactorial dyslipidemia with an LDL-C \geq 160 mg/dL may fall in the “at risk” stratification in the AHA Scientific Statement if obesity, insulin resistance, or other risk factors are present.⁴ In “at risk” individuals, treatment recommendations are to initiate therapeutic lifestyle change for 6 months and if LDL-C remains above goal (LDL-C <130 mg/dL), to add a statin. Lifestyle advice is the same as that for the “moderate risk” individuals described above.

Current Clinical Practice in the United States

Lipid screening in the United States is inconsistent in pediatric populations and this may be due to conflicting screening guidelines, perceived low yield or impact of universal screening, and uncertainty about dyslipidemia treatment.⁸⁴ Recent studies investigating screening practices in large U.S. health care organizations have found universal screening rates of 2 to 9 percent in children between 9 and 11 years of age.⁸⁵⁻⁸⁹ Higher weight status, non-white race or ethnicity, and the presence of comorbid conditions were associated with higher screening rates in these studies.

Data from the CASCADE FH Registry provide information about FH detection and treatment in the U.S. pediatric population in the context of referral populations from lipid clinics.⁹⁰ In a sample of 493 children and adolescents <18 years old from the FH Registry, covering data from 2014-2018, the mean age of FH diagnosis was 9.4 years of age. This is in the context of AAP recommendations to selectively screen children 2 to 8 years of age with family history of CVD or dyslipidemia, or in the presence of other risk factors, and universal screening between 9 and

11 years and again between 17 and 21 years. Of those eligible for lipid-lowering therapy based on age, LDL-C level, and family history, 72 percent were taking a statin and 7 percent a supplement (phytosterols, omega-3 fatty acids, psyllium), yet only 28 percent achieved their LDL-C goal. Genetic testing appeared to be rare, with just 2 percent having a confirmed FH genetic mutation.

Previous USPSTF Recommendation

In 2016, the USPSTF concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents 20 years or younger (**Grade: I statement**).¹ This was consistent with the previous 2007 USPSTF recommendation.⁹¹

The USPSTF has two other recommendations related to cardiovascular disease prevention in children and adolescents. The USPSTF recommends that clinicians screen for obesity in children and adolescents 6 years and older and offer or refer them to comprehensive, intensive behavioral interventions to promote improvements in weight status (**2017 B recommendation**).⁹² Additionally, the USPSTF found insufficient evidence on screening for high blood pressure in children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood (**2020 I statement**).⁹³

In 2022, the USPSTF recommended that clinicians prescribe a statin in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10 percent or greater (**B recommendation**).⁹⁴ The Task Force also recommends clinicians selectively offer a statin to adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors and a calculated 10-year CVD event risk of 7.5 to 10 percent (**C recommendation**). Additionally, the USPSTF concluded that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use in adults 76 years and older (**I statement**).⁹⁴ However, the USPSTF recommendation is not intended for individuals with known FH or with LDL-C ≥ 190 mg/dL who are considered to be at very high CVD risk.

A 2016 systematic evidence review was conducted on screening for dyslipidemia in younger adults ages 21-39 years; however, the authors identified no studies meeting inclusion criteria, and the USPSTF did not make recommendations for this population.⁹⁵

Chapter 2. Methods

Scope and Purpose

This systematic review is a combined update of two prior reports^{2,3} to support the 2016 USPSTF recommendation on screening for lipid disorders in children and adolescents.¹ Previously, separate reports were issued for familial hypercholesterolemia (FH) and multifactorial dyslipidemia, defined as lipid elevations from causes other than FH. Our update includes studies published since the previous reviews and studies from the previous reviews that met updated inclusion criteria.

Analytic Framework and Key Questions

We followed USPSTF procedures and methods to define study inclusion and exclusion criteria (**Appendix A Table 1**) and developed an analytic framework (**Figure 1**) with five Key Questions (KQs).

KQ1. Does screening for familial hypercholesterolemia (FH) or multifactorial dyslipidemia in asymptomatic children and adolescents delay or reduce the incidence of health outcomes (e.g., CVD events* or mortality) or improve intermediate outcomes (e.g., serum lipid levels and atherosclerotic markers) in children, adolescents, or adults?

KQ2. What is the diagnostic yield of serum lipid screening for FH or multifactorial dyslipidemia in children and adolescents?

KQ3. What are the harms of screening for FH or multifactorial dyslipidemia in children and adolescents?

KQ4. Does treatment of FH or multifactorial dyslipidemia with behavioral interventions, lipid-lowering medications, or both in children and adolescents delay or reduce the incidence of health outcomes (e.g., CVD events* or mortality) or improve intermediate outcomes (e.g., serum lipid levels and atherosclerotic markers) in children, adolescents, or adults?

KQ5. What are the harms of treatment of FH or multifactorial dyslipidemia in children and adolescents?

* CVD events are defined as MI or ischemic stroke.

Data Sources and Searches

We considered all studies from the previous reviews on this topic for inclusion in the current review and performed a comprehensive search for new literature. We searched MEDLINE, and the Cochrane Central Register of Controlled Clinical Trials for relevant studies published

between January 2015 and May 16, 2022. Studies included in the previous USPSTF reviews were evaluated for inclusion against the eligibility criteria for the current review. A research librarian developed and executed the search, which was peer-reviewed by a second research librarian (**Appendix A**). Additionally, due to an expansion in the scope of the current review to broaden eligible thresholds for defining multifactorial dyslipidemia, we performed a targeted review of previously excluded studies.

We also examined the reference lists of other previously published reviews, meta-analyses, and primary studies to identify additional potential studies for inclusion. We supplemented our searches with suggestions from experts and articles identified through news and table-of-contents alerts. We conducted ongoing surveillance for relevant literature through September 23, 2022. One new study was identified;⁹⁶ however, it did not substantively change the review's interpretation of findings or conclusions and is not addressed further. We also searched ClinicalTrials.gov (<https://ClinicalTrials.gov/>) for ongoing trials. We managed all literature search results in EndNote® X9 (Thomson Reuters, New York, NY).

Study Selection

Detailed inclusion and exclusion criteria were developed to guide study selection (**Appendix A Table 1**). Two reviewers independently reviewed the titles and abstracts of all identified articles to determine whether studies met these criteria. Two reviewers then independently evaluated the full text of potentially relevant studies. Disagreements regarding the abstract and/or full text review were resolved by discussion and consultation with a third reviewer if necessary. We used DistillerSR (Evidence Partners, Ottawa, Canada) to conduct abstract and full-text review, where records were kept of all included and excluded studies.

Study selection details specific to each KQ are provided below. For all KQs, we required that studies be conducted among children and adolescents 20 years of age or younger and in countries categorized as “Very High” on the 2019 Human Development Index (as defined by the United Nations Development Programme).⁹⁷ Studies needed to be conducted in primary care or a setting referable from primary care. We required that studies be published in the English language.

KQ1 and KQ3 (Benefits and Harms of Screening)

For studies evaluating the benefits and harms of lipid screening, we included RCTs or controlled clinical trials (CCTs) of universal or selective screening using a serum lipid panel compared to no screening or usual care. Populations with homozygous FH, those already being followed for dyslipidemia, or with diagnoses associated with secondary dyslipidemia were excluded, as were populations with an established family history of FH. Screening could have been performed with a fasting or nonfasting lipid measurement, which included one or more of the following lipid components: TC, LDL-C, HDL-C, non-HDL-C, or TG. Interventions consisting solely of apolipoprotein screening were excluded as were studies of genetic screening alone or cascade screening for FH. Screening based exclusively on apolipoproteins or genetic screening were excluded because these are not common screening practices in U.S. primary care. Cascade

screening was excluded because this represents a case finding approach as opposed to population screening. Further, rigorous cascade screening is not currently implementable in the United States due to HIPAA and lack of current infrastructure.

KQ1 studies evaluating benefits needed to report a health outcome, intermediate outcome, or intermediate behavioral health outcome for inclusion. Eligible health outcomes were MI, ischemic stroke, CVD mortality, or all-cause mortality. Intermediate outcomes were serum lipid concentrations (TC, LDL-C, HDL-C, TG, or non-HDL-C), atherosclerosis markers (carotid intima-media thickness, calcium score, or pathological findings), or BMI, and intermediate behavioral outcomes were physical activity, sedentary behavior, or dietary intake.

KQ3 studies evaluating harms needed to report psychosocial effects of screening, overdiagnosis, or false positives or false negatives if there was a confirmatory test. We excluded studies reporting the psychosocial functioning of children with elevated lipids versus normal lipids, as these studies address questions of association between lipids and psychosocial variables but not screening. We did not include studies evaluating the accuracy of calculated Friedwald or novel approaches versus direct measurement for LDL because we were not focused on a comparative question of lab assays. Further, we did not include studies evaluating the accuracy of fasting versus nonfasting lipid measurements as we sought to identify the harms of screening compared to no screening or usual care. Finally, we did not include studies that addressed the diagnostic accuracy of serum lipids or clinical FH criteria against a genetic test for FH.

KQ2 (Diagnostic Yield)

For studies evaluating the diagnostic yield of serum lipid screening, we included recent, large cohort studies that conducted universal or selective lipid screening and reported screen positivity for any stated threshold of elevated lipids. We initially looked for studies reporting positive predictive value of a first elevated screening lipid result for a second confirmatory test. No studies used a confirmatory test, so we accepted studies reporting screen positivity based on a single lipid test. As for KQ1, screening could have been performed with a fasting or nonfasting lipid measurement, which included one or more of the following lipid components: TC, LDL-C, HDL-C, TG, or non-HDL-C. Lipid screening needed to be population-based or conducted in a community setting, in primary care, or in a setting referable from primary care.

Because of a very large body of potentially included studies, we limited the evidence base to large, recent, US-based cohorts to ensure greatest applicability. Specifically, we required samples to be larger than 1,000 participants and to have data collected after the year 2000. The minimum study size of 1,000 participants represents relatively broad criteria selected to increase geographic representation in the United States as well as inclusive representation of racial and ethnic groups. For cohorts with multiple publications and multiple measurements over time, we identified the largest or most recent publication for each specific population strata as follows: age, sex, race and ethnicity, BMI status, and family history. Publications focusing on other participant characteristics (e.g., vitamin D status, grip strength, stature) were excluded.

KQ4 and KQ5 (Benefits and Harms of Treatment)

For KQ4 and KQ5 studies evaluating the benefits and harms of treatment, we included RCTs of lipid-lowering medications, behavioral interventions to promote healthy diet or physical activity, and dietary supplements. Apheresis and revascularization interventions were excluded. We required a comparator group of no treatment or usual care. For children and adolescents with FH, usual care was defined by contemporary treatment recommendations,⁴ including therapeutic lifestyle change and a statin if LDL-C remained above goal after lifestyle intervention. Thus, a study in an FH population that included a statin as a control and a statin plus another agent in the intervention group (IG) would be acceptable. Studies in FH populations that used outdated usual care pharmacotherapy interventions were excluded. In populations without FH, brief diet advice was an acceptable control group (CG), but more intensive lifestyle counseling was considered too intensive as a comparator. Comparative effectiveness studies, such as studies of low-dose versus higher-dose agents, were not included for efficacy or harms.

For KQ5 studies evaluating the harms of treatment, we included nonrandomized studies of interventions (NRSIs) in addition to RCTs.⁹⁸ As for RCTs, a comparator group of no treatment or usual care was required in NRSIs. Pre-post study designs were excluded.

Treatment studies could have populations that were identified in any manner, including cascade screening, but children and adolescents with homozygous FH or a dyslipidemia diagnosis associated with secondary dyslipidemia were excluded.

KQ4 studies needed to report a health outcome, intermediate outcome, or intermediate behavioral health outcome for inclusion. Eligible health outcomes were MI, ischemic stroke, CVD mortality, or all-cause mortality. Intermediate outcomes were serum lipid concentrations (TC, LDL-C, HDL-C, TG, or non-HDL-C), atherosclerosis markers (carotid intima-media thickness, calcium score, or pathological findings), or BMI, and intermediate behavioral outcomes were physical activity, sedentary behavior, or dietary intake. KQ5 studies evaluating harms needed to report a harm outcome related to lipid-lowering medications (e.g., adverse events, long-term safety) or lifestyle modification (e.g., nutritional harms, psychosocial measures).

Quality Assessment

Two reviewers applied USPSTF design-specific criteria⁹⁹ to assess the methodological quality of all eligible studies (**Appendix A Table 2**). Previously included studies were re-rated for consistency with newly included studies. We assigned each study a quality rating of “good,” “fair,” or “poor.” Discordant quality ratings were resolved by discussion or adjudicated by a third reviewer as needed. Studies rated as poor-quality were not eligible for the review.

For cohort studies evaluating yield of screening tests for elevated lipids (KQ2), we developed a brief set of critical appraisal questions tailored to this type of study and outcome. These questions addressed bias in sample selection, differences in those participating and not participating in the study, the extent of missing data, consistent and appropriate outcome measurement, and selective reporting bias. Specifically, we evaluated whether the screening test

was the same for every participant in a study, for example whether lipid tests were universally fasting or nonfasting. Studies in which both modalities were used but reporting was not stratified could at best be rated as fair. Further, evidence of sampling bias was considered a fatal flaw and studies with sampling bias were rated as poor—for example, yield studies with the aim of describing screening practices where screening was rare and those screened had different characteristics than those not screened. For a yield study to be rated as good, we required information about whether nonrespondents were different from respondents and whether those with missing data were different from those with complete data.

Good-quality RCTs were those that met all or nearly all the specified quality criteria. Specifically, comparable groups were assembled initially and maintained throughout the study, followup was 90 percent or higher, assessment procedures were described and blinded if they involved direct interviews, randomization methods were described, and allocation was concealed. Fair-quality studies did not meet all criteria but did not have serious threats to their internal validity related to design, execution, or reporting. To be rated as poor-quality, intervention studies generally had several important limitations, including at least one of the following risks of bias: very high attrition (generally >40%); differential attrition between intervention arms (generally >20%); lack of baseline comparability between groups without adjustment; or problematic issues in trial conduct, analysis, or reporting of results (e.g., possible selective reporting; inappropriate exclusion of participants from analyses; questionable validity of allocation or assessment procedures).

For nonrandomized studies of interventions evaluated for harms outcomes only (KQ5), good quality studies had to have a low risk of bias in all of the following domains: baseline and time-varying confounding, participant selection, intervention classification, departure from intended interventions, missing data, outcome measurement, and selective reporting.¹⁰⁰ Fair-quality studies did not meet all criteria but did not have serious threats to their internal validity related to design, execution, or reporting. To be rated as poor-quality, intervention studies generally had several important limitations, including lack of an appropriate control group, unclear or biased participant selection, problematic categorization of treatment status, differential followup in treated and untreated groups, or outcome measurement that was poorly described or did not use standardized procedures.

Data Abstraction

For all included studies, one reviewer extracted key elements into standardized abstraction forms in DistillerSR (Evidence Partners, Ottawa, Canada). A second reviewer checked the data for accuracy. Extracted data elements included general characteristics of the study (e.g., author, year, study design, country), clinical and demographic characteristics of the sample and setting (e.g., age, sex, race and ethnicity, baseline lipid values), intervention details (e.g., screening intervention and threshold for KQ2 studies or treatment details for KQ4 and KQ5 studies), analytic methods (e.g., adjustments), and outcomes of interest as prespecified in the inclusion criteria. For KQ2 studies of screening yield, we abstracted results for the prevalence of abnormal lipids in the overall study population and in population strata defined by age, sex, race and ethnicity, BMI status, and family history. We abstracted prevalence for thresholds for

elevated lipids as defined by study authors. For treatment studies (KQ4 and KQ5), we abstracted only the longest followup for outcomes if multiple timepoints were reported. For harms outcomes (KQ5), we abstracted dichotomous versions of lab outcomes (e.g., the proportion of individuals with elevated values above a stated threshold), as the clinical meaning of small changes in continuous measures for these lab outcomes is unknown. For KQ4 and KQ5 studies, we audited the availability of subgroup analyses.

Data Synthesis, and Analysis

All results were synthesized separately for FH and multifactorial dyslipidemia populations. Results for the evidence related to the prevalence of FH and elevated lipids (KQ2) were synthesized narratively and summarized in tables. For KQ2 studies, numerators and denominators were back-calculated as appropriate and confidence intervals were computed if not reported for the prevalence rate. For treatment studies (KQ4 and KQ5), we synthesized results by intervention type (e.g., statins, bile acid sequestrant, ezetimibe, fibrate, PCSK9 inhibitor, combination drug therapy, and lifestyle counseling). Except for statins, which had the largest body of evidence, these interventions did not allow for quantitative pooling due to the limited number of contributing studies; these data are summarized narratively and in tables. For continuous lipid measures, the body of evidence for statins allowed for meta-analysis of TC, LDL-C, and HDL-C. Due to either high statistical heterogeneity (commonly $I^2 > 50$) or to small number of trials to be pooled, the random effects restricted maximum likelihood method with the Knapp-Hartung correction was applied in meta-analyses.^{101, 102} We used change from baseline in each group as the measure for analysis and crude effect estimates were calculated if between group results were not reported; we favored adjusted over unadjusted effect estimates. For pooling statin studies with multiple randomized groups with differing statin intensity, we selected the highest intensity dose group. Statin intensity categorizations were based on 2018 guidelines for the management of cholesterol in adults,³¹ as intensity categorizations are not established for pediatric populations. Studies with multiple randomized groups of differing intensity were evaluated qualitatively to assess dose-response relationships.

Statistical heterogeneity among pooled studies was evaluated using standard χ^2 tests and the magnitude of heterogeneity was estimated using the I^2 statistic. Due to the limited number of trials for pooled analyses of statins ($k < 10$), assessment of small study effects and publication bias were not performed.^{103, 104}

For the dichotomous measure of the proportion of individuals meeting LDL-C goals, we computed the crude absolute risk difference (ARD) between treatment and control groups. Due to the limited number of studies and differing LDL-C thresholds in studies, we used visual displays and tables to describe the results and did not pool.

All quantitative analyses were performed using Stata 16.1 (StataCorp, College Station, TX).

Grading the Strength of the Body of Evidence

The strength of evidence for each outcome was graded using an adaptation of the Evidence-based Practice Center approach,¹⁰⁵ which is based on a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.¹⁰⁶ This adaptation explicitly addresses four of the five Evidence-based Practice Center-required domains: consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations, risk of bias). We do not evaluate the fifth domain—directness—as it is implied in the structure of the KQs (i.e., pertains to whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there was insufficient evidence for a particular outcome). Study quality summarizes the quality ratings of the individual trials included for an outcome and indicates the degree to which the results are likely to have adequately low risk of bias. The limitations domain highlighted important restrictions in answering the overall KQ (e.g., lack of replication of interventions, nonreporting of outcomes important to patients or nonreporting of outcomes in some trials).

The overall strength of evidence was graded as “high,” “moderate,” “low,” or “insufficient.” “High” indicates high confidence that the evidence reflects the true effect, and that further research is very unlikely to change our confidence in the estimate of effects. “Moderate” indicates moderate confidence that the evidence reflects the true effect, and that further research may change our confidence in the estimate of effect and may change the estimate. “Low” indicates low confidence that the evidence reflects the true effect, and that further research is likely to change our confidence in the estimate of effect and to change the estimate. A grade of “insufficient” indicates that evidence is either unavailable or does not permit estimate of an effect. At least two independent reviewers rated the overall strength of evidence for each intervention type. We resolved discrepancies through consensus discussion involving more reviewers.

Contextual Questions

In addition to the systematically reviewed questions (KQs 1-5), we also addressed contextual questions (CQs) to aid with the broader interpretation of the evidence. Contextual questions are important considerations that may not be readily answerable from the available RCT literature. Two CQs were prespecified in our research plan:

CQ1. What is the association between lipid-related childhood and adolescent intermediate outcomes and adult health outcomes?

CQ2. What is the optimal timing of statin treatment initiation in FH?

CQs are not systematically reviewed. Evidence for CQs was identified based on literature retrieved for the systematic search for KQs as well as targeted searches and scanning bibliographies of relevant articles. A best evidence approach was used to identify most recent, applicable, and robust evidence. CQs are addressed in the Discussion.

Expert Review and Public Comment

The draft Research Plan was posted for public comment on the USPSTF website from May 13 to June 9, 2021. The USPSTF received comments regarding the selection of outcomes, expansion of the screening population to the family, and the inclusion of adult health outcomes in the Analytic Framework. In response, the USPSTF added BMI, physical activity, sedentary behavior, and dietary intake as intermediate outcomes. The USPSTF retained the focus of the screening population on children for this review because of other available lipid-related USPSTF recommendations in adults, and because of the current prevalence of lipid screening in the general adult population. Adult health outcomes were retained in the Analytic Framework in accordance with USPSTF methods. A final Research Plan was posted on the USPSTF website on August 19, 2021. The draft version of this report was reviewed by three invited experts and five individuals at USPSTF Federal Partner agencies. Experts were selected based on their expertise with both methodologic and content aspects of the review and were selected to obtain diverse informed perspectives. All expert comments were considered, and the report was updated to improve clarity, ensure accuracy, and address scientifically relevant concerns.

USPSTF and AHRQ Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and key questions and to resolve issues around scope for the final evidence synthesis. AHRQ staff provided oversight for the project, coordinated the systematic review, reviewed the draft report, and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Description of Included Studies

The results for this review will be presented by condition: familial hypercholesterolemia (FH) and multifactorial dyslipidemia. Within each condition, results are organized by KQ and intervention type.

We reviewed 7,058 abstracts and assessed 272 full-text articles for inclusion (**Appendix B Figure 1**). Overall, we included 43 studies (reported in 67 publications) across included conditions. Twenty-six studies were in children and adolescents with familial hypercholesterolemia (FH), 9 studies in children and adolescents with multifactorial dyslipidemia, and 9 studies in a children and adolescents with FH or multifactorial dyslipidemia. One yield study reported on both populations. The full lists of included studies and excluded studies (with reasons for exclusion) are available in **Appendix C** and **Appendix D**, respectively.

There were no included studies for screening benefits and harms (KQ1 and KQ3). A total of seven studies were included for the diagnostic yield of serum lipid screening (KQ2), three for FH and five for multifactorial dyslipidemia (with one study reporting on both populations). A total of 33 RCTs were included for treatment benefits (KQ4): 22 RCTs in FH, four RCTs in multifactorial dyslipidemia, and seven RCTs were in a combination of FH and multifactorial dyslipidemia populations (**Table 6**). A total of 31 studies were included for treatment harms (KQ5): 20 studies in FH, four studies in multifactorial dyslipidemia, and seven studies of populations with FH or multifactorial dyslipidemia (**Table 7**).

KQ1. Does Screening for FH or Multifactorial Dyslipidemia in Asymptomatic Children and Adolescents Delay or Reduce the Incidence of Health Outcomes (e.g., CVD Events or Mortality) or Improve Intermediate Outcomes (e.g., Serum Lipid Levels and Atherosclerotic Markers) in Children, Adolescents, or Adults?

Summary of Findings

No studies meeting criteria were identified.

FH

No studies meeting criteria were identified.

Multifactorial Dyslipidemia

No studies meeting criteria were identified.

KQ2. What Is the Diagnostic Yield of Serum Lipid Screening for FH or Multifactorial Dyslipidemia in Children and Adolescents?

Summary of Findings

No studies performed a confirmatory lipid or genetic test; thus, evidence is limited to screen-positivity (prevalence) rather than diagnostic yield of lipid screening for identifying FH. We included three fair-quality U.S. studies (n=395,465) reporting prevalence of FH ranging from 0.2 to 0.4 percent (1:250 to 1:500) using diagnostic criteria exclusively based on lipid levels (LDL-C \geq 190 mg/dL or TC \geq 270 mg/dL). Targeted screening in those with a family history of hypercholesterolemia or premature CVD would miss many cases of children with LDL-C \geq 160 mg/dL.

No studies performed a confirmatory lipid test; thus, evidence is limited to screen-positivity (prevalence) rather than diagnostic yield of lipid screening for identifying multifactorial dyslipidemia. We included five fair-quality studies (n=142,257) reporting prevalence of multifactorial dyslipidemia showing that lipid abnormalities are common, being generally more common for the parameters of HDL-C and TG. Prevalence ranged from 7.1 to 9.4 percent for elevated TC (\geq 200 mg/dL), 6.4 to 7.4 percent for elevated LDL-C (\geq 130 mg/dL), 12.1 to 22.2 percent for low HDL-C ($<$ 40 mg/dL), 8.0 to 17.3 percent for elevated TG (using various thresholds), and 6.4 to 13.0 percent for elevated non-HDL-C (\geq 145 mg/dL). Prevalence of any lipid abnormality in 6- to 19-year-olds was 19.2 percent based on NHANES data (2013-2016, n=4,381). Older age and higher BMI were associated with higher prevalence of multifactorial dyslipidemia. Conclusions for prevalence by race and ethnicity are limited by sparse reporting and inconsistent patterns among lipid parameters. Prevalence by sex was inconsistent across the cohorts and for different lipid measures. Overall, prevalence estimates from NHANES were generally lower than other geographically limited databases.

FH

Study and Participant Characteristics

We identified no studies that performed a confirmatory lipid or genetic test; thus evidence is limited to screen-positivity (prevalence) rather than diagnostic yield of lipid screening for identifying FH. We included three fair-quality studies (in 4 articles) that reported prevalence of FH in child and adolescent populations in the United States (n=395,465) (**Table 8; Appendix E Table 1**).^{69, 70, 107, 108}

One publication used National Health and Nutrition Examination Survey (NHANES) data from nonpregnant participants 12 to 19 years of age from 1999-2012.⁷⁰ The NHANES survey combines in-home interviews with mobile examinations and laboratory tests; about 98 percent of participants reported fasting for at least eight hours. FH was defined as LDL-C \geq 190 mg/dL.

A second study aimed to estimate the prevalence of FH in a Texas blood donor program using data from all donors aged 16 years or older between January 2002 and December 2016.¹⁰⁷ Authors used de-identified data from the Carter BloodCare database, with a sample of 321,718 blood donors aged 16 to 20 years. FH was defined as a nonfasting total cholesterol \geq 270 mg/dL (MEDPED criteria).

A third study using a state-wide sample is the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) study,¹⁰⁸ a cardiovascular risk detection screening program including evaluation for obesity, dyslipidemia, hypertension, and prediabetes. This study included fifth grade children enrolled in schools in West Virginia, who were screened between 1998 and 2015 (n=60,404). A total of 39 percent of eligible 5th graders in the state participated. Serum sampling methods changed over the 17-year program and included fingerstick capillary sampling and venous serum specimens using fasting and nonfasting samples. Significant likelihood of FH was defined as LDL-C $>$ 190 mg/dL while “probable FH” was defined as LDL-C $>$ 160 mg/dL in this cohort. An earlier CARDIAC publication (n=20,266) investigated the prevalence of children with a fasting LDL-C \geq 160 mg/dL and a positive family history of premature cardiovascular disease between years 2003 and 2008.⁶⁹

Population characteristics were not reported in the adolescent age group for NHANES 1999-2012 or the Carter BloodCare donors (**Table 9**). The mean age of participants in the CARDIAC study was 11 years with approximately half female participants.¹⁰⁸ The majority of participants were White (93%), 3 percent were Black, 1 percent Latino, 1 percent Asian, and 1 percent of “other” race. Nineteen percent of participants had a BMI in the 85-94.9th percentile for BMI, and 28 percent had a BMI in the 95-98.9th percentile. Approximately one-third of participants had a family history of heart disease or high total cholesterol.

Outcomes (Results)

No included studies used a second confirmatory or genetic test. Outcomes reported in these studies included only screen positivity from a single screen, therefore diagnostic yield cannot be calculated.

Results are reported in **Table 10, Figure 2**. Overall prevalence ranged from 0.2 percent to 0.4 percent (1:250 to 1:500) in the three datasets using the cut point of LDL-C $>$ or \geq 190 mg/dL.

In the 321,718 screened donors aged 16-20 years from the Carter BloodCare dataset, 0.3 percent (or 1:321) screened positive for FH using MEDPED criteria TC \geq 270 mg/dL.¹⁰⁷

In the fifth-grade cohort of the West Virginia CARDIAC program, 1.1 percent screened positive for “probable FH,” (LDL-C $>$ 160 mg/dL) and 0.2 percent screened positive for “significant likelihood of FH” (LDL-C $>$ 190 mg/dL).¹⁰⁸ A separate CARDIAC publication from screening

years 2003-2008 found that of 14,468 students with a positive family history of premature CVD, 1.2 percent had a fasting LDL-C \geq 160 mg/dL.⁶⁹ A total of 1.7 percent of 5798 students *without* a family history of premature CVD had a fasting LDL-C \geq 160 mg/dL.⁶⁹

Multifactorial Dyslipidemia

Study and Participant Characteristics

No studies performed a confirmatory lipid test; thus evidence is limited to screen-positivity (prevalence) rather than diagnostic yield of lipid screening for identifying multifactorial dyslipidemia. We included five fair-quality studies (in 8 articles) that reported the prevalence of multifactorial dyslipidemia in child and adolescent populations in the United States (n=142,257) (**Table 11-12; Appendix E Table 2**).^{52, 69, 108-113} The primary NHANES publication (n=26,047) included a nationally representative sample of children and adolescents aged 6-19 years screened from 1999-2016; however, only subsets of this population sample are available for the outcomes discussed below.^{52, 110, 112} The NHANES survey combines in-home interviews with mobile examinations and laboratory tests; the overall examination response rate was 81 percent. The threshold for abnormal lipids, using both fasting and nonfasting lipids were TC \geq 200 mg/dL, LDL-C \geq 130 mg/dL, HDL-C $<$ 40 mg/dL, TG \geq 130 mg/dL, and non-HDL-C \geq 145 mg/dL. Fasting values were only obtained for adolescents aged 12-19 years who had morning exams.⁵²

The HEALTHY study (n=6,097) recruited middle schools from seven different geographic areas with student populations at increased risk for type 2 diabetes, defined by authors as having at least 50 percent of students eligible for free or reduced-price lunch or belonging to a racial or ethnic minority group.¹⁰⁹ Sixth-grade students in each school were invited to health screenings from 2006-2009, and 58 percent of all eligible students participated in screening. Abnormal fasting lipid levels were defined by the “high” cut points as described by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents Summary Report: TC \geq 200 mg/dL, LDL-C \geq 130 mg/dL, TG \geq 130 mg/dL, and HDL-C \leq 40 mg/dL. The aim of this study was to investigate the utility of BMI to identify cardiometabolic risk and reports prevalence only by BMI strata.

The Study of Latinos (SOL)–Youth Study (n=1,137) included participants ages 10-16 years, whose parents or legal guardians previously participated in the Hispanic Community Health Study/Study of Latinos.¹¹³ The sample included Latino youth from four cities including New York City, Chicago, Miami, and San Diego. Data were collected between 2012 and 2014. This study explored various thresholds for abnormal lipids, with thresholds defined by the World Health Organization (WHO), the Adult Treatment Panel III report (ATP III) and the International Diabetes Federation (IDF).

The remaining two studies, The Poudre Valley Health System (PVHS) Healthy Hearts Club and CARDIAC, recruited from schools within a single state.^{108, 111} The PVHS Healthy Hearts Club study (n=9,694) provided cardiovascular screening to 4th grade students who attended a participating school in one of six Northern Colorado school districts from years 1992-2013.¹¹¹ These students received nonfasting lipid screening, and authors defined thresholds for acceptable

TC <170 mg/dL; borderline TC \geq 170–199 mg/dL; high TC \geq 200 mg/dL; low HDL-C <40 mg/dL; and high non-HDL-C \geq 145 mg/dL.

CARDIAC (n=99,282) is discussed above in the FH section. Abnormal lipid values relevant for multifactorial dyslipidemia were LDL-C >130 mg/dL and HDL-C <40 mg/dL.

Participant characteristics were variably reported among these studies (**Table 12**). The mean ages ranged from 10 to 16 years, and approximately half were female in these cohorts. The SOL youth study was conducted in 100 percent Latino youth by design, reporting specific ethnicities as 49 percent Mexican, 14 percent Dominican, 10 percent Mixed Hispanic, 10 percent Puerto Rican, 6 percent Central American, 6 percent Cuban, and 4 percent South American.¹¹¹ HEALTHY reported about half of participants were Latino (53%), followed by Black students (19%), White students (19%), and other race/ethnicity (8%). CARDIAC reported the majority of participants were White (93%), 3 percent were Black, 0.8 percent Latino, 0.5 percent Asian, and 0.5 percent other.¹⁰⁸ BMI characteristics were reported in four studies^{108, 109, 111}; the percent overweight (BMI 85-94th percentile) ranged from 13 to 20, and the percent obese (BMI \geq 95th percentile) ranged from 8 to 30. HEALTHY reported that most students were in Tanner stage 3 at screening (40%), and approximately 46 percent of students had one or more cardiometabolic risk factors.¹⁰⁹

Outcomes (Results)

No included studies used a confirmatory test, therefore diagnostic yield cannot be calculated. Outcomes reported in these studies included only screen positivity from a single screen. Furthermore, while the vast majority of individuals with abnormal lipids have multifactorial dyslipidemia, a very small proportion may have FH as there were no upper thresholds to the lipid levels.

High TC

Three studies reported the percentage of participants who had a TC \geq 200 mg/dL and prevalence ranged from 7.1 percent to 9.4 percent (**Table 13; Figure 3**). Higher prevalence of abnormal TC was seen in higher BMI populations; results were mixed about differences in prevalence by sex (**Figures 4-6**). NHANES (2009-2016; n=10,661; mean age: 12 years) reported that 7.1 percent (95% CI, 6.4% to 7.8%) had high TC (fasting or nonfasting).⁵² In an overlapping NHANES cohort analysis (2011-2014; n=4358), adolescents ages 16-19 years had a higher prevalence of elevated TC compared to younger children ages 6-8 years (8.9% [95% CI, 7.2% to 10.5%] vs 6.0% [95% CI, 4.5% to 7.5%], $p<0.05$).¹¹² In the same years (n=4361), the percentage of females having high TC was significantly higher than males (8.9% [95% CI, 7.6% to 10.1%] vs 5.9% [95% CI, 4.9% to 6.8%]; $p<0.05$).¹¹² The NHANES 2009-2016 cohort analysis found that among youths aged 6-19 years, non-Hispanic Black youths had the highest prevalence of high TC (8.3% [95% CI, 7.2% to 9.3%]), followed by White (7.5% [95% CI, 6.3% to 8.7%]), and Mexican participants (6.9% [95% CI, 5.7% to 8.1%]).⁵² A smaller NHANES sample from 2011-2014 was the only publication with separate reporting for Asian populations, and found that non-Hispanic Asian youths had the highest prevalence of high TC (10.9% [95% CI, 8.0% to 13.8%]), followed by Black (9.6% [95% CI, 7.9% to 11.3%]), White (7.3% [95% CI, 5.8% to 8.9%]), and Hispanic

(6.3% [95% CI, 5.0% to 7.6%]) youths aged 6-19 years.¹¹² The prevalence of high TC in Asians was significantly different ($p<0.05$) from both White and Hispanic participants, while the prevalence in Black youths was found to be significantly different ($p<0.05$) from Hispanic participants.¹¹² However, these results should be interpreted with caution due to the small sample size of Asian youth. In subgroup analyses by BMI status, in 2009-2016 ($n=8268$), NHANES reported that children aged 6-19 years in the $\geq 95^{\text{th}}$ percentile for BMI had a higher percentage of participants with TCs ≥ 200 mg/dL (10.7% [95% CI, 9.0 to 12.4%]), compared with BMI percentiles $5^{\text{th}}-85^{\text{th}}$ and $85^{\text{th}}-94^{\text{th}}$ (5.5% [95% CI, 4.8% to 6.3%] and 7.0% [95% CI, 5.5% to 8.5%] respectively).^{52, 112}

The West Virginia CARDIAC program (1999-2016) reported that a total of 4747 (8.6% [95% CI, 8.4% to 8.8%]) students had high TC.¹⁰⁸ They also reported that prevalence of elevated TC (fasting or nonfasting) was greater in higher BMI categories and found that children in the $\geq 95^{\text{th}}-99^{\text{th}}$ percentile had the highest prevalence of abnormal TC (13.0% [95% CI, 12.4% to 13.6%]), compared with BMI percentiles $\leq 85^{\text{th}}$, $85^{\text{th}}-95^{\text{th}}$ and $>99^{\text{th}}$ (6.1, 9.2, and 12.2 percent, respectively).

For the HEALTHY study ($n=6097$; mean age: 11 years) data are only available by BMI strata.¹⁰⁹ The prevalence of high TC increased progressively with higher BMI strata, with the highest prevalence in those with BMI $\geq 95^{\text{th}}$ percentile (9.3% [95% CI, 8.0% to 10.6%]).

PVHS ($n=9,694$ fourth-grade students; mean age: 10 years) had an estimated prevalence of 9.4 percent (95% CI, 8.8% to 10.1%) of high, nonfasting TC in their screened cohort.¹¹¹ Prevalence was the same (9.4% [95% CI, 8.6% to 10.2%]) in both females and males in this cohort and was highest amongst students with BMI $\geq 95^{\text{th}}$ percentile (15.1% [95% CI, 12.6% to 17.6%]).¹¹¹

High LDL-C

Two studies reported the prevalence of high LDL-C, using a threshold of ≥ 130 mg/dL; these ranged from 6.4 to 7.4 percent with higher prevalence in higher BMI categories (**Table 14; Figure 3**). The CARDIAC cohort reported that 7.4 percent (95% CI, 7.2% to 7.6%) of 54,784 students screened in years 1999-2016 had a high LDL-C (fasting or nonfasting).¹⁰⁸ More recent data from students who were screened with a nonfasting lipid profile in 2016-2017 ($n=3648$), showed that 3.8 percent (95% CI, 3.2% to 4.4%) had a high LDL-C.¹¹⁰ Using screening data from 1999-2016, CARDIAC explored prevalence by BMI category, and found that youth in each of the higher BMI categories had a significantly higher prevalence of high LDL-C compared to those in lower BMI categories¹⁰⁸ (BMI $95^{\text{th}}-99^{\text{th}}$ percentile: 11.4% [95% CI, 10.8% to 12.0%]; BMI $>99^{\text{th}}$ percentile: 11.0% [95% CI, 10.0% to 12.0%] vs. BMI $\leq 85^{\text{th}}$ percentile: 4.8% [95% CI, 4.6% to 5.0%] and BMI $85^{\text{th}}-94^{\text{th}}$ percentile: 8.5% [95% CI, 8.0% to 9.0%], respectively) (**Figure 6**).¹⁰⁸

NHANES reported that the prevalence of high fasting or nonfasting LDL-C in youths aged 12-19 years, screened in 2007-2014 ($n=2042$), was 6.4 percent (95% CI, 4.9% to 7.8%).⁵² In the same years, the prevalence of high LDL-C was highest among Black youths of the same age range (8.2% [95% CI: 5.9% to 10.6%]), followed by White youths (7.8% [95% CI, 5.6% to 10.1%]), and Mexican youths (4.3 % [95% CI, 2.2% to 6.4%]) (**Figure 5**). NHANES also found that those

in the $\geq 95^{\text{th}}$ percentile for BMI had a higher percentage of participants with high LDL-C (10.0%), compared with BMI percentiles 5^{th} - 85^{th} and 85^{th} - 94^{th} (5.1% [95% CI, 3.5% to 6.6%] and 6.8% [95% CI, 3.6% to 10.0%], respectively) (**Figure 6**).⁵²

For the HEALTHY study, prevalence is only available by BMI strata.¹⁰⁹ The prevalence of high LDL-C among participants increased progressively with higher BMI. For youth in the $\geq 95^{\text{th}}$ percentile for BMI, the prevalence of high LDL-C was 6.8 percent (95% CI, 5.6% to 7.9%) (**Figure 6**).¹⁰⁹

Abnormal HDL-C

Four studies reported the prevalence of low HDL-C levels, defined as HDL-C < 40 mg/dL, and reported prevalence ranging from 12.1 to 22.2 percent, again with higher prevalence in older age groups, higher BMI categories, and in Hispanic children. (**Table 15; Figures 3-5, 7**). NHANES (2013-2016; $n=6457$) reported a 12.1% prevalence rate for low, nonfasting HDL-C (95% CI, 10.4% to 13.7%).⁵² The prevalence of abnormal HDL-C increased with age in those screened in years 2011-2014 ($n=4358$), estimated as 7.7 percent (95% CI, 6.0% to 9.4%) in ages 6-8 years, 10.3% (95% CI, 8.4% to 12.2%) in ages 9-11 years, 14% (95% CI, 12.0% to 16.0%) in ages 12-15 years, and 18.4% (95% CI, 16.1% to 20.6%) in ages 16-19 years.¹¹² Over the same time period, the percentage of females having low HDL-C was significantly lower ($p < 0.05$) than the percentage among males (12.0% [95% CI, 10.6% to 13.4%] vs. 14.8% [95% CI, 13.3% to 16.2%], respectively).¹¹² The NHANES 2013-2016 analysis found the highest prevalence of low HDL-C among Mexican youths (14.8% [95% CI, 12.3% to 17.3%]), followed by White youths (12.5% [95% CI, 9.9% to 15.0%]), and Black youths (6.5% [95% CI, 4.9% to 8.0%]) ages 6 to 19 years.⁵² An analysis of 2011-2014 NHANES data, which provided separate reporting of Asian youths of the same age group, found that Hispanic youths had the highest prevalence for abnormal HDL-C (15.6% [95% CI, 13.7% to 17.5%]), followed by White youths (14.4% [95% CI, 12.3% to 16.5%]), Asian youths (8.2% [95% CI, 5.6% to 10.8%]), and Black youths (7.4 [95% CI, 5.9% to 8.9%]).¹¹² The prevalence of abnormal HDL-C for Black and Asian youths within this sample was found to be significantly different from both White and Hispanic ($p < 0.05$).¹¹² However, these results should be interpreted with caution due to the small sample size of Asian youth. In 2013-2016 ($n=4205$), NHANES found those in the $\geq 95^{\text{th}}$ percentile for BMI had a higher percentage of participants with low HDL-C (29.3% [95% CI, 26.3% to 32.4%]), compared with those in the 5^{th} - 85^{th} percentiles for BMI and the 85^{th} - 94^{th} percentiles (5.7% [95% CI, 4.0% to 7.3%] and 11.5% [95% CI, 8.2% to 14.9%], respectively).⁵²

CARDIAC reported that a total of 9,851 out of 55,034 students screened in years 1999-2016 had low HDL-C (17.9% [95% CI, 17.2% to 18.6%]).¹⁰⁸ In their 2016-2017 cohort ($n=3648$), prevalence was slightly lower at 16 percent (95% CI, 14.8% to 17.2%) (548 of 3,648 students).¹¹⁰ Using screening data from 1999-2016, CARDIAC explored prevalence by BMI category, and found that students with BMI $\geq 99^{\text{th}}$ percentile have the highest prevalence: 44.7% (95% CI: 43.1% to 46.3%), followed by 31.1 percent (95% CI, 30.3% to 32.0%) among students in the BMI 95^{th} - 99^{th} percentile, 17.9 percent (95% CI, 17.2% to 18.6%) among students with BMI in the 85^{th} - 94^{th} percentile, and 9 percent (95% CI, 8.7% to 9.3%) among students with BMI $\leq 85^{\text{th}}$ percentile.¹⁰⁸

The HEALTHY study screened 6,097 students in the years 2006-2009 (mean age: 11 years) and reported the prevalence of low, fasting HDL-C only by BMI strata.¹⁰⁹ The prevalence of low fasting HDL-C increased progressively by BMI strata and was 32.2 percent (95% CI, 30.0% to 34.4%) in those in the $\geq 95^{\text{th}}$ percentile.¹⁰⁹

The SOL Youth study (2012-2014; n=1137; mean age: 13 years) reported the prevalence of fasting low HDL-C using various cutoffs among Latino youth in years 2012-2014.¹¹³ Using the cutoff of HDL-C <40 mg/dL, the prevalence of low HDL-C was estimated to be 12.6 percent (95% CI, 10.7% to 14.5%). Prevalence was similar in males and females with overlapping confidence intervals (males: 13.4% [95% CI, 10.6 to 16.2], females: 11.8% [95% CI, 9.1 to 14.4]). . At a cutoff of <35 mg/dL, prevalence was 3.3 percent overall (95% CI, 2.3 to 4.3) and similar in males and females (males: 3.6% [95% CI, 2.1 to 5.1], females: 3.1% [1.7 to 4.5]).¹¹³

The PVHS study had an estimated 22.2 percent (95% CI, 21.4% to 23.0%) prevalence of nonfasting, low HDL-C in students screened from 1992-2013 (n=9694; mean age: 10 years).¹¹¹ The study found the prevalence of low-HDL-C among males and females to be 21.2 percent (95% CI, 20.0% to 22.4%) and 23.2 percent (95% CI, 22.0% to 24.4%), respectively. Additionally, the study found prevalence to be highest among those in $\geq 95^{\text{th}}$ percentile for BMI (47.5% [95% CI, 44.0% to 51.0%]), followed by 32.9 percent (95% CI, 30.3% to 35.5%) in the 85th – 94th percentile, and 17.8 percent (95% CI, 16.9% to 18.7%) in those in $\leq 85^{\text{th}}$ percentile for BMI.¹¹¹

High TG

Four studies reported the prevalence of high TG levels; two studies defined this as TG ≥ 130 mg/dL, two studies used TG ≥ 150 mg/dL, and one study used TG ≥ 110 mg/dL with prevalence ranges 8.0 to 17.3 percent (**Table 16; Figures 3-5, 7**).

TG ≥ 130 mg/dL

NHANES 2007-2014 (n=2045) reported the prevalence of high TG (fasting and nonfasting) in youths aged 12-19 years as 10.2 percent (95% CI, 8.3% to 12.1%).⁵² From the same cohort, prevalence of high TG was highest among Mexican youths (15.8% [95% CI, 12.2% to 19.3%]), followed by 11.9 percent (95% CI, 9.6% to 14.3%) in White youths, and 4.8 percent (95% CI, 3.2% to 6.4%) in Black youths. NHANES also found that those in the $\geq 95^{\text{th}}$ percentile for BMI had a higher percentage of participants with high TG (22.3% [95% CI, 17.1% to 27.5%]), compared with BMI percentiles 5th-85th and 85th-94th (5.9% [95% CI, 4.1% to 7.8%] and 14.5% [95% CI, 9.8% to 19.2%]), respectively.⁵²

The HEALTHY study of 6,097 youths (mean age: 11 years) screened in years 2006-2009 reports the prevalence of high fasting TG only by BMI strata.¹⁰⁹ The study reported progressively higher prevalence with increasing BMI strata with a prevalence of 29.1 percent (95% CI, 27.0% to 31.2%) for those in the $\geq 95^{\text{th}}$ percentile for BMI.¹⁰⁹

TG ≥150 mg/dL

CARDIAC (1999-2016) reported that 6384 of 55,034 students (11.6% [95% CI, 11.3% to 11.9%]) had high TG.¹⁰⁸ In the same cohort, CARDIAC explored prevalence by BMI category, and found students in the BMI ≥99th percentile had the highest prevalence (31.1% [95% CI, 29.6% to 32.6%]), followed by 23.3 percent (95% CI, 22.5% to 24.1%) among students in the BMI 95th-99th percentile, 12.2 percent (95% CI, 11.6% to 12.8%) among students in the BMI 85th-94th percentile, and 4.1 percent (95% CI, 3.9% to 4.3%) for students in the BMI ≤85th percentile.¹⁰⁸

The SOL Youth study had an estimated 8.0 percent prevalence (95% CI, 6.4% to 9.6%) of high, nonfasting TG among Latino youths in years 2012-2014 (n=1137; mean age: 13 years).¹¹³ The prevalence point estimate was higher for males than females, but confidence intervals overlapped (males: 9.5% [95% CI, 7.1 to 11.9]; females: 6.4% [95% CI, 6.4 to 8.4]).¹¹³

TG ≥110 mg/dL

The SOL Youth study had an estimated 17.3 percent prevalence (95% CI, 15.1% to 19.5%) of high, nonfasting TG among Latino youths in years 2012-2014 (n=1137; mean age: 13 years) using a lower threshold of ≥110 mg/dL.¹¹³ Prevalence was similar in males and females with overlapping confidence intervals (males: 17.7% [95% CI, 14.6 to 20.8]; females: 16.9 [95% CI: 13.8 to 20.0])..¹¹³

Abnormal Non-HDL-C

Two studies reported abnormal non-HDL-C lipid levels, defined as ≥145 mg/dL; the prevalence was 6.4 percent and 13.0 percent, with higher prevalence associated with increasing age, and higher BMI categories (**Table 17; Figures 3-5**). NHANES (2013-2016, n=6456) reported the prevalence of nonfasting high non-HDL-C as 6.4 (95% CI, 5.6% to 7.3%).⁵² The prevalence of high non-HDL-C increased with age in those screened in years 2011-2014 (n=4358), ranging from 6.3 percent (95% CI, 4.8% to 7.8%) in ages 6-8 through 12.0 percent (95% CI, 10.1% to 13.9%) in ages 16-19; the prevalence of non-HDL-C in the oldest age group was found to be significantly different from ages 6-8 years, 9-11 years, and 12-15 years (p<0.05).¹¹² In the cohort (n=4361), the percent of females having high non-HDL-C was significantly higher (p<0.05) than in males (9.4% [95% CI, 8.1% to 10.6%] vs. 7.5% [95% CI, 6.4% to 8.6%], respectively).¹¹² An analysis of 2013-2016 NHANES data found the highest prevalence among Mexican youths (7.4% [95% CI, 6.4% to 8.3%]), followed closely by White youths (7.1% [95% CI, 5.7% to 8.5%]), and Black youths (5.6% [95% CI, 3.7% to 7.4%]).⁵² A separate NHANES analysis of 2011-2014 cohort data that had separate reporting on Asian youths, found that Asian youths had the highest prevalence of non-HDL-C abnormalities (10.4% [95% CI, 7.5% to 13.3%]), followed by Hispanic (8.7% [95% CI, 7.2% to 10.2%]), White (8.5% [95% CI, 6.8% to 10.2%]), and Black youths (8.2% [95% CI, 6.6% to 9.8%]).¹¹² However, these results should be interpreted with caution due to the small sample size of Asian youth. In 2013-2016 (n=4205), NHANES found those in the ≥95th percentile for BMI had a higher percentage of participants with high non-HDL-C (14.1% [95% CI, 11.7% to 16.5%]), compared with 5th-85th and 85th-94th

BMI percentiles (2.8% [95% CI, 2.0% to 3.6%] and 8.9% [95% CI, 6.7% to 11.1%], respectively).⁵²

The PVHS study had an estimated 13.0 percent prevalence (95% CI, 12.3% to 13.7%) of high nonfasting non-HDL-C among participants screened in years 1992-2013 (n=9694; mean age: 10 years).¹¹¹ The prevalence of high non-HDL-C was almost the same between males and females (13% [95% CI, 12.0% to 13.9%] vs. 12.9% [95% CI, 12.0% to 13.8%], respectively). Additionally, these authors found prevalence to be highest among those in $\geq 95^{\text{th}}$ percentile for BMI (27.0% [95% CI, 23.9% to 30.1%]), followed by 19.6 percent (95% CI: 17.4% to 21.8%) in the 85th – 94th percentile, and 10.4 percent (95% CI, 9.7% to 11.1%) in those in $\leq 85^{\text{th}}$ percentile for BMI.¹¹¹

Any Abnormal Lipid Value

One study reported that 19.2 percent of participants had one or more abnormal lipid levels in TC, HDL-C, or non-HDL-C; this study included children of different ages and variable thresholds for abnormal lipids (**Table 18**). NHANES (2013-2016; n=4381; age range 6-19 years) reported that 19.2 percent (95% CI, 17.6% to 20.8%) of all participants screened positive for abnormal fasting or nonfasting lipid values, which they defined as TC ≥ 200 mg/dL, HDL-C < 40 mg/dL, or non-HDL ≥ 145 mg/dL.⁵² Within this sample, NHANES found that older children, ages 12-19 years, had a higher percentage of abnormal lipid levels compared with children ages 6-11 years (21.8% [95% CI, 19.6% to 24.0%] vs 15.2% [95% CI, 13.1% to 17.3%] respectively).

Combination of Abnormal Lipid Values

One study reported a threshold of a combination of abnormal LDL-C and HDL-C (**Table 18**). The West Virginia CARDIAC program (1999-2016; n=99,282; mean age 11 years) reported that 25.0 percent (95% CI, 24.7% to 25.3%) of all fifth grade participants screened positive for abnormal, fasting or nonfasting lipid values defined as a combination of an LDL-C > 130 mg/dL and HDL-C < 40 mg/dL.¹⁰⁸

KQ3. What Are the Harms of Screening for FH or Multifactorial Dyslipidemia in Children and Adolescents?

Summary of Findings

No studies meeting criteria were identified.

Familial Hypercholesterolemia (FH)

No studies meeting criteria were identified.

Multifactorial Dyslipidemia

No studies meeting criteria were identified.

KQ4. Does Treatment of FH or Multifactorial Dyslipidemia With Behavioral Interventions, Lipid-Lowering Medications, or Both in Children and Adolescents Delay or Reduce the Incidence of Health Outcomes (e.g., CVD Events or Mortality) or Improve Intermediate Outcomes (e.g., Serum Lipid Levels and Atherosclerotic Markers) in Children, Adults, or Both?

Summary of Findings

FH

No treatment trials reported long-term health outcomes. We included 22 fair- to good-quality trials (n=2257) examining the effectiveness of various lipid lowering treatments for FH including pharmacotherapy, behavioral counseling, and dietary supplements. Overall, this evidence body demonstrated that pharmacotherapy appears beneficial for TC and LDL-C outcomes with variable and mixed results for TG and HDL-C, with the largest evidence available for statins; behavioral counseling was not effective; and supplements showed mixed results with the best evidence supporting plant sterol spreads. Treatment trials in FH populations represented a heterogeneous set of interventions with differing doses, formulations, and intensities. Trials were generally small, short-term, and none reported health outcomes. Nearly all drug trials were industry funded.

Ten fair- to good-quality randomized, controlled trials (RCTs) (n=1230) of statins comprised the largest body of evidence addressing FH treatment with followup for up to 2 years, but only one trial is new in this update. Pooled analyses demonstrated that statins were associated with an 81-82 mg/dL greater mean difference in TC and LDL-C compared to placebo at up to 2 years followup (TC: k= 7, n=706, mean difference (MD) in change -82.1 mg/dL [95% CI -101.1 to -63.2], I^2 83.0%; LDL-C: k= 8, n=742, MD in change -81.3 mg/dL [95% CI, -97.6 to -65.0, I^2 81.6%]). Within-trial comparisons demonstrated that higher doses were generally associated with greater reductions in TC and LDL-C compared to lower doses, but confidence intervals overlapped. Pooled analysis showed no statistically significant difference in HDL-C (k=6, n=643, MD in change 1.6 mg/dL [95% CI -0.2 to 3.4], I^2 0%). We included one good- and two fair-quality bile acid sequestrant trials (n=332) (none newly identified) that demonstrated that this drug was generally associated with a significantly greater reduction in TC compared to placebo ranging from -22.1 to -40.6 mg/dL and LDL-C ranging from -13.2 to -45.9 mg/dL at 8 weeks. Bile acid sequestrants were not associated with statistically significant reductions in TG and results were mixed for HDL-C, with some variation in effect by dose. We included one good-quality ezetimibe trial (n=138) showing a statistically significant reduction in TC (MD in change -64.0 mg/dL [95% CI, -81.1 to -46.9]), LDL-C (MD in change -63.0 mg/dL [95% CI, -

79.5 to -46.5]), and non-HDL-C (MD in change -65.0 mg/dL [95% CI, -82.2 to -47.8]). Changes in HDL-C and TG were not significant.

We included one very small newly included fair-quality fibrate trial (n=14) reporting a statistically significant improvement in TC (MD in change -84.9 mg/dL [95% CI, -126.2 to -43.6]) but not HDL-C or TG at 13 weeks; however, this drug is not available in the U.S and not FDA-approved in children. One new good-quality PCSK9 inhibitor trial (n=158) demonstrated that evolocumab was associated with a statistically significant reduction in LDL-C as measured by percent change (-38.3% [95% CI, -45.5% to -31.1%]) and absolute mean change (-68.6 mg/dL [95% CI, -83.1 to -54.0]) with greater achievement of goal LDL-C <100 mg/dL (62.5% vs 2.3%, ARD 60.2% [95% CI, 49.6 to 70.9]) at 24 weeks. We included one previously included trial of combination drug therapy of a statin plus ezetimibe compared to a statin alone (n=248) showing that the two drug intervention was associated with a greater reduction in TC (MD in change -40.1 mg/dL [95% CI, -51.1 to -29.2]), LDL-C (MD in change -37.5 mg/dL [95% CI, -48.0 to -27.0]), TG (-9.5 median difference in percent change, p<0.01), and non-HDL-C (MD -40.0 mg/dL [95% CI, -51.0 to -28.9]) compared to the single-drug intervention control group at 33 weeks.

We included one very small, fair-quality behavioral counseling trial in an FH population (n=21) which was newly identified that reported no statistically significant improvement in lipid levels, overlapping confidence intervals for physical activity outcomes, and mixed results for dietary outcomes at 12 weeks.

We included four fair-quality randomized crossover supplement trials (n=116) in FH populations; all were newly identified trials. The two trials of plant sterol food spreads demonstrated statistically significant reductions of 20.5 to 30.5 mg/dL in TC and 22.4 to 30.1 mg/dL in LDL-C at 4 to 8 weeks. The 2 trials of omega-3 fatty acids did not show a statistically significant difference in lipid level changes between the intervention and control groups.

Multifactorial Dyslipidemia

No treatment trials reported long-term health outcomes. We included four fair- to good-quality trials (n=1,008) examining the effectiveness of various lipid lowering treatments for multifactorial dyslipidemia. Overall, this body of evidence showed that behavioral counseling interventions were associated with non-sustained, short-term TC and LDL-C reductions with some improvements in dietary intake. Dietary interventions were heterogeneous with variable intensity, duration, and followup; supplements did not improve lipid outcomes based on small, short-term studies.

There were no included trials of drug interventions in child and adolescent populations with multifactorial dyslipidemia. We included two behavioral counseling trials (n=934), including one fair-quality newly identified trial and one good-quality previously included trial. The trials represented heterogeneous dietary interventions with variable intensity, duration and followup. These trials demonstrated 3-6 mg/dL short-term statistically significant greater reductions in TC and LDL-C and improvements in dietary intake outcomes in the intervention group compared to the control group, but findings did not persist at longer followup. The trial with the more

intensive intervention reported significantly greater reductions in TC and LDL-C at 3 years compared to the control group (TC: MD -3.3 mg/dL [95% CI, -6.4 to -0.2]; LDL-C: MD -3.3 mg/dL [95% CI, -6.0 to -0.6]) but not at 7.4 years (TC: MD -1.1 [95% CI -5.0 to 2.8]; LDL-C: MD -1.9 [95% CI -4.7 to 0.9]). The trial with the less intensive, home-based intervention reported statistically significant LDL-C reduction compared to the control group at 3 months (MD -6.7 mg/dL (CIs not available), $p < 0.05$), however, differences were no longer significant at 1 year.

We included two small, fair-quality supplement intervention trials ($n=74$) examining flaxseed and fish oil in populations with multifactorial dyslipidemia; one of these trials was newly identified. Both studies had short duration of 4 to 8 weeks. These trials reported no statistically significant difference in TC or LDL-C, and flaxseed was associated with a statistically significant worsening of TG and HDL-C in the intervention group. There were no differences in BMI or total caloric intake.

Multifactorial Dyslipidemia/FH

We included seven fair- to good-quality supplement trials ($n=288$) in populations of children and adolescents with FH or multifactorial dyslipidemia which evaluated a wide range of supplement interventions. Overall, there was insufficient evidence to make conclusions about the effectiveness of supplements to improve lipid or other outcomes with one to three trials for each supplement type and short duration trials of 5 to 16 weeks.

All studies were newly identified. Only one trial, which evaluated the fiber glucomannan, showed a statistically significant improvement in TC, LDL-C, and non-HDL-C (-10 to -11 mg/dL). Two other fiber trials, however, showed no statistically significant improvements in TC or LDL-C. One psyllium fiber trial showed a 60.2 mg/dL reduction in TG while other fiber trials showed no difference in TG. A hempseed trial showed no statistically significant reductions in any lipid parameter.

FH

Drug Therapy Intervention: Statins

Trial and Participant Characteristics

We identified eight fair-¹¹⁴⁻¹²¹ and two good-^{122, 123} quality trials ($n=1,230$) that examined the effectiveness of statin treatment in children and adolescents with FH. One trial was newly identified in this update.¹¹⁴ Overall, the evidence is relatively dated. When data collection years were reported they ranged from 1990 to 2014; trials that did not report data collection years were published between 1998 and 2003. Five trials were multinational,^{114, 116-118, 120} one was conducted in the US,¹²³ three in the Netherlands,^{115, 121, 122} and one in Canada.¹¹⁹ Trial sizes were generally small, ranging from 50¹²¹ to 214.¹²² FH criteria varied and included a combination of one or more genetic, serum lipid, or family history criteria (**Figure 8; Table 19**). Most trials did not report recruitment setting or method; one trial reported recruitment from a lipid clinic¹¹⁹ and one

trial reported recruitment of a consecutive sample of treatment-naïve patients from an academic center.¹²²

Mean age ranged from 11¹¹⁴ to 15^{121, 123} years and the total age range of eligible participants was 6 to 18 years (**Figure 9; Table 20**).^{121, 123} One trial had all female participants¹²³ and one was exclusively male¹¹⁶; percent female ranged from 31¹¹⁷ to 55¹¹⁴ in the remaining trials. The five trials^{115-118, 123} reporting race and ethnicity indicated that the vast majority of participants were White, ranging from 80¹²³ to 93 percent.¹¹⁸ In the three trials reporting smoking history^{116, 121, 122} smoking ranged from 0¹²¹ to 11 percent.¹²² Where reported,^{116, 118, 122} family history of premature CAD/CVD was common, ranging from 34¹²² to 89¹¹⁸ percent. Two trials reported baseline Tanner staging showing a wide range in sexual maturity of participants in the study. All trials reported baseline fasting lipid values. Ranges of mean fasting lipid values were: TC 274^{120, 121} to 316¹¹⁶; LDL-C 208^{120, 121} to 250¹¹⁶; HDL-C 44¹¹⁶ to 52¹¹⁴ and TG 62¹¹⁵ to 111¹¹⁶ (**Figure 10**).

Intervention Characteristics

The trials administered various statin types and doses including Atorvastatin 10-20 mg,¹¹⁷ Lovastatin 10-40 mg,^{116, 123} Pravastatin 5-40 mg,^{115, 122} Pitavastatin 1-4 mg,¹¹⁴ Rosuvastatin 5-20 mg,¹¹⁴ and Simvastatin 10-40 mg (**Figure 11; Table 21**).¹¹⁹⁻¹²¹ Three trials had multiple intervention arms with different statin doses in addition to the placebo arm.^{114, 115, 118} Drug intensity, as defined by AHA/ACC guidelines for adults,³¹ was low to moderate in these trials, with the exception of one high-intensity arm in the trial by Avis and colleagues (Rosuvastatin 20 mg).¹¹⁸ Five trials had drug titration protocols.^{116, 117, 120, 121, 123} All trials had 4-12 week run-in diets which were typically followed the fat-restricted, NCEP Step 1 diet guidelines (**Appendix A Table 4**). Some trials specifically advised that all participants maintain the diet during the trial period.^{116, 117, 119, 122, 123} Followup measures occurred immediately following the completion of the treatment and ranged from 6¹¹⁹ to 104 weeks¹²² (**Figure 12**). LDL-C treatment goals were established in only four trials and varied: LDL-C <110 mg/dL,^{114, 118} ≤130 mg/dL,¹¹⁷ and <95th percentile for age and sex.¹¹⁵ The control groups received placebo in all trials. Adherence to treatment was high in the three reporting trials. Even the longest 104-week trial reported that overall, 87 percent of pills were taken¹²²; the second trial reported an overall 93 percent adherence at 12-week followup¹¹⁵ and the third trial reported that 88 to 91 percent of participants in the three intervention arms took ≥80% of pills at 12-week followup.¹¹⁸

Outcomes (Results)

In pooled analyses, statins were associated with an 81-82 mg/dL greater mean difference in TC and LDL-C compared to placebo at up to 104 weeks followup (TC: k= 7, n=706, MD in change -82.1 mg/dL [95% CI -101.1 to -63.2], *I*² 83.0%; LDL-C: k= 8, n=742, MD in change -81.3 mg/dL [95% CI, -97.6 to -65.0, *I*² 81.6%]) (**Figures 13-15; Tables 22-23**). The only trial using a high-intensity statin¹¹⁸—Rosuvastatin 20 mg/day—showed the highest reduction in TC and LDL-C (TC: MD in change -119.0 [95% CI, -139.1 to -98.9]; LDL-C: MD in change -118.0 [95% CI, -136.4 to -99.6]); however, confidence intervals overlapped with trials using moderate- and low-intensity statins. In terms of percent change, statins were associated with a 25 to 33 percent greater reduction in TC and LDL-C, respectively, at up to 48 weeks (k=5, n=526, MD in % change TC: -25.3% [95% CI, -33.0 to -17.5]; LDL-C: k=6, n=577, MD in % change -33.4%

[95% CI -42.0 to -24.8]) (**Figures 13, 16-17; Tables 24-25**). There was no difference in change in HDL-C between the groups ($k=6$, $n=643$, MD in change 1.6 mg/dL [95% CI -0.2 to 3.4], $I^2=0\%$) (**Figure 18**). Studies that could not be included in pooled analyses showed consistent results (**Table 26**).^{114, 115, 118, 120} There were insufficient data to pool TG because values were most often reported as medians (**Figure 19**). Results for TG were mixed and significant in 3 of 9 reporting trials, with mean between-group differences ranging from -8.0 to -12.4 mg/dL where reported in trials showing benefit (**Table 27**).^{117, 120, 121} Four trials reported the proportion of participants meeting LDL-C goals (**Table 28**).^{114, 115, 117, 118} In the highest-dose statin arms in each trial, 11.1 to 60.0 percent of participants met study-specified LDL-C goals, with no control group participants meeting goals (**Figure 20**). Three studies included multiple intervention groups evaluating different statin doses.^{114, 115, 118} Point estimates for reductions in TC and LDL-C were consistently greater in higher-dose arms within a trial, but confidence intervals also consistently overlapped.

One statin trial reported cIMT outcomes. The 2-year trial by Wiegman and colleagues showed a statistically significant between-group mean difference in change in mean combined carotid IMT favoring the statin group (MD in change 0.01 mm [95% CI, 0.00 to 0.02]; $p=0.03$).¹²²

Drug Therapy Intervention: Bile Acid Sequestrants

Trial and Participant Characteristics

We identified one good-quality¹²⁴ and two fair-quality trials^{125, 126} ($n=332$) examining the effectiveness of bile acid sequestrants to improve lipid levels in children with FH (**Tables 29-30**). All three trials were included in the prior review. One trial was multinational and recruited from 41 sites in Australia, Austria, Canada, the Czech Republic, Hungary, Israel, the Netherlands, New Zealand, Norway, Slovakia, South Africa and the United States and was conducted between 2005 and 2007.¹²⁴ The other two trials were conducted in Norway.^{125, 126} Participants were recruited from lipid clinics in the two trials reporting recruitment method.^{125, 126} Two trials included adolescents with FH aged 10 to 16 or 17 years^{124, 126} and the other trial included a younger age range—prepubescent females ages 6 to 10 years and males ages 6 to 11 years with FH.¹²⁵ Definitions of FH varied in the trials. Mean age ranged from 8 years to 14 years (**Figure 9**) with 37 to 44 percent of trial participants female. Only the larger multinational trial reported race and ethnicity: 87 percent were White, 3 percent were Black, and 4 percent were Asian.¹²⁴ At baseline, one trial reported that 24 percent of participants were on statin therapy¹²⁴ and the other trials did not report baseline lipid lowering medication use. In the three trials, mean fasting TC ranged from 265¹²⁴ to 320¹²⁵ mg/dL, mean LDL-C ranged from 199¹²⁴ to 245¹²⁶ mg/dL, mean HDL-C ranged from 43¹²⁶ to 47,¹²⁴ and mean or median TG ranged from 76¹²⁵ to 95¹²⁴ mg/dL (**Figure 21**).

Intervention Characteristics

Different bile acid sequestrant formulations were evaluated in the three trials, including cholestyramine 8 mg/day (after 1 week titration from 4 mg/d),¹²⁵ colestipol 10 mg daily or 5g twice per day,¹²⁶ or colesevelam 1.875 g/day and 3.75 g/day (**Table 31**).¹²⁴ All participants were on a low fat or NCEP Step 1 diet (**Appendix E Table 4**) prior to and/or during the randomized

drug period. Treatment duration and followup were 8 weeks in two trials¹²⁴ and 52 weeks (1 year) in the other trial (**Figure 12**).¹²⁵ The control groups received placebo in all trials. Overall adherence in the intervention groups was 68¹²⁶ and 87¹²⁴ percent in the 8-week trials. In the longer trial, 61 in the intervention group completed 1 year of therapy, having taken a median of 77 percent of all doses.¹²⁵

Outcomes (Results)

The three bile acid sequestrant trials demonstrated that this intervention was generally associated with a significantly greater reduction in TC and LDL-C, with some variation in effect by dose (**Figures 22-25; Tables 32-37**).¹²⁴⁻¹²⁶ For TC, statistically significant reductions ranged from -22.1 to -40.6 mg/dL; TC reduction for colestevam was significant only in the higher dose trial.¹²⁴ For LDL-C, reductions were statistically significant in all trials; two trials reported difference in mean values that ranged from -13.2 to -45.9 mg/dL at 8 weeks. Changes in HDL-C were only statistically significant in one trial, occurring in the intervention group randomized to the higher dose of colestevam (3.75 g/day), showing a 2.9 mg/dL greater change (calculated 95% CI, -0.5 to 6.3; $p=0.008$ in adjusted analyses).¹²⁴ There were no statistically significant reductions in TG in any of the trials.¹²⁴⁻¹²⁶ In the trial of colestevam, more participants in the higher dose 3.75 g/day group achieved LDL-C goal (<100 mg/dL) (7.9% in the IG vs 0% in the CG; ARD 7.9% [95% CI, 1.3 to 14.6]). There was no statistically significant difference in the proportion achieving goal in the lower-dose 1.875 g/day group (3.2% in the IG vs 0% in the CG; ARD 3.2% [95% CI, -1.2 to 7.5]).¹²⁴

Drug Therapy Intervention: Ezetimibe

Trial and Participant Characteristics

We identified one good-quality trial ($n=138$), examining the effectiveness of the cholesterol absorption inhibitor, ezetimibe, to improve lipid levels in children with FH (**Tables 29-30**).¹²⁷ This trial was included in the previous review. The trial collected data between 2009 and 2012 and recruited from 29 sites across nine countries including the US, Canada, Colombia, France, Greece, Italy, Norway, the Netherlands, and Israel. Participants were aged 6-10 years with heterozygous FH diagnosed by genotype or clinical criteria or clinically important non-FH defined as LDL >159 to <400 mg/dL while on lipid lowering diet for ≥ 3 months. Ninety-one percent of participants had FH and, thus, this trial was considered an FH trial; stratified results are reported by type of hyperlipidemia. Mean age was 8 years and 57 percent of participants were female. Most participants were White (80%), with 15 percent reporting multiracial heritage, 1 percent Black, and 3 percent Asian. Mean baseline fasting TC was 293 mg/dL, LDL-C was 227 mg/dL, HDL-C was 50 mg/dL and TG was 85 mg/dL (**Figure 21**).

Intervention Characteristics

After a drug washout period of up to 13 weeks, there was a 5-week placebo run-in with diet stabilization period in all participants (**Table 31**). The intervention group ($n=93$) then received oral ezetimibe 10 mg daily and the control group ($n=45$) received placebo tablets for 12 weeks.

Overall adherence in the trial was high with a mean of 95 percent medication compliance at each visit in both the placebo and control groups.

Outcomes (Results)

At 12 weeks, ezetimibe was associated with a statistically significant reduction in TC (MD in change -64.0 mg/dL [95% CI, -81.1 to -46.9]), LDL-C (MD in change -63.0 mg/dL [95% CI, -79.5 to -46.5]), and non-HDL-C (MD in change -65.0 mg/dL [95% CI, -82.2 to -47.8]) (**Figures 22-25; Table 32-36**).¹²⁷ Changes in HDL and TG were not significant. The outcome of percent change in LDL-C from baseline was reported for subgroups of participants with FH and clinically important non-FH. LDL reductions appeared smaller in participants with non-FH but only 12 participants were analyzed in this subgroup, so confidence intervals were wide and overlapped those for participants with FH.

Drug Therapy Intervention: Fibrate

Trial and Participant Characteristics

We identified one very small fair-quality randomized crossover trial (n=14) examining the effectiveness of fibrates to improve lipid levels in children with FH (**Table 29-30**).¹²⁸ The drug, bezafibrate, is not available in the U.S and not FDA-approved in children; currently, there are no fibrates that are FDA-approved in children. This trial was not included in the previous review. The study was conducted in the UK. Participants were aged 4-15 years with FH diagnosed by serum lipid levels and family history who previously failed dietary treatment and refused to continue taking cholestyramine. Mean age was 11 years and 57 percent of participants were female. Race and ethnicity were not reported. Mean baseline fasting TC was 359 mg/dL, HDL-C 39 mg/dL, TG 89 mg/dL, and baseline LDL-C was not reported (**Figure 21**).

Intervention Characteristics

In a randomized crossover design, participants were allocated to receive bezafibrate 10-20 mg/kg/day twice per day or placebo for three months and were then crossed over to receive the other treatment for three additional months (**Table 31**). Prior to the trial, all children were treated with dietary modification (low saturated fat and increased polyunsaturated fat diet) which did not reduce lipid levels adequately and were then placed on a bile acid sequestrant which was eventually refused in all subjects. Participants had a washout period from any cholesterol medications for at least three months prior to randomization. Adherence was high with 93 percent of participants having bezafibrate detected in the urine during the active treatment period. All children reported a preference for bezafibrate compared with prior cholestyramine resin treatment.

Outcomes (Results)

At 13 weeks, bezafibrate was associated with statistically significant improvement in TC but not HDL-C or TG (**Figures 22, 24-25; Tables 32, 34-35**). Active treatment with bezafibrate was

associated with an 84.9 mg/dL greater reduction in TC compared to the control group (95% CI, -126.2 to -43.6).

Drug Therapy Intervention: PCSK9 Inhibitors

Trial and Participant Characteristics

We identified one new good-quality trial (n=158), examining the effectiveness of a PCSK9 inhibitor, evolocumab, to improve lipid levels in children and adolescents with heterozygous FH (**Tables 29-30**).¹²⁹ The trial collected data between 2016 and 2019 and recruited from 47 sites across 23 countries in North America, Latin America, Europe and the Asia-Pacific region. Participants were ages 10-17 years with heterozygous FH diagnosed either by genetic testing or clinical diagnostic criteria. Lipid inclusion criteria were LDL-C \geq 130 mg/dL and \leq 400 mg/dL while on a low-fat diet and stable lipid-lowering therapy for at least 4 weeks prior to screening. Mean age was 14 years and 56 percent of participants were female. Most participants self-identified as White (86%) and representation from other races or ethnicities was not reported, however, 16 percent of participants were recruited from Latin America and 4 percent were recruited from the Asia-Pacific region. Approximately one-third of participants had overweight or obesity. At baseline, 79 percent were taking a moderate or high intensity statin medication and 13 percent were additionally taking ezetimibe. Mean fasting TC was 250 mg/dL, mean LDL-C was 184 mg/dL, mean HDL-C was 47 mg/dL, and mean TGs were 84 mg/dL (**Figure 21**).

Intervention Characteristics

The intervention group (n=104) received evolocumab 420 mg via monthly subcutaneous injection for 24 weeks (**Table 31**). The injections could be self-administered or administered by a designee or health professional. The control group (n=53) received monthly placebo subcutaneous injections. Adherence was high in the intervention group with 96 percent of participants completing the trial.

Outcomes (Results)

At 24 weeks, evolocumab was associated with a large and statistically significant reduction in LDL-C as measured by percent change (-38.3% [95% CI, -45.5% to -31.1%]) and absolute mean change (-68.6 mg/dL [95% CI, -83.1 to -54.0]) (**Figure 23; Tables 33, 36-37**). Likewise, evolocumab was associated with a statistically significant difference in non-HDL (-35.1% [95% CI, -42.0% to -28.2%]). More participants in the PCSK9 intervention group reached LDL goals, either as defined by LDL-C <100 mg/dL (62.5% vs 2.3%, ARD 60.2 [95% CI, 49.6 to 70.9]) or by >50% reduction in LDL (44.8% vs 2.3%, ARD 42.5% [95% CI, 31.6 to 53.4]). Evolocumab was not associated with statistically significant changes in cIMT over 24 weeks as assessed from several measures of cIMT thickness. For example, the mean change in difference between the intervention and placebo groups in the average of largest left and right common carotid artery was -0.01 mm (95% CI, -0.03 to 0.01).

Drug Therapy Intervention: Combination Therapy

Trial and Participant Characteristics

One fair-quality RCT (n=248) examined the effectiveness of a two-drug intervention (simvastatin and ezetimibe) compared to single drug therapy (simvastatin alone) to lower lipids in adolescents with FH (**Tables 29-30**).¹³⁰ This multinational RCT included male and post-menarchal female adolescents ages 10-17 years with Tanner stage ≥ 2 and FH. Mean age was 14 years with 43 percent female participants. Participants were mostly White (82%), with few Black (2%) or Asian (4%) participants, and 13 percent reported as 'other' race/ethnicity. Mean baseline fasting LDL-C was 222 mg/dL (**Figure 21**).

Intervention Characteristics

The intervention group was randomized to receive simvastatin 10, 20 or 40 mg per day plus ezetimibe 10 mg/d for 6 weeks; then all intervention arms received the same dose of simvastatin (40 mg/d) and ezetimibe (10 mg/d) for 27 weeks (**Table 31**).¹³⁰ The control groups were randomized to receive simvastatin 10, 20 or 40 mg plus one placebo tablet.

Outcomes (Results)

At 33 weeks, the two-drug intervention was associated with a significant improvement in all lipid parameters compared with the single-drug intervention, except for HDL-C, which showed no statistically significant difference (**Figures 22-24; Tables 32-37**). The two-drug intervention showed a greater reduction in TC (MD in change -40.1 mg/dL [95% CI, -51.1 to -29.2]), LDL-C (MD in change -37.5 mg/dL [95% CI, -48.0 to -27.0]), TG (-9.5 median difference in percent change, $p < 0.01$), and non-HDL-C (MD in change -40.0 mg/dL [95% CI, -51.0 to -28.9]) compared to the single-drug intervention control group. The intervention group was more likely to reach the LDL-C goal of < 110 mg/dl than the control group (62.7% v 26.7%, ARD 36.0% [95% CI, 24.5 to 47.6]).

Behavioral Counseling Interventions

Trial and Participant Characteristics

We identified one new fair-quality trial (n=21) that examined the effectiveness of behavioral counseling interventions to improve lipid levels and dietary and physical activity habits in children and adolescents with FH (**Table 38-39**).¹³¹ This U.S. trial recruited children and adolescents ages 10-18 years with FH from outpatient lipid clinics. Data were collected in 2018-2019. Mean age was 14 years; half of participants were female; 82 percent were White and 18 percent Asian. Eighteen percent had an overweight weight status and 9 percent had an obese weight status. At baseline, approximately one-quarter (23%) were on behavioral treatment only and most (77%) were on statin medications. Mean fasting TC was 193 mg/dL, LDL 127 mg/dL, and HDL 50 mg/dL.

Intervention Characteristics

This RCT tested a low-intensity intervention of one in-person 60-minute individual session with a dietician and four followup sessions via email or phone over a 12-week period (**Table 40**). The intervention consisted of 26 behavioral change techniques aimed to reduce total and saturated fat and cholesterol; increase intake of unsaturated fat, fiber, fruits and vegetables, and plant stanol or sterol fortified foods; reduce sedentary behavior and increase PA. The control group participants received usual care (annual outpatient lipid clinic visit) and were placed on a waitlist to receive the intervention after the trial. Adherence to the initial session and first three followup sessions was complete (100%) and the majority (60%) completed the fourth follow-up sessions.

Outcomes (Results)

At 12 weeks, results were mixed across lipid, physical activity, and dietary outcomes. There were no statistically significant differences between the intervention and control groups for changes in any serum lipid outcomes (TC, LDL-C, HDL-C) (**Figures 22-24; Table 41**). No statistical testing was done for adiposity and activity outcomes, including median changes in BMI, body fat percentage, moderate and vigorous physical activity, and sedentary time (**Appendix E Table 3**). General trends for these outcomes were more favorable for the intervention group compared to the control group, with overlapping ranges in both groups. The intervention was associated with statistically significant improvement in some but not all dietary measures. For example, more participants in the intervention group met dietary goals of consuming 2 g/d of plant stanols or sterols (90% v 0%) and the intervention group ate 2 additional portions of fruits/vegetables per day compared with the control group (adjusted difference, 2.2 portions [95% CI 1.2 to 3.2]) There was a statistically significant 5 percent difference between the intervention and control groups in fat intake as measured by percent of total energy intake (-5.3% [95% CI -8.9 to -1.5]), but the reduction in saturated fat intake was not statistically significant and intake of recommended fats—monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA)—either showed a statistically significant reduction (MUFA: -3.2% of total energy [95% CI -5.3 to -1.01]) or no difference (PUFA). No statistical differences were seen in cholesterol or fiber intake.

Supplement Interventions

Trial and Participant Characteristics

We identified four new fair-quality randomized crossover trials (n=116) that examined the effectiveness of supplements to improve lipid levels in children and adolescents with FH (**Tables 42-43**).¹³²⁻¹³⁵ Trials were set in the Netherlands,¹³² Finland,¹³³ Norway,¹³⁴ and the US.¹³⁵ Trial sizes were generally small, ranging from 14 to 41 participants. The trials recruited children and adolescents ranging in age from 2 to 21 years of age with heterozygous FH based on varied criteria using serum lipids, genetic mutation confirmation, or family history (**Figure 9**). Mean ages ranged from age 9 to 10 years; the trial with older participants—ranging from 9 to 19 years—did not report mean age.¹³⁵ The trials included approximately half female participants. Race and ethnicity were not reported. Mean baseline fasting lipids in the trials were: TC 271-297

mg/dL, LDL-C 208-219 mg/dL, HDL-C 42-53 mg/dL; mean TG varied substantially in the trials from 50-133 mg/dL (**Figure 21**).

Intervention Characteristics

The supplements included plant sterols,^{132, 134} the omega-3 fatty acid docosahexaenoic acid (DHA),¹³⁵ and a combination of plant sterol/stanol and omega fatty acids administered as rapeseed margarine plus sitostanol ester (**Table 44**).¹³³ Supplements were administered as food spreads or capsules, and interventions were short term, ranging from 4 to 8 weeks (**Figure 12**). The intervention groups received 15 g spread containing 2.3 g/d of plant sterols (sitosterol and campesterol) over 4 weeks,¹³² 20 g spread of 1.76 g/d plant sterol esters over 8 weeks,¹³⁴ 24 g/d rapeseed margarine containing 3g/d sitostanol ester over 6 weeks,¹³³ or 6 capsules per day containing 1.2 g DHA over 6 weeks.¹³⁵ The control groups received control spreads¹³²⁻¹³⁴ or corn/soy oil capsules.¹³⁵ Adherence was high in all trials as measured by returned spread tubs (>90% of spread consumed)¹³²⁻¹³⁴ and pill counts (reported as “excellent compliance”).¹³⁵

Outcomes (Results)

Two of four supplement trials showed statistically significant TC and LDL-C reductions favoring the intervention groups; these were trials evaluating 1.76 g/d or 2.3 g/d plant sterols (**Figures 22-25; Tables 45-48**).^{132, 134} De Jongh and colleagues reported that the 4 week plant sterol intervention was associated with a 30 mg greater reduction in TC (-30.5 mg/dL [95% CI, -39.4 to -23.2]) and LDL-C (-30.1 mg/dL [95% CI, -38.6 to -23.2]) compared to the control group.¹³² The 8 week trial by Amundsen and colleagues similarly reported significant reductions in TC (-20.5 mg/dL [95% CI, -36.1 to -8.6]) and LDL-C (-22.4 mg/dL [95% CI, -34.5 to -6.5]) compared to the control group.¹³⁴ The trial evaluating the supplement combination of plant sterol/stanol and omega fatty acids administered as rapeseed margarine plus sitostanol ester found a similar magnitude of TC and LDL-C reduction, but failed to reach statistical significance compared to the control group (TC: MD -31.3 mg/dL [95% CI, -67.7 to 5.1]; LDL-C -31.7 mg/dL [95% CI, -67.2 to 3.8]).¹³³ In the trial evaluating the omega-3 fatty acid DHA, TC and LDL-C increased in the intervention group compared to the control group but differences were not statistically significant and confidence intervals were wide (TC: MD 9.0 mg/dL [95% CI, -45.7 to 63.7]; LDL-C 10.0 mg/dL [95% CI, -45.2 to 65.2]).¹³⁵ There were no statistically significant differences between the intervention and control groups for HDL-C or TG.

Multifactorial Dyslipidemia

Drug Therapy Interventions

There were no included trials of drug interventions in child and adolescent populations with multifactorial dyslipidemia.

Behavioral Counseling Interventions

Trial and Participant Characteristics

We identified two behavioral counseling trials—one fair-quality¹³⁶ and one good-¹³⁷ quality—in children and adolescents with multifactorial dyslipidemia (N total=934) (**Tables 49-50**). One trial was included in the prior review, and one was newly included. The Dietary Intervention Study in Children (DISC) (n=663) was a 7-year U.S. study initiated in the 1980s that recruited prepubertal children aged 7 to 10 years with LDL-C $\geq 80^{\text{th}}$ and $< 98^{\text{th}}$ percentiles for age and sex.¹³⁷ These participants were recruited from multiple settings including schools, pediatric practices, and HMO mailing lists. The Children's Health Project (CHP) (n=271) was a 1-year UK study initiated in the early 1990s that recruited children ages 4 to 10 years from a cholesterol screening program at nine suburban pediatric practices.¹³⁶ The children had initially elevated TC screening results (>176 mg/dL) and subsequently elevated mean fasting LDL-C and weighed $\geq 85\%$ and $< 130\%$ of ideal body weight.

The mean ages were 9 years¹³⁷ and 6 years¹³⁶ in the two trials (**Figure 26**). Approximately half of participants were female in both trials, and the majority were White (86% and 87%). Eight and 10 percent of participants were Black in DISC and CHP, respectively.^{136, 137} In DISC, one-third to one-half of participants' parents were college graduates and CHP participants were from middle to upper income families with parents with high educational attainment. Mean fasting LDL-C was similar in both trials (131 mg/dL¹³⁷ and 122 mg/dL¹³⁶) (**Figure 27**). The DISC trial additionally reported mean fasting TC (200 mg/dL), HDL-C (57 mg/dL) and TG (80 mg/dL).¹³⁷

Intervention Characteristics

The two behavioral counseling intervention trials were heterogeneous with respect to intervention contact time and duration, but both exclusively focused on dietary change without including physical activity messages (**Table 51; Appendix E Table 4**). The DISC trial randomized the intervention group (n=334) to an intensive intervention over 7 years.¹³⁷ The intervention group attended sessions focused on dietary interventions that included 19 case manager-led individual sessions and 31 group sessions led by dietitians, behaviorists, and health educators in an academic medical center. The primary goal of the intervention was adherence to a diet low in total and saturated fat, low in cholesterol, and high in fiber. There were no physical activity messages or goals in this intervention. The control group (n=329) received usual care that informed parents of their child's high cholesterol and recommendations to see their physicians as well as publicly available educational publications on heart-healthy eating. At year 3, the participants with lipid levels exceeding thresholds for monitoring were reviewed and referred to physicians. The intervention group had high adherence: attendance was 89 percent or higher through the first 3 years and declined to 72 percent during year 5. Adherence further declined to 37 percent at the end of year 7 (defined as attending 2 or more individual or group visits per year).

The CHP trial randomized families to two intervention groups of low intensity and a control group.¹³⁶ The first intervention group (n=92) was assigned to a home-based social cognitive theory-based intervention that included 10 audiotape story books with accompanying picture

books, child activity books, and a parent manual to be reviewed over 10 weeks. The second intervention group (n=90) involved the child and at least one parent attending one in person 45-to-60-minute counseling session with a pediatric registered dietician and home print materials with access to the dietician by phone with any questions after the session. Both interventions consisted of dietary messages consistent with the NCEP Step 1 diet (**Appendix A Table 4**); no physical activity messages or goals were included. The control group (n=89) received no intervention. Adherence to the first intervention was moderate with 64 percent of children listening to all stories and 95 percent listening to at least half; 63 percent completed at least half of the activities. About half (46%) of the parents reported reading the entire manual and another 15 percent reported reading at least half of the manual. Adherence to the second intervention was presumably complete given that there was only one visit, but only 2 percent contacted the dietician by phone for the 3-month period.

Outcomes (Results)

Lipid lowering results were mixed in the two studies of behavioral counseling interventions, with greater TC and LDL-C reduction seen in the intervention with more contact time (**Figures 28-31; Table 52**). Improvements for some dietary outcomes were seen in both interventions, with benefit diminishing at longer followup. The DISC intervention was associated with significantly greater reductions in TC and LDL-C at 3 years compared to the control group (TC: MD -3.3 mg/dL [95% CI, -6.4 to -0.2]; LDL-C: MD -3.3 mg/dL [95% CI, -6.0 to -0.6]) but not at 7.4 years (TC: MD -1.1 [95% CI -5.0 to 2.8]; LDL-C: MD -1.9 [95% CI -4.7 to 0.9]). The intervention was not associated with significant differences in HDL-C or TG or at either timepoint. While 3-month results for the home-based CHP intervention showed statistically significant LDL-C reduction compared to the control group (MD in change -6.7 mg/dL (CIs not available), $p < 0.05$), differences were no longer significant at 1 year. Change in LDL-C was not significantly different between the dietician counseling intervention and control at 3 months or 1 year. No other lipid outcomes were reported.

Behavioral counseling interventions were associated with improvements in several dietary intake outcomes at shorter followup periods up to 3 years, but when longer followup was reported, improvements were attenuated (**Appendix E Table 5**). For example, cholesterol intake was statistically significantly lower in the intervention group in the DISC trial at 3 years (MD -18.1 mg/1000 kcal [95% CI -25.7 to -10.4]) but not at 7.4 years and results in the CHP trial showed no significant difference.^{136, 137} In the DISC trial, percent calories from fat declined more in the intervention group at 3 years (MD -4.2% [95% CI, -5.1 to -3.4]) and 7.4 years (MD -1.5% [95% CI, -2.43 to -0.57]) compared to the control group. Similarly, mean change in percent calories from fat was lower in the CHP interventions at one year (home-based intervention: MD in change -1.3% [calculated 95% CI, -3.1 to 0.5]; $p < 0.05$ in adjusted analyses; dietician-based intervention: MD in change -2.3% [95% CI, -4.1 to -0.5]). DISC reported a statistically significant improvement in saturated fat intake at 3 years (MD -2.1% [95% CI, -2.5 to -1.7]) and 7.4 years (MD -0.9% [95% CI, -1.4 to -0.4]). Similarly, at 3 months, both interventions in CHP showed a comparable reduction in grams of saturated fat intake that were significantly greater than the control group (home-based intervention: MD in change -3.8 g [95% CI, -6.15 to -1.45]; dietician-based intervention: MD in change -4.2 g [95% CI, -6.42 to -1.98]). The clinical importance of these small changes in dietary intake outcomes is uncertain.

Supplement Interventions

Trial and Participant Characteristics

We identified two small fair-quality trials examining the effectiveness of dietary supplements to reduce lipids in children and adolescents with multifactorial dyslipidemia (n=72) (**Tables 53-54**). One randomized controlled trial (n=32)¹³⁸ evaluated a flaxseed supplement and the other was a randomized crossover trial (n=42)¹³⁹ examining the omega-3 fatty acid supplement of fish oil; the latter trial was newly identified in this update. The trials were conducted in Canada¹³⁸ and the US.¹³⁹ One trial included children and adolescents ages 8 to 18 years with elevated LDL-C (135-193 mg/dL), a family history of hypercholesterolemia or premature CVD, and were on the Step II diet (**Appendix A Table 4**),¹³⁸ while the crossover trial included adolescents ages 10 to 17 years with elevated fasting TG (≥ 150 mg/dL and < 750 mg/dL) but LDL-C < 160 mg/dL.¹³⁹ Both trials recruited participants from lipid referral clinics.

The mean ages were 13¹³⁸ and 14¹³⁹ years in the two trials (**Figure 26**). Approximately one-third to one-half of participants were female in the two trials, and in the one trial reporting race, the majority were White (86% White participants, 5% Black participants, 7% Latino participants, 2% reported as ‘other’ race/ethnicity).¹³⁹ Mean fasting lipid values in the two trials were: TC, 194 mg/dL¹³⁹ and 208 mg/dL¹³⁸; LDL-C, 112 mg/dL¹³⁹ and 138 mg/dL¹³⁸; HDL-C 39 mg/dL¹³⁹ and 49 mg/dL;¹³⁸ and TG 112 mg/dL¹³⁸ and 272 mg/dL¹³⁹ (**Figure 27**).

Intervention Characteristics

The intervention group in the RCT received 30 g/d of flaxseed baked into muffins and breads for 4 weeks and the control group received identical muffins and breads containing whole wheat flour in place of the flaxseed (**Table 55**).¹³⁸ Both groups complied with an NCEP Step 2 diet (**Appendix A Table 4**) for a minimum of 6 months prior to trial enrollment. The intervention group in the randomized crossover trial received 4 g/d of fish oil for 8 weeks while the control group received a corn oil placebo.¹³⁹ Adherence in the flaxseed trial was high based on self-reported intake logs (IG: 85%, CG: 80%)¹³⁸ and adherence was not reported in the fish oil trial.

Outcomes (Results)

There were no statistically significant differences in TC or LDL-C in either trial (**Figures 28-31; Table 56**). Results for TG were mixed, with the fish oil intervention associated with significant improvement (-36 mg/dL [CIs not available], p=0.04),¹³⁹ and the flaxseed intervention associated with a significant increase in TG (MD in change 29.2 mg/dL [95% CI, 4.4-53.2]).¹³⁸ The flaxseed trial similarly reported significant worsening of HDL-C in the control group (MD in change -7.4 mg/dL [95% CI -11.6 to -3.1]).¹³⁸ There was no difference in BMI or total caloric intake between the groups in the flaxseed trial (**Appendix E Table 6**).¹³⁸

Multifactorial Dyslipidemia/FH

Supplement Interventions

Trial and Participant Characteristics

We identified six fair-quality¹⁴⁰⁻¹⁴⁵ and one good-quality¹⁴⁶ trials (n=288) examining the effectiveness of various supplements that included children and adolescents with either FH or multifactorial hyperlipidemia (**Tables 57-59**). The supplements included: omega-3 fatty acids,^{141, 146} fiber,^{140, 143, 145} hazelnuts,¹⁴² and probiotics.¹⁴⁴ One trial was conducted in the US,¹⁴³ and the other six were conducted in Italy.^{140-142, 144-146} The trials included children and adolescents ranging from 5 to 18 years with FH and multifactorial dyslipidemia (**Figure 32**). Inclusion criteria varied and comprised various serum lipid thresholds and/or family history of hyperlipidemia or CVD. Children were recruited from outpatient hospital-based pediatric clinics or lipid clinics. Mean ages were 8 to 12 years. The proportion of participants with FH varied widely, from 5 percent to 69 percent^{140, 141, 144-146}; one study reported “most” had FH¹⁴³ and another study did not specify participants’ diagnoses.¹⁴² Four of the trials explicitly described participants meeting criteria for familial combined hyperlipidemia, sometimes comprising a substantial proportion of participants (8% to 60%).^{140, 141, 144, 145} Between 20¹⁴⁰ and 58¹⁴⁴ percent of participants were female among trials. No trials reported race or ethnicity. Reporting of weight status in the trials was inconsistent; 4 trials reported no participants with BMI \geq 85th percentile^{140, 141, 144, 146} and 2 trials reported between 8 and 22 percent of participants had mild or borderline overweight.^{141, 142} Ranges of mean fasting lipid values were: TC 201 mg/dL¹⁴³ to 252 mg/dL,¹⁴⁶ LDL-C 136 mg/dL¹⁴¹ to 175 mg/dL,¹⁴⁶ HDL-C 46 mg/dL¹⁴³ to 60 mg/dL,^{142, 146} TG 68 mg/dL (median)¹⁴² to 196 mg/dL,¹⁴³ and non-HDL-C 154 mg/dL¹⁴¹ to 192 mg/dL¹⁴⁶ (**Figure 33**).

Intervention Characteristics

The intervention groups in the two omega-3/6 fatty acid trials received one 500 mg gel capsule of DHA+EPA or 500 mg gel capsule of DHA alone over 16 weeks in one trial¹⁴⁶ and 3 g/d of hempseed oil in capsules for 8 weeks in the other trial (**Figure 12; Table 60**).¹⁴¹ Intervention groups in the fiber trials received 500 mg glucomannan gel caps for 8 weeks,¹⁴⁰ age dependent dosing of glucomannan capsules twice per day with lunch and dinner (2-3 g/d),¹⁴⁵ and ready to eat cereals with 6 g/d of psyllium fiber for 4-5 weeks.¹⁴³ The intervention group in the hazelnut trial received one daily weight-based portion (15-30 g) of hazelnuts with or without skin for 8 weeks.¹⁴² The intervention group in the probiotic trial received one daily probiotic capsule one hour before dinner of *B. animalis* subspecies *lactis* MB 109, *B. bifidum* MB 109, and *B. longum* subspecies *longum* BL04 (1x10⁹ CFU each species) for 12 weeks.¹⁴⁴ Run-ins included 4 weeks^{140, 144} to 3-month dietary counseling¹⁴¹⁻¹⁴³ on some form of low total fat, low saturated fat, low cholesterol diet. The control groups received placebo^{140, 143, 144, 146} or usual care.^{141, 142, 145} Adherence was high when measured ranging from 89 percent¹⁴⁴ to 97 percent¹⁴⁶ based on capsule counts and 82 percent for cereal consumption in one trial.¹⁴³ Three trials did not report adherence.^{141, 142, 145}

Outcomes (Results)

Of the 7 supplement trials conducted in populations with multifactorial dyslipidemia or FH, only one, which evaluated the fiber glucomannan, showed a statistically significant reduction in multiple lipid values (**Figures 34-37; Tables 61-65**): TC (-10.8 mg/dL [-18.5 to -3.1]), LDL-C (-10.1 mg/dL [-17.4 to -2.9]), and non-HDL-C (-11.2 mg/dL [-18.0 to -4.5]).¹⁴⁰ However, this is in the context of two other fiber trials showing no statistically significant reduction in TC or LDL-C (the other 2 fiber studies did not report non-HDL-C).^{143, 145} The remaining trials showed no difference in TC. None of the studies reported a statistically significant change in HDL-C.^{140-143, 145, 146} Only one trial, evaluating psyllium fiber, reported a statistically significant reduction in TG (-60.2 mg/dL [-115.9 to -92.0]) while the other trials showed no statistically significant difference between groups for this outcome.^{140-142, 145, 146} The trials evaluating omega-3/6 (DHA, EPA¹⁴⁶ and hempseed oil¹⁴¹), probiotics,¹⁴⁴ and hazelnuts¹⁴² showed no statistically significant reductions in any lipid parameter.

One trial of omega-3/6 (hempseed oil) in participants with multifactorial dyslipidemia or FH also reported non-lipid outcomes and showed no difference in BMI between the groups (**Appendix E Table 7**).¹⁴¹

KQ5. What Are the Harms of Treatment of FH or Multifactorial Dyslipidemia in Children and Adolescents?

Summary of Findings

Familial Hypercholesterolemia

Overall, harms reported in pharmacotherapy trials were similar in the intervention and control groups, however, most studies were relatively short term and small with few events leading to imprecise estimates. Further, the clinical importance of transient elevations in lab values was unknown.

In the statin trials, transaminitis of 3 times or more the upper limit of normal occurred in 0 to 4.5 percent in intervention groups and 0 to 1.9 percent in control groups. The largest trial (n=214) with 2-year followup reported no cases in the statin group and only 2 cases of AST more than 3 times the upper limit of normal in the control group. In the 10-year observational followup of this trial, transaminitis at this threshold was similarly rare (ALT: 1 case of >3 times elevation in the statin group; AST: 1 case of >3 each in the statin and control group). Abnormal creatine kinase of 10 times or greater the upper limit of normal was reported as zero in two trials, and up to 4.5 percent in the statin groups and up to 1.7 percent in the control groups. One trial's 10-year observational followup reported no instances of elevated creatine kinase in participants on statins and in 2 non-FH siblings not taking statins. Two observational studies evaluated statin harms in populations with dyslipidemia without specification of type of dyslipidemia. One fair-quality observational study evaluated the association of statins and new onset diabetes (n=9,393) showing no difference in new diabetes diagnoses over up to 9 years followup in those taking statins compared to controls. One fair-quality observational study (n=943) reported ALT more

than 3 times the upper limit of normal with a frequency of 4.4 percent in the statin group and 1.5 percent in the control group over 3.5 years of observation.

No significant differences between Tanner stages or other hormonal adverse events were reported in the RCTs or longer observational followup. Harms in the three bile acid sequestrant trials (n=332) were similar in the intervention and control groups, however, the trials were generally small with few events and significance testing was not reported. Harms in the ezetimibe trial (n=138), PCSK9 inhibitor trial (n=158), and combination statin plus ezetimibe versus statin trial (n=248) showed similar rates of total adverse events in the intervention and control groups. The small fibrate trial (n=14) reported one instance of transient ALT elevation and one instance of alkaline phosphatase elevation in the intervention group. The diet and physical activity counseling intervention did not mention harms and three supplement trials in FH reported that there were no adverse events.

Multifactorial Dyslipidemia

Overall, behavioral counseling interventions do not appear to be associated with important harms and there is inadequate evidence to make conclusions about harms of supplements in this population.

The two behavioral counseling trials in children with multifactorial dyslipidemia (n=934) reported no adverse effects in terms of growth and development, nutrient adequacy, and psychosocial outcomes in the dietary intervention group compared to the control group. The flaxseed trial (n=32) reported no adverse events and the fish oil trial (n=42) reported gastrointestinal symptoms, fishy taste, and frequent nose bleeds.

Multifactorial Dyslipidemia/FH

Overall, fiber supplements appear to be associated with GI side effects and there is inadequate evidence to make conclusions about harms of other supplements in these populations. Evidence is limited by few studies and short trial durations of 5 to 16 weeks.

Five of the seven supplement trials in populations with FH or multifactorial dyslipidemia reported harms, with two trials reporting no adverse events, however the fiber trials reported various gastrointestinal side effects of 0 to 22.2 percent in intervention groups and 0 to 5.0 percent in control groups, and the probiotic trial reported three cases of abdominal pain (5.4% v 2.8%).

FH

Drug Therapy Intervention: Statins

Trial and Participant Characteristics

All 10 RCTs of statin interventions in children and adolescents with FH included for KQ4 also reported harms (**Table 19**).¹¹⁴⁻¹²³ These harms were dermatologic,^{115, 116, 120} gastrointestinal,^{115-118, 120, 123} hormonal,^{115-117, 120, 122, 123} hepatic,^{114-118, 120, 122, 123} and musculoskeletal.^{114-116, 118, 120, 122, 123} Overall total adverse events and withdrawals were reported in all but one trial.¹¹⁹ Most trials were generally short-term, ranging from 6 to 28 weeks.^{114-119, 121, 123} Two longer trials were 48 weeks¹²⁰ and 2 years.¹²² Thus, much of the evidence reflects short-term harms only.

Three NRSI were also included for harms of statins (**Table 66**). Longer-term harms in children and adolescents with FH are available from one good-quality NRSI study (n=309) which was a 10-year observational followup of the included Wiegman et al 2-year RCT.^{122, 147} Inclusion criteria were children 8-18 years with FH diagnosis based on genetic confirmation or serum LDL-C threshold who previously participated in the 2 year statin trial; at the end of the trial, all participants with FH received the statin. The control group was non-FH siblings of the participants, none of whom were taking statins. This study was conducted in the Netherlands and collected data between 1997 and 2011.

Two fair-quality NRSIs from the United States included participants with hyperlipidemia without specifying whether the hyperlipidemia was FH or multifactorial.^{148, 149} One study (n=9,393) had the aim of evaluating whether statin use was associated with the risk of type 2 diabetes¹⁴⁸ and included children and adolescents 8 to 20 years from an insurance database with data collected between 2003 and 2014.¹⁴⁸ The other smaller study (n=943) aimed to evaluate the hepatotoxicity of statins in individuals 21 years or younger from a lipid clinic with one or more serum ALT measurements available; data were collected for 3.5 years between 2010 and 2014.¹⁴⁸

Outcomes (Results)

The harms reported in the statin intervention groups and control groups were similar, however, most studies were small with few events leading to imprecise estimates (**Figures 38-40; Appendix E Tables 8-18**). Total adverse events were reported in seven trials and were similar in the intervention and control groups, ranging between 0 to 70.1 percent in statin groups and 0 to 73.8 percent in control groups.^{115-118, 121-123} Total adverse event reporting was broad in the trials reporting high total adverse event rates and often included minor transient symptoms such as diarrhea or respiratory tract infections, which are unlikely to be intervention-related. For example, in the study reporting the highest rates of total adverse events (IG: 70.1%, CG: 73.8%), more than half of these events were respiratory tract infections. Gastrointestinal^{115-117, 120, 123} and dermatologic^{115, 116, 120} side effects were similar in the intervention and control groups. Transaminitis (elevated ALT or AST) of any severity ranged from 0 to 22.2 percent in the statin groups and 0 to 5.5 percent in the control groups.^{114-117, 120, 122, 147} However, transaminitis of 3

times or more the upper limit of normal, which is a typical threshold in clinical practice for discontinuation and rechallenge with another statin, occurred in 0 to 4.5 percent in the intervention groups and 0 to 1.9 percent in the control groups. The largest trial (n=214) of longest duration (2 years) by Wiegman and colleagues reported no cases of transaminitis greater than 3-fold elevation in the statin group and two cases in the control group.¹²² One NRSI¹⁴⁷ (n=309) which was a 10 year observational followup of the 2 year trial by Wiegman and colleagues and used non-FH siblings not taking statins as the control group, reported similar rates of transaminitis in the statin and control groups; 1 treated FH individual and no untreated non-FH siblings had ALT >3 times normal and 1 treated FH individual and 1 untreated non-FH siblings had AST >3 times normal. Abnormal creatine kinase of any severity occurred in 0 to 15.4 in the intervention groups and 0 to 1.7 percent in control groups.^{114, 116, 118, 120, 122, 123, 147} Abnormal creatine kinase of at least 10 or more times the upper limit of normal was reported as zero in two trials^{116, 123} and up to 4.5 percent in the intervention groups and up to 1.7 percent in the control groups in two other trials reporting this threshold.^{118, 120} In the NRSI (n=309) which was a 10-year observational followup of the Wiegman et al 2-year RCT, elevated creatine kinase was diagnosed in no participants on statins and two non-FH siblings not taking statins.¹⁴⁷ No significant differences between Tanner stages or other hormonal adverse events were reported.^{115-117, 120, 122, 123, 147}

The NRSI reporting on hepatotoxicity measures reported slightly higher rates of elevated ALT in participants on statins compared to those not on statins, but statistical testing was not performed due to the rarity of events (**Appendix E Table 11**).¹⁴⁸ Desai et al reported ALT elevations of greater than 3 times the upper limit of normal with a frequency of 4.4 percent in the statin group and 1.5 percent in the control group over 3.5 years of observation.

The NRSI reporting on the association of statin use with new onset diabetes found no statistically significant association (**Appendix E Table 18**).¹⁴⁹ Joyce et al reported that 17 of 869 (2.0%) of participants taking statins developed new onset diabetes compared to 146 of 8524 (1.7%) in the control group (HR 1.11 [95% CI, 0.65 to 1.90]) over up to 9 years followup. This nonsignificant difference was similar when the analysis was limited to participants with pure hypercholesterolemia which is a surrogate for FH (HR 1.11 (95% CI, 0.58 to 2.12)).

Drug Therapy Intervention: Bile Acid Sequestrants

Outcomes (Results)

The harms reported in the three bile acid sequestrant trials appeared similar, however the trials were generally small with few events and significance testing was not reported (**Table 29; Appendix E Table 19-23**).¹²⁴⁻¹²⁶ Total adverse events, reported in one trial, were similar between the groups (3.75 g dose: 6.3%, 1.875 g dose: 10.8%, control: 10.8%).¹²⁴ Withdrawals due to adverse events were low in two of three trials, ranging from 0 to 4.6 percent in intervention groups and were 0 percent in control groups.^{124, 126} However, there was one outlier trial with a high withdrawal rate due to adverse events in both the intervention and control groups, largely due to lack of palatability of the drug or placebo (38.9% v 27.8%).¹²⁵ Individual gastrointestinal side effects such as diarrhea, intestinal obstruction, abdominal pain, and vomiting were reported in 0 to 13.6 percent of participants taking bile acid sequestrants and 0 to 11.5

percent taking placebo.^{124, 125} Elevations in creatine phosphokinase (with no specified threshold) were reported in 1.6 percent of the high dose group, 3.1 percent of the low dose groups, and none in the control group.¹²⁴ In the one trial reporting nutritional deficiencies, folate deficiency and vitamin D deficiency were 4.5 percent and 13.6 percent, respectively, in the intervention group and 0 percent in the control group.

Drug Therapy Intervention: Ezetimibe

Outcomes (Results)

In the one trial of ezetimibe compared to placebo, harms generally occurred in the same rates in both groups (**Table 29; Appendix E Table 19-23**).¹²⁷ There were no reported serious drug-related adverse events in either group. There were few withdrawals due to drug-related adverse events (IG: 2/92 [2.2%], CG: 0/45 [0%]). There were three total withdrawals in the intervention group due to ALT elevation, prurigo, and an epileptic event in a patient with congenital epilepsy. One case of transaminitis (ALT ≥ 3 times ULN) occurred in an intervention group participant (1.1% [1/92]) and no cases occurred in the control group. There were no reported elevations in CK (defined as ≥ 10 times ULN with or without muscle symptoms or ≥ 5 times ULN with symptoms), rhabdomyolysis, pancreatitis, or cholecystitis. The one adverse event with a statistically significant difference between groups was diarrhea, occurring more frequently in the control group (-7.8% difference [95% CI, -19.8 to -1.1]).

Drug Therapy Intervention: Fibrate

Outcomes (Results)

Two adverse events were reported in the small trial of fibrate compared to placebo (**Table 29; Appendix E Table 21-22**).¹²⁸ There was one participant in the intervention group with a transiently elevated abnormal alkaline phosphatase (7.1% [1/14]) and one participant with a transient elevation in ALT that normalized by the end of the third month of treatment (7.1% [1/14]). No drug-related clinical adverse events were reported.

Drug Therapy Intervention: PCSK9 Inhibitors

Outcomes (Results)

In the one trial of PCSK9 inhibitors, there were similar rates of total adverse events in the intervention and control groups (62% v 64%) (**Table 29; Appendix E Tables 19-23**).¹²⁹ Total adverse event reporting, however, was broad and included minor and transient events which are unlikely to be intervention-related, such as nasopharyngitis and headache. There were no serious adverse events related to the drug. There was one withdrawal due to adverse events in the intervention group where drug-related arthropathy led to discontinuation (1.0% [1/104]). One intervention group participant experienced an injection site reaction (1.0% [1/104]).

Drug Therapy Intervention: Combination Therapy

Outcomes (Results)

In the one combination drug therapy trial comparing treatment with ezetimibe and a statin to a statin alone, there were similar rates of total adverse events in both groups (83% v 84%) (**Table 29; Appendix E Table 19-23**).¹³⁰ As with other drug interventions, adverse event reporting was broad and included minor or transient symptoms which are unlikely to be intervention-related, such as diarrhea, headache, or sinusitis. Two participants in the combination drug therapy group withdrew due to adverse events (2/122 [1.6%]) and one participant in the control group withdrew due to a laboratory adverse event (1/118 [0.8%]). Six participants in the combination drug therapy group (5%) and three participants in the single drug therapy group (2%) experienced ALT elevations, however, varied thresholds were used by individual investigators and did not always reach 3 times the upper limit of normal. There were no clinically significant adverse effects on growth, sexual maturation, or hormones. Gastrointestinal, dermatologic, and musculoskeletal outcomes appeared similar in both groups; however, significance testing was not reported.

Behavioral Counseling Interventions

Outcomes (Results)

The one behavioral counseling trial included for the FH population did not address harms.¹³¹

Supplement Interventions

Outcomes (Results)

In three of the four supplement trials conducted in FH populations (**Table 42**), authors explicitly reported that there were no adverse events.^{132, 134, 135} The other trial did not address harms.¹³³

Multifactorial Dyslipidemia

Behavioral Counseling Interventions

Outcomes (Results)

The two behavioral counseling trials in children with multifactorial dyslipidemia reported that growth and development, nutrient adequacy, and psychosocial outcomes were similar between the intervention and control groups (**Table 49; Appendix E Table 24-25**).^{136, 137} In the DISC trial, there was no difference in growth and development measures including BMI (3 y: MD - 0.04 kg/m² [95% CI, -0.3 to 0.2]; 7 y: MD -0.1 kg/m² [95% CI, -0.5 to 0.4]), height (MD 0.6 cm [95% CI, -0.02 to 1.2]; 7 y: -0.3 cm [-1.0 to 0.4]), weight (3 y: MD 0.3kg [-0.5 to 1.0]), and Tanner staging (6 y: reported as not statistically different) between the dietary intervention and

control groups. Likewise, CHP reported similar height and weight z-score changes in the intervention and control groups at 1 year.¹³⁶ Serum ferritin, red cell folate, serum retinol, serum zinc and albumin were similar in the dietary intervention and control groups in the DISC trial.¹³⁷ Psychosocial outcomes were similar for anxiety, behavioral issues, and suicidality in the DISC trial. Depression scores, however, as assessed using the Child Depression Inventory (CDI) were better in the intervention group at 3 years (OR for CDI \geq 14 score: 0.24 [95% CI, 0.09 to 0.65]).¹³⁷ In the CHP trial, behavior problems, as assessed in 4 to 6 year-olds using the Conners Parent Rating Scale, and health beliefs and self-perceived competence, as assessed in 6- to 10-year-olds using the Perceived Competence Scale, were similar in the intervention and control groups.¹³⁶

Supplement Interventions

Outcomes (Results)

In the flaxseed supplement trial, authors explicitly reported that there were no adverse events or withdrawals due to adverse events (**Table 53; Appendix E Table 26**).¹³⁸ In the fish oil supplement trial, intervention-related adverse events included gastrointestinal symptoms, fishy taste and frequent nose bleeds resulting in dose reductions in two participants; authors did not report prevalence of adverse events by group.¹³⁹ There were no withdrawals due to adverse events in the fish oil supplement trial.

Multifactorial Dyslipidemia/FH

Supplement Interventions

Outcomes (Results)

Five of the seven supplement trials reported a harm outcome, and reporting was varied among studies (**Table 57; Appendix E Table 27**). One trial each reported withdrawals due to adverse events¹⁴⁰ or serious drug related adverse events,¹⁴⁴ and there were no events in any group. Two trials explicitly stated that there were no adverse events.^{145, 146} In the glucomannan study by Guardamagna and colleagues, the intervention group reported frequent gastrointestinal effects (4/18 [22.2%] vs 0/18) and increased satiety (2/18 [11.1%] vs 0/18 [0%]) but the study size was small and number of events was low.¹⁴⁰ There were a few reported cases of abdominal pain in the probiotic trial intervention group (2/37 [5.4%] vs 1/36 [2.8%]) but again study size was small and the number of events was low.¹⁴⁴ The small psyllium fiber trial reported diarrhea more frequently in the control group with (IG: 0%, CG: 5%).¹⁴³

Chapter 4. Discussion

Summary of Evidence

We conducted a systematic review to support the USPSTF in updating its recommendation on lipid screening in children and adolescents. We have included seven new studies of diagnostic yield, 16 new treatment trials, and two new non-randomized studies of interventions. Despite the inclusion of new evidence, our conclusions are similar to those of the prior reviews^{2, 3} (**Tables 67-69**). There is no direct evidence from population-based screening trials addressing the benefits and harms of pediatric lipid screening for intermediate, behavioral, or health outcomes. Our updated review shows that dyslipidemia is common in contemporary pediatric populations in the United States with a prevalence of 19.2 percent for any lipid abnormality and heterozygous FH prevalence (as defined by phenotype) estimated at 0.2 to 0.4 percent (1:250 to 1:500). The body of evidence on treatment benefit is strongest for statins in FH children and adolescents with pooled analysis showing beneficial effects on TC and LDL-C; these results were based on mostly small, short-term studies with the longest trial of 2 years. Most of the evidence for statin harms is from small, short-term studies. Limited longer-term evidence shows few withdrawals due to adverse events, slightly higher rates of liver and musculoskeletal lab elevations, and no significant differences in Tanner staging or hormonal adverse events between statin and placebo groups. These safety and efficacy findings are consistent with another recent systematic review¹⁵⁰ and 1-to-20-year observational followup studies of children and adolescents on statins.^{71, 151-158} The trials of bile acid sequestrants, fibrates and PCSK9 inhibitors in FH populations show reductions in one or more lipid parameters and are generally associated with low withdrawals due to adverse events. There is scant evidence on behavioral counseling interventions and supplements in FH; two small plant sterol supplement trials show improvement in TC and LDL-C at 4-8 weeks. The body of evidence on treatment of multifactorial dyslipidemia is sparse, being limited to two short term behavioral counseling interventions showing modest short-term benefits in lipid levels that did not persist with longer follow-up. These results are consistent with short-term quality improvement projects in specialty settings that have shown that clinician advice targeting lifestyle modifications have shown promising results especially for LDL-C reductions.¹⁵⁸ Two supplement studies of flaxseed and fish oil showing no benefit in lipid levels. Supplement trials recruiting both FH and multifactorial dyslipidemia populations show mixed results on lipid outcomes for fiber supplements and data on other supplements were too limited to make conclusions. Fiber supplements were commonly associated with gastrointestinal side effects and limited evidence from other supplements reported no adverse events, no serious adverse events or no AEs leading to withdrawals.

Single Screening Test Identifies Distinct Conditions

Our review's juxtaposition of the bodies of evidence for FH and multifactorial dyslipidemia highlights a few key points. First, the natural history of the two conditions varies dramatically. While a single screening lipid panel would identify both conditions, FH is far less common and more prognostically severe and multifactorial dyslipidemias are highly prevalent and less severe. Second, the strength of the bodies of treatment literature are quite distinct for different

dyslipidemias. Some have argued that the rationale for universal lipid screening in childhood is solely or primarily to identify those with FH because identifying FH has more potential benefit in reducing premature CVD events and death. There is existing direct RCT evidence from our review that statin therapy in FH reduces lipid levels and slows progression of atherosclerosis; additional observational evidence shows treatment in childhood reduces CVD mortality compared to delayed treatment in adulthood.¹⁵⁹ While the treatment evidence for multifactorial dyslipidemias is scant, some have suggested that early identification of any dyslipidemia could lead to earlier non-pharmacologic interventions or pharmacologic management for significantly elevated LDL-C and potentially improve health outcomes.¹⁶⁰ However, screening would identify nearly one-fifth of children who would be labeled as having dyslipidemia based on having at least one abnormal lipid parameter. There is no direct evidence to suggest an effective intervention for this twenty percent of children and adolescents other than to recommend healthy lifestyle habits which should be recommended to all children and adolescents. As reported in this review, there is no trial evidence supporting that any intervention in children with multifactorial dyslipidemia leads to improved lipid levels. Further, a systematic review of statin treatment in children with dyslipidemia secondary to obesity identified no studies.¹⁶¹

More detailed evidence is discussed below about indirect pathways that have been proposed to link childhood screening and early treatment of both FH and multifactorial dyslipidemias to health outcomes.

Indirect Linkages From Child Lipids to Adult Health Outcomes

In the absence of direct evidence that lipid screening in childhood is associated with improved long term health outcomes, and because any health outcomes resulting from screening and treatment in childhood would require decades to realize, several indirect linkages have been proposed as suggested in the framework in **Figure 41**.

The association between elevated adult lipids and adult CVD events (**Figure 41, line c**) is well established and is founded upon a causal relationship between lipids and coronary atherosclerosis.¹⁶² If youth lipids independently predict CVD events (**Figure 41, line a**), then there may be grounds to initiate early treatment if the net benefit of treatment is positive. Similarly, if there is a strong persistence between youth and adult lipids (**Figure 41, line b**), then early measurement of cholesterol may identify individuals at risk for future CVD events.¹⁶³ On the other hand, if abnormal lipids in youth are transient, then more caution in initiating treatment in the young may be warranted.

Association Between Youth Lipids and Adult Health Outcomes (Figure 41, line a)

Multiple robust streams of evidence suggest that abnormal lipids in childhood and young adulthood are highly associated with adult CVD events. In 2022, the i3C Consortium published a pooled analysis of seven prospective cohort studies (n=38,589) that followed participants who

had cardiovascular risk factors measured in childhood over a mean of 35 years and evaluated the association of childhood measures with subsequent cardiovascular events in adulthood.⁴⁹ In the context of loss to followup over long periods, outcome ascertainment for fatal events was more reliable than for nonfatal events because of the use of national death registries, so we focus on fatal events here. Levels of cardiovascular risk factors in childhood (ages 3 to 19 years) were highly associated with fatal cardiovascular events in adulthood.

Hazard ratios for a fatal CVD event in adulthood were 1.30 (95% CI, 1.14 to 1.47) per unit increase in the z-score for TC (which describes standard deviations from the mean). For log-transformed TG, this HR was 1.50 (95% CI, 1.33 to 1.70). When a combined score of multiple adult cardiovascular risk factors (smoking, BMI, SBP, TG, and TC) is considered in the analysis of the relationship of combined childhood risk factors to later fatal CVD events, the child risk factors are no longer statistically significant. This could suggest that childhood risk factors predict adult fatal CVD events largely because they track to adult risk factor levels. This control for adult risk factors is only available as a combined score for multiple risk factors and is not available for lipids alone. When adult risk factors are considered as a trajectory from childhood (change in combined risk score from childhood to adulthood), both child and adult measures are statistically significant, underscoring the importance of changes over time, but again this analysis is only for combined risk factors and not lipids exclusively. One broad limitation of these i3c analyses is that individual CVD risk factors are not examined independently. Analyses were adjusted for sex, race, cohort, mean age at year of child measurement, and parent education. Furthermore, the i3C cohorts remain relatively young (ages 40 years to early 50 years) so the analyses to date focus on early CVD.

In a pooled analysis of 36,030 participants from six US-based cohort studies, Zhang and colleagues investigated the independent association between exposure to high lipids in young adulthood (age 18 to 39 years) and later CVD events, taking into account exposure to elevated lipids in later adulthood (≥ 40 years).¹⁶⁴ This analysis is unique in its focus on cumulative exposure to elevated lipids, with a mean of 5 measurements over time per person and a median followup period of 17 years. Exposure to LDL-C levels 100 mg/dL or above in young adulthood was associated with an adjusted hazard ratio of 1.64 (95% CI, 1.27 to 2.11) for CHD, defined as myocardial infarction or CHD death, compared with LDL <100 mg/dL in young adulthood. This hazard ratio controls for later exposure to elevated lipids as well as other cardiometabolic risk factors and clinical characteristics and underscores the prognostic value of early adulthood lipid levels. Reinforcing this cumulative exposure hypothesis are data showing that adults with FH have increased CVD risk compared with adults without FH with similar lipid profiles.¹¹

Limited evidence from the i3C and Zhang et al analyses suggest no differences in the associations between childhood lipids and adulthood CVD outcomes by race and ethnicity (limited to Black and White individuals), however robust evidence is lacking.^{49, 164}

Another analysis method using a Mendelian randomization study came to similar conclusions. In a meta-analysis of nine single nucleotide polymorphisms (SNPs) in six different genes that are associated with lower LDL-C but not competing CVD risk factors, Mendelian randomization analyses suggested that lower LDL-C levels throughout the lifespan are associated with substantially lower CHD in adulthood compared to the current practice of initiating treatment for

lipid-lowering later in life.¹⁶² This analysis suggests that the cumulative long-term LDL-C levels plays a critical role in the natural history of atherosclerotic heart disease.

Additionally, a 2021 systematic review by Pool and colleagues¹⁶⁵ identified three publications from one cohort study, the Princeton Followup Study, that reported significant associations between TG in childhood and adult CVD events with HRs ranging from 5.4 to 6.1.

Tracking of Youth Lipids to Adult Lipids (Figure 41, line b)

There is no standardized measure for reporting “tracking,” so reporting among studies is variable and no single pooled measure can summarize the persistence of elevated lipids between youth and adulthood. Taken together, however, evidence suggests that tracking of TC or LDL-C from young childhood to adolescence and then to adulthood is moderate, but much less strong for TG. These tracking data should be considered in the context of known growth and maturation-related variations in children. Lipid levels are very low in cord blood at birth, increase slowly in the first 2 years of life, peak prior to puberty, and decrease during adolescence before rising again during late adolescence and young adulthood.^{30, 166} Males experience a decrease in HDL-C levels during late puberty, whereas HDL-C levels remain stable in females until menopause.²¹ Because of this variation in lipid levels over the life course, and the associated limitations with fixed cutpoints that are not age- and sex-specific, assessing the persistence of elevated lipid values is likely sensitive to the ages and intervals at which measurements are occurring.

The most comprehensive analysis of lipid levels beginning in childhood is from the i3C consortium, which is a combined analysis of seven prospective cohort studies (n=38,589) that followed participants over a mean of 35 years and reported Pearson correlations for TC and TG between young childhood (3-11 years) and adolescence (12-19 years), and between childhood (3-19 years) and adulthood (≥ 20 years).⁴⁹ In analyses of TC, the correlation between young childhood and adolescence was 0.74 and was 0.58 between childhood and adulthood. In analyses of TG, the correlation between young childhood and adolescence was 0.40 and was 0.44 between childhood and adulthood. In a study reporting sensitivity and specificity measures, the sensitivity and specificity of LDL-C ≥ 130 mg/dL in adolescence (12-18 years) were 65 percent and 75 percent for LDL-C ≥ 160 mg/dL in adulthood after 20.2 years of followup; the diagnostic performance was similar for TC.¹⁶⁷ Persistence of elevated values can also be assessed by the proportion of a population remaining in the highest quintile of the distribution after followup. In studies reporting this measure, which had followup ranging from 4 to 27 years, between 40 and 60 percent of participants age 5-18 years at initial measurement remained in the highest quintile after followup for various lipid measures (TC, HDL-C, TG).^{163, 168, 169} Unsurprisingly, these studies found that shorter followup intervals and higher childhood age better tracked with adult lipid values. An analysis by Kelder and colleagues found that 79 percent of 3rd graders remained within plus or minus one quintile of their initial quintile after 6 years followup for TC and HDL-C.¹⁶⁹ These studies were conducted in the general population so are less relevant to the FH population for whom there is a more extensive genetic component.

Linkage of Adult Lipids to CVD Events (Figure 41, line c)

A robust literature base supports the association between elevated adult lipid levels and cardiovascular disease events both in the observational epidemiologic literature⁴⁵ as well as the statin treatment trials.¹⁷⁰ Most recently, scientists have introduced the concept of “cholesterol-years” similar to the paradigm of pack-years in tobacco exposure.¹⁷¹ Several recent analyses have focused on cumulative LDL-C exposure as an important risk factor for incident CVD. A 2021 meta-analysis of four U.S. cohorts (Atherosclerosis Risk in Communities study (ARIC), Multi-Ethnic Study of Atherosclerosis (MESA), Framingham Heart Study-Offspring (FHS-O), Coronary Artery Risk Development in Young Adults study (CARDIA) with 18,288 participants ages 18 to 60 years with data spanning 1971 to 2017 demonstrated that higher total cumulative LDL-C—as measured by cumulative levels, time-weighted average, and slope—during young adulthood and middle age—were associated with increased risk of incident CHD events (MI, CHD deaths).¹⁷² The point estimates for the HRs comparing the top to the bottom quartiles for these cumulative LDL-C variables ranged from 1.26 to 1.97. These findings remained significant even after adjusting for the most recent LDL-C during middle age, however, this association was not found for other CVD outcomes such as stroke or heart failure. One 2020 IPD meta-analysis of 13 international cohorts (n=34,072) similarly found that elevated mean LDL-C and lower mean HDL-C measures in adulthood (baseline ages mostly 40’s to 60’s) were associated with higher incident CVD events (MI, stroke or vascular death) but unlike the previous analyses, the annualized progression of these lipid values (slope) in individual participants was not associated with incident CVD events.¹⁷³ Additional study designs supporting this concept of cumulative exposure are Mendelian randomization studies. One aforementioned meta-analysis of Mendelian randomization studies (n=312,321) showed that naturally random allocation to a lower LDL-C exposure, mediated by nine polymorphisms in six genes, was associated with a 54 percent CHD risk reduction for each 39 mg/dL lower LDL-C.¹⁶² This risk reduction is equivalent to a 3 times greater reduction in the risk of CHD per unit of lower LDL-C than statin treatment in adulthood.

Association Between Youth Lipids to Adult Subclinical CVD (cIMT), and Adult cIMT to CVD Events (Figure 41, line d)

Another pathway connecting youth lipids to health outcomes would be for youth lipids to be associated adult subclinical CVD (e.g., cIMT) and for adult subclinical CVD in turn to be associated with CVD events, or for youth cIMT to be associated with CVD events. Cohort data consistently show associations between child lipids levels and adult cIMT, and extended followup from a treatment trial initiated in childhood further reinforces this association. Further, single adult cIMT measurements appear to be associated with CVD events. Overall, the evidence base for indirect linkages associating cIMT to CVD events through the lifecourse is weaker than the evidence for the lipid pathway.

A 2020 publication from the i3C Consortium, which followed 4,582 youth ages 3 to 19 years from 4 prospective cohorts for a mean of 26 years, found that youth with dyslipidemia were at a markedly higher relative risk of having an elevated carotid artery intima-media thickness (cIMT) in adulthood compared to youth with normal lipid levels.¹⁷⁴ An LDL-C ≥ 130 mg/dL in childhood or adolescence was associated with a 26 percent increase in cIMT $\geq 90^{\text{th}}$ percentile in adulthood

(RR 1.26 [95% CI, 1.04 to 1.51]); estimates were adjusted for age, sex, BMI, SBP, cohort and length of followup. When analyzed by age groups, only LDL-C ≥ 130 mg/dL in youth 15-17 years was statistically significantly associated with cIMT $\geq 90^{\text{th}}$ percentile in adulthood, however this finding may be related to reduced power in age strata. The risk of cIMT $\geq 90^{\text{th}}$ percentile was attenuated and no longer statistically significant for individuals whose LDL-C was abnormal in youth and lowered to normal levels in adulthood (RR 1.16 [95% CI, 0.96 to 1.40]).

A 2021 systematic review by Pool and colleagues¹⁶⁵ found longitudinal community-based population data showing a consistent association of higher childhood LDL-C and TC and thicker cIMT in adulthood, mixed findings for HDL-C, and no association between childhood TG and cIMT in adulthood. In studies stratifying cIMT findings by age, associations were present in adolescence but were not significant in early childhood.

Evidence from 20-year followup of statin therapy initiated in childhood (between 8 and 18 years, mean 14 years) is available from a small study of 214 children who were randomized between 1997 to 1999 to statins or placebo.¹⁵⁹ Comparative data are available from 95 unaffected siblings and 156 parents with FH who did not receive statin treatment until much later in life (estimated mean age 32 years). This analysis showed that after 20 years, mean cIMT values converged in statin-treated children with FH and their unaffected siblings, with mean values falling from baseline in children with FH and rising in unaffected siblings.

Further, subclinical atherosclerotic changes appear early in children with FH which supports a link between lipids and cIMT. Data from an international study of 196 children with FH and 64 unaffected siblings found that statistically significant differences in cIMT were present between children with and without FH as early as 8 years of age.⁴⁰ Another study also comparing children with FH and unaffected siblings further found that the progression of cIMT was 5 times greater in children with FH.⁴¹ By adulthood, atherosclerotic burden in individuals with FH has increased substantially because of continued exposure to high LDL-C.

Single cIMT measurements in adults have been shown to be associated with incident CVD, however, there is conflicting evidence about whether cIMT changes (progression or regression) over time are associated with CVD risk or if cIMT added to traditional risk calculation has added predictive value. This literature is limited by clinical heterogeneity in cIMT measurement methodology and reporting. One meta-analysis of eight observational studies in adults (n=37,197) showed a nonlinear relationship between a single CIMT measurement and MI or stroke.¹⁷⁵ Based on five cohorts, the HR for MI per 1SD increase in common carotid artery IMT adjusted for age and sex was 1.26 (95% CI, 1.21 to 1.30) and the HR for stroke per 1 SD increase in common carotid artery IMT adjusted for age and sex was 1.32 (95% CI, 1.27 to 1.38). The PROG-IMT IPD meta-analysis of 16 cohorts (n=36,984) with a mean followup of 7 years showed that while mean cIMT from two ultrasound visits 2 to 7 years apart (median 4 y) was associated with CVD risk (adjusted HR 1.16 [95% CI 1.10 to 1.22]), the annual cIMT progression was not associated with the combined CVD endpoint (adjusted HR 0.98 [95% CI, 0.95 to 1.01]).¹⁷⁶ On the other hand, a meta-analysis of 119 treatment trials (n=100,667) with a mean followup of 3.7 years showed that across all interventions, each 10 $\mu\text{m}/\text{year}$ reduction of cIMT progression resulted in a relative risk for CVD of 0.91 (95% credible interval 0.87 to 0.94), with an additional relative risk for CVD of 0.92 (0.87-0.97) being achieved independent of cIMT

progression.¹⁷⁷ cIMT has also been evaluated as a nontraditional risk factor that may improve the predictive performance of traditional CVD risk scoring. A systematic review of 13 studies reported highly variable results for various model performance measures quantifying the incremental predictive value of cIMT. For example the change in the c-statistic from adding cIMT to traditional risk assessment was 0.007 to 0.035 and overall net reclassification index (NRI) values varied from 3.1 percent to 28.4 percent.¹⁷⁸ Limitations of existing cIMT studies include heterogeneity of measurement method population, age, and followup time.

Age to Initiate Statins in FH

There is no direct comparative effectiveness evidence to determine the exact age to start statin treatment for heterozygous FH, but earlier initiation is supported by indirect observational evidence. Net screening benefit depends on the indirect evidence that screening would correctly identify children with the condition and that earlier identification and treatment would result in improved outcomes compared to identification and treatment in adulthood. The screening benefits for those diagnosed with FH could be substantial as the condition's natural history includes premature CVD with events occurring in the second or third decade of life.

Expert consensus guidelines recommend pharmacotherapy with statins for heterozygous FH at age 8 years or older. These recommendations for early initiation aim to reduce cumulative exposure to high LDL-C and are based on indirect evidence showing that markers of atherosclerosis are evident as early as age 8 years in children with FH compared to unaffected siblings or healthy controls; these subclinical atherosclerotic markers include higher cIMT and endothelial dysfunction (flow mediated dilation), and arterial stiffness (pulse wave velocity, arterial compliance).^{40, 41, 179, 180} There is observational evidence supporting early treatment improvements in intermediate and health outcomes. At 10-20 year followup, cIMT progression rates converge in children with pathogenic variant-confirmed FH treated with statins and their unaffected siblings.^{147, 159} One compelling observation from a 20-year followup from the statin trial by Wiegman and colleagues demonstrated that early initiation of statins in adolescence was associated with an improved cumulative CVD-free survival at 39 years of age.¹⁵⁹ Those with pathogenic variant-confirmed FH who started statins in youth (mean statin initiation age of 14.0 +/- 3.1 years) had higher rates of CVD-free survival compared to their parents, for whom statins were not available until adulthood (99% v 74% CVD-free survival; HR 11.8 [95% CI, 3.0 to 107.0] adjusted for sex, smoking status).¹⁵⁹ Currently, the FDA has approved seven statins in children as young as 8 to 10 years of age with heterozygous FH.

Other Potential Benefits of Pediatric Lipid Screening

Some have argued that lipid screening can lead to additional benefits beyond identifying children with dyslipidemia. For example, universal lipid screening can lead to the discovery of secondary comorbid conditions (e.g., diabetes, hypothyroidism) through additional testing, whereby treatment of these comorbid disorders could lead to further improved health outcomes. Presumably, identification of dyslipidemia in children could also accelerate the identification of this condition in other family members via cascade testing (FH-mutation testing in relatives of

someone with an FH mutation), with earlier diagnosis and treatment leading to additional benefits. However, there is limited direct evidence about additional benefits of screening beyond the child. For any type of dyslipidemia, there is a moderate correlation of abnormal lipids amongst siblings. For example, one analysis shows the sibling of a child with LDL-C ≥ 130 mg/dL has more than a five-fold chance of also having LDL-C above this level (OR 5.45 [95% CI, 4.31 to 6.90]).¹⁸¹ The remaining evidence on additional potential benefits to the family of screening come from the FH literature. One UK study (n=10,095) of children ages 1-2 years assessed the efficacy and feasibility of screening for cholesterol levels and testing for FH mutations during an immunization visit and found that for every 1,000 children screened 8 persons (4 children and 4 parents) were identified as having positive FH results.¹⁸² Using results from this original study, authors have published cost effectiveness analyses demonstrating that a combination of cascade testing (FH-mutation testing in relatives of someone with an FH mutation) and child-parent screening (testing children for cholesterol and FH mutations during 1-year immunization visits and parents of FH-positive children) was cost effective and the most rapid strategy for identifying FH in the UK population.^{183, 184} The authors report that this combination strategy of cascade screening plus child-parent screening can identify one new FH individual for every 70 children screened. While soliciting family history of premature CVD or dyslipidemia has been suggested to make FH screening more efficient, family history has been shown to be inaccurate⁶⁸ and a substantial number of FH children would be missed if screening was limited to those with family history of premature CVD.⁶⁹

Others have surmised that screening and identification of dyslipidemia in children and adolescents with elevated BMI may make weight management interventions more effective; however, limited evidence does not support this hypothesis.^{185, 186}

Limitations of Our Approach

We did not address ApoB, Lp(a), or VLDL outcomes in this review as we focused on lipids generally ordered in primary care for screening purposes. We did not systematically review the accuracy (sensitivity/specificity) of FH diagnostic criteria and our findings accepted FH as defined by study authors for all key questions. We recognize that FH is genetically heterogeneous and that the relationship between the FH genotype and FH phenotype as expressed by elevated LDL-C is not straightforward.^{10, 18, 187, 188} We also did not include other less common monogenic or polygenic dyslipidemias, so our estimates of the positivity rates for screening may be an underestimate of familial dyslipidemias.

Limitations of the Studies and Future Research Needs

No studies performed a confirmatory lipid or genetic test; thus, evidence for children and adolescents is limited to screen-positivity (prevalence) from a single lipid test rather than diagnostic yield of lipid screening for FH. A recent study in adults that used a regression model including genetic testing data from the UK Biobank to estimate FH prevalence in the US found a similar FH prevalence (0.38%) to what we found for children and adolescents in our review (0.2% to 0.4%).¹⁸⁹ FH diagnostic criteria in yield studies were limited to lipid levels alone; this is

inconsistent with treatment trial criteria which also included genetic, family, or clinical history components in addition to lipid levels. Treatment trials were generally small with relatively short followup, with most trial durations of less than 6 months. Only one statin trial had a followup as long as 2 years. With the exception of statins evaluated in the FH population, the bodies of evidence for any specific intervention in either the FH or multifactorial dyslipidemia population were extremely sparse, often consisting of just one to three studies. Behavioral counseling and supplement trials were generally small, with short term followup leading to uncertainty regarding long term adherence and benefit persistence. Outcomes for treatment trials were limited to intermediate outcomes with insufficient followup periods to assess long-term health effects or harms. Obtaining such health outcome data may be quite difficult. In order to report on health outcomes for CVD events occurring in adulthood, these trials would need to be conducted over a period of decades while maintaining adequate followup, and further may be difficult to interpret because of the contemporary relevance of the population studied. While one statin treatment trial and one trial of PCSK9 inhibitors reported cIMT as an intermediate outcome, no studies reported other measures of atherosclerosis such as coronary artery calcium scores. We did not identify any behavioral counseling trials in children with concurrent dyslipidemia and elevated BMI reporting lipid effects of such interventions.

We identified a few relevant US-based yield and registry studies that are following children with FH over time and intend to report long-term change in lipid levels, CVD outcomes, and/or adverse events (**Appendix F**). Additionally, we identified two ongoing relevant treatment studies: one trial of a PCSK9 inhibitor in children and adolescents with heterozygous FH and one trial of omega-3 treatment for dyslipidemia in children with obesity 10 to 18 years of age.

Future research needs include:

- Population-based trials evaluating the effectiveness of lipid screening in pediatric populations
- Standardized definitions for FH in clinical practice and trials
- Additional placebo-controlled RCTs in FH populations would likely be considered unethical because of poor CVD prognosis in this population. Thus, additional observational long-term reporting of health outcomes and statin safety (including diabetes, transaminitis) in those with FH for whom statins were initiated at various timepoints in childhood and adolescence would provide additional data for long-term benefits and harms; siblings unaffected with FH could serve as appropriate controls.
- Behavioral counseling intervention trials in children with multifactorial dyslipidemia with and without elevated BMI and behavioral counseling as adjunct to pharmacotherapy in children with FH

Conclusions

There is no direct evidence from population-based screening trials addressing the benefits and harms of pediatric lipid screening for intermediate, behavioral, or health outcomes. Dyslipidemia is common in contemporary pediatric populations, with nearly one in five children in the United States having any lipid abnormality. Heterozygous FH prevalence as defined by phenotype in

U.S. pediatric cohorts is estimated at 0.2 to 0.4 percent (1:250 to 1:500). The body of evidence on treatment benefit is strongest for statins in FH children and adolescents based on pooled results showing beneficial effects on TC and LDL-C from mostly small, short-term studies, with the longest trial of 2 years and safety data from individual trials and non-randomized studies showing few withdrawals due to adverse events. There are fewer non-statin pharmacotherapy trials in FH populations showing reductions in one or more lipid parameters and generally low withdrawals due to adverse events. There is scant evidence on behavioral counseling interventions and supplements in FH. The body of evidence on treatment of multifactorial dyslipidemia is sparse, consisting of a few behavioral counseling interventions and supplements that did not reduce lipids at longest followup time point. Supplement trials recruiting both FH and multifactorial dyslipidemia populations were too few for any single supplement and insufficient to make conclusions about efficacy or safety.

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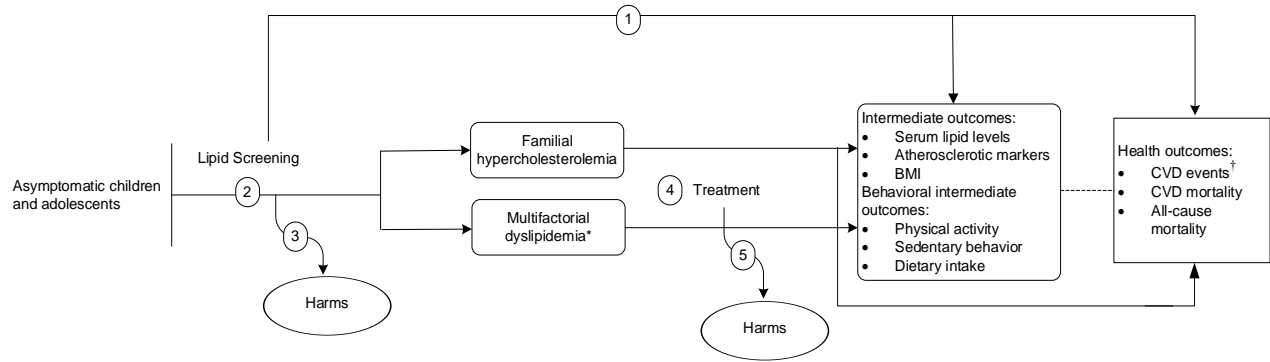
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Figure 1. Analytic Framework

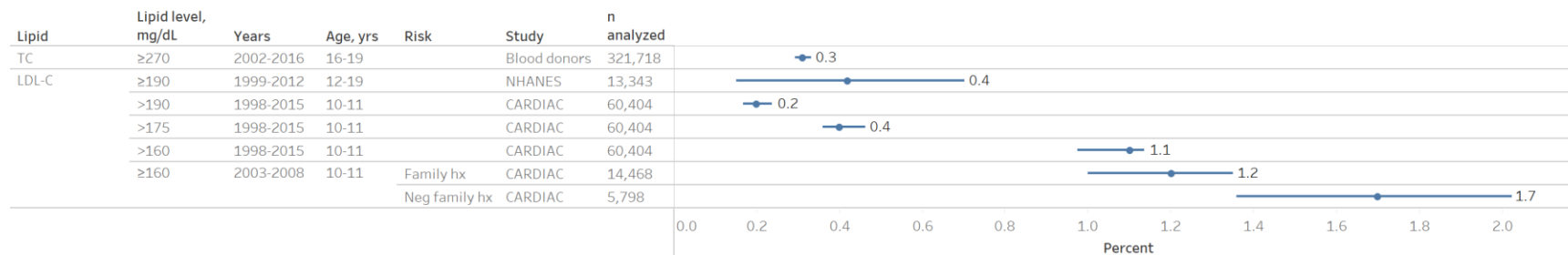


*Multifactorial dyslipidemia is defined as dyslipidemia not due to familial hypercholesterolemia

[†]CVD events are defined as MI or ischemic stroke.

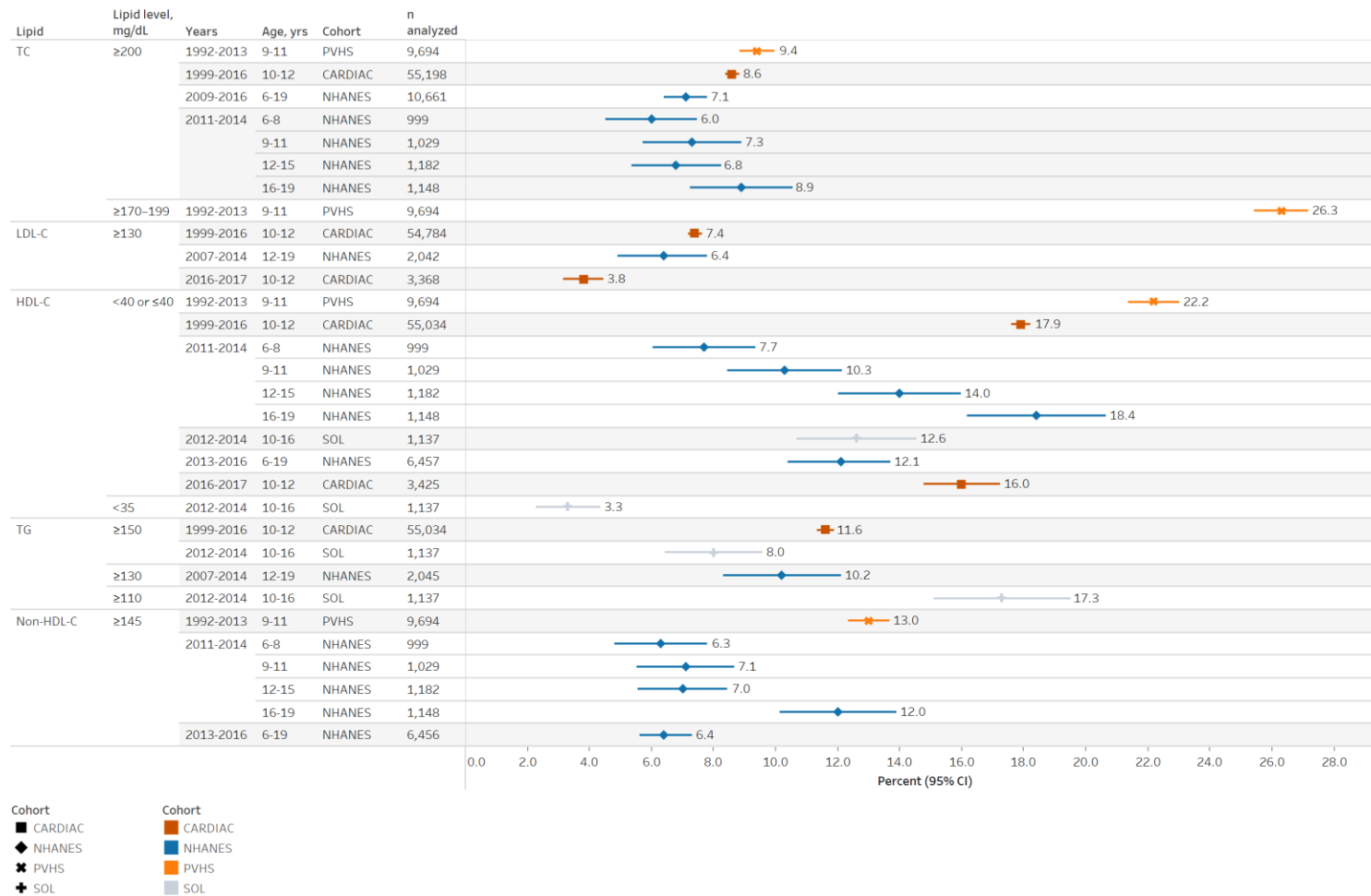
Abbreviations: BMI = body mass index; CVD = cardiovascular disease

Figure 2. Familial Hypercholesterolemia (FH): Prevalence of FH in US Cohorts Included for Key Question 2



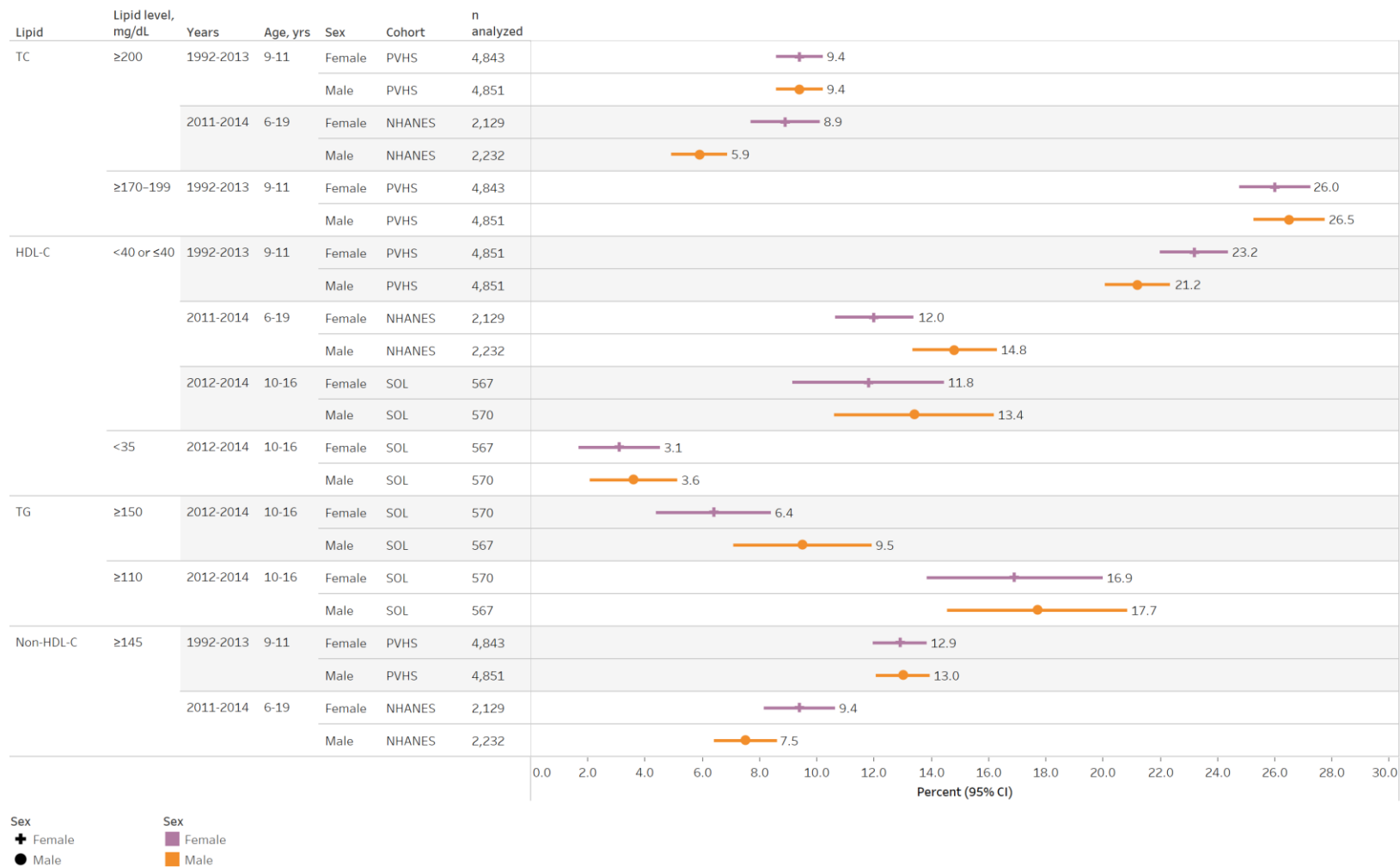
Abbreviations: CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; hx = history; LDL-C = low-density lipoprotein-cholesterol; Neg = negative; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol; US = United States; yrs = years

Figure 3. Multifactorial Dyslipidemia (MFD): Prevalence of MFD in US Cohorts Included for Key Question 2



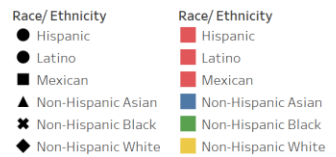
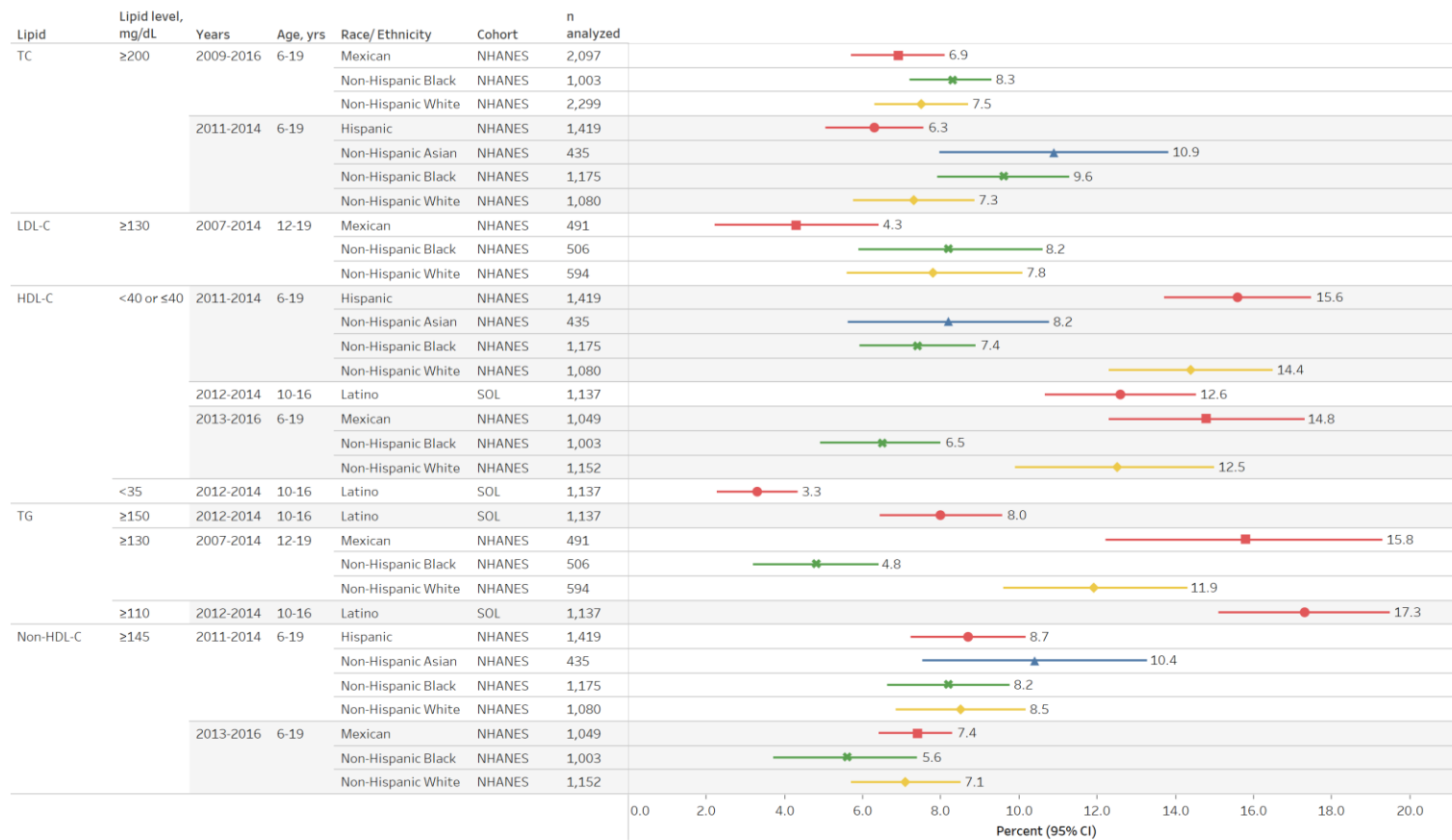
Abbreviations: CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; PVHS = The Poudre Valley Health System; SOL = Study of Latinos; TC = total cholesterol; TG = triglycerides; US = United States; yrs = years

Figure 4. Multifactorial Dyslipidemia (MFD): Prevalence of MFD in US Cohorts Included for Key Question 2, by Sex



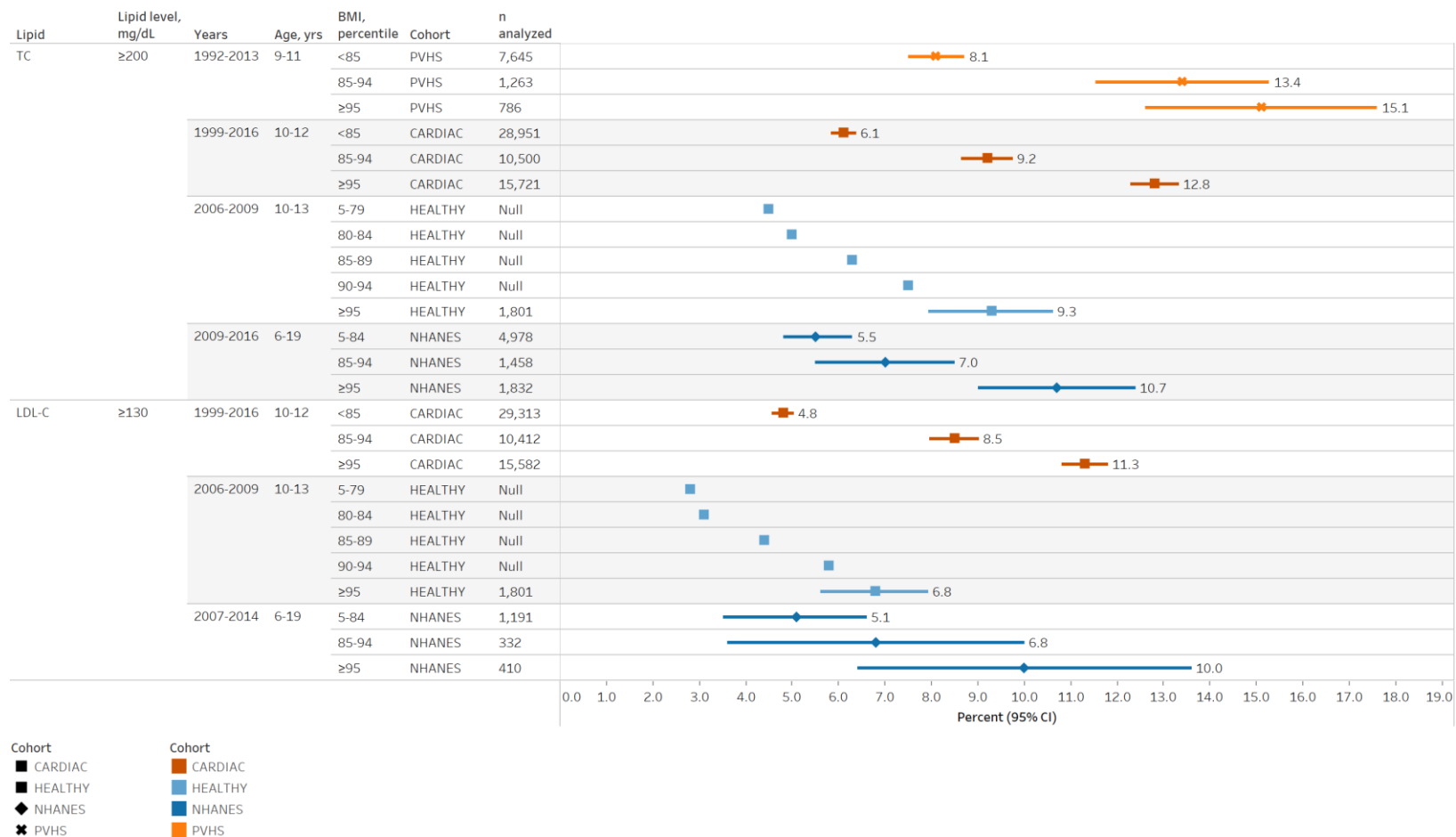
Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; PVHS = The Poudre Valley Health System; SOL = Study of Latinos; TC = total cholesterol; TG = triglycerides; US = United States; yrs = years

Figure 5. Multifactorial Dyslipidemia (MFD): Prevalence of MFD in US Cohorts Included for Key Question 2, by Race/Ethnicity



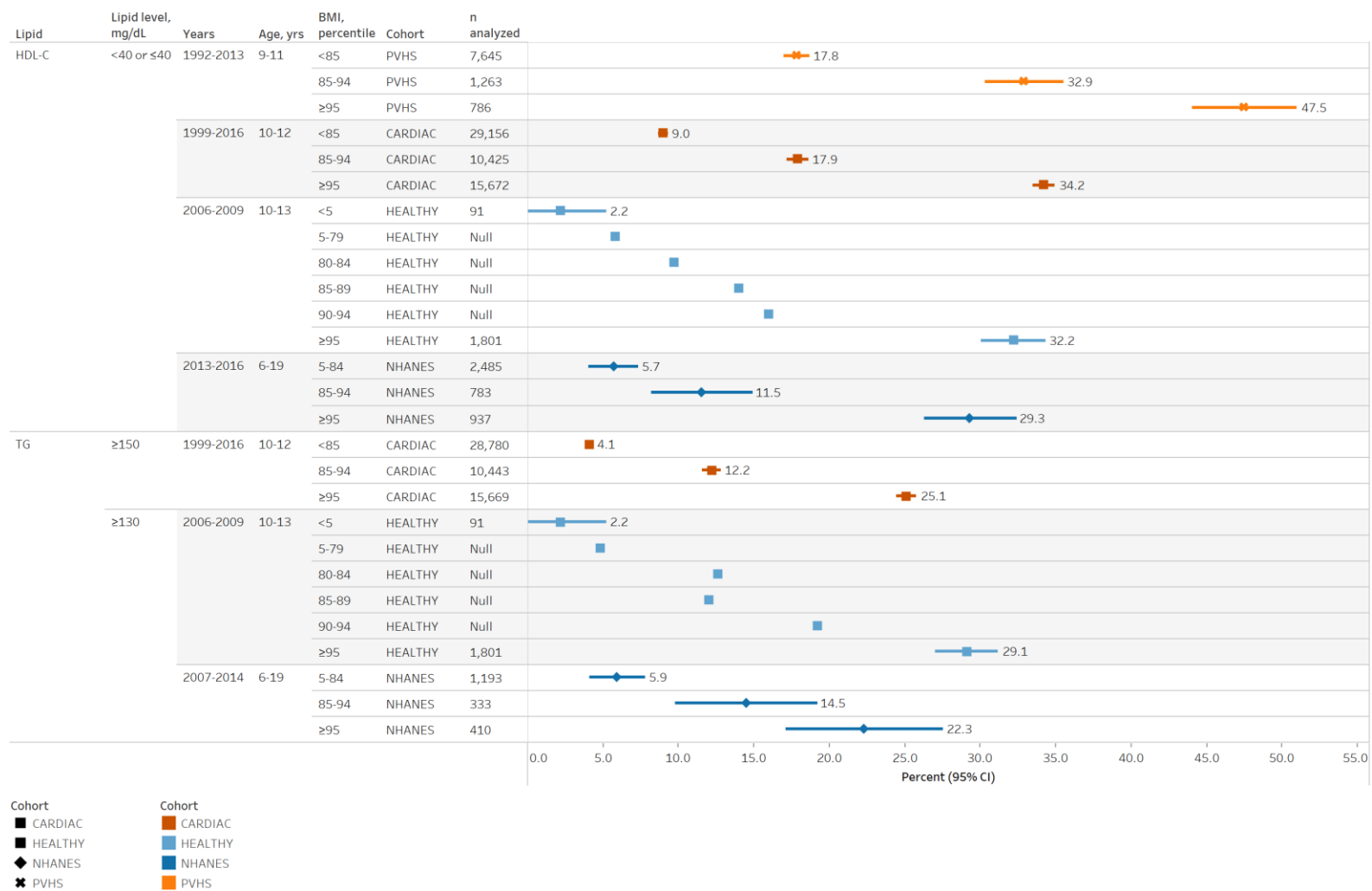
Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; SOL = Study of Latinos; TC = total cholesterol; TG = triglycerides; US = United States

Figure 6. Multifactorial Dyslipidemia (MFD): Prevalence of High Total Cholesterol and Low-Density Lipoprotein Cholesterol Levels in US Cohorts Included for Key Question 2, by BMI



Abbreviations: BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; PVHS = The Poudre Valley Health System; TC = total cholesterol; US = United States; yrs = years

Figure 7. Multifactorial Dyslipidemia (MFD): Prevalence of Abnormal High-Density Lipoprotein Cholesterol and High Triglyceride Levels in US Cohorts Included for Key Question 2, by BMI



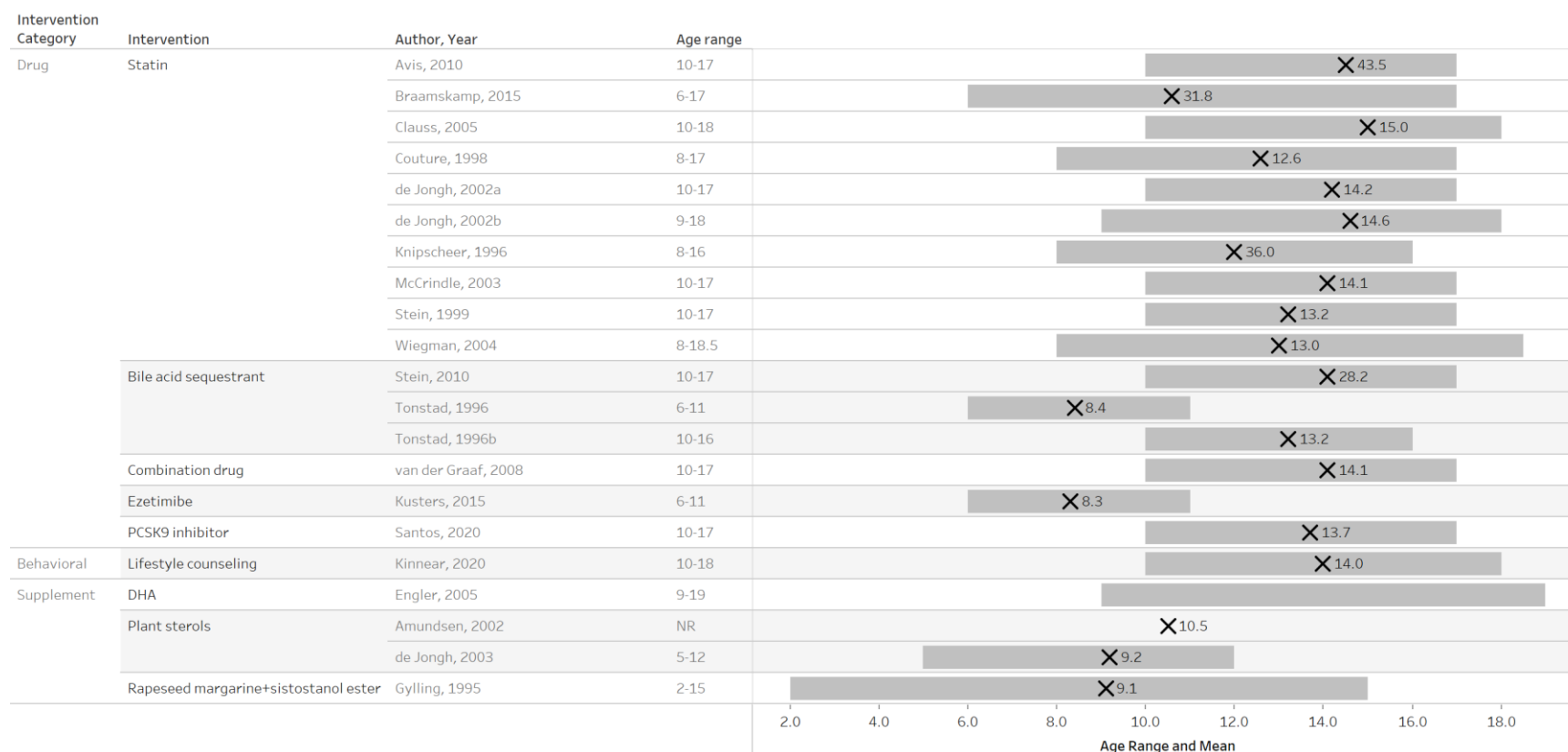
Abbreviations: BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; PVHS = The Poudre Valley Health System; TG = triglycerides; US = United States; yrs = years

Figure 8. Familial Hypercholesterolemia (FH): Statin Intervention Trials—FH Criteria Reported (Key Question 4)

Author, Year	Baseline TC, mg/dL	Baseline LDL-C, mg/dL	Elevated LDL-C, mg/dL				Genetic FH confirmation	Parental/family history of FH	Parental/family history of hyperlipidemia	Parental/family premature CVD/CAD
			>130-140	>155-160	>190-220	>130 + risk factor				
Avis, 2010	298	233		●			●		●	
Braamskamp, 2015	303	234		●		●				
Clauss, 2005	282	211		●			●			
Couture, 1998	287	223	●			●				
de Jongh, 2002a	274	209		●			●			
de Jongh, 2002b	274	209	●			●		●		
Knipscheer, 1996	301	247	●					●	●	
McCrintle, 2003	288	222			●	●	●		●	
Stein, 1999	317	251			●			●	●	
Wiegman, 2004	301	238		●			●			

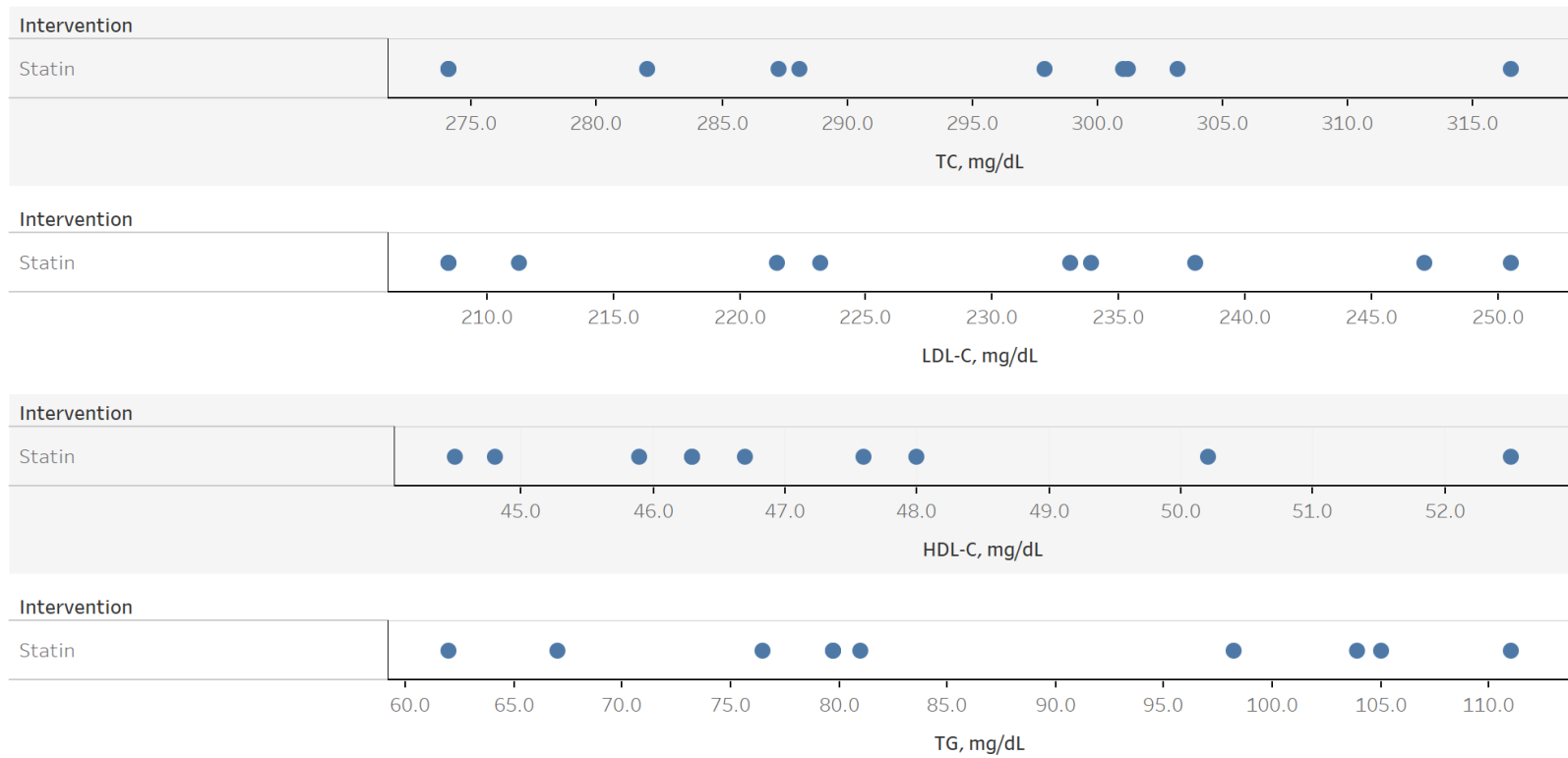
Abbreviations: CAD = coronary artery disease; CVD = cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; TC = total cholesterol

Figure 9. Familial Hypercholesterolemia: All Treatment Intervention Trials—Mean Age and Age Ranges, by Intervention (Key Question 4)



Abbreviations: DHA = Docosahexaenoic acid; PCSK9 = Proprotein convertase subtilisin/kexin type 9

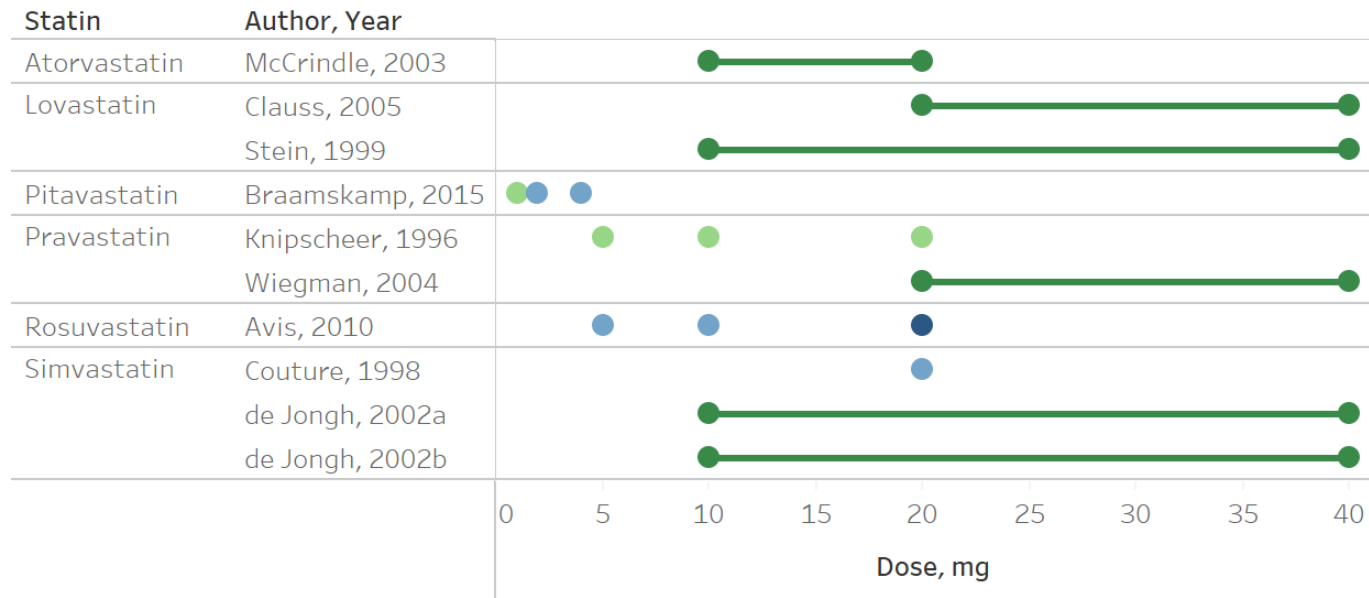
Figure 10. Familial Hypercholesterolemia (FH): Statin Intervention Trials—Baseline Lipid Levels (Key Question 4)



Note: Each circle corresponds to the mean lipid level at baseline for an individual study.

Abbreviations = HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; TC = total cholesterol; TG = triglycerides

Figure 11. Familial Hypercholesterolemia: Statin Intervention Trials—Daily Dose in Each Trial (Key Question 4)

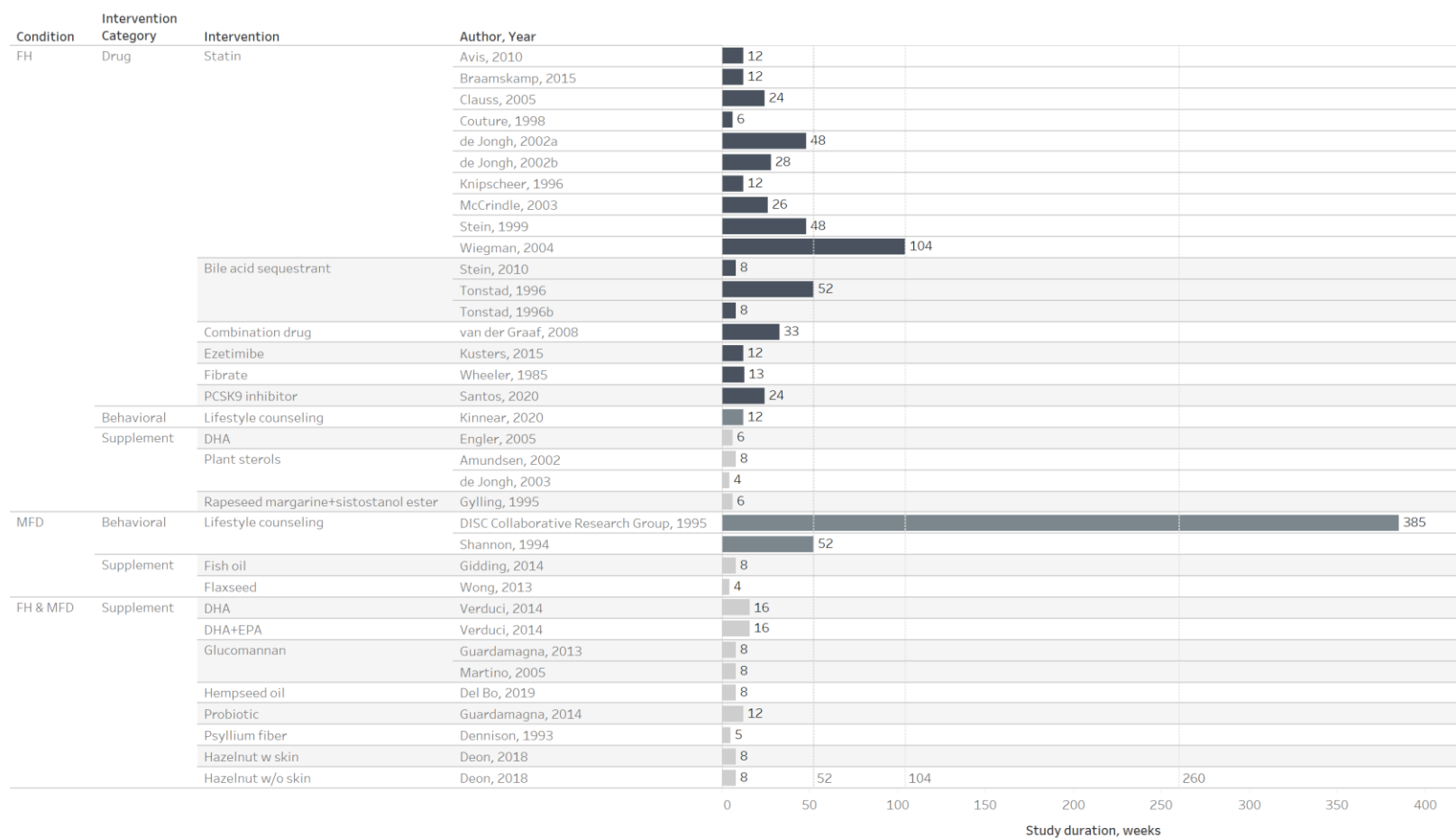


Statin Intensity

- High
- Moderate
- Low to Moderate
- Low

Abbreviations: mg = milligram

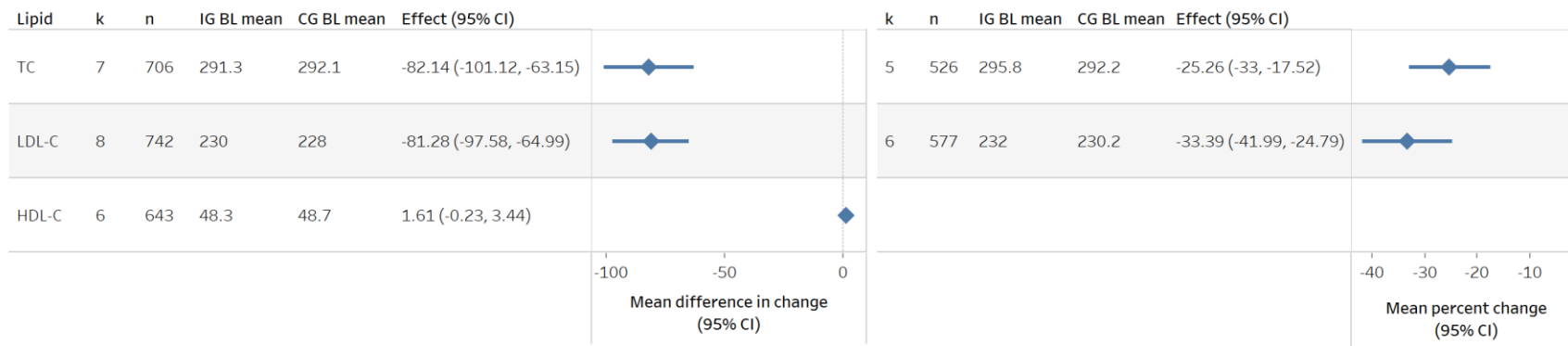
Figure 12. Familial Hypercholesterolemia (FH), Multifactorial Dyslipidemia (MFD), & MFD/FH: All Treatment Intervention Trials—Study Duration, by Condition (Key Question 4)



Intervention Category
 ■ Drug
 ■ Behavioral
 ■ Supplement

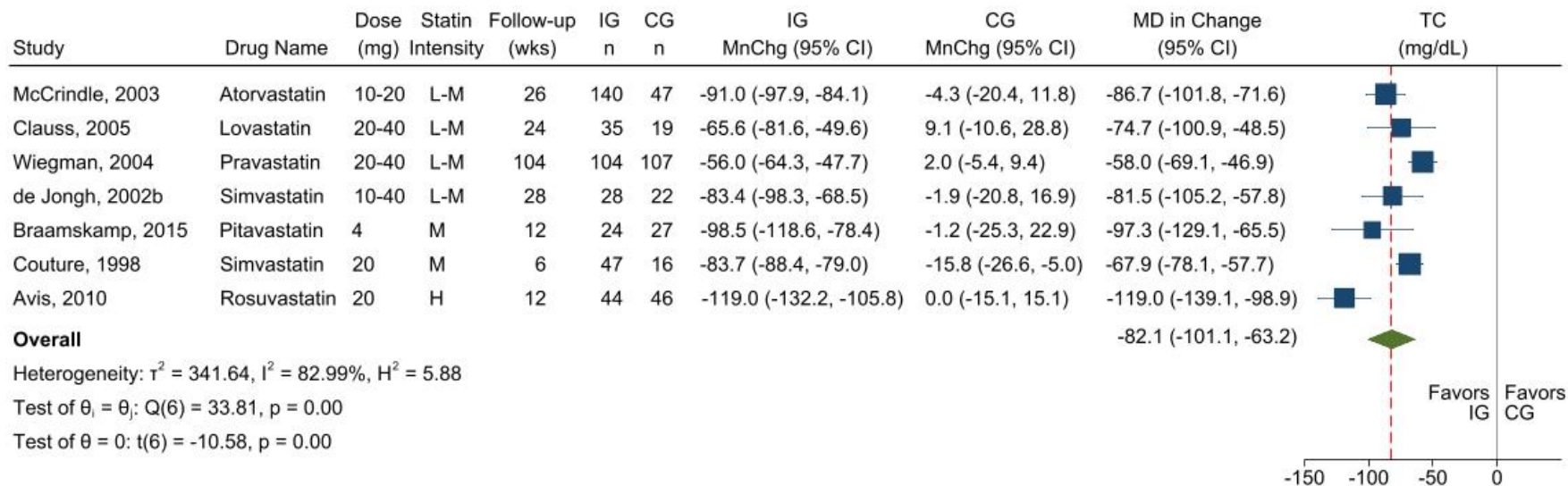
Abbreviations: DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; FH = familial hypercholesterolemia; MFD = multifactorial dyslipidemia; PCSK9 = Proprotein convertase subtilisin/kexin type 9

Figure 13. Familial Hypercholesterolemia: Statin Intervention Trials—Meta Plot of Total Cholesterol, Low-Density Lipoprotein, and High-Density Lipoprotein Results (Key Question 4)



Abbreviations: BL = baseline; CG = control group; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; IG = intervention group; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; TC = total cholesterol; TG = triglycerides

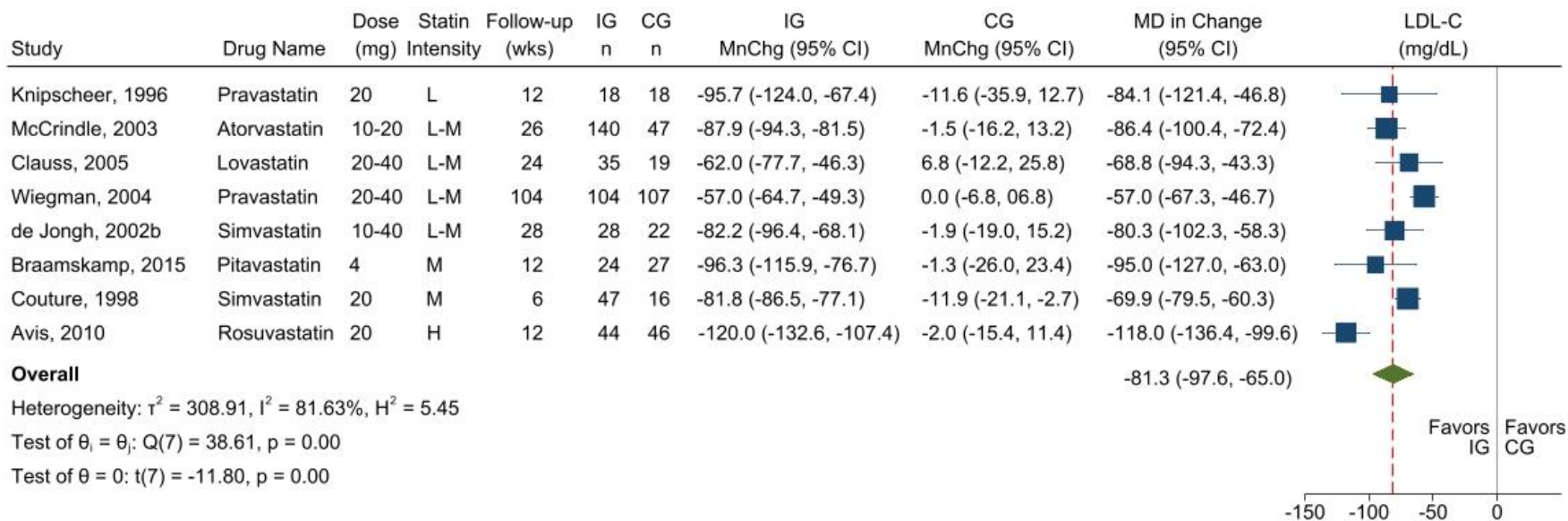
Figure 14. Familial Hypercholesterolemia: Statin Intervention Trials—Pooled Analysis of Mean Difference in Change in Total Cholesterol (mg/dL) of Highest Statin Intensity in Intervention Arm Compared With Placebo (k=7, n=706) (Key Question 4)



Random-effects ML model with Knapp-Hartung confidence intervals
 Sorted by: Statin Intensity and Drug Name

Abbreviations: CG = control group; CI = confidence interval; H = high intensity statin; IG = intervention group; L = low intensity statin; M = moderate intensity statin; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; TC = total cholesterol; wks = weeks

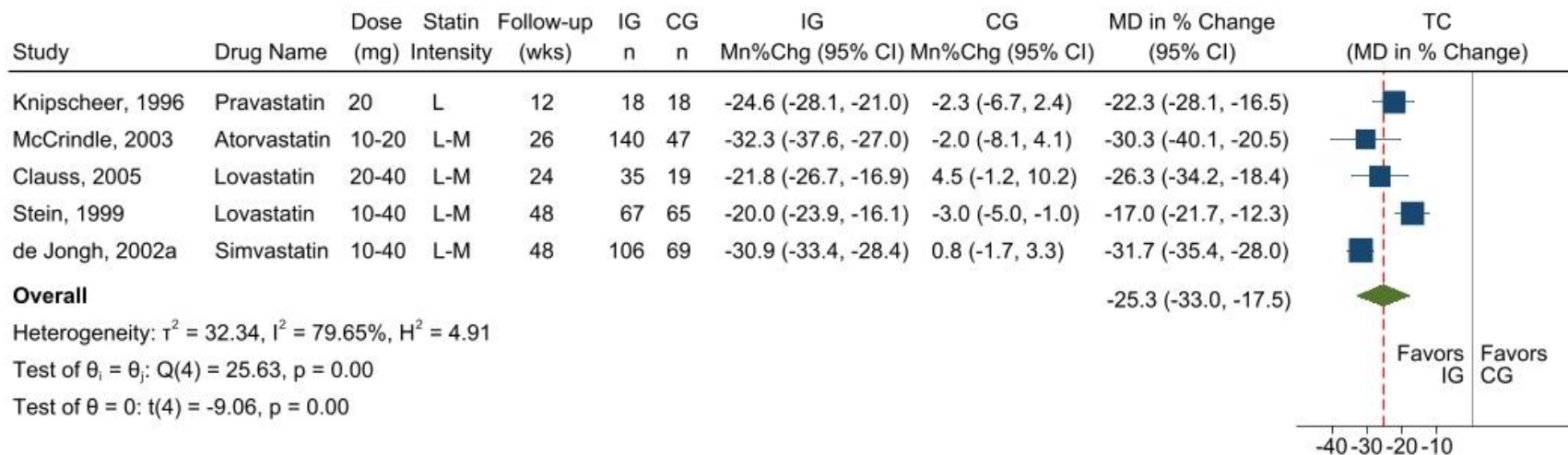
Figure 15. Familial Hypercholesterolemia: Statin Intervention Trials—Pooled Analysis of Mean Difference in Change in Low-Density Lipoprotein Cholesterol (mg/dL) of Highest Statin Intensity in Intervention Arm Compared With Placebo (k=8, n=742) (Key Question 4)



Random-effects ML model with Knapp-Hartung confidence intervals
 Sorted by: Statin Intensity and Drug Name

Abbreviations: CG = control group; CI = confidence interval; H = high intensity statin; IG = intervention group; L = low intensity statin; LDL-C = low-density lipoprotein cholesterol; M = moderate intensity statin; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; wks = weeks

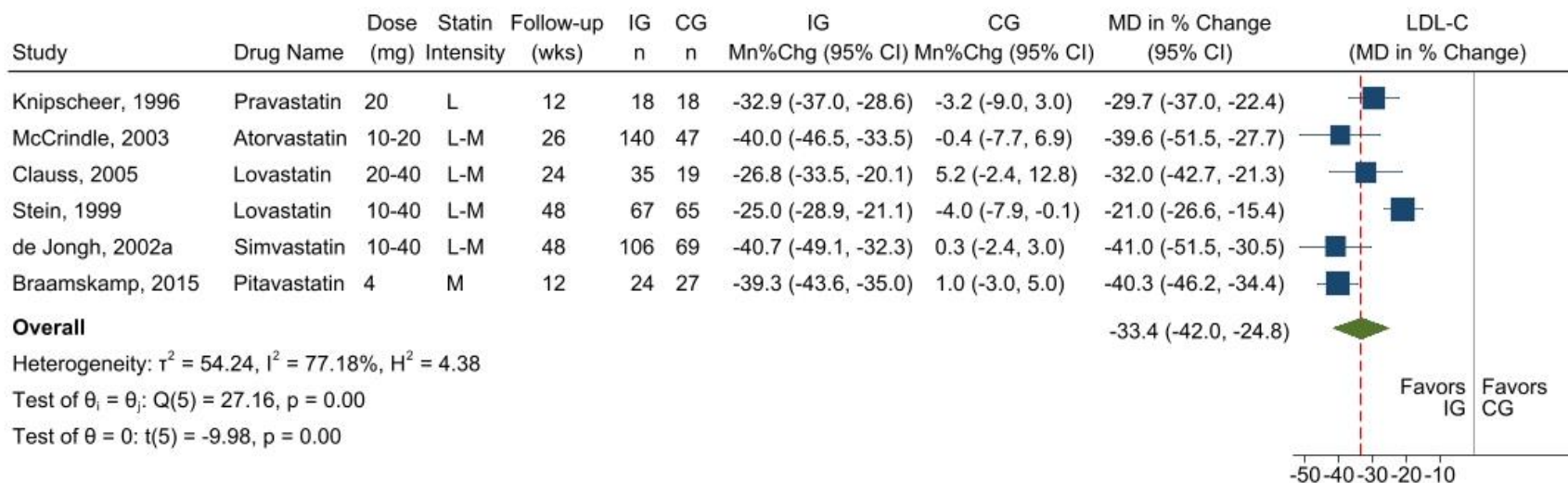
Figure 16. Familial Hypercholesterolemia: Statin Intervention Trials—Pooled Analysis of Mean Difference in Percent Change in Total Cholesterol of Highest Statin Intensity in Intervention Arm Compared With Placebo (k=5; n=526) (Key Question 4)



Random-effects ML model with Knapp-Hartung confidence intervals
 Sorted by: Statin Intensity and Drug Name

Abbreviations: CG = control group; CI = confidence interval; H = high intensity statin; IG = intervention group; L = low intensity statin; M = moderate intensity statin; MD = mean difference; mg/dL = milligrams per deciliter; Mn%Chg = mean percent change; TC = total cholesterol; wks = weeks

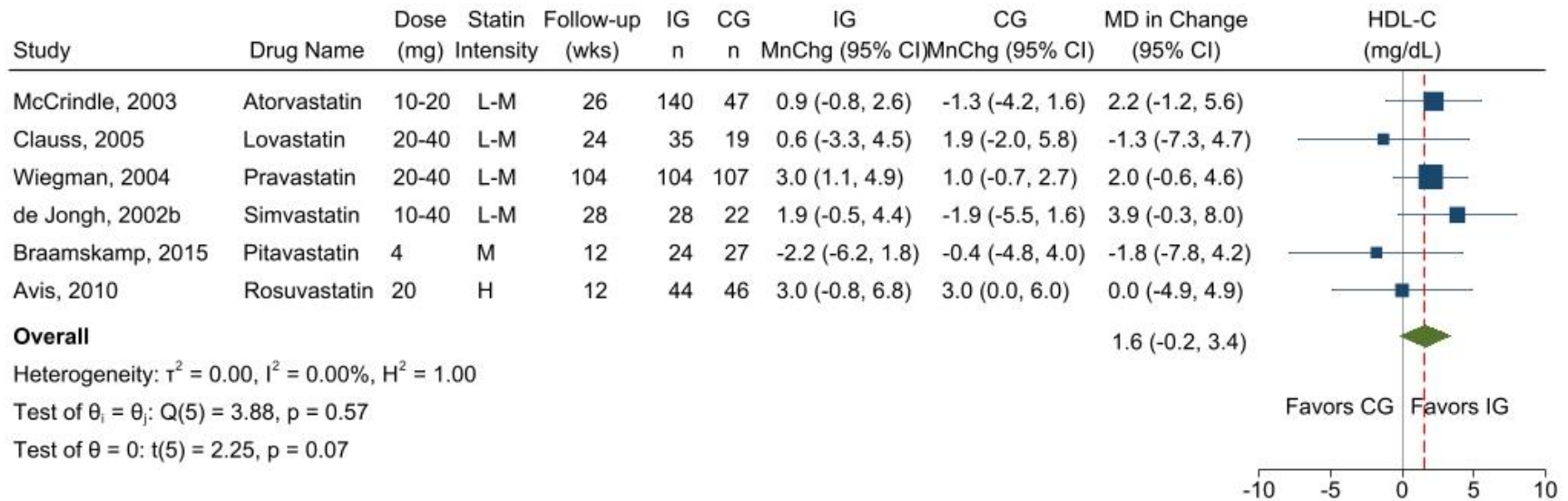
Figure 17. Familial Hypercholesterolemia: Statin Intervention Trials—Pooled Analysis of Mean Difference in Percent Change in Low-Density Lipoprotein Cholesterol of Highest Statin Intensity in Intervention Arm Compared With Placebo (k=6, n=577) (Key Question 4)



Random-effects ML model with Knapp-Hartung confidence intervals
 Sorted by: Statin Intensity and Drug Name

Abbreviations: CG = control group; CI = confidence interval; H = high intensity statin; IG = intervention group; L = low intensity statin; LDL-C = low-density lipoprotein cholesterol; M = moderate intensity statin; MD = mean difference; mg/dL = milligrams per deciliter; Mn%Chg = mean percent change; wks = weeks

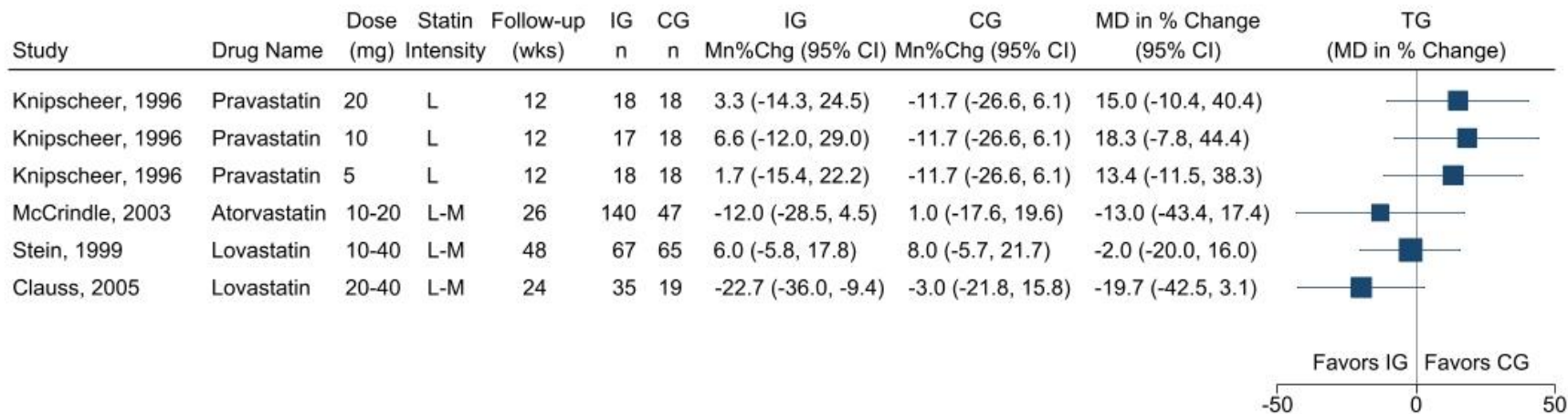
Figure 18. Familial Hypercholesterolemia: Statin Intervention Trials—Pooled Analysis of Mean Difference in Change in High-Density Lipoprotein Cholesterol (mg/dL) of Highest Statin Intensity in Intervention Arm Compared With Placebo (k=6, n=643) (Key Question 4)



Random-effects ML model with Knapp-Hartung confidence intervals
 Sorted by: Statin Intensity and Drug Name

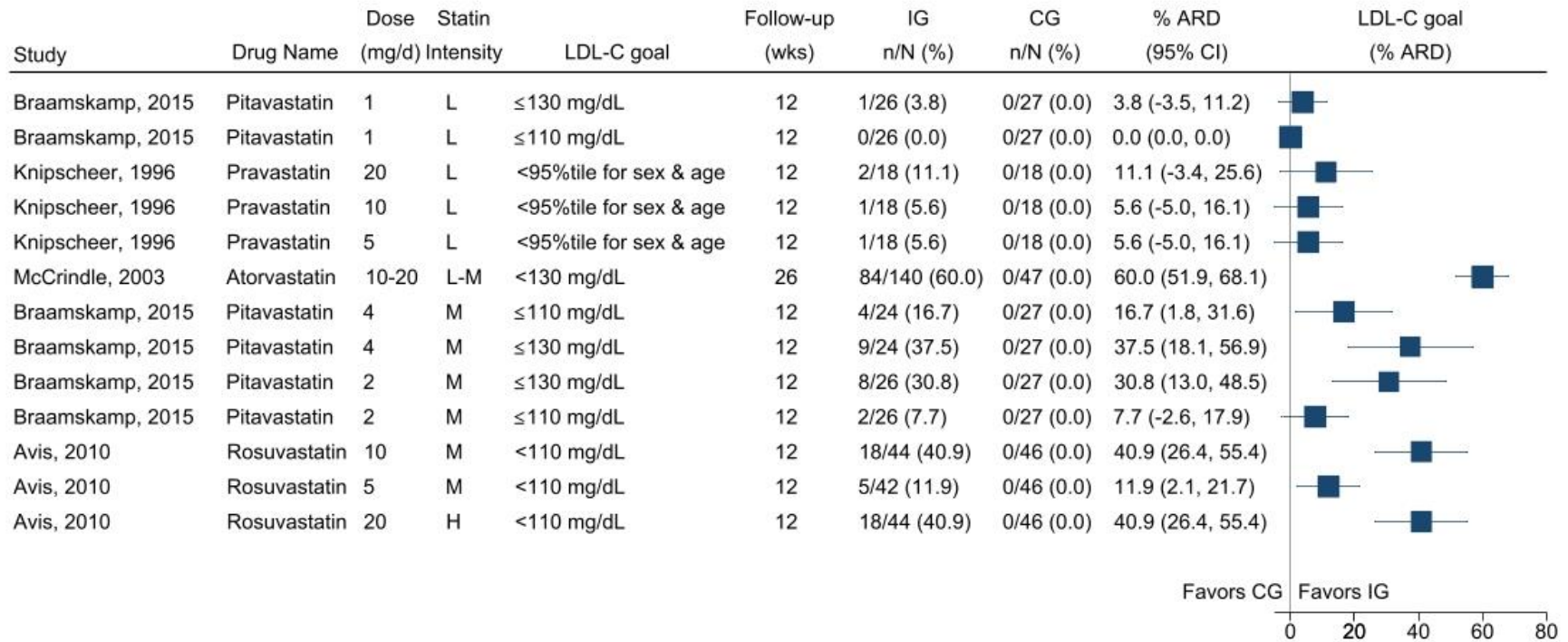
Abbreviations: CG = control group; CI = confidence interval; H = high intensity statin; HDL-C = high-density lipoprotein cholesterol; IG = intervention group; L = low intensity statin; M = moderate intensity statin; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; wks = weeks

Figure 19. Familial Hypercholesterolemia: Statin Intervention Trials—Mean Difference in Percent Change in Triglycerides Compared With Placebo, Sorted by Statin Intensity (k=4, n=387) (Key Question 4)



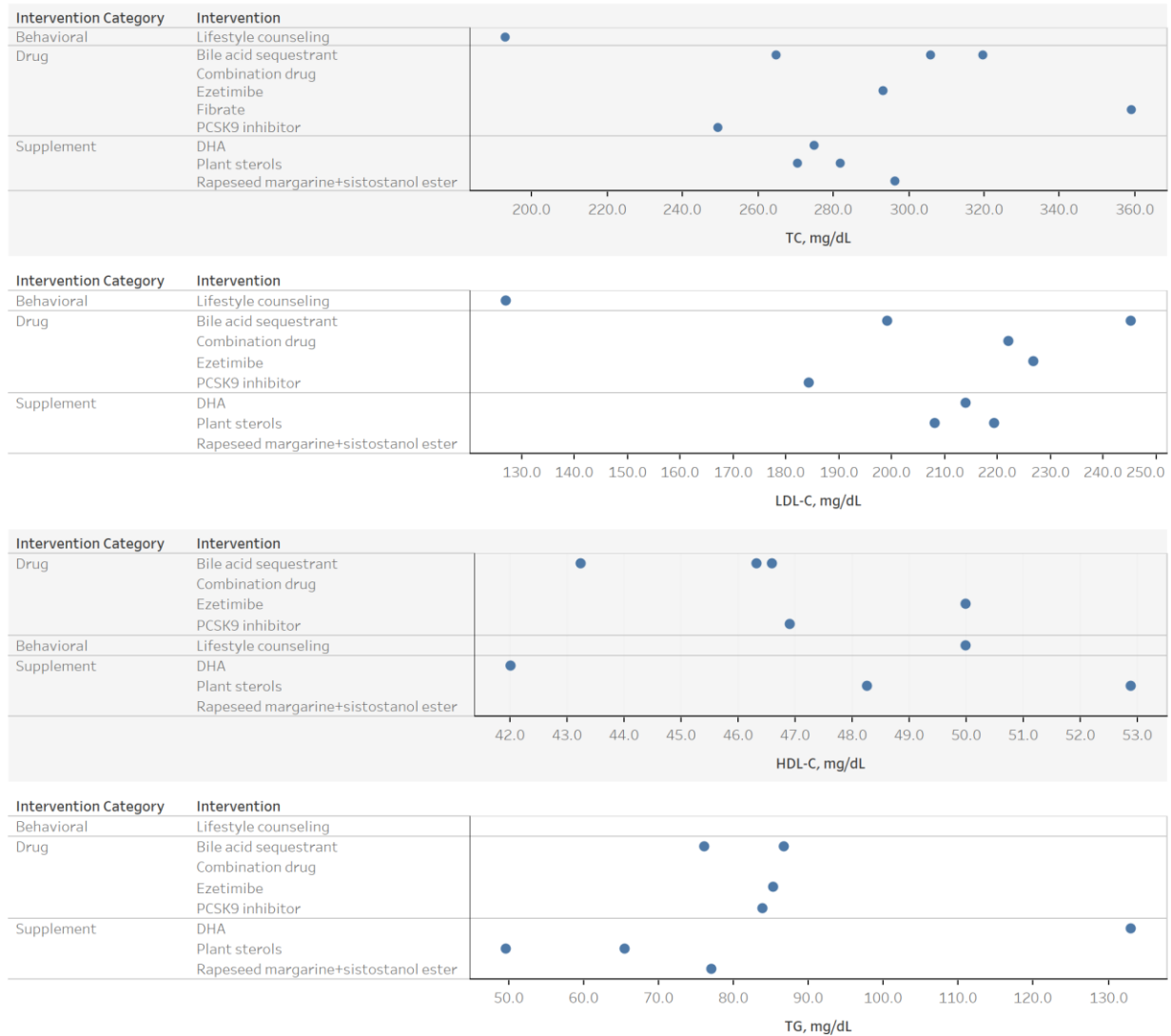
Abbreviations: CG = control group; CI = confidence interval; H = high intensity statin; IG = intervention group; L = low intensity statin; M = moderate intensity statin; MD = mean difference; mg/dL = milligrams per deciliter; Mn%Chg = mean percent change; TG = triglycerides; wks = weeks

Figure 20. Familial Hypercholesterolemia: Statin Intervention Trials—Absolute Risk Difference (%) of Low-Density Lipoprotein Cholesterol at Goal, Sorted by Statin Intensity (k=4, n=364) (Key Question 4)



Abbreviations: ARD = absolute risk difference; CG = control group; CI = confidence interval; H = high intensity statin; IG = intervention group; L = low intensity statin; LDL-C = low-density lipoprotein cholesterol; M = moderate intensity statin; MD = mean difference; mg/d = milligrams per day; mg/dL = milligrams per deciliter; wks = weeks

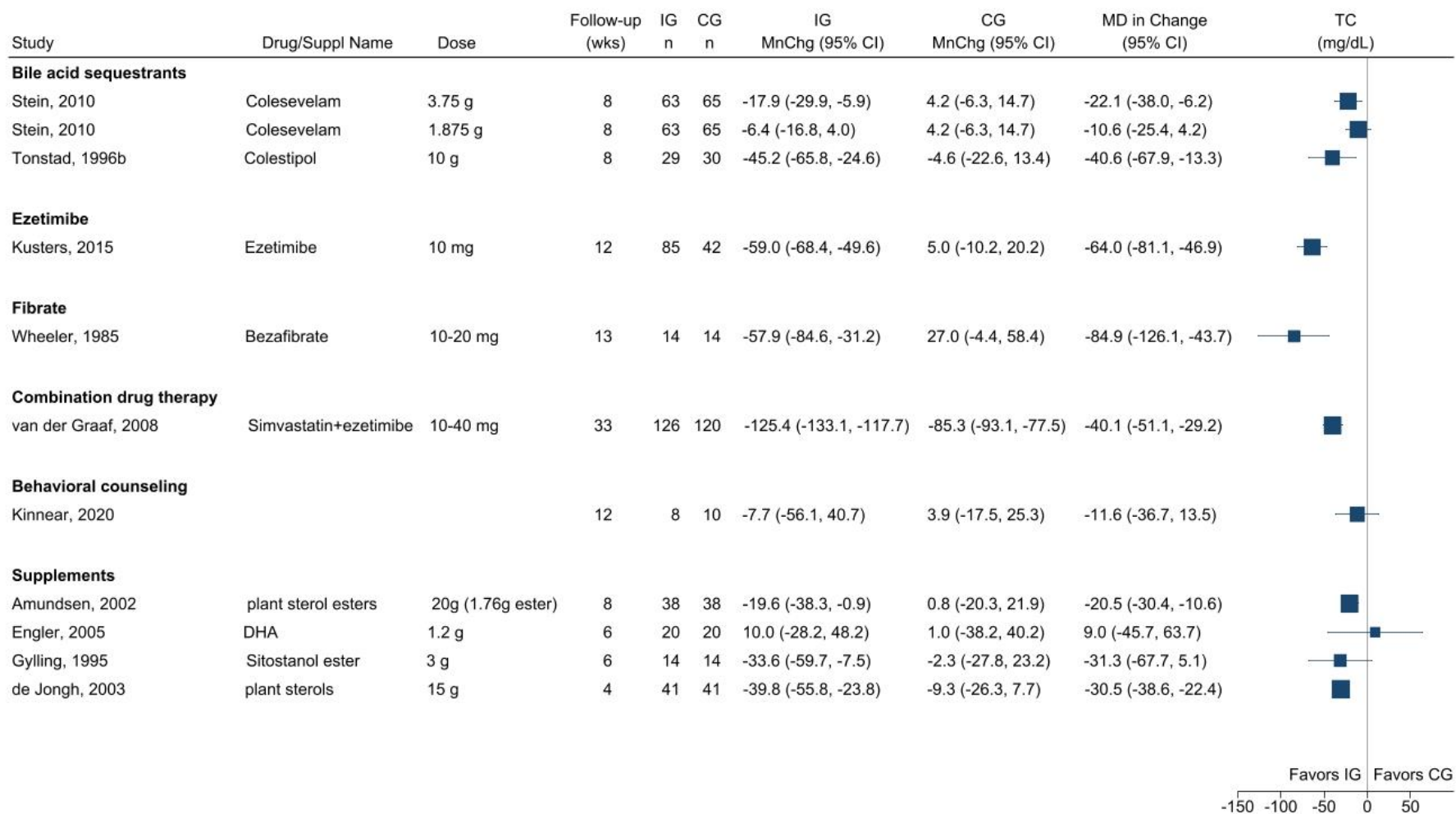
Figure 21. Familial Hypercholesterolemia: Non-Statin Intervention Trials—Baseline Lipid Levels, by Intervention (Key Question 4)



NOTE: Each dot represents mean lipid level from a study.

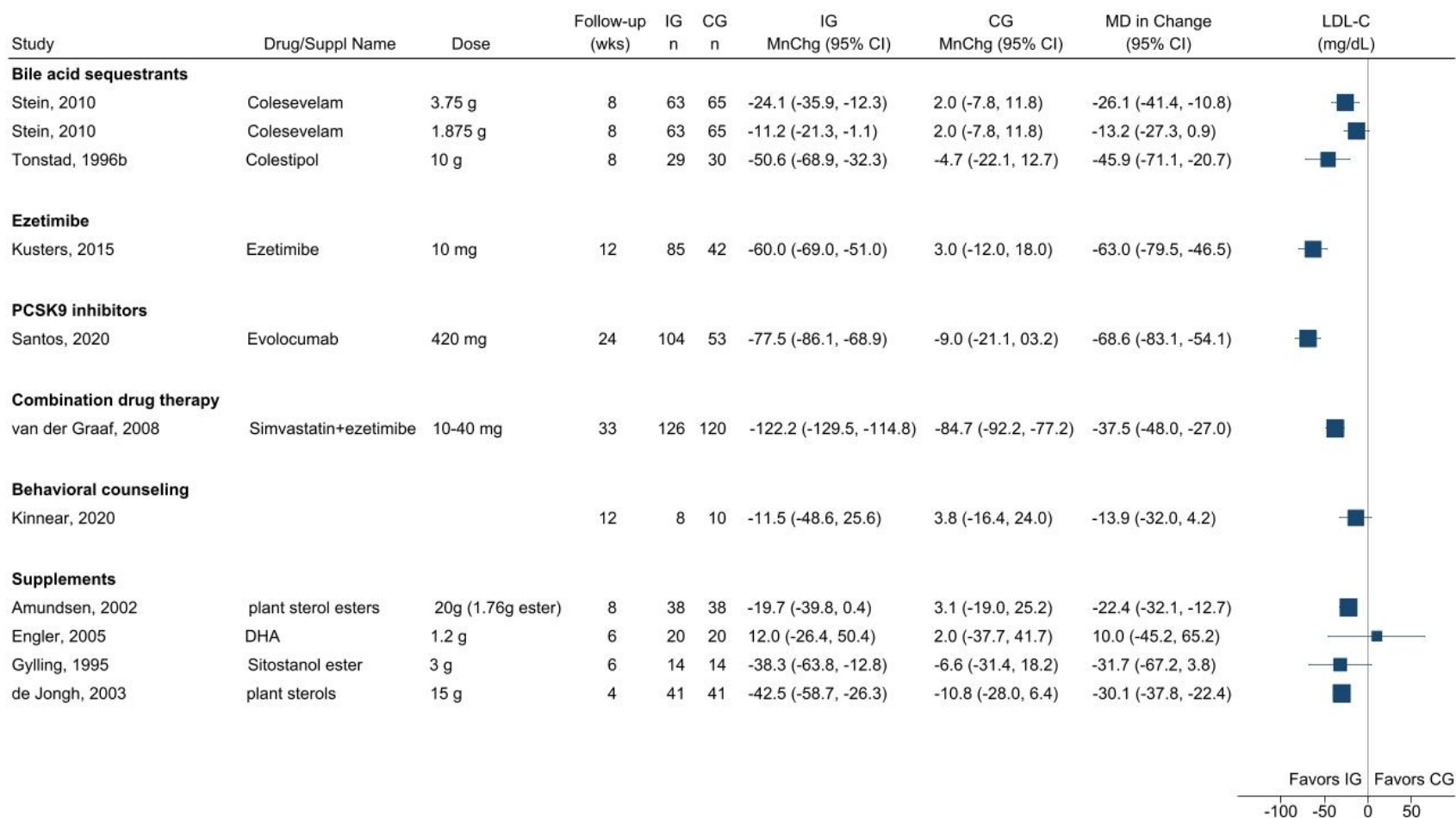
Abbreviations: DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; PCSK9 = Proprotein convertase subtilisin/kexin type 9; TC = total cholesterol; TG = triglycerides

Figure 22. Familial Hypercholesterolemia: Non-Statin Intervention Trials—Mean Difference in Change in Total Cholesterol Compared With Controls (k=10) (Key Question 4)



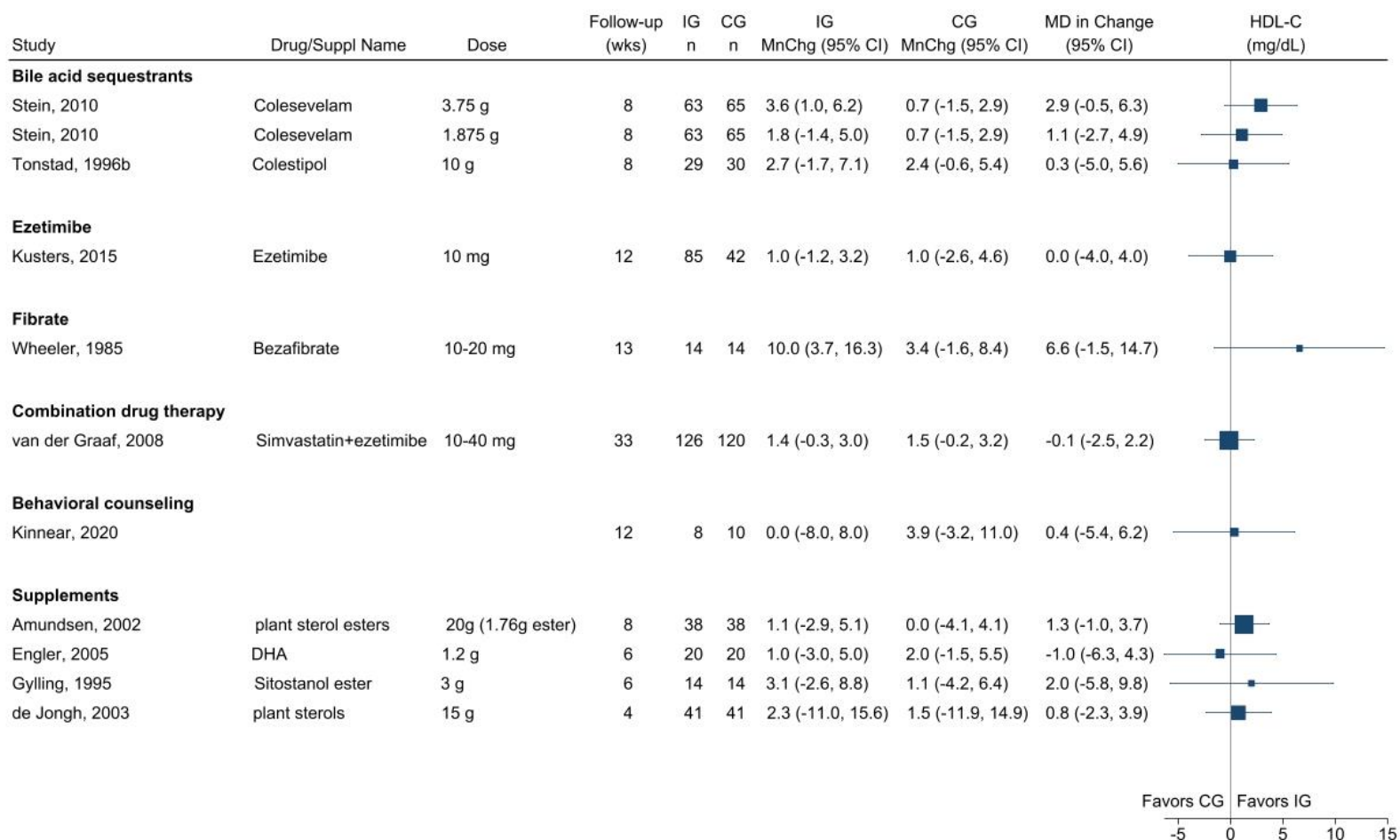
Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; g = gram(s); IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; TC = total cholesterol; wks = weeks

Figure 23. Familial Hypercholesterolemia: Non-Statin Intervention Trials—Mean Difference in Change in Low-Density Lipoprotein Cholesterol Compared With Controls (k=10) (Key Question 4)



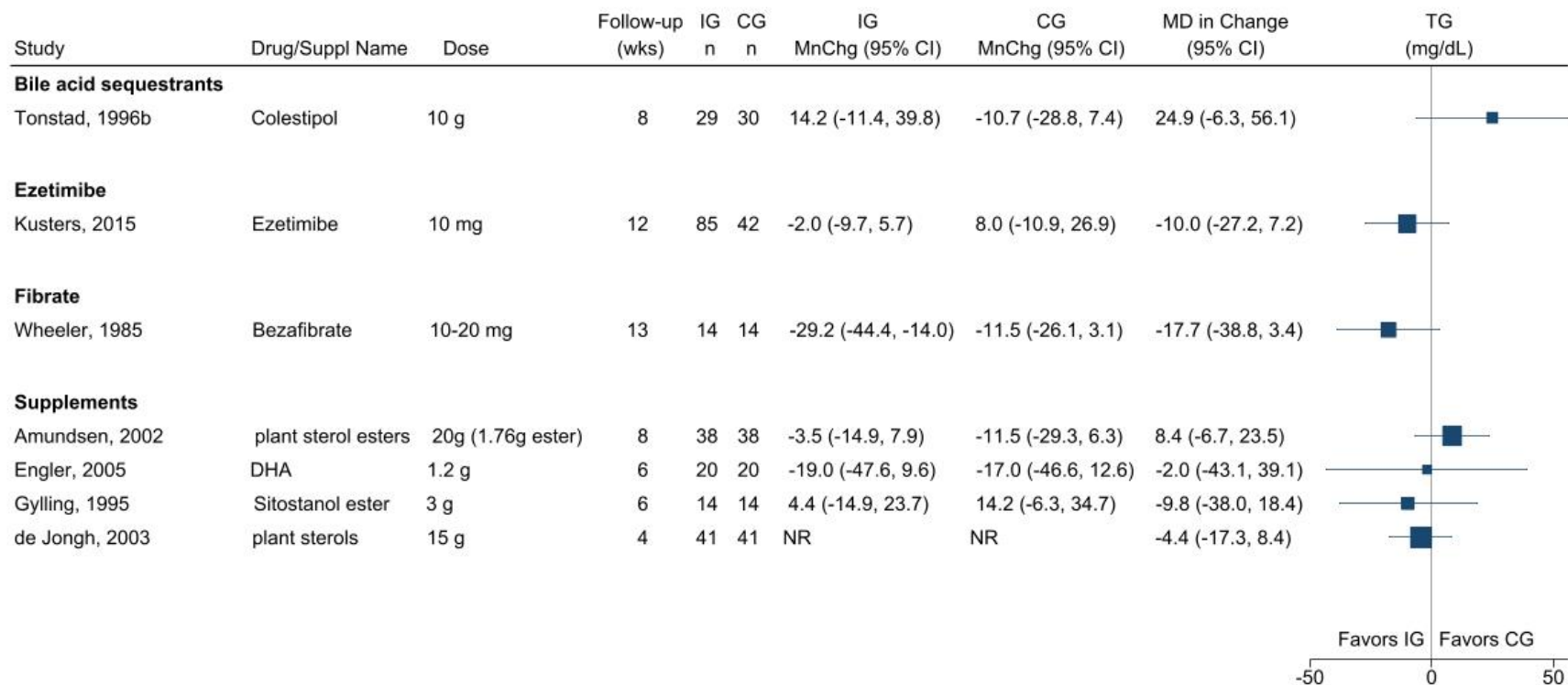
Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; g = gram(s); IG = intervention group; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; wks = weeks

Figure 24. Familial Hypercholesterolemia: Non-Statin Intervention Trials—Mean Difference in Change in High-Density Lipoprotein Cholesterol Compared With Controls (k=10) (Key Question 4)



Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; g = gram(s); HDL-C = high-density lipoprotein cholesterol; IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; wks = weeks

Figure 25. Familial Hypercholesterolemia: Non-Statin Intervention Trials—Mean Difference in Change in Triglycerides Compared With Controls (k=7) (Key Question 4)



Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; g = gram(s); IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; TG = triglycerides; wks = weeks

Figure 26. Multifactorial Dyslipidemia: All Treatment Intervention Trials—Mean Age and Age Ranges (Key Question 4)

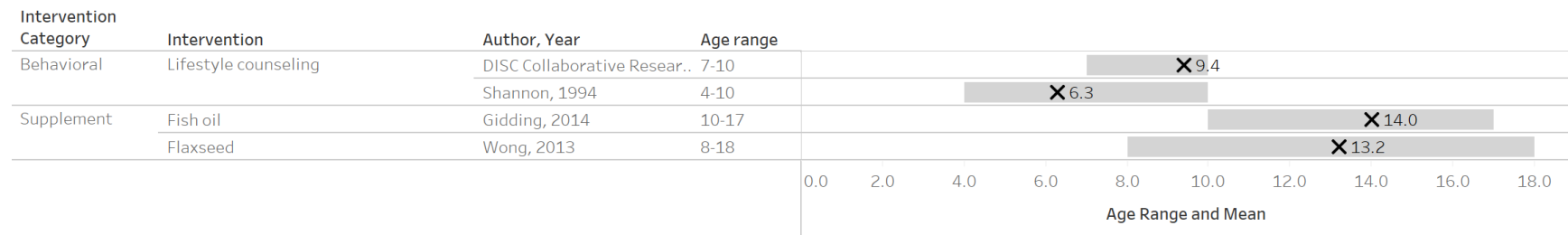
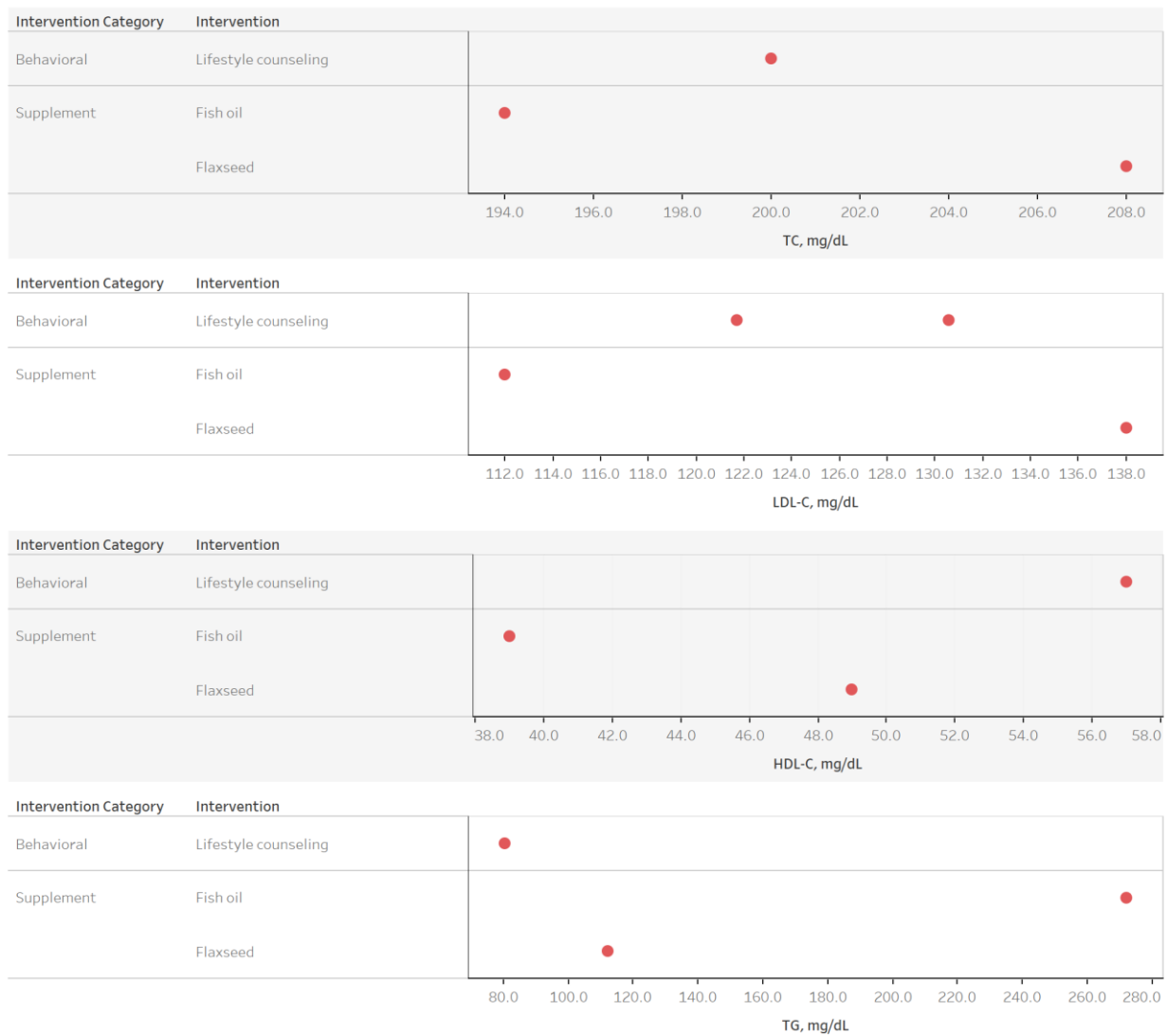
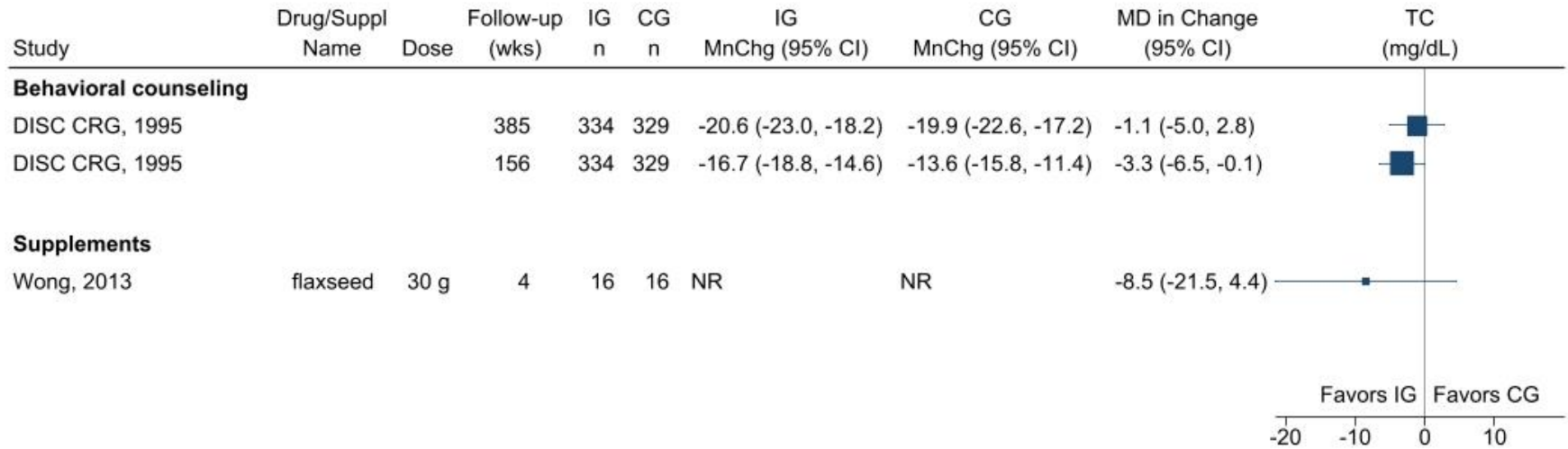


Figure 27. Multifactorial Dyslipidemia: All Treatment Intervention Trials—Baseline Lipid Levels for Each Study, Grouped by Intervention Type (Key Question 4)



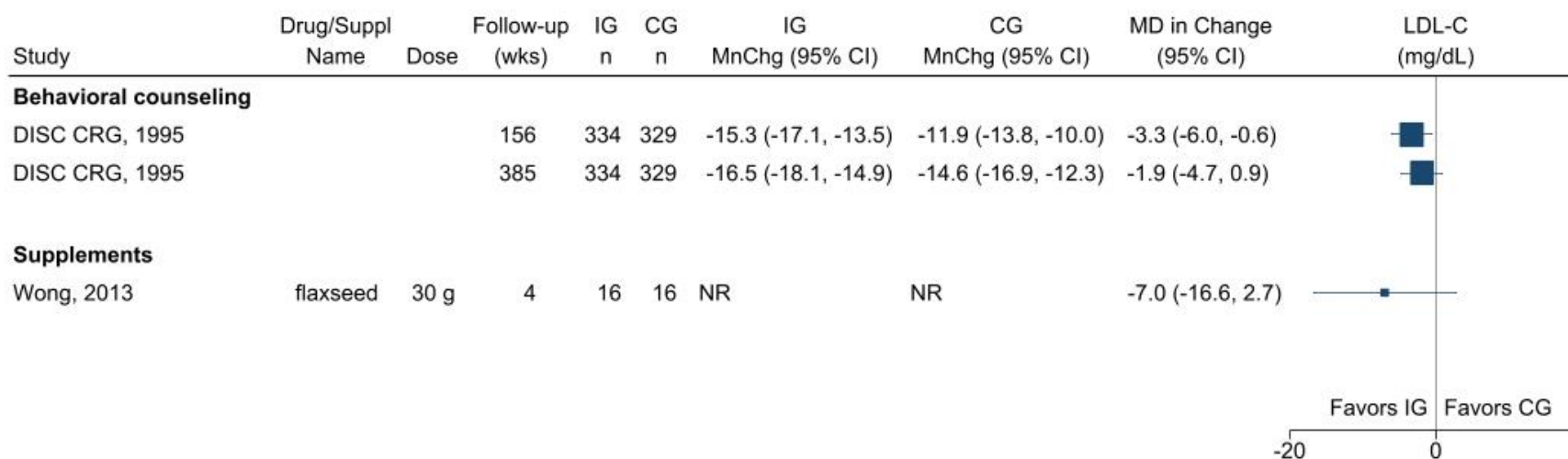
Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; TC = total cholesterol; TG = triglycerides

Figure 28. Multifactorial Dyslipidemia: All Intervention Trials—Mean Difference in Change in Total Cholesterol Compared With Controls (k=2) (Key Question 4)



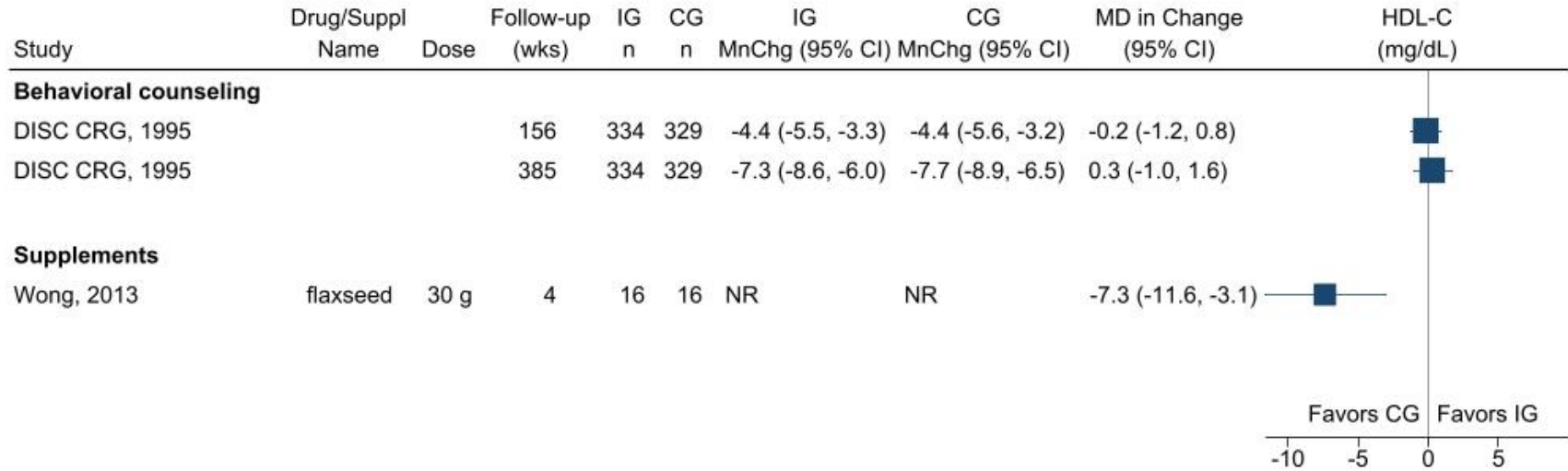
Abbreviations: CG = control group; CI = confidence interval; DISC CRG = The Dietary Intervention Study in Children Collaborative Research Group; g = gram(s); IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; TC = total cholesterol; wks = weeks

Figure 29. Multifactorial Dyslipidemia: All Intervention Trials—Mean Difference in Change in Low-Density Lipoprotein Cholesterol Compared With Controls (k=2) (Key Question 4)



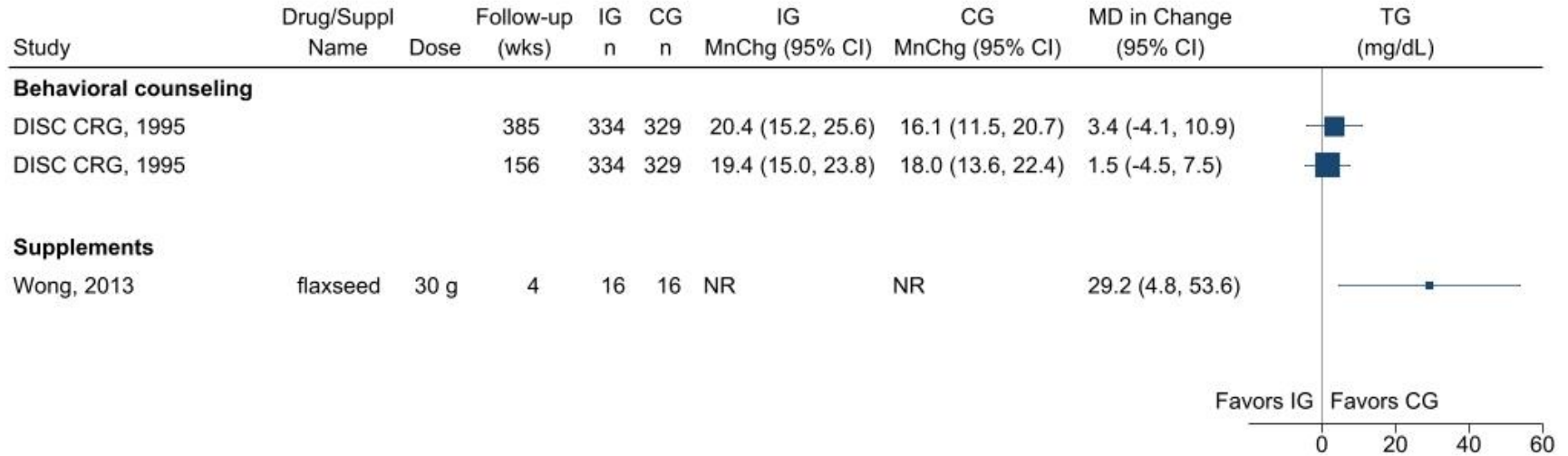
Abbreviations: CG = control group; CI = confidence interval; DISC CRG= The Dietary Intervention Study in Children Collaborative Research Group; g = gram(s); IG = intervention group; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; wks = weeks

Figure 30. Multifactorial Dyslipidemia: All Intervention Trials—Mean Difference in Change in High-Density Lipoprotein Cholesterol Compared With Controls (k=2) (Key Question 4)



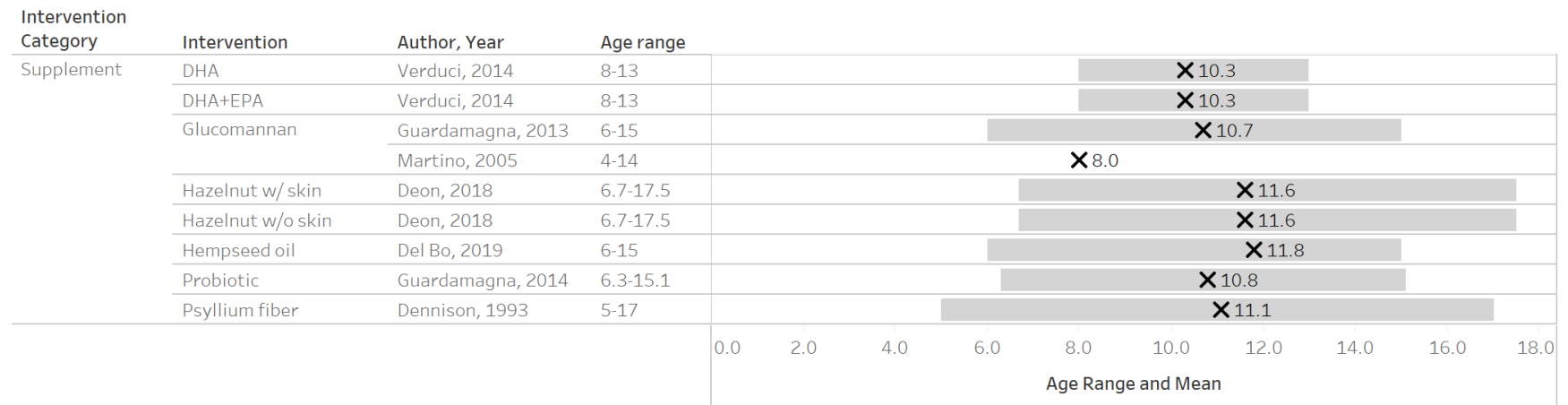
Abbreviations: CG = control group; CI = confidence interval; DISC CRG= The Dietary Intervention Study in Children Collaborative Research Group; g = gram(s); HDL-C = high-density lipoprotein cholesterol; IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; wks = weeks

Figure 31. Multifactorial Dyslipidemia: All Intervention Trials—Mean Difference in Change in Triglycerides Compared With Controls (k=2) (Key Question 4)



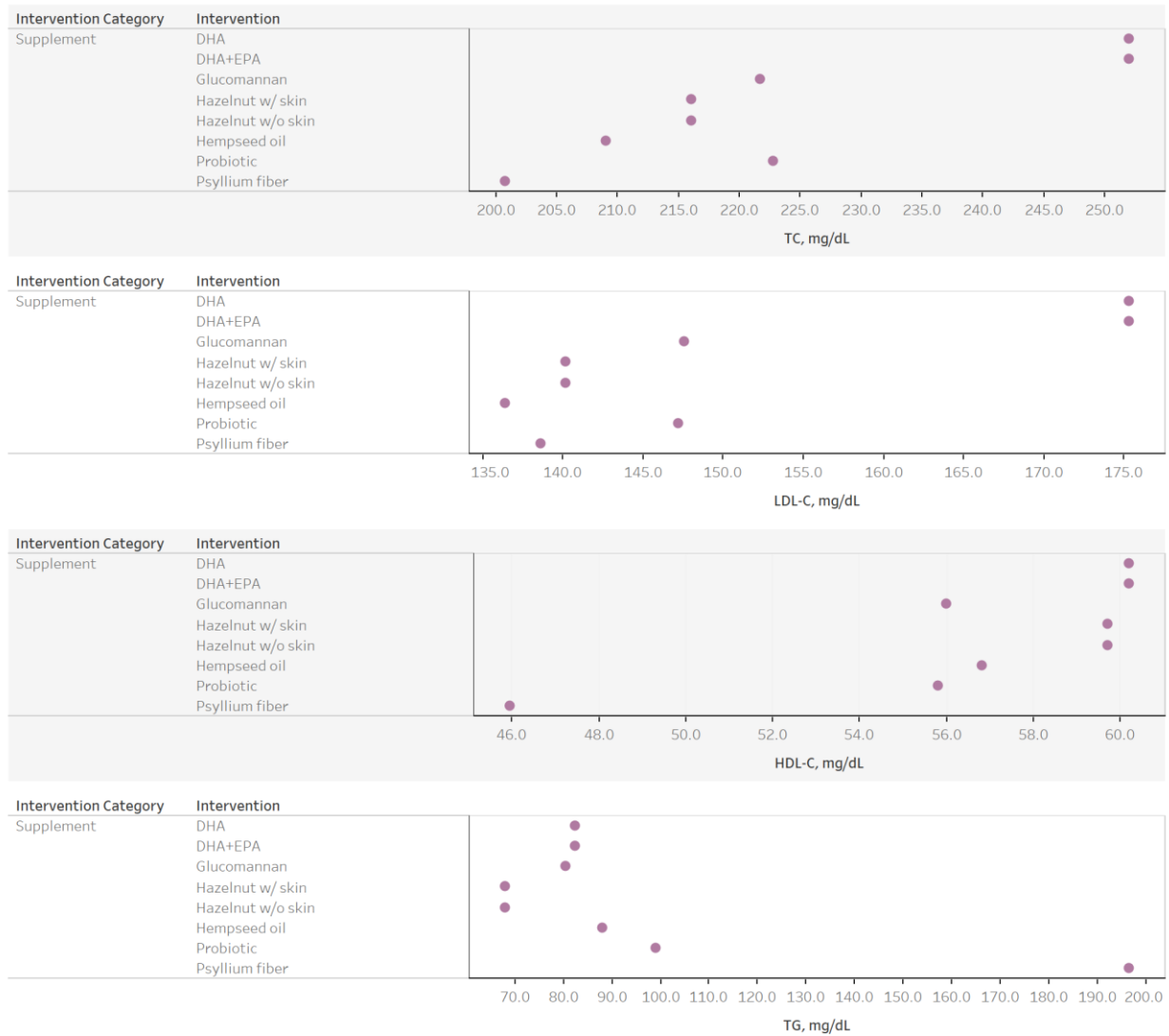
Abbreviations: CG = control group; CI = confidence interval; DISC CRG= The Dietary Intervention Study in Children Collaborative Research Group; g = gram(s); IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; TG = triglycerides; wks = weeks

Figure 32. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: All Intervention Trials—Mean Age and Age Ranges, by Intervention (Key Question 4)



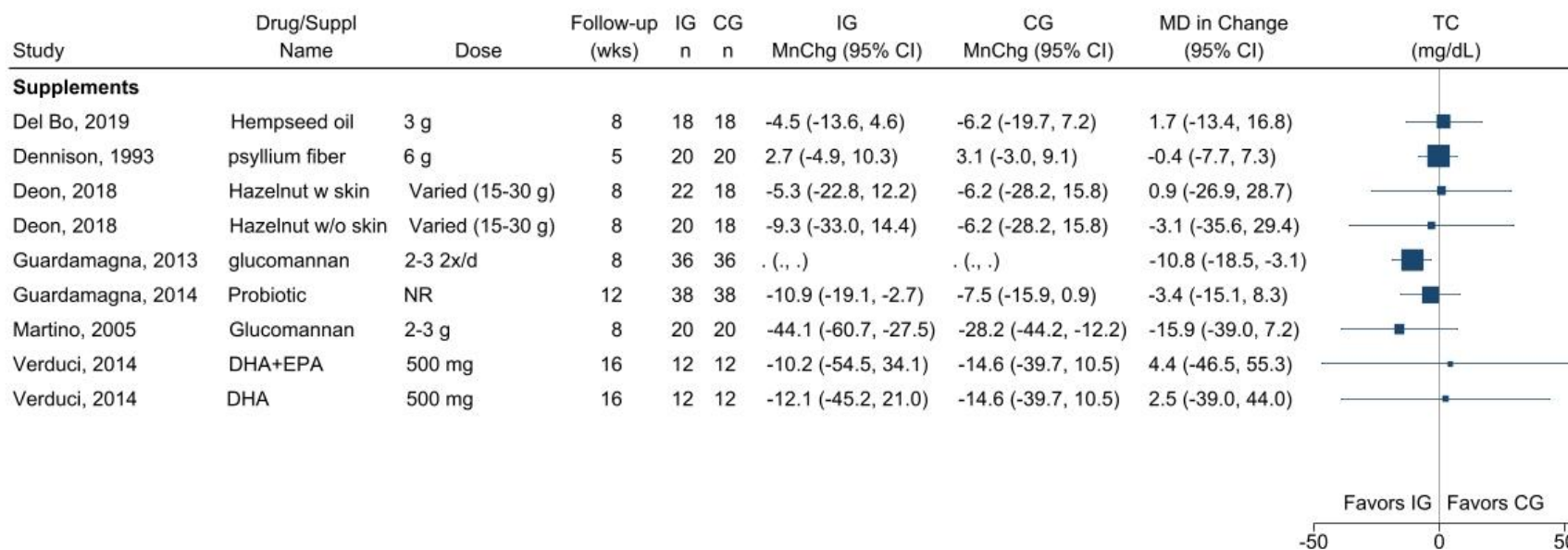
Abbreviations: DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; w/ = with; w/o = without

Figure 33. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: All Intervention Trials—Baseline Lipid Levels, by Intervention (Key Question 4)



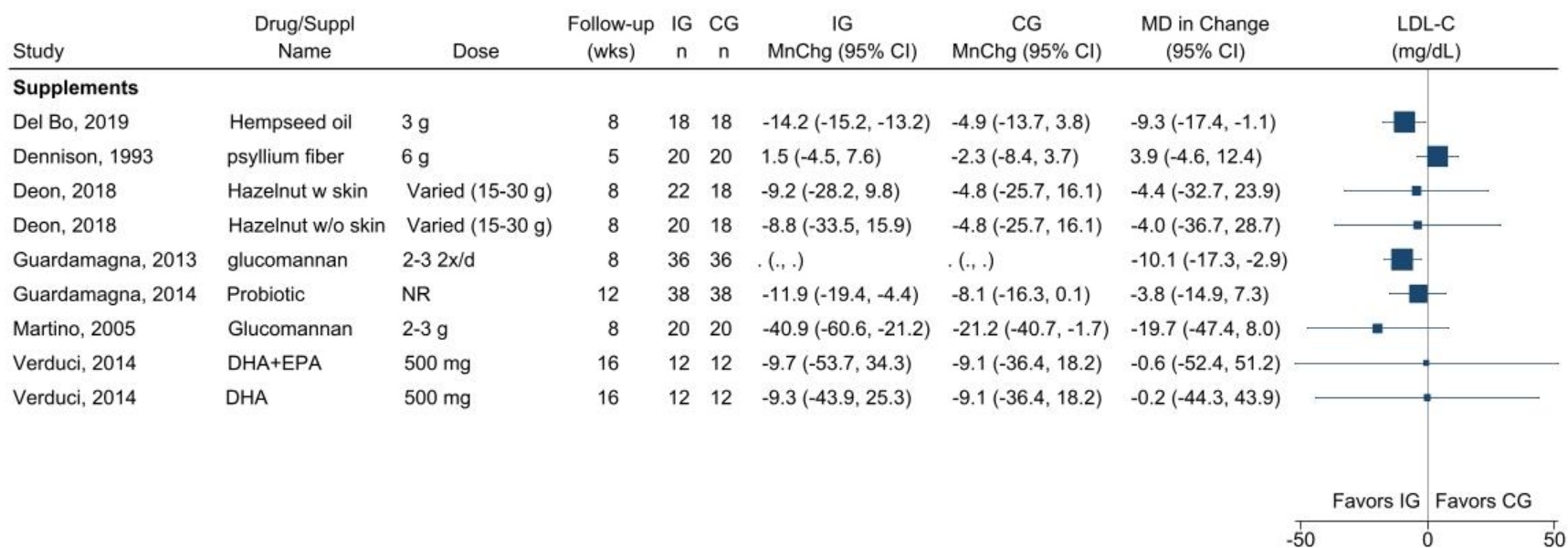
Abbreviations: DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; HDL-C = high-density lipoprotein cholesterol; LDL-C = lowdensity lipoprotein cholesterol; mg/dL = milligrams per deciliter; TC = total cholesterol; TG = triglycerides; w/ = with; w/o = without

Figure 34. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: All Intervention Trials—Mean Difference in Change in Total Cholesterol Compared With Controls (k=7) (Key Question 4)



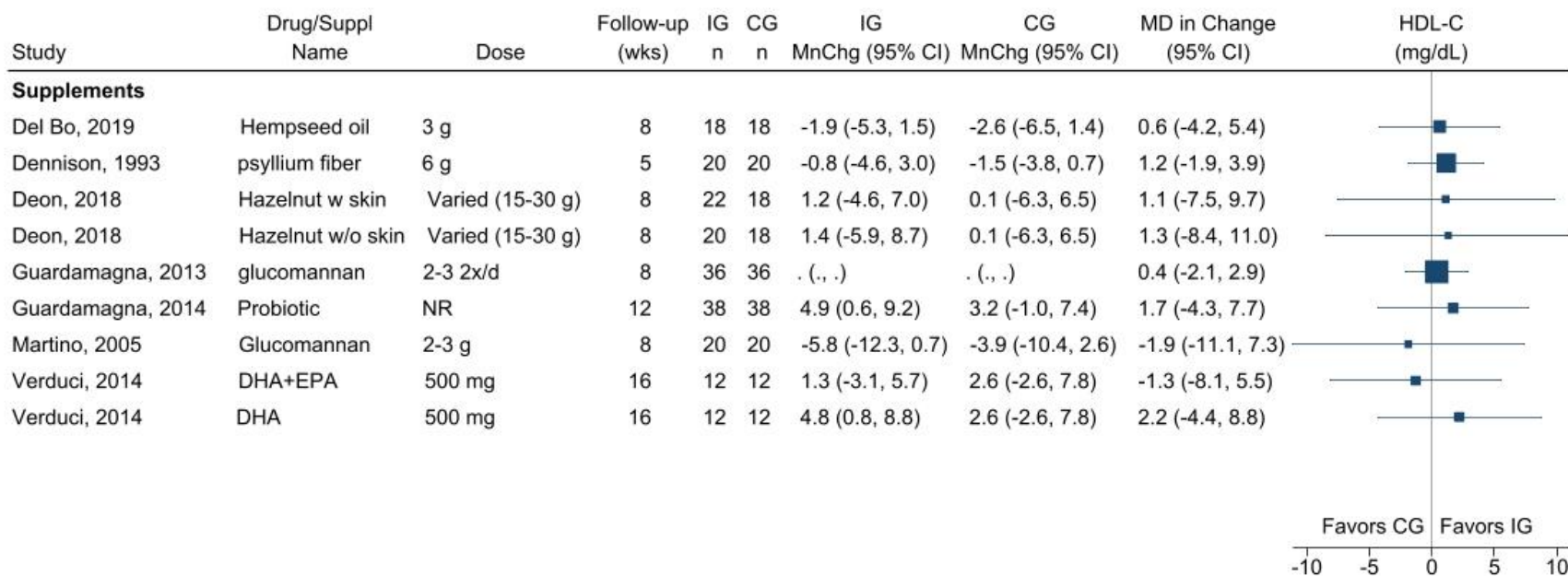
Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; g = gram(s); IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; TC = total cholesterol; w/ = with; wks = weeks; w/o = without

Figure 35. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: All Intervention Trials—Mean Difference in Change in Low-Density Lipoprotein Cholesterol Compared With Controls (k=7) (Key Question 4)



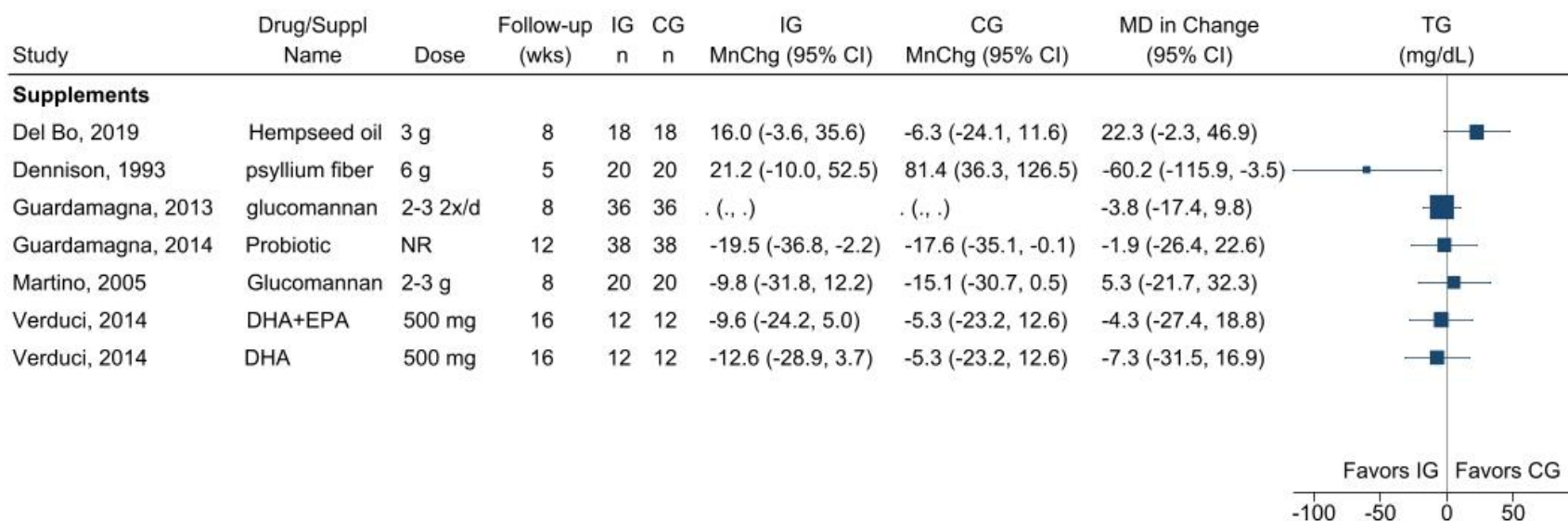
Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; g = gram(s); IG = intervention group; LDL-C = low-density lipoprotein cholesterol; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; w/ = with; wks = weeks; w/o = without

Figure 36. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: All Intervention Trials—Mean Difference in Change in High-Density Lipoprotein Cholesterol Compared With Controls (k=7) (Key Question 4)



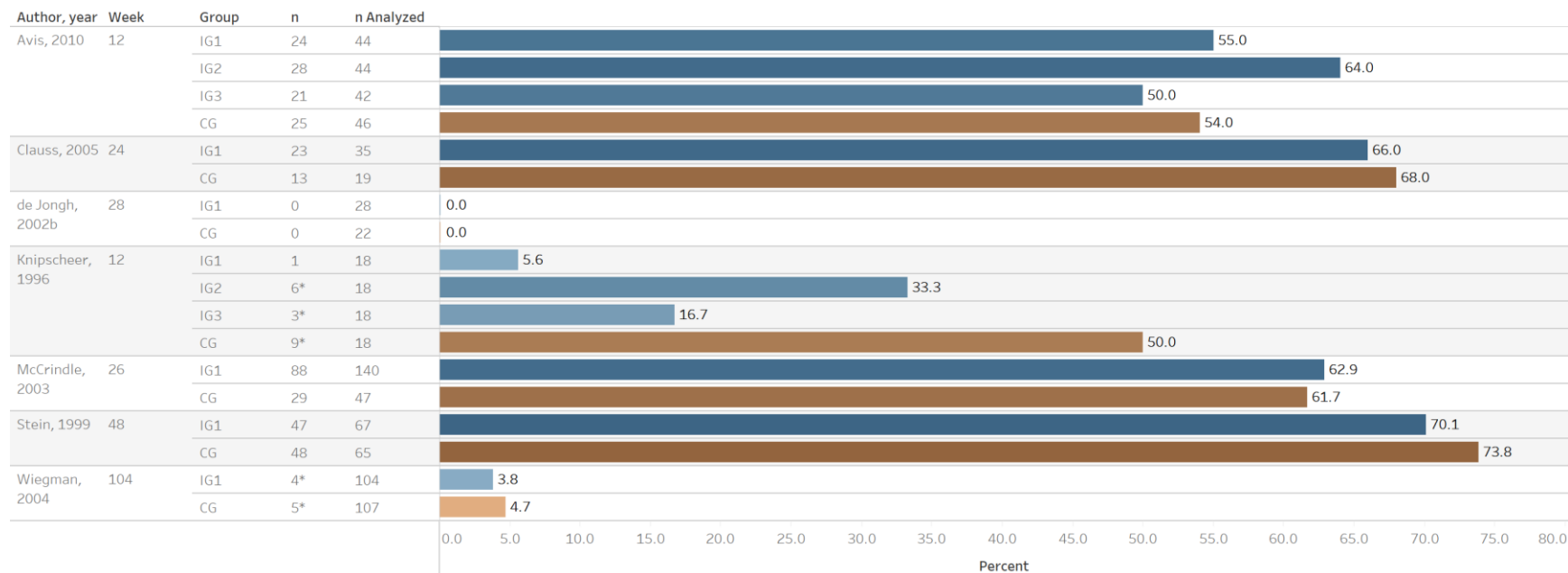
Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; g = gram(s); HDL-C = high-density lipoprotein cholesterol; IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; w/ = with; wks = weeks; w/o = without

Figure 37. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: All Intervention Trials—Mean Difference in Change in Triglycerides Compared With Controls (k=6) (Key Question 4)



Abbreviations: CG = control group; CI = confidence interval; DHA = Docosahexaenoic acid; EPA = Eicosapentaenoic acid; g = gram(s); IG = intervention group; MD = mean difference; mg/dL = milligrams per deciliter; MnChg = mean change; NR = not reported; TG = triglycerides; w/ = with; wks = weeks; w/o = without

Figure 38. Familial Hypercholesterolemia: Statin Intervention Trials—Total Adverse Events (Key Question 5)

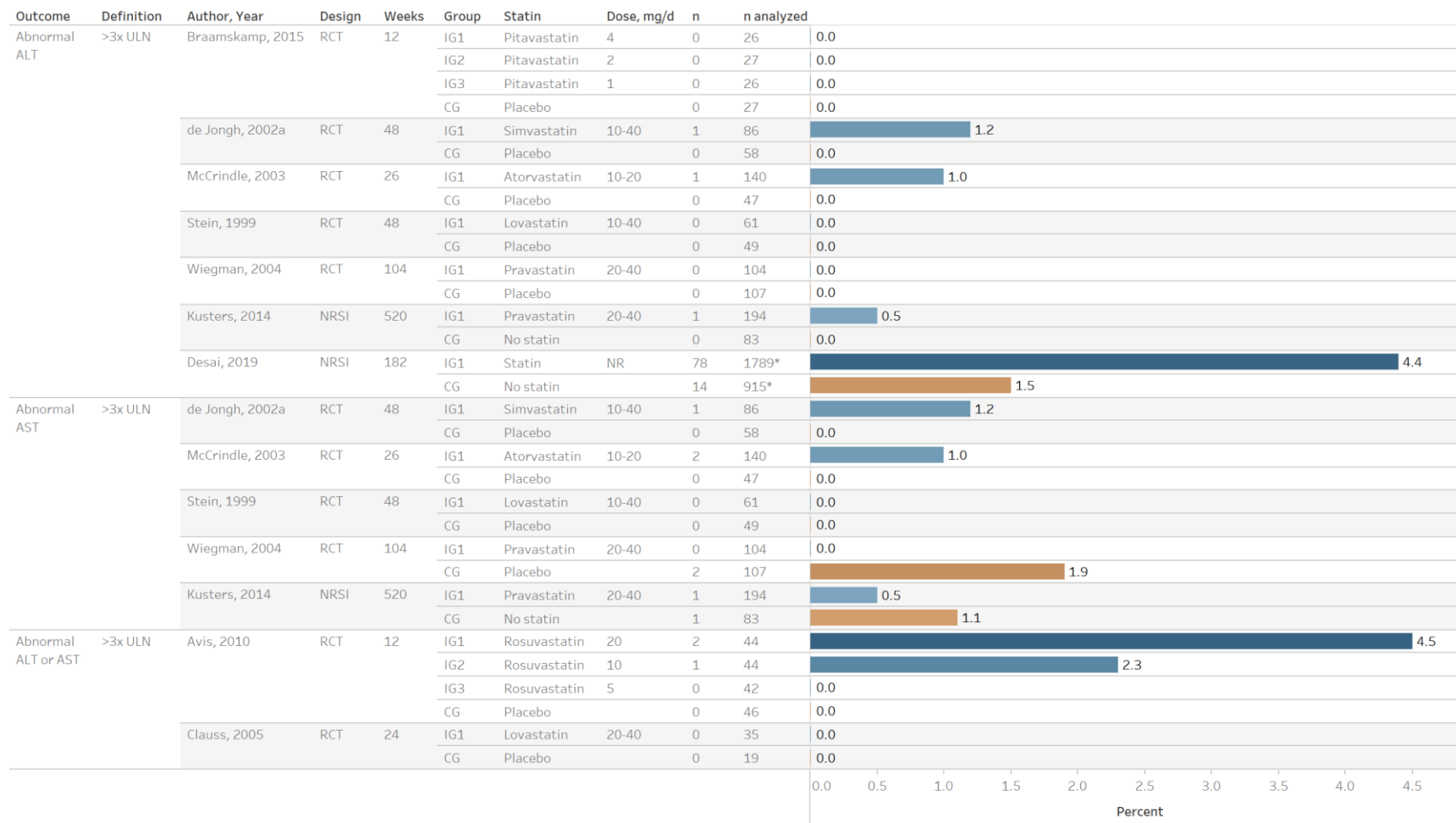


NOTE: Blue and orange colors indicate intervention (blue) or control (orange). Darker shading corresponds to higher percentages.

* Number of events, not people.

Abbreviations: CG = control group; IG = intervention group

Figure 39. Familial Hypercholesterolemia: Statin Intervention Trials—Liver Enzyme Adverse Events (Key Question 5)

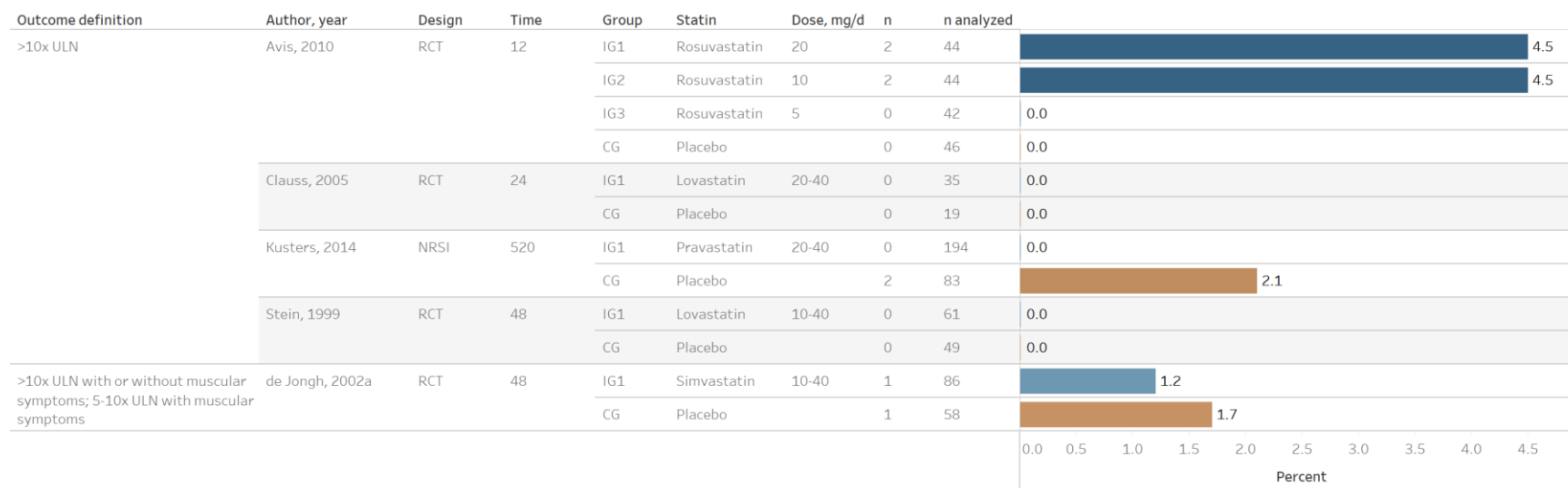


NOTE: Blue and orange colors indicate intervention (blue) or control (orange). Darker shading corresponds to higher percentages.

* Number of individual tests, not people.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate transaminase; CG = control group; IG = intervention group; mg/d = milligrams per day; n = number; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial; ULN = upper limit of normal.

Figure 40. Familial Hypercholesterolemia: Statin Intervention Trials—Abnormal Creatinine Kinase Level Results (Key Question 5)



NOTE: Blue and orange colors indicate intervention (blue) or control (orange). Darker shading corresponds to higher percentages.

Abbreviations: CG = control group; IG = intervention group; mg/d = milligrams per day; n = number; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial; ULN = upper limit of normal.

Figure 41. Indirect Linkages From Child Intermediate Outcomes to Adult Health Outcomes

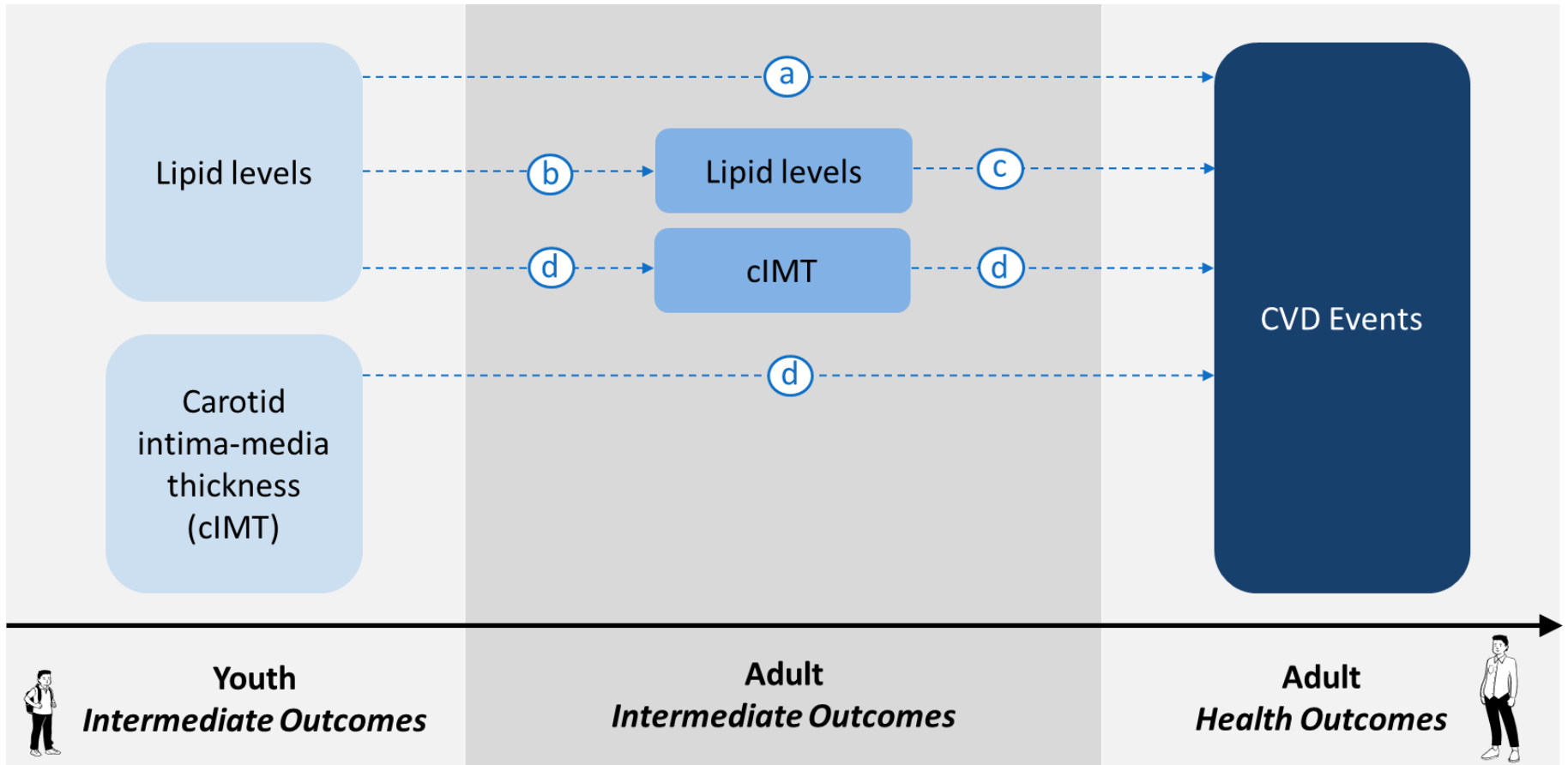


Table 1. MEDPED Criteria to Diagnose FH (United States)^{18*}

Age (years)	Total cholesterol (LDL-C) levels, mg/dL			
	First-degree relative [†]	Second-degree relative [†]	Third-degree relative [†]	General population
<20	220 (155)	230 (165)	240 (170)	270 (200)
20-29	240 (170)	250 (180)	260 (185)	290 (220)
30-39	270 (190)	280 (200)	290 (210)	340 (240)
≥40	290 (205)	300 (215)	310 (225)	360 (260)

*Expected to diagnose FH with 98% specificity and sensitivity ranging from 54% in the general population to 88% in first-degree relatives

[†]First: parents, offspring, brother, and sister. Second: aunts, uncles, grandparents, nieces, nephews. Third: first cousins, siblings of grandparents.

Abbreviations: FH= familial hypercholesterolemia LDL-C = low-density lipoprotein cholesterol; MEDPED = Make Early Diagnosis to Prevent Early Death Program; mg/dL = milligrams per deciliter

Table 3. Dutch Lipid Clinic Network Diagnostic Criteria for FH¹⁹¹

Diagnosis	Requirements	Criteria
Definite FH	(a) + (b) OR (a) + (c)	(a) Total cholesterol levels, mg/dL Age ≥16 years: >290 Age <16 years: >260
		Or
		LDL-C levels, mg/dL Adults: >190 Children: >155
		(b) Tendon xanthomas in patient or in 1 st or 2 nd -degree [†] relative
Possible FH	(a) + (d) OR (a) + (e)	(c) DNA-based evidence of an LDL-C receptor mutation or familial defective apoB-100
		(d) Family history of MI before age 50 in 2 nd -degree relative or before age 60 in 1 st -degree relative
		(e) Family history of raised total cholesterol in 1 st -degree relative or >290 mg/dL in 2 nd -degree relative

*Table adapted from Marks, 2003¹⁹⁰

†First: parents, offspring, brother and sister. Second: aunts, uncles, grandparents, nieces, nephews.

Abbreviations: apoB = apolipoprotein type B; DNA = deoxyribonucleic acid; FH= familial hypercholesterolemia; LDL-C = low-density lipoprotein-cholesterol; mg/dL = milligrams per deciliter; MI = myocardial infarction

Table 3. Dutch Lipid Clinic Network Diagnostic Criteria for FH¹⁹¹

Criteria		Points
Family history	1 st -degree* relative with known premature (men aged <55 years; women <60 years) coronary or vascular disease or 1 st -degree relative with known LDL-C >95 th percentile	1
	1 st -degree relative with tendon xanthomata and/or corneal arcus, or child(ren) <18 years with LDL-C >95 th percentile	2
Clinical history	Patient with premature coronary artery disease (men aged <55 years; women <60 years)	2
	Patient with premature cerebral or peripheral vascular disease (men aged <55 years; women <60 years)	1
Physical examination†	Tendon xanthomas	6
	Corneal arcus at age <45 years	4
LDL-C levels (without treatment)	≥325 mg/dL†	8
	251 to 325 mg/dL	5
	191 to 250 mg/dL	3
	155 to 190 mg/dL	1
DNA analysis	Functional mutation in the <i>LDLR</i> , <i>apoB</i> , or <i>PCSK9</i> genes	8
<p><i>Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained</i></p> <p><i>A 'definite' FH diagnosis requires >8 points</i></p> <p><i>A 'probable' FH diagnosis requires 6 to 8 points</i></p> <p><i>A 'possible' FH diagnosis requires 3 to 5 points</i></p>		

*1st-degree: parents, offspring, brother, and sister.

†Exclusive of each other (i.e., maximum 6 points if both are present)

Abbreviations: apoB = apolipoprotein type B; DNA = deoxyribonucleic acid; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; mg/dL = milligrams per deciliter; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Table 4. Acceptable, Borderline-High and High Plasma Lipid, Lipoprotein and Apolipoprotein Concentrations (mg/dL*) to Define Multifactorial Dyslipidemia in Children and Adolescents^{30†}

Category	Acceptable	Borderline	High‡
TC	< 170	170 to 199	≥ 200
LDL-C	< 110	110 to 129	≥ 130
Non-HDL-C	< 120	120 to 144	≥ 145
ApoB	< 90	90 to 109	≥ 110
TG (0 to 9 years)	< 75	75 to 99	≥ 100
TG (10 to 19 years)	< 90	90 to 129	≥ 130
Category	Acceptable	Borderline	Low‡
HDL-C	> 45	40 to 45	< 40
ApoA-1	> 120	115 to 120	< 115

*To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non-HDL-C by 38.6; for triglycerides (TG), divide by 88.6

†Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children (1992). Non-HDL-C values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut points for LDL-C. Values for plasma ApoB and ApoA-1 are from the National Health and Nutrition Examination Survey III.

‡The cut points for high and borderline high represent approximately the 95th and 75th percentiles, respectively. Low cut points for HDL-C and ApoA-1 represent approximately the 10th percentile

Abbreviations: ApoA-1 = apolipoprotein A-1; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter TC; total cholesterol; TG = triglycerides

Table 5. Lipid Screening Recommendations in Pediatric Populations From Other Organizations

Organization, Year	Year published	Universal screening recommendation	Selective screening recommendation
UK National Screening Committee ¹⁹²	2020	Systematic population screening program for FH not recommended	-
National Institute for Health and Care Excellence (NICE) ¹⁹³	2019	-	In children aged 0–10 years at risk of FH because of 1 affected parent, offer a DNA test at the earliest opportunity. If testing of a child at risk has not been undertaken by the age of 10 years, offer an additional opportunity for a DNA test. In children at risk of homozygous FH because of two affected parents or because of the presence of clinical signs, for example, cutaneous lipid deposits (xanthomata), LDL-C concentration should be measured before the age of 5 years or at the earliest opportunity thereafter. If the LDL-C concentration is greater than 425 mg/dL then a clinical diagnosis of homozygous FH should be considered.
European Society of Cardiology/European Atherosclerosis Society ¹⁹¹	2019	-	A diagnosis of FH should be considered in people with relatives with premature CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C (>150 mg/dL in children), and in first-degree relatives of FH patients. FH should be diagnosed using clinical criteria and confirmed, when possible, via DNA analysis. Once the index case is diagnosed, family cascade screening is recommended. Testing for FH is recommended from the age of 5 years, or earlier if homozygous FH is suspected.
HEART UK ¹⁹⁴	2019	-	Cascade testing of children should be undertaken by age 10 years in families where an FH mutation has been identified, by testing for the mutation identified in the index case. In FH families where the genetic basis is unknown, LDL-C concentrations can be used for cascade screening.
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/	2018	In children and adolescents without cardiovascular risk factors or family	In children and adolescents with a family history of either early CVD (MI, documented angina, or

Table 5. Lipid Screening Recommendations in Pediatric Populations From Other Organizations

Organization, Year	Year published	Universal screening recommendation	Selective screening recommendation
NLA/PCNA Guideline on the Management of Blood Cholesterol ³¹		history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non-HDL-C once between the ages of 9 and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities	atherosclerosis by angiography in parents, siblings, grandparents, aunts, or uncles (<55 for men and <65 for women) or significant hypercholesterolemia (≥ 240 mg/dL, LDL-C ≥ 190 mg/dL, non-HDL-C ≥ 220 mg/dL, or known primary hypercholesterolemia), it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect FH or rare forms of hypercholesterolemia.
Canadian Cardiovascular Society ¹⁹⁵	2018	Universal cholesterol level screening should be considered for detection of FH in children with reverse cascade screening of parents when warranted	Cascade screening protocols should be implemented at the local, provincial, and national level in Canada and offered to first-degree relatives of patients with FH.
American Academy of Pediatrics (AAP) ^{30, 63, 196}	2017	Endorsement and adoption of NHLBI 2012 recommendation Screen once (fasting or nonfasting) between 9 and 11 years of age, and once between 17 and 21 years of age.	Selective screening (fasting lipid profile) between 2 and 8 years of age if (a) parent, grandparent, aunt/uncle, or sibling with MI, angina, stroke, CABG/stent/angioplasty at <55 years in males and <65 years in females, (b) parent with TC ≥ 240 mg/dL or known dyslipidemia, (c) child has diabetes, hypertension, BMI $\geq 95^{\text{th}}$ percentile, or smokes cigarettes, or (d) child has a moderate or high-risk medical condition. Selective screening (fasting lipid profile) between 12 and 16 years of age if there is new knowledge of one of the criteria above, but BMI cutpoint of $\geq 85^{\text{th}}$ percentile
American Association of Clinical Endocrinologists and American College of Endocrinology ^{197, 198}	2017	-	Screen children at risk for FH (e.g., family history of premature cardiovascular disease or elevated cholesterol) at 3 years of age, again between ages 9 and 11, and again at age 18. Adolescents >16 years should be screened every 5 years or more frequently if they have ASCVD risk factors, overweight or obesity, other elements of insulin resistance syndrome, or a family history of premature ASCVD.
American Academy of Family Physicians (AAFP) ¹⁹⁹	2016	Endorsement of the USPSTF recommendation. The current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and	-

Table 5. Lipid Screening Recommendations in Pediatric Populations From Other Organizations

Organization, Year	Year published	Universal screening recommendation	Selective screening recommendation
International FH Foundation ²⁰⁰	2015	adolescents 20 years or younger Targeted, opportunistic and universal screening strategies should be employed to detect index cases	<p>Targeted, opportunistic and universal screening strategies should be employed to detect index cases.</p> <p>Children with xanthomata or other physical findings of homozygous FH, or at risk of homozygous FH should be screened as early as possible and definitely by 2 years of age.</p> <p>Children with suspected heterozygous FH should be screened between the ages of five and 10 years; age at screening should be similar in males and females.</p> <p>Secondary causes of hypercholesterolaemia should first be excluded.</p> <p>Children should be genetically tested for FH only after a pathogenic variant (mutation) has been identified in a parent or first degree relative; Children may initially be genetically tested for FH when parents or first degree relatives are unknown or deceased, or as an accepted screening practice in certain countries, such as the Netherlands.</p> <p>Age-, gender- and country-specific plasma LDL-C concentration thresholds should be used to make the phenotypic diagnosis; because of biological variation, two fasting LDL-cholesterol values are recommended.</p> <p>A plasma LDL-C of ≥ 190 mg/dL indicates high probability of FH in the absence of a positive parental history of hypercholesterolaemia or premature CHD; an LDL-C of 155 mg/dL or above indicates high probability of FH in the presence of a positive parental history of hypercholesterolaemia or premature CHD.</p>
National Heart, Lung, and Blood Institute's (NHLBI) Expert Panel on Integrated Guidelines for	2012	Screen once (fasting or nonfasting) between 9 and 11 years of age, and once between 17 and 21 years of	<p>Same as AAP (first row)</p> <p>Selective screening (fasting lipid profile) between 2 and 8 years of age if (a) parent, grandparent, aunt/uncle, or</p>

Table 5. Lipid Screening Recommendations in Pediatric Populations From Other Organizations

Organization, Year	Year published	Universal screening recommendation	Selective screening recommendation
Cardiovascular Health and Risk Reduction in Children and Adolescents ³⁰		age.	sibling with MI, angina, stroke, CABG/stent/angioplasty at <55 years in males and <65 years in females, (b) parent with TC ≥240 mg/dL or known dyslipidemia, (c) child has diabetes, hypertension, BMI ≥95 th percentile, or smokes cigarettes, or (d) child has a moderate or high-risk medical condition. Selective screening (fasting lipid profile) between 12 and 16 years of age if there is new knowledge of one of the criteria above, but BMI cutpoint of ≥85 th percentile

Abbreviations: AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA = American Academy of Physician Assistants; ABC = Association of Black Cardiologists; ACC = American College of Cardiology; ACPM = American College of Preventive Medicine; ADA = American Diabetes Association; AGS = American Geriatrics Society; AHA = American Heart Association; APhA = American Pharmacists Association; ASPC = American Society for Preventive Cardiology; BMI = body mass index; CHD= coronary heart disease; CVD = cardiovascular disease; DNA = deoxyribonucleic acid; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; NHLBI = National Heart, Lung, and Blood Institute; NLA = National Lipid Association; PCNA = Preventive Cardiovascular Nurses Association; TC = total cholesterol; UK = United Kingdom; USPSTF = United States Preventive Services Task Force

Table 6. Included Studies for Treatment Benefits, by Population and Intervention Category (Key Question 4), k=33

Intervention Category	Intervention Type	Conditions included	Total Number of Studies (n)	Number of New Studies
Drug (k=21)	Statin (k=10)	FH	10 (n=1230)	1
		MFD	0	-
	Drug Combination* (k=1)	FH	1 (n=248)	0
		MFD	0	-
	Bile acid sequestrants (k=3)	FH	3 (n=332)	0
		MFD	0	-
	PCSK9 inhibitor (k=1)	FH	1 (n=158)	1
		MFD	0	-
	Ezetimibe (k=1)	FH	1 (n=138)	0
		MFD	0	-
Fibrate (k=1)	FH	1 (n=14)	1	
	MF	0	-	
Behavioral (k=3)	Lifestyle counseling (k=3)	FH	1 (n=21)	1
		MFD	2 (n=934)	1
Supplement (k=13)	Various†	FH	4 (n=116)	4
		MFD	2 (n=74)	1
		FH / MFD	7 (n=288)	7
All intervention categories (k=33)	All intervention types	FH	22 (n=2257)	8
		MFD	4 (n=1008)	2
		FH / MFD	7 (n=288)	7

* Interventions included combinations of simvastatin + ezetimibe

† Supplement interventions include DHA, DHA plus EPA, fish oil, flaxseed, glucomannan, hazelnuts (with or without skin), hempseed oil, plant sterols, probiotics, psyllium fiber, rapeseed margarine, sistostanol esters

Abbreviations: FH = familial hypercholesterolemia; MFD = multifactorial dyslipidemia; PCSK9 = proprotein convertase subtilisin/kexin type 9

Table 7. Included Studies for Treatment Harms, by Population and Intervention Category (Key Question 5); k=31

Intervention Category	Intervention Type	Conditions included	Total Number of Studies (n)	Number of New Studies
Drug (k=19)	Statin (k=12)	FH	12 (n=11,812)	3
		MFD	0	-
	Drug Combination* (k=1)	FH	1 (n=248)	0
		MFD	0	-
	Bile acid sequestrants (k=3)	FH	3 (n=332)	0
		MFD	0	-
	PCSK9 inhibitor (k=1)	FH	1 (n=158)	1
		MFD	0	-
	Ezetimibe (k=1)	FH	1 (n=138)	0
		MFD	0	-
	Fibrate (k=1)	FH	1 (n=14)	1
		MFD	0	-
Behavioral (k=2)	Lifestyle counseling (k=2)	FH	0	-
		MFD	2 (n=934)	1
Supplement (k=10)	Various †	FH	3 (n=102)	3
		MFD	2 (n=74)	1
		FH / MFD	5 (n=186)	5
All Interventions (k=31)	All intervention types	FH	22 (n=12,804)	8
		MFD	4 (n=1008)	2
		FH / MFD	5 (n=186)	5

* Intervention included combinations of simvastatin + ezetimibe

† Supplement interventions include DHA, DHA plus EPA, fish oil, flaxseed, glucomannan, hazelnuts (with or without skin), hempseed oil, plant sterols, probiotics, psyllium fiber, rapeseed margarine

Abbreviations: FH = familial hypercholesterolemia; MFD = multifactorial dyslipidemia; PCSK9 = proprotein convertase subtilisin/kexin type

Table 8. Familial Hypercholesterolemia: Study Characteristics of US Cohorts Included for Key Question 2

Cohort name Quality	N	Population	FH definition (mg/dL)	Years of data collection	Recruitment target	Recruitment Methods	Brief screening details	Fasting?
NHANES ⁷⁰ Fair	13,343	Nonpregnant NHANES participants 12 to 19 years of age between years 1999-2012	LDL-C ≥190	1999- 2012	National	NHANES participants; Combined in- home interviews with mobile examinations and laboratory tests.	Mobile examination with laboratory test; lipid profiles measured from morning peripheral blood draws.	Yes*
Blood donors ¹⁰⁷ Fair	321,718	Youth and adults aged 16 years or older who voluntarily donated blood	MEDPED criteria: TC ≥270	2002- 2016	Single state	Deidentified data were obtained from the Carter BloodCare database	Nonfasting TC measured from donors who voluntarily donated blood to Carter BloodCare between 2002- 2016.	No
CARDIAC ¹⁰⁸ Fair	60,404	5 th grade students enrolled in West Virginia schools	Significant likelihood of FH: LDL-C ≥190 Suggestive of FH: LDL-C ≥160	1998- 2015	Single state	Universal screening in participating schools	Cardiovascular risk detection screening program including evaluation for obesity, dyslipidemia, hypertension, and prediabetes	Mixed†

*97.6% reported fasting for ≥8 hours

†Fasting until 1st semester 2012, thereafter, non-fasting lipids reported for abnormal lipids

Abbreviations: CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; FH= familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MEDPED = Make Early Diagnosis to Prevent Early Death Program; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol; US = United States

Table 9. Familial Hypercholesterolemia: Population Characteristics of US Cohorts Included for Key Question 2

Cohort name	Mean age (range)	Female, %	Race/ethnicity, %	BMI	Smoking, %	% With Family History of CVD and Definition
NHANES, 1999-2012 ⁷⁰	NR* (12-19)	NR	NR	NR	NR	NR
Blood donors, 2002-2016 ¹⁰⁷	NR† (16-20)	NR	NR	NR	NR	NR
CARDIAC, 1998-2015 ¹⁰⁸	11 ‡ (NR)	53	White: 93 Black: 3 Asian: 1 Native American: NR Latino: 1 Other: 1	85 th -94.9 th percentile: 19 95 th -98.9 th percentile: 28	Smoking in the home: 33.7	Heart disease, unspecified: 32 Family hx of high TC, 34

*Baseline population characteristics were not available for this age group

†Baseline population characteristics only reported for overall cohort, which included adults (n=1,178,102 [3,038,420 donations]): Median age: 32 years; Female: 52.6%; Race/ethnicity, %: White: 64.8; Latinx: 14.7; AA: 7.6; Asian: 2.7; Other: 1.6; Unknown: 8.6

‡Baseline population characteristics based on n=99,282 (1999-2016)

Abbreviations: BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CVD = cardiovascular disease; hx = history; TC = total cholesterol; US = United States

Table 10. Familial Hypercholesterolemia: Prevalence of FH in US Cohorts Included for Key Question 2

Cohort name, Year	Fasting status	Definition (lipid values in mg/dL)	Population Description	Time of screening	N analyzed	N screen positive	% screen positive
NHANES, 1999-2012 ⁷⁰	Fasting	LDL-C ≥190	12-19 yrs	1999-2012	13,343	NR	0.42 (95% CI: 0.15, 0.70)
Blood donors, 2002-2016 ¹⁰⁷	Nonfasting	MEDPED criteria for FH: TC ≥270	<20 yrs	2002-2016	321,718	1001	0.31
CARDIAC, 1998-2015 ^{69, 108}	Mixed	LDL-C >160	5 th graders	1998-2015	60,404	637	1.1
	Mixed	LDL-C >175	5 th graders	1998-2015	60,404	248	0.4
	Mixed	LDL-C >190	5 th graders	1998-2015	60,404	122	0.2
	Fasting ⁶⁹	LDL-C ≥160	5 th graders with a family history of premature CVD* ⁶⁹	2003-2008	14,468	170	1.2
	Fasting ⁶⁹	LDL-C ≥160	5 th graders without a family history of premature CVD* ⁶⁹	2003-2008	5798	98	1.7

* Positive family history based on NCEP criteria: parents or grandparents with documented coronary artery disease before age of 55 years. Premature CHD was defined as coronary disease that occurred before age 55, evidenced by (1) a myocardial infarction (“heart attack”) that required hospitalization, (2) coronary bypass surgery, (3) coronary angioplasty and/or stent placement, (4) or death that resulted from CHD event

Abbreviations: CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease; FH= familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MEDPED = Make Early Diagnosis to Prevent Early Death Program; mg/dL = milligrams per deciliter; NCEP = National Cholesterol Education Program; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol

Table 11. Multifactorial Dyslipidemia: Study Characteristics of US Cohorts Included for Key Question 2

Cohort name Quality	N	Population	MFD definition (mg/dL)	Years of data collection	Recruitment target	Recruitment Methods	Brief screening details	Fasting?
NHANES ⁵² Fair	26,047	Youths ages 6-19 years who participated in an NHANES examination from 1999 to 2016	TC ≥200 LDL-C ≥130 HDL-C <40 TG ≥130 Non-HDL-C ≥145	1999-2000 through 2015-2016	National	Random, population-based selection	Home interviews, mobile exams and lab tests in youths aged 6 to 19 years; fasting TG and apo-B in a subset of adolescents aged 12 to 19 years	Mixed*
HEALTHY study ¹⁰⁹ Fair	6,097	Middle school students aged 10-13 at increased risk for type 2 diabetes	TC ≥200 LDL-C ≥130 HDL-C ≤40 TG ≥130	2006-2009	Multi-center	Middle schools with student populations at increased risk for type 2 diabetes, defined by authors as ≥50% eligible for free or reduced-price lunch or belonging to a racial or ethnic minority group. 6 th graders invited to health screenings in fall 2006	Fasting blood draw to assess cardiovascular risk factors	Fasting
Study of Latinos (SOL) Youth study ¹¹³ Fair	1,137	Participants ages 10-16 whose parents/legal guardians participated in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)	Multiple thresholds: NCEP ATP III: HDL-C <40 TG ≥110 WHO: HDL-C <35 TG ≥150	2012-2014	Multi-state	All eligible children in households from the Hispanic Community Health Study/ Study of Latinos from four cities (Bronx, Chicago, Miami, and San Diego).	Blood specimens taken after overnight fast	Fasting

Table 11. Multifactorial Dyslipidemia: Study Characteristics of US Cohorts Included for Key Question 2

Cohort name Quality	N	Population	MFD definition (mg/dL)	Years of data collection	Recruitment target	Recruitment Methods	Brief screening details	Fasting?
			IDF (ages 10-15): HDL-C <50 (10-15 y) HDL-C <40 (16+ y) TG ≥150					
The Poudre Valley Health System (PVHS), Healthy Hearts Club ¹¹¹ Fair	9,694	4 th grade students who received a cardiovascular screening	TC ≥200 HDL-C <40 non-HDL-C ≥145	1992-2013	Single state	Schools were selected based on willingness to participate.	Nonfasting cholesterol screening data collected every year 1992-2013 (except 1997 and 1999).	Non-fasting
CARDIAC ¹⁰⁸ Fair	99,282	5 th grade students enrolled in West Virginia schools	LDL-C ≥130 HDL-C <40	1999-2016	Single state	5 th grade students enrolled in West Virginia schools	Cardiovascular risk detection screening program including evaluation for obesity, dyslipidemia, hypertension, and prediabetes	Mixed †

*Fasting values only obtained for adolescents aged 12-19 who had morning exams

†Fasting till 1st semester 2012, thereafter, non-fasting lipids reported for abnormal lipids

Abbreviations: CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol; TG = triglycerides; Trig = triglycerides; US = United States; WHO = World Health Organization

Table 12. Multifactorial Dyslipidemia: Population Characteristics of Included US Cohorts for Key Question 2

Cohort name, Year	Mean age (range)	Female, %	Race/ethnicity, %	BMI	Smoking, %	% With Family History of CVD and Definition	Other BL Char
NHANES, 1999-2016 ⁵²	12* (6-19)	51	NR	NR	NR	NR	NR
Study of Latinos (SOL) Youth study, 2012-2014 ¹¹³	13 (10-16)	50	Latino: 100 49% Mexican, 14% Dominican, 10% Mixed Hispanic, 10% Puerto Rican, 6% Central American, 6% Cuban 4% South American, 1.9% Other	NR	NR	NR	
HEALTHY study, 2006-2009 ¹⁰⁹	11 (10-13)	52	White: 19 Black: 20 Asian: NR Native American: NR Latino: 53 Other: 8	Overweight, BMI percentile 85-94: 20 Obese, BMI percentile ≥95: 30	NR	NR	Tanner stage: 1: 10% 2: 26% 3: 40% 4: 22% 5: 2% Metabolic risk factors: ≥1: 46% ≥2: 19% ≥3: 7%
The Poudre Valley Health System (PVHS), Healthy Hearts Club, 1992-2013 ¹¹¹	10 (NR)	50	Middle school student populations with ≥50% of students belonging to a racial or ethnic minority group	Overweight, BMI percentile 85-94: 13 Obese, BMI percentile ≥95: 8	NR	NR	Middle school student populations with ≥50% of students eligible for free or reduced-price lunch
CARDIAC, 1999-2016 ¹⁰⁸	11 (NR)	53	White: 93 Black: 3 Asian: 1 Native American: NR	85-94.9 %tile: 19 95-98.9 %tile: 28	Smoking in the home: 34	Heart disease, unspecified: 32 Family hx of	NR

Table 12. Multifactorial Dyslipidemia: Population Characteristics of Included US Cohorts for Key Question 2

Cohort name, Year	Mean age (range)	Female, %	Race/ethnicity, %	BMI	Smoking, %	% With Family History of CVD and Definition	Other BL Char
			Latino: 1 Other: 1			high TC, 34	

* Sample sizes and characteristics varied between cycles according to sampling strategy (eg, intentional oversampling of adolescents in 1999-2006 and of non-Hispanic Asians in 2011-2016); n=26,047

Abbreviations: BL = baseline; BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CVD = cardiovascular disease; MFD = multifactorial dyslipidemia; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol

Table 13. Multifactorial Dyslipidemia: Prevalence of High Total Cholesterol (≥ 200 mg/dL)

Cohort name	Fasting status	Group	Subgroups	Time of screening	N analyzed	N screen positive	% screen positive (95% CI)
NHANES* ^{52, 112}	Mixed†	All participants	-	2009-2016	10,661	757	7.1 (6.4, 7.8)
		Age	Ages 6-8	2011-2014	999	60	6.0 (4.5, 7.5) ‡
			Ages 9-11	2011-2014	1029	75	7.3 (5.7, 8.9)
			Ages 12-15	2011-2014	1182	80	6.8 (5.4, 8.2)
			Ages 16-19	2011-2014	1148	102	8.9 (7.2, 10.5)
		BMI	5 th -85 th percentile	2009-2016	4978	274	5.5 (4.8-6.3)
			85 th -94 th percentile	2009-2016	1458	102	7.0 (5.5-8.5)
			$\geq 95^{\text{th}}$ percentile	2009-2016	1832	196	10.7 (9.0-12.4)
		Sex	Males	2011-2014	2232	132	5.9 (4.9, 6.8)
			Females	2011-2014	2129	189	8.9 (7.6, 10.1)§
		Ethnicity/ Race	Non-Hispanic White	2009-2016	2299	172	7.5 (6.3, 8.7)
			Non-Hispanic Black	2009-2016	1003	83	8.3 (7.2, 9.3)
			Mexican	2009-2016	2097	145	6.9 (5.7, 8.1)
			Non-Hispanic White	2011-2014	1080	79	7.3 (5.8, 8.9)
Non-Hispanic Black	2011-2014		1175	113	9.6 (7.9, 11.3) ¶		
Non-Hispanic Asian	2011-2014		435	47	10.9 (8.0, 13.8) ¶#		
Hispanic	2011-2014	1419	89	6.3 (5.0, 7.6)			
CARDIAC ¹⁰⁸	Mixed**	All participants	-	1999-2016	55,198	4747	8.6 (8.4, 8.8)
		BMI	$\leq 85^{\text{th}}$ percentile	1999-2016	28,951	1,766	6.1 (5.8, 6.4) ††
			85 th -94 th percentile	1999-2016	10,500	966	9.2 (8.6, 9.8) ††
			95 th -99 th percentile	1999-2016	12,131	1,577	13.0 (12.4, 13.6) ††
			>99 th percentile	1999-2016	3590	438	12.2 (11.1, 13.3) ††
HEALTHY study ¹⁰⁹	Fasting	BMI	<5 th percentile	2006-2009	91	6	6.5 (1.5, 11.7)
			5 th -79 th percentile	2006-2009	NR	NR	4.5 (NR)
			80 th -84 th percentile	2006-2009	NR	NR	5.0 (NR)
			85 th -89 th percentile	2006-2009	NR	NR	6.3 (NR)
			90 th -94 th percentile	2006-2009	NR	NR	7.5 (NR)
			$\geq 95^{\text{th}}$ percentile	2006-2009	1801	167	9.3 (8.0, 10.6)
The Poudre	Nonfasting	All participants	-	1992-2013	9694	911	9.4 (8.8, 10.1)

Table 13. Multifactorial Dyslipidemia: Prevalence of High Total Cholesterol (≥ 200 mg/dL)

Cohort name	Fasting status	Group	Subgroups	Time of screening	N analyzed	N screen positive	% screen positive (95% CI)
Valley Health System (PVHS), Healthy Hearts Club ¹¹¹		BMI	$\leq 85^{\text{th}}$ percentile	1992-2013	7645	619	8.1 (7.5, 8.7)
			85 th -94 th percentile	1992-2013	1263	169	13.4 (11.5, 15.3)
			$\geq 95^{\text{th}}$ %	1992-2013	786	119	15.1 (12.6, 17.6)
		Sex	Males	1992-2013	4851	456	9.4 (8.6, 10.2)
			Females	1992-2013	4843	455	9.4 (8.6, 10.2)
		<i>Borderline TC ≥ 170–199 mg/dL</i>	<i>All participants</i>	1992-2013	9694	2545	26.3 (25.4, 27.2)
			<i>BMI $\leq 85^{\text{th}}$ percentile</i>	1992-2013	7645	1949	25.5 (24.5, 26.5)
			<i>BMI 85th-94th percentile</i>	1992-2013	1263	357	28.3 (25.8, 30.8)
			<i>BMI $\geq 95^{\text{th}}$ percentile</i>	1992-2013	786	242	30.8 (27.6, 34.0)
			<i>Males</i>	1992-2013	4851	1286	26.5 (25.2, 27.7)
		<i>Females</i>	1992-2013	4843	1259	26.0 (24.8, 27.2)	

* Per study authors, NHANES (1999-2016) maximal sample size was reported. N estimate was based on population-weighted data from the National Health and Nutrition Examination Survey (1999-2016).

†Fasting values only obtained for adolescents aged 12-19 who had morning exams

‡FN: Significantly different from ages 16-19 (p <0.05).

§Significantly different from boys (p <0.05)

¶ Significantly different from Hispanic (p <0.05)

Significantly different from non-Hispanic white (p < 0.05)

** Fasting till 1st semester 2012, thereafter, non-fasting lipids reported for abnormal lipids ††Significantly different from other BMI subgroups, p <0.05: prevalence less than BMI 85th-94th, BMI 95th-99th and BMI >99th %tiles

‡‡Not significantly different from subgroup BMI >99th %tile; and significantly different from the other subgroups, p <0.05: prevalence more than BMI <85th and BMI 85th-94th %tiles

Abbreviations: BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CI = confidence interval; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol

Table 14. Multifactorial Dyslipidemia: Prevalence of High Low-Density Lipoprotein Cholesterol (LDL-C ≥130 mg/dL)

Cohort name	Fasting	Group	Subgroup	Time of screening	N analyzed	N screen positive	% screen positive (95% CI)
NHANES* ⁵²	Mixed†	Age	Ages 12-19	2007-2014	2042	131	6.4 (4.9, 7.8)
		BMI	5 th -<85 th percentile	2007-2014	1191	61	5.1 (3.5-6.6)
			85 th -94 th percentile	2007-2014	332	23	6.8 (3.6-10.0)
			≥95 th percentile	2007-2014	410	41	10.0 (6.4-13.6)
			Race	Non-Hispanic Black, ages 12-19	2007-2014	506	41
		Mexican, ages 12-19	2007-2014	491	21	4.3 (2.2-6.4)	
		Non-Hispanic White, ages 12-19	2007-2014	594	46	7.8 (5.6-10.1)	
HEALTHY ¹⁰⁹	Fasting	BMI	<5 th percentile	2006-2009	91	2	2.2 (0.0, 5.2)
			5 th -79 th percentile	2006-2009	NR	NR	2.8 (NR)
			80 th -84 th percentile	2006-2009	NR	NR	3.1 (NR)
			85 th -89 th percentile	2006-2009	NR	NR	4.4 (NR)
			90 th -94 th percentile	2006-2009	NR	NR	5.8 (NR)
			≥95 th percentile	2006-2009	1801	122	6.8 (5.6, 7.9)
CARDIAC ^{108, 110}	Mixed‡	All participants	-	1999-2016	54,784	4054	7.4 (7.2, 7.6)
			-	2016-2017	3,648	128	3.8 (3.2, 4.4)
		BMI	≤85 th percentile	1999-2016	29,313	1,407	4.8 (4.6, 5.0)§
			85 th -94 th percentile	1999-2016	10,412	885	8.5 (8.0, 9.0)§
			95 th -99 th percentile	1999-2016	12,018	1,370	11.4 (10.8, 12.0)¶
			>99 th percentile	1999-2016	3564	392	11.0 (10.0, 12.0)¶

* Per study authors, NHANES (1999-2016) maximal sample size was reported. N estimate was based on population-weighted data from the National Health and Nutrition Examination Survey (1999-2016).

†Fasting values only obtained for adolescents aged 12-19 who had morning exams

‡ Fasting till 1st semester 2012, thereafter, non-fasting lipids reported for abnormal lipids

§ Significantly different than the other BMI subgroups, p <0.05: prevalence less than BMI 85th-94th, BMI 95th-99th, and BMI >99th %tiles

¶ Not significantly different from subgroup BMI 95th-99th %tile; significantly different from the other subgroups, p <0.05: prevalence more than BMI <85th and BMI 85th-94th %tiles

Abbreviations: BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey

Table 15. Multifactorial Dyslipidemia: Prevalence of Abnormal High-Density Lipoprotein Cholesterol Results (HDL-C <40 mg/dL)

Cohort name	Fasting status	Group	Subgroup	Time of screening	N analyzed	N screen positive	% screen positive (95% CI)
NHANES* ^{52, 112}	Mixed†	All participants	-	2013-2016	6457	781	12.1 (10.4, 13.7)
		Age	Ages 6-8	2011-2014	999	77	7.7 (6.0, 9.4)
			Ages 9-11	2011-2014	1029	106	10.3 (8.4, 12.2)
			Ages 12-15	2011-2014	1182	165	14.0 (12.0, 16.0)
			Ages 16-19	2011-2014	1148	211	18.4 (16.1, 20.6)
		Sex	Males	2011-2014	2232	330	14.8 (13.3, 16.2)
			Females	2011-2014	2129	255	12.0 (10.6, 13.4)‡
		BMI	5 th -<85 th percentile	2013-2016	2485	142	5.7 (4.0-7.3)
			85 th -94 th percentile	2013-2016	783	90	11.5 (8.2-14.9)
			≥95 th percentile	2013-2016	937	275	29.3 (26.3-32.4)
		Race/Ethnicity	Non-Hispanic White	2013-2016	1152	144	12.5 (9.9-15.0)
			Non-Hispanic Black	2013-2016	1003	65	6.5 (4.9-8.0)
			Mexican	2013-2016	1049	155	14.8 (12.3-17.3)
Non-Hispanic White	2011-2014		1080	156	14.4 (12.3, 16.5)		
Non-Hispanic Black	2011-2014		1175	87	7.4 (5.9, 8.9)§		
Non-Hispanic Asian	2011-2014		435	36	8.2 (5.6, 10.8)§		
Hispanic	2011-2014		1419	221	15.6 (13.7, 17.5)		
HEALTHY study ¹⁰⁹	Fasting	BMI	<5 th percentile	2006-2009	91	2	2.2 (0.0, 5.2)
			5 th -79 th percentile	2006-2009	NR	NR	5.8 (NR)
			80 th -84 th percentile	2006-2009	NR	NR	9.7 (NR)
			85 th -89 th percentile	2006-2009	NR	NR	14.0 (NR)
			90 th -94 th percentile	2006-2009	NR	NR	16.0 (NR)
			≥95 th percentile	2006-2009	1801	580	32.2 (30.0, 34.4)
Study of Latinos (SOL) Youth study ¹¹³	Fasting	<40 mg/dL	All participants	2012-2014	1137	143	12.6 (10.7, 14.5)
			Males	2012-2014	570	76	13.4 (10.6, 16.2)
			Females	2012-2014	567	67	11.8 (9.1, 14.4)
		<35 mg/dL	All participants	2012-2014	1137	38	3.3 (2.3, 4.3)
			Males	2012-2014	570	20	3.6 (2.1, 5.1)
			Females	2012-2014	567	18	3.1 (1.7, 4.5)
The Poudre Valley Health System (PVHS), Healthy Hearts Club ¹¹¹	Nonfasting	All participants	-	1992-2013	9694	2152	22.2 (21.4, 23.0)
		Sex	Males	1992-2013	4851	1028	21.2 (20.0, 22.4)
			Females	1992-2013	4851	1124	23.2 (22.0, 24.4)
		BMI	≤85 th percentile	1992-2013	7645	1361	17.8 (16.9, 18.7)
			85 th -94 th percentile	1992-2013	1263	416	32.9 (30.3, 35.5)
			≥95 th percentile	1992-2013	786	373	47.5 (44.0, 51.0)

Table 15. Multifactorial Dyslipidemia: Prevalence of Abnormal High-Density Lipoprotein Cholesterol Results (HDL-C <40 mg/dL)

Cohort name	Fasting status	Group	Subgroup	Time of screening	N analyzed	N screen positive	% screen positive (95% CI)
CARDIAC ^{108, 110}	Mixed¶	All participants	-	1999-2016	55,034	9851	17.9 (17.2, 18.6)
			-	2016-2017	3,648	548	16.0 (14.8, 17.2)
		BMI	≤85 th percentile	1999-2016	29,156	2,624	9.0 (8.7, 9.3)#
			85 th -94 th percentile	1999-2016	10,425	1,866	17.9 (17.2, 18.6)
			95 th -99 th percentile	1999-2016	12,093	3,761	31.1 (30.3, 32.0)
			>99 th percentile	1999-2016	3579	1,600	44.7 (43.1, 46.3)

* Per study authors, NHANES (1999-2016) maximal sample size was reported. N estimate was based on population-weighted data from the National Health and Nutrition Examination Survey (1999-2016).

†Fasting values only obtained for adolescents aged 12-19 who had morning exams

‡ Significantly different from boys (p <0.05)

§ Significantly different from Hispanic (p <0.05) & significantly different from non-Hispanic white (p < 0.05)

¶ Fasting till 1st semester 2012, thereafter, non-fasting lipids reported for abnormal lipids

Significantly different from other BMI subgroups, p <0.05: prevalence less than BMI 85th-94th, BMI 95th-99th and BMI >99th %tiles

Abbreviations: BMI = body mass index; CARDIAC = Artery Risk Detection in Appalachian Communities; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; NHANES = National Health and Nutrition Examination Survey; WHO = World Health Organization

Table 16. Multifactorial Dyslipidemia: Prevalence of High Triglyceride Level Results (Various Thresholds)

TG Threshold	Cohort	Fasting	Group	Subgroup	Time of screening	N analyzed	N screen positive	% screen positive (95% CI)
≥130 mg/dL (k=2)	NHANES* ⁵²	Mixed†	Age	12-19 yrs	2007-2014	2045	209	10.2 (8.3, 12.1)
			BMI	5 th -<85 th percentile	2007-2014	1193	70	5.9 (4.1-7.8)
				85 th -94 th percentile	2007-2014	333	48	14.5 (9.8-19.2)
				≥95 th percentile	2007-2014	410	91	22.3 (17.1-27.5)
				Race/Ethnicity	Mexican, ages 12-19	2007-2014	491	78
			Non-Hispanic White, ages 12-19	2007-2014	594	71	11.9 (9.6-14.3)	
			Non-Hispanic Black, ages 12-19	2007-2014	506	24	4.8 (3.2-6.4)	
	HEALTHY study ¹⁰⁹	Fasting	BMI	<5 th percentile	2006-2009	91	2	2.2 (0, 5.2)
				5 th -79 th percentile	2006-2009	NR	NR	4.8 (NR)
				80 th -84 th percentile	2006-2009	NR	NR	12.6 (NR)
				85 th -89 th percentile	2006-2009	NR	NR	12.0 (NR)
90 th -94 th percentile				2006-2009	NR	NR	19.2 (NR)	
≥95 th percentile				2006-2009	1801	524	29.1 (27.0, 31.2)	
Elevated TG ≥150 mg/dL (k=2)	Study of Latinos (SOL) Youth study ¹¹³	Fasting	All participants	-	2012-2014	1137	91	8.0 (6.4, 9.6)
			Sex	Males	2012-2014	570	54	9.5 (7.1, 11.9)
				Females	2012-2014	567	36	6.4 (4.4, 8.4)
	CARDIAC ¹⁰⁸	Mixed‡	All participants	-	1999-2016	55,034	6384	11.6 (11.3, 11.9)
			BMI	≤85 th percentile	1999-2016	28,780	1,180	4.1 (3.9, 4.3)
				85 th -94 th percentile	1999-2016	10,443	1,274	12.2 (11.6, 12.8)
				95 th -99 th percentile	1999-2016	12,090	2,817	23.3 (22.5, 24.1)
>99 th percentile	1999-2016	3579		1,113	31.1 (29.6, 32.6)			
≥110 mg/dL (k=1)	Study of Latinos (SOL) Youth study ¹¹³	Fasting	All participants	-	2012-2014	1137	197	17.3 (15.1, 19.5)
			Sex	Males	2012-2014	570	101	17.7 (14.6, 20.8)
				Females	2012-2014	567	96	16.9 (13.8, 20.0)

* Per study authors, NHANES (1999-2016) maximal sample size was reported. N estimate was based on population-weighted data from the National Health and Nutrition Examination Survey (1999-2016).

† Fasting values only obtained for adolescents aged 12-19 who had morning exams

‡ Fasting till 1st semester 2012, thereafter, non-fasting lipids reported for abnormal lipids

Abbreviations: BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CI = confidence interval; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; TG = triglycerides

Table 17. Multifactorial Dyslipidemia: Prevalence of Abnormal Non-High-Density Lipoprotein Results (Non-HDL-C \geq 145 mg/dL)

Cohort	Fasting	Group	Subgroup	Time of screening	N analyzed	N screen positive	% screen positive (95% CI)
NHANES* ^{52, 112}	Mixed†	All participants	-	2013-2016	6456	413	6.4 (5.6, 7.3)
		Age	Ages 6-8	2011-2014	999	63	6.3 (4.8, 7.8)
			Ages 9-11	2011-2014	1029	73	7.1 (5.5, 8.7)
			Ages 12-15	2011-2014	1182	83	7.0 (5.5, 8.4)
			Ages 16-19	2011-2014	1148	138	12.0 (10.1, 13.9)‡
		Sex	Males	2011-2014	2232	167	7.5 (6.4, 8.6)
			Females	2011-2014	2129	200	9.4 (8.1, 10.6)§
		BMI	5 th -<85 th percentile	2013-2016	2485	70	2.8 (2.0-3.6)
			85 th -94 th percentile	2013-2016	783	70	8.9 (6.7-11.1)
			\geq 95 th percentile	2013-2016	937	132	14.1 (11.7-16.5)
		Race/Ethnicity	Non-Hispanic White	2013-2016	1152	82	7.1 (5.7, 8.5)
			Non-Hispanic Black	2013-2016	1003	56	5.6 (3.7, 7.4)
			Mexican	2013-2016	1049	78	7.4 (6.4, 8.3)
			Non-Hispanic White	2011-2014	1080	92	8.5 (6.8, 10.2)
			Non-Hispanic Black	2011-2014	1175	96	8.2 (6.6, 9.8)
Non-Hispanic Asian	2011-2014		435	45	10.4 (7.5, 13.3)		
Hispanic	2011-2014	1419	123	8.7 (7.2, 10.2)			
The Poudre Valley Health System (PVHS), Healthy Hearts Club ¹¹¹	Nonfasting	All participants	-	1992-2013	9694	1255	13.0 (12.3, 13.7)
		Sex	Males	1992-2013	4851	630	13 (12.0, 13.9)
			Females	1992-2013	4843	625	12.9 (12.0, 13.8)
		BMI	5 th -<85 th percentile	1992-2013	7645	795	10.4 (9.7, 11.1)
			85 th -94 th percentile	1992-2013	1263	248	19.6 (17.4, 21.8)
			\geq 95 th percentile	1992-2013	7645	212	27.0 (23.9, 30.1)

* Per study authors, NHANES (1999-2016) maximal sample size was reported. N estimate was based on population-weighted data from the National Health and Nutrition Examination Survey (1999-2016).

† Fasting values only obtained for adolescents aged 12-19 who had morning exams

‡ Significantly different from ages 6-8, 9-11, and 12-15 (p <0.05)

§ Significantly different from boys (p <0.05)

Abbreviations: BMI = body mass index; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey

Table 18. Multifactorial Dyslipidemia: Prevalence of Any Abnormal Lipid Level and Combination of Abnormal Lipid Values

Definition (lipid values in mg/dL)	Cohort	Fasting	Group	Subgroup	Time of screening	N analyzed	N screen positive	% Screen positive (95% CI)
Abnormal HDL-C, non-HDL-C, or TC TC ≥200 HDL-C <40 Non-HDL-C ≥145	NHANES* ⁵²	Mixed	All participants	-	2013-2016	4381	841	19.2 (17.6, 20.8)
			Age	6-11 yrs	2013-2016	2041	310	15.2 (13.1, 17.3)
				12-19 yrs	2013-2016	2340	510	21.8 (19.6, 24.0)
Abnormal LDL-C and HDL-C LDL-C >130 HDL-C <40	CARDIAC ¹⁰⁸	Mixed	All participants	-	1999-2016	99,282	24,821	25.0 (24.7, 25.3)

* Per study authors, NHANES (1999-2016) maximal sample size was reported. N estimate was based on population-weighted data from the National Health and Nutrition Examination Survey (1999-2016).

Abbreviations: CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CI = confidence interval; HDL-C = high-density cholesterol; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NHANES = National Health and Nutrition Examination Survey; TC = total cholesterol

Table 19. Familial Hypercholesterolemia: Statin Intervention Trials—Study Characteristics (Key Question 4)

Prior Include	Author, Year Study Name Quality	Brief Population Description*	FH Criteria	Country	Years of data collection	N
X	Avis, 2010 ¹¹⁸ PLUTO Fair	Adolescents aged 10-17 years in Tanner stage \geq II	Genetic test; fasting LDL-C \geq 190 mg/dL; or LDL-C $>$ 160 mg/dL if there was a family history of premature CVD or if the patient had \geq 2 other risk factors for CVD	Multinational	2006-2008	177
	Braamskamp, 2015 ¹¹⁴ PASCAL Fair	Children and adolescents aged 6-17 years with LDL-C \geq 160 mg/dL, or \geq 130 mg/dL with \geq 1 risk factor	Genetic testing; non-FH children eligible if LDL-C \geq 160 mg/dL or \geq 130 mg/dL with \geq 1 risk factors†	Multinational	2012-2014	106
X	Clauss, 2005 ¹²³ Good	Postmenarchal adolescent females aged 10-17 years	1 parent with FH; LDL-C 160-400 mg/dL and TG $<$ 350 mg/dL	US	1999-2000	54
X	Couture, 1998 ¹¹⁹ Fair	Children and adolescents aged 8-17 years	Plasma LDL-C $>$ 95 th percentile for age and sex while on lipid-lowering diet; all had genetic confirmation	Canada	NR	63
X	de Jongh, 2002a ¹²⁰ Fair	Children and adolescents aged 10 to 17 years	LDL-C 158-398 mg/dL and 1 parent with confirmed diagnosis of heFH	Multinational	NR	175
X	de Jongh, 2002b ¹²¹ Fair	Children and adolescents aged 9-18 years	LDL-C $>$ 95 th percentile for age and sex; documented family history of hyperlipidemia with LDL-C $>$ 95 th percentile for age and gender before treatment, or a personal diagnosis of FH by genetic test	Netherlands	NR	50
X	Knipscheer, 1996 ¹¹⁵ Fair	Children and adolescents aged 8-16	Plasma LDL-C $>$ 95 th percentile for age and sex during lipid-lowering diet and hypercholesterolemia present in siblings, parents, or grandparents, or clinical manifestations of premature atherosclerosis $<$ 50 y in 1 st or 2 nd degree relatives.	Netherlands	NR	72
X	McCrinkle, 2003 ¹¹⁷ Fair	Adolescents aged 10-17 years with FH or severe hypercholesterolemia and Tanner stage \geq 2	Known FH or severe hypercholesterolemia and plasma LDL-C \geq 190 mg/dL or plasma LDL-C concentrations \geq 160 mg/dL and a positive family history of FH or documented premature CV disease in a 1 st or 2 nd degree relative; TG levels \leq 400 mg/dL ‡	Multinational	NR	187

Table 19. Familial Hypercholesterolemia: Statin Intervention Trials—Study Characteristics (Key Question 4)

Prior Include	Author, Year Study Name Quality	Brief Population Description*	FH Criteria	Country	Years of data collection	N
X	Stein, 1999 ¹¹⁶ Fair	Adolescent males aged 10-17 years	LDL-C \geq 189 to 503 mg/dL after \geq 4 months AHA diet and \geq 1 parent had LDL-C value of \geq 189 mg/dL not associated with a disorder known to cause secondary LDL-C elevation, or if LDL-C values were \geq 220 to 503 mg/dL and a parent had died of CAD with no available lipid values	Multinational	1990-1994	132
X	Wiegman, 2004 ¹²² Good	Children and adolescents aged 8-18 years	1 parent with definite clinical or molecular diagnosis of FH; 2 fasting samples with LDL-C levels \geq 155 mg/dL and TG levels $<$ 350 mg/dL after 3 months on fat-restricted diet	Netherlands	1997-2001	214

* Defining adolescent as age 10-19 years based on WHO, however some have argued for broader definition²⁰¹

† 97.2% of study population had FH and results were not stratified by FH/MF, so this study is categorized as FH

‡ Distribution of FH vs MFD NR; assuming primarily FH based on baseline LDL-C 221.5 mg/dL

Abbreviations: AHA = American Heart Association; CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; FH= familial hypercholesterolemia; heFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; RCTs = randomized controlled trials; TG = triglycerides; US = United States

Table 20. Familial Hypercholesterolemia: Statin Intervention Trials—Population Characteristics (Key Question 4)

Author, Year	Mean age, years (Age range)	% Female	Race/ ethnicity	% Smoking	% With Family History of CVD and Definition	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
Avis, 2010 ¹¹⁸ PLUTO	14 (10-17)	45	White: 93 Black: NR Asian: NR Native American: NR Latino: NR Other: NR	NR	89% family hx of premature CVD	298	233	47	81*
Braamskamp, 2015 ¹¹⁴ PASCAL	11 (6-17)	55	NR	NR	NR	303	234	52	76*
Clauss, 2005 ¹²³	15 (10-18)	100	White: 80 Black: NR Asian: NR Native American: NR Latino: NR Other: NR	NR	NR	282	211	48	105
Couture, 1998 ¹¹⁹	13 (8-17)	41	NR	NR	NR	287	223	45	98
de Jongh, 2002a ¹²⁰	14 (10-17)	43	NR	NR	NR	274	208	46	80†
de Jongh, 2002b ¹²¹	15 (9-18)	48	NR	0	NR	274	208	50	NR‡
Knipscheer, 1996 ¹¹⁵	12 (8-16)	35	White: 92 Black: 7 Asian: 1 Native American: 0 Latino: 0 Other: 0	NR	NR	301	247	46	62
McCrinkle, 2003 ¹¹⁷	14 (10-17)	31	White: 92 Black: 2 Asian: 2 Native American: NR Latino: NR Other: 5	NR	NR	288	222	46	104
Stein, 1999 ¹¹⁶	13 (10-17)	0	White: 93 Black: NR	3	Evidence of CAD: 37	316	250	44	111

Table 20. Familial Hypercholesterolemia: Statin Intervention Trials—Population Characteristics (Key Question 4)

Author, Year	Mean age, years (Age range)	% Female	Race/ ethnicity	% Smoking	% With Family History of CVD and Definition	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
			Asian: NR Native American: NR Latino: NR Other: NR		37% family history of evidence of CAD				
Wiegman, 2004 ¹²²	13 (8-18)	53	NR	11	34% family hx of premature CVD	301	238	48	67*

*Calculated as a mean of IG and CG medians (this calculation was only made if sample sizes were >100)

†Median

‡Median (IQR) in IG: 70 (44–161) mg/dL; CG: 95 (30–159) mg/dL. Cannot calculate overall mean due to sample size

Abbreviations: BL = baseline; CAD = coronary artery disease; CVD = cardiovascular disease; FH= familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; RCTs = randomized controlled trials; TC = total cholesterol; TG = triglycerides

Table 21. Familial Hypercholesterolemia: Statin Interventions—Intervention Characteristics (Key Question 4)

Author, Year Study Name	IG n	IG Brief Description	Intensity*	Run-in Background diet/PA	Duration and Longest FU, wks	Tx goals	CG n	CG Descr
McCrinkle, 2003 ¹¹⁷	140	Atorvastatin 10-20 mg/day	Moderate	4-wk NCEP step 1 diet run-in Step 1 diet	26	Dose titrated to 20 mg/day at week 4 in patients not achieving LDL-C ≤130 mg/dL.	47	Placebo
Stein, 1999 ¹¹⁶	67	Lovastatin 10-40 mg/day	Moderate	8 wk diet run-in with AHA pediatric diet (similar to NCEP Step 1) and 4 wk placebo run-in	48	NR	65	Placebo
Clauss, 2005 ¹²³	35	Lovastatin 20-40 mg/day	Moderate	4-wk diet and placebo run in Step I or similar diet	24	NR	19	Placebo
Braamskamp, 2015 ¹¹⁴ PASCAL	26	Pitavastatin 4 mg/d	Moderate	5 wk diet run-in NR	12	Minimal LDL-C goal 130 mg/dL; ideal goal 110 mg/dL	27	Placebo
	27	Pitavastatin 2 mg/d	Moderate	5 wk diet run-in NR	12	Minimal LDL-C goal 130 mg/dL; ideal goal 110 mg/dL	27	Placebo
	26	Pitavastatin 1 mg/d	Moderate	5 wk diet run-in NR	12	Minimal LDL-C goal 130 mg/dL; ideal goal 110 mg/dL	27	Placebo
Knipscheer, 1996 ¹¹⁵	18	Pravastatin 20 mg	Low	8 wk diet and placebo run-in. Run-in diet 50% carbohydrate energy, 20% protein 20%, 30% fat 30%, with unsaturated:saturated ratio of 2:1 and daily intake cholesterol <300 mg	12	LDL-C <95 th percentile for sex and age	18	Placebo

Table 21. Familial Hypercholesterolemia: Statin Interventions—Intervention Characteristics (Key Question 4)

Author, Year Study Name	IG n	IG Brief Description	Intensity*	Run-in Background diet/PA	Duration and Longest FU, wks	Tx goals	CG n	CG Descr
	18	Pravastatin 10 mg	Low	8 wk diet and placebo run-in. Run-in diet 50% carbohydrate energy, 20% protein 20%, 30% fat 30%, with unsaturated:saturated ratio of 2:1 and daily intake cholesterol <300 mg	12	LDL-C <95%tile for sex and age	18	Placebo
	18	Pravastatin 5 mg	<Low	8 wk diet and placebo run-in. Run-in diet 50% carbohydrate energy, 20% protein 20%, 30% fat 30%, with unsaturated:saturated ratio of 2:1 and daily intake cholesterol <300 mg	12	LDL-C <95%tile for sex and age	18	Placebo
Wiegman, 2004 ¹²²	106	Pravastatin 20-40 mg/day	Low to moderate depending on age	12 wk fat-restricted diet Fat-restricted diet and maintenance of habitual physical activity. Recommended intake of total fat 30% and 10% as saturated fat.	104	NR	108	Placebo.
Avis, 2010 ¹¹⁸ PLUTO	44	Rosuvastatin 20 mg/day	High	6-wk diet-only run-in NR	12	LDL-C <110 mg/dL	46	Placebo
	44	Rosuvastatin 10 mg/day	Moderate	6-wk diet-only run-in NR	12	LDL-C <110 mg/dL	46	Placebo
	42	Rosuvastatin 5 mg/day	Moderate	6-wk diet-only run-in	12	LDL-C <110 mg/dL	46	Placebo

Table 21. Familial Hypercholesterolemia: Statin Interventions—Intervention Characteristics (Key Question 4)

Author, Year Study Name	IG n	IG Brief Description	Intensity*	Run-in Background diet/PA	Duration and Longest FU, wks	Tx goals	CG n	CG Descr
				NR				
Couture, 1998 ¹¹⁹	NR	Simvastatin 20 mg/day	Moderate	4 wk placebo run-in. All lipid lowering medications discontinued 6 wk prior to run-in AHA Phase I diet with focus on unrestricted daily caloric intake depending on age and physical activity	6	NR	NR	Placebo
de Jongh, 2002a ¹²⁰	106	Simvastatin 10-40 mg/d	Moderate	4 wk diet and placebo run-in NR	48	NR	69	Placebo
de Jongh, 2002b ¹²¹	28	Simvastatin 10-40 mg/day	Moderate	NR	28	NR	22	Placebo

*Statin intensity was categorized based on 2018 guidelines for the management of cholesterol in adults.³¹ When the statin was titrated, intensity was categorized as the maximum dose of the titration. Intensity categorizations are not established for pediatric populations.

Abbreviations: AHA = American Heart Association; CG = control group; Descr = description; FH = familial hypercholesterolemia; FU = follow up; IG = intervention group; LDL-C = low-density lipoprotein cholesterol; mg/d = milligrams per day; mg/dL = milligrams per deciliter; NCEP = National Cholesterol Education Program; PA = physical activity; RCTs = randomized controlled trials; TX = treatment

Table 22. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Mean Difference in Change in Total Cholesterol (mg/dL) (Key Question 4)

Author, Year	Statin	Daily dose (mg)	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Avis, 2010 ¹¹⁸	Rosuvastatin	20	12	44	46	-119.00 (-132.20 to -105.80)	0.00 (-15.06 to 15.06)	-119.00 (-139.10 to -98.90), <0.001
		10	12	44	46	-102.00 (-115.80 to -88.20)	0.00 (-15.06 to 15.06)	-102.00 (-122.48 to -81.52), <0.001
		5	12	42	46	-93.00 (-108.86 to -77.14)	0.00 (-15.06 to 15.06)	-93.00 (-114.86 to -71.14), <0.001
Braamskamp, 2015 ¹¹⁴	Pitavastatin	4	12	24	27	-98.50 (-118.57 to -78.43)	-1.20 (-25.33 to 22.93)	-97.30 (-129.14 to -65.46), <0.0001
		2	12	26	27	-70.40 (-86.13 to -54.67)	-1.20 (-25.33 to 22.93)	-69.20 (-98.24 to -40.16), <0.0001
		1	12	26	27	-54.60 (-70.98 to -38.22)	-1.20 (-25.33 to 22.93)	-53.40 (-82.78 to -24.02), <0.0001
Clauss, 2005 ¹²³	Lovastatin	20-40	24	35	19	-65.60 (-81.61 to -49.59)	9.10 (-10.60 to 28.80)	-74.70 (-100.85 to -48.55), <0.001
Couture, 1998 ¹¹⁹	Simvastatin	20	6	47	16	-83.70 (-88.37 to -79.03)	-15.80 (-26.62 to -4.98)	-67.90 (-78.07 to -57.73), <0.0001
de Jongh, 2002b ¹²¹	Simvastatin	10-40	28	28	22	-83.40 (-98.27 to -68.52)	-1.93 (-20.81 to 16.95)	-81.47 (-105.16 to -57.78), 0.0001
McCrinkle, 2003 ¹¹⁷	Atorvastatin	10-20	26	140	47	-91.00 (-97.87 to -84.13)	-4.30 (-20.43 to 11.83)	-86.70 (-101.78 to -71.62), <0.001
Wiegman, 2004 ¹²²	Pravastatin	20-40	104	106	108	-56.00 (-64.26 to -47.74)	2.00 (-5.39 to 9.39)	-58.00 (-69.07 to -46.93), <0.001

Abbreviations: BL = baseline; CI = confidence interval; CG = control group; FU = follow up; IG = intervention group; MD = mean difference; mg = milligram; NR = not reported; wks = weeks

Table 23. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Mean Difference in Change in Low-Density Lipoprotein Cholesterol (mg/dL) (Key Question 4)

Author, Year	Statin	Daily dose (mg)	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Avis, 2010 ¹¹⁸	Rosuvastatin	20	12	44	46	-120.00 (-132.57 to -107.43)	-2.00 (-15.38 to 11.38)	-118.00 (-136.39 to -99.61), <0.001
		10	12	44	46	-101.00 (-113.62 to -88.38)	-2.00 (-15.38 to 11.38)	-99.00 (-117.43 to -80.57), <0.001
		5	12	42	46	-95.00 (-109.44 to -80.56)	-2.00 (-15.38 to 11.38)	-93.00 (-112.66 to -73.34), <0.001
Braamskamp, 2015 ¹¹⁴	Pitavastatin	4	12	24	27	-96.30 (-115.90 to -76.70)	-1.30 (-25.97 to 23.37)	-95.00 (-127.05 to -62.95), <0.0001
		2	12	26	27	-66.30 (-80.65 to -51.95)	-1.30 (-25.97 to 23.37)	-65.00 (-93.82 to -36.18), <0.0001
		1	12	26	27	-55.10 (-70.91 to -39.29)	-1.30 (-25.97 to 23.37)	-53.80 (-83.35 to -24.25), <0.0001
Clauss, 2005 ¹²³	Lovastatin	20-40	24	35	19	-62.00 (-77.70 to -46.30)	6.80 (-12.25 to 25.85)	-68.80 (-94.33 to -43.27), <0.001
Couture, 1998 ¹¹⁹	Simvastatin	20	6	47	16	-81.80 (-86.47 to -77.13)	-11.90 (-21.15 to -2.65)	-69.90 (-79.54 to -60.26), <0.0001
de Jongh, 2002b ¹²¹	Simvastatin	10-40	28	28	22	-82.24 (-96.40 to -68.08)	-1.93 (-19.03 to 15.17)	-80.31 (-102.33 to -58.29), 0.0001
Knipscheer, 1996 ¹¹⁵	Pravastatin	20	12	18	18	-95.70 (-124.03 to -67.37)	-11.60 (-35.89 to 12.69)	-84.10 (-121.42 to -46.78), <0.05
		10	12	18	18	-50.90 (-72.43 to -29.37)	-11.60 (-35.89 to 12.69)	-39.30 (-71.90 to -6.70), <0.05
		5	12	18	18	-49.40 (-65.30 to -33.50)	-11.60 (-35.89 to 12.69)	-37.80 (-66.83 to -8.77), <0.05
McCrintle, 2003 ¹¹⁷	Atorvastatin	10-20	26	140	47	-87.90 (-94.32 to -81.48)	-1.50 (-16.22 to 13.22)	-86.40 (-100.37 to -72.43), <0.001
Wiegman, 2004 ¹²²	Pravastatin	20-40	104	106	108	-57.00 (-64.69 to -49.31)	0.00 (-6.82 to 6.82)	-57.00 (-67.26 to -46.74), <0.001

Abbreviations: BL = baseline; CI = confidence interval; CG = control group; FU = follow up; IG = intervention group; MD = mean difference; mg = milligram; NR = not reported; wks = weeks

Table 24. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Mean Difference in Percent Change in Total Cholesterol (Key Question 4)

Author, Year	Statin	Daily dose (mg)	FU, wks	IG n	CG n	IG Mean % Change from BL (95% CI)	CG Mean % Change from BL (95% CI)	MD in % Change (95% CI), p-value
Avis, 2010 ¹¹⁸	Rosuvastatin	20	12	44	46	-39.0 (NR)	0.0 (NR)	-39.0 (NR), <0.001
		10	12	44	46	-34.0 (NR)	0.0 (NR)	-34.0 (NR), <0.001
		5	12	42	46	-30.0 (NR)	0.0 (NR)	-30.0 (NR), <0.001
Braamskamp, 2015 ¹¹⁴	Pitavastatin	4	12	24	27	-31.3 (NR)	0.9 (NR)	-32.2 (NR), <0.0001
		2	12	26	27	-24.2 (NR)	0.9 (NR)	-25.1 (NR), <0.0001
		1	12	26	27	-17.8 (NR)	0.9 (NR)	-18.7 (NR), <0.0001
Clauss, 2005 ¹²³	Lovastatin	20-40	24	35	19	-21.8 (-26.7 to -16.9)	4.5 (-1.2 to 10.2)	-26.3 (-34.2, -18.4)
de Jongh, 2002a ¹²⁰	Simvastatin	10-40	48	106	69	-30.90 (-33.37 to -28.43)	0.80 (-1.71 to 3.31)	-31.70 (-35.35 to -28.05), <0.001
Knipscheer, 1996 ¹¹⁵	Pravastatin	20	12	18	18	-24.60 (-28.10 to -21.00)	-2.30 (-6.70 to 2.40)	-22.30 (-28.07 to -16.53), <0.05
		10	12	17	18	-17.20 (-21.10 to -13.10)	-2.30 (-6.70 to 2.40)	-14.90 (-20.99 to -8.81), <0.05
		5	12	18	18	-18.20 (-21.90 to -14.20)	-2.30 (-6.70 to 2.40)	-15.90 (-21.86 to -9.94), <0.05
McCordle, 2003 ¹¹⁷	Atorvastatin	10-20	26	140	47	-32.3 (-37.6 to -27.0)	-2.0 (-8.1 to 4.1)	-30.3 (-40.1, -20.5)
Stein, 1999 ¹¹⁶	Lovastatin	10-40	48	67	65	-20.00 (-23.92 to -16.08)	-3.00 (-4.96 to -1.04)	-17.00 (-21.72 to -12.28), <0.001

Abbreviations: BL = baseline; CI = confidence interval; CG = control group; FU = follow up; IG = intervention group; MD = mean difference; mg = milligram; NR = not reported; wks = weeks

Table 25. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Mean Difference in Percent Change in Low-Density Lipoprotein Cholesterol (Key Question 4)

Author, Year	Statin	Daily dose (mg)	FU, wks	IG n	CG n	IG Mean % Change from BL (95% CI)	CG Mean % Change from BL (95% CI)	MD in % Change (95% CI), p-value
Avis, 2010 ¹¹⁸	Rosuvastatin	20	12	44	46	-50.0 (NR)	-1.0 (NR)	-51.0 (NR), <0.001
		10	12	44	46	-45.0 (NR)	-1.0 (NR)	-46.0 (NR), <0.001
		5	12	42	46	-38.0 (NR)	-1.0 (NR)	-39.0 (NR), <0.001
Braamskamp, 2015 ¹¹⁴	Pitavastatin	4	12	24	27	-39.3 (-43.6 to -35.0)	1.0 (-3.0 to 5.0)	-40.3 (-46.2, -34.4), <0.0001
		2	12	26	27	-30.1 (-34.2 to -26.0)	1.0 (-3.0 to 5.0)	-31.1 (-36.9, -25.3), <0.0001
		1	12	26	27	-23.5 (-27.6 to -19.4)	1.0 (-3.0 to 5.0)	-24.5 (-30.3, -18.7), <0.0001
Clauss, 2005 ¹²³	Lovastatin	20-40	24	35	19	-26.8 (-33.5 to -20.1)	5.2 (-2.4 to 12.8)	-32.0 (-42.7, -21.3)
de Jongh, 2002a ¹²⁰	Simvastatin	10-40	48	106	69	-40.70 (-49.13 to -32.27)	0.30 (-2.40 to 3.00)	-41.00 (-51.51 to -30.49), <0.001
Knipscheer, 1996 ¹¹⁵	Pravastatin	20	12	18	18	-32.9 (-37.0 to -28.6)	-3.2 (-9.0 to 3.0)	-29.7 (-37.0, -22.4), <0.05
		10	12	18	18	-23.8 (-28.5 to -18.8)	-3.2 (-9.0 to 3.0)	-20.6 (-28.4, -12.8), <0.05
		5	12	18	18	-23.3 (-27.9 to -18.4)	-3.2 (-9.0 to 3.0)	-20.1 (-27.8, -12.4), <0.05
McCordle, 2003 ¹¹⁷	Atorvastatin	10-20	26	140	47	-40.0 (-46.5 to -33.5)	-0.4 (-7.7 to 6.9)	-39.6 (-51.5, -27.7)
Stein, 1999 ¹¹⁶	Lovastatin	10-40	48	67	65	-25.00 (-28.92 to -21.08)	-4.00 (-7.92 to -0.08)	-21.00 (-26.61 to -15.39), <0.001

Abbreviations: BL = baseline; CI = confidence interval; CG = control group; FU = follow up; IG = intervention group; MD = mean difference; mg = milligram; NR = not reported; wks = weeks

Table 26. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Mean Difference in Change in High-Density Lipoprotein Cholesterol (mg/dL) (Key Question 4)

Author, Year	Statin	Daily dose (mg)	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Avis, 2010 ¹¹⁸	Rosuvastatin	20	12	44	46	3.00 (-0.84 to 6.84)	3.00 (-0.04 to 6.04)	0.00 (-4.88 to 4.88), 0.5
		10	12	44	46	5.00 (1.89 to 8.11)	3.00 (-0.04 to 6.04)	2.00 (-2.35 to 6.35), 0.2
		5	12	42	46	2.00 (-1.63 to 5.63)	3.00 (-0.04 to 6.04)	-1.00 (-5.71 to 3.71), 0.4
Braamskamp, 2015 ¹¹⁴	Pitavastatin	4	12	24	27	-2.20 (-6.25 to 1.85)	-0.40 (-4.80 to 4.00)	-1.80 (-7.83 to 4.23), 0.25
		2	12	26	27	-1.80 (-6.19 to 2.59)	-0.40 (-4.80 to 4.00)	-1.40 (-7.62 to 4.82), 0.32
		1	12	26	27	2.60 (-2.47 to 7.67)	-0.40 (-4.80 to 4.00)	3.00 (-3.70 to 9.70), 0.16
Clauss, 2005 ¹²³	Lovastatin	20-40	24	35	19	0.60 (-3.27 to 4.47)	1.90 (-1.97 to 5.77)	-1.30 (-7.28 to 4.68), NSD
de Jongh, 2002a ¹²⁰	Simvastatin	10-40	48	106	69	Mean % Chg: 3.30 (0.09 to 6.51)	Mean % Chg: -0.40 (-4.28 to 3.48)	MD in % Chg: 3.70 (-1.34 to 8.74), NSD
de Jongh, 2002b ¹²¹	Simvastatin	10-40	28	28	22	1.93 (-0.50 to 4.36)	-1.93 (-5.48 to 1.62)	3.86 (-0.31 to 8.03), 0.080
Knipscheer, 1996 ¹¹⁵	Pravastatin	20	12	18	18	Mean % Chg: 10.80 (3.40 to 18.80)	Mean % Chg: 4.30 (-2.70 to 11.80)	MD in % Chg: 6.50 (-4.08 to 17.08), NSD
		10	12	18	18	Mean % Chg: 5.50 (-1.70 to 13.20)	Mean % Chg: 4.30 (-2.70 to 11.80)	MD in % Chg: 1.20 (-9.20 to 11.60), NSD
		5	12	18	18	Mean % Chg: 3.80 (-3.10 to 11.20)	Mean % Chg: 4.30 (-2.70 to 11.80)	MD in % Chg: -0.50 (-10.68 to 9.68), NSD
McCrinkle, 2003 ¹¹⁷	Atorvastatin	10-20	26	140	47	0.90 (-0.77 to 2.57)	-1.30 (-4.24 to 1.64)	2.20 (-1.15 to 5.55), NR*
McCrinkle, 2003 ¹¹⁷	Lovastatin	10-40	48	67	65	Mean % Chg: 1.00 (-2.92 to 4.92)	Mean % Chg: -1.00 (-4.92 to 2.92)	MD in % Chg: 2.00 (-3.61 to 7.61), NSD
Stein, 1999 ¹¹⁶	Pravastatin	20-40	104	106	108	3.00 (1.08 to 4.92)	1.00 (-0.71 to 2.71)	2.00 (-0.57 to 4.57), 0.09

* The imputed MD in change from BL (95% CI) are unadjusted compared to the study's adjusted p-value of 0.02.

Abbreviations: BL = baseline; CG = control group; Chg = change; CI = confidence interval; FU = follow up; IG = intervention group; MD = mean difference; mg = milligram; NSD = no significant difference; NR = not reported; wks = weeks

Table 27. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Mean Difference in Percent Change in Triglyceride Levels (Key Question 4)

Author, Year	Statin	Daily dose (mg)	FU, wks	IG n	CG n	IG Mean % Change from BL (95% CI)	CG Mean % Change from BL (95% CI)	MD in % Change (95% CI), p-value
Avis, 2010 ¹¹⁸	Rosuvastatin	20	12	44	46	-16.00 (NR)	-7.00 (NR)	NR, 0.1
		10	12	44	46	-15.00 (NR)	-7.00 (NR)	NR, 0.1
		5	12	42	46	-13.00 (NR)	-7.00 (NR)	NR, 0.8
Braamskamp, 2015 ¹¹⁴	Pitavastatin	4	12	24	27	0.30 (NR)	2.00 (NR)	NR, 0.85
		2	12	26	27	-5.90 (NR)	2.00 (NR)	NR, 0.38
		1	12	26	27	-7.60 (NR)	2.00 (NR)	NR, 0.28
Clauss, 2005 ¹²³	Lovastatin	20-40	24	35	19	-22.70 (-36.03 to -9.37)	-3.00 (-21.82 to 15.82)	-19.70 (-42.49 to 3.09), 0.067
de Jongh, 2002a ¹²⁰	Simvastatin	10-40	48	106	69	Med % Chg (Range): -8.7 (-73.1 to -204.1)	Med % Chg (Range): -4.3 (-49.2 to -141.30)	NR, <0.05
de Jongh, 2002b ¹²¹	Simvastatin	10-40	28	28	22	Mean Chg (95% CI): -16.82 (-28.94 to -4.69)	Mean Chg (95% CI): -8.85 (-28.82 to 11.12)	MD in Chg (95% CI): -7.97 (-30.32 to 14.39), NR*
Knipscheer, 1996 ¹¹⁵	Pravastatin	20	12	18	18	3.30 (-14.30 to 24.50)	-11.70 (-26.60 to 6.10)	15.00 (-10.37 to 40.37), NSD
		10	12	17	18	6.60 (-12.00 to 29.00)	-11.70 (-26.60 to 6.10)	18.30 (-7.77 to 44.37), NSD
		5	12	18	18	1.70 (-15.40 to 22.20)	-11.70 (-26.60 to 6.10)	13.40 (-11.51 to 38.31), NSD
McCordle, 2003 ¹¹⁷	Atorvastatin	10-20	26	140	47	-20.00 (-28.67 to -11.33)	-7.60 (-23.40 to 8.20)	-12.40 (-29.94 to 5.14), NR†
Stein, 1999 ¹¹⁶	Lovastatin	10-40	48	67	65	6.00 (-5.76 to 17.76)	8.00 (-5.72 to 21.72)	-2.00 (-19.98 to 15.98), NSD
Wiegman, 2004 ¹²²	Pravastatin	20-40	104	106	108	Med Chg (IQR): -12 (-35 to 16)	Med Chg (IQR): 1 (-20 to 22)	NR, 0.21

* Study reported statistical significance between treatments (IG vs CG, p=0.041) based on absolute values and log-transformation of TG, not accounting for MD in change from BL

†The imputed MD in change from BL (95% CI) are unadjusted compared to the study's adjusted p-value of 0.03.

Abbreviations: BL = baseline; CG = control group; Chg = change; CI = confidence interval; FU = follow up; IG = intervention group; IQR = interquartile range; Med = median; MD = mean difference; Med = median; mg = milligram; NR = not reported; NSD = no significant difference; wks = weeks

Table 28. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Proportion Achieving Low-Density Lipoprotein Cholesterol Goal (Absolute Risk Difference, %) (Key Question 4)

Author, year	Statin	LDL-C Goal (mg/dL)	Daily Dose, mg	Statin intensity	IG N	IG n/N (%)	CG N	CG n/N (%)	% ARD (95% CI)
Avis, 2010 ¹¹⁸	Rosuvastatin	<110	20	H	44	18/44 (40.9)	46	0/46 (0.0)	40.91 (26.38 to 55.44)
			10	M	44	18/44 (40.9)	46	0/46 (0.0)	40.91 (26.38 to 55.44)
			5	M	42	5/42 (11.9)	46	0/46 (0.0)	11.90 (2.11 to 21.70)
Braamskamp, 2015 ¹¹⁴	Pitavastatin	≤110	4	M	24	4/24 (16.7)	27	0/27 (0.0)	16.67 (1.76 to 31.58)
		≤130	4	M	24	9/24 (37.5)	27	0/27 (0.0)	37.50 (18.13 to 56.87)
		≤110	2	M	26	2/26 (7.7)	27	0/27 (0.0)	7.69 (-2.55 to 17.93)
		≤130	2	M	26	8/26 (30.8)	27	0/27 (0.0)	30.77 (13.03 to 48.51)
		≤110	1	L	26	0/26 (0.0)	27	0/27 (0.0)	0.00 (0.00 to 0.00)
		≤130	1	L	26	1/26 (3.8)	27	0/27 (0.0)	3.85 (-3.55 to 11.24)
Knipscheer, 1996 ¹¹⁵	Pravastatin	<95 th percentile for sex and age	20	L	18	2/18 (11.1)	18	0/18 (0.0)	11.11 (-3.41 to 25.63)
			10	L	18	1/18 (5.6)	18	0/18 (0.0)	5.56 (-5.03 to 16.14)
			5	L	18	1/18 (5.6)	18	0/18 (0.0)	5.56 (-5.03 to 16.14)
McCrinkle, 2003 ¹¹⁷	Atorvastatin	<130	10-20	L-M	140	84/140 (60.0)	47	0/47 (0.0)	60.00 (51.88 to 68.12)

Abbreviations: ARD = absolute risk difference; CG = control group; CI = confidence interval; H = high intensity; IG = intervention group; L = low intensity; LDL-C = low-density lipoprotein cholesterol; M = moderate intensity; mg/dL = milligrams per deciliter

Table 29. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Study Characteristics, by Intervention (Key Question 4-5)

Intervention	Author, Year Quality	Brief Population Description*	FH Criteria	Country	Years of data collection	N
Bile acid sequestrant	Tonstad, 1996 ¹²⁵ Fair	Children aged 6 to 11 years with FH in Tanner's stage 1	TC >260 mg/dl and TG <200 mg/dl, if one parent had baseline TC ≥300 and TG <200, or tendon xanthoma, and if autosomally dominant inheritance of hypercholesterolemia was present in other members of the pedigree	Norway	NR	72
	Tonstad, 1996b ¹²⁶ Fair	Adolescents aged 10 to 16 years with FH	TC ≥300 mg/dL and tendon xanthoma in one or both parents and in relatives in a manner compatible with autosomal dominant inheritance, or on the detection of an LDL-C receptor mutation.	Norway	NR	66
	Stein, 2010 ¹²⁴ Good	Children and adolescents aged 10-17 years with FH	LDL-C >160 mg/dl or >130 mg/dl on stable NCEP diet and stable statin therapy	Multinational Conducted across 41 sites in Australia, Austria, Canada, the Czech Republic, Hungary, Israel, the Netherlands, New Zealand, Norway, Slovakia, South Africa, and the United States.	2005-2007	194
Ezetimibe	Kusters, 2015 ¹²⁷ Good	Children and adolescents aged 6-10 years with heterozygous FH or clinically important nonFH (LDL-C >160 mg/dL while on a lipid-lowering diet for ≥3 months) 91% FH; 9% MFD	Clinical criteria for heterozygous FH included LDL-C levels >189 to <400 mg/dL with a family history of hypercholesterolemia consistent with dominant autosomal transmission, or LDL-C >159 to <400 mg/dL and at least 1 of the following: (1) genotype confirmed heterozygous FH; (2) at least 1 biological parent with genotype-confirmed heterozygous FH and a historic untreated LDL-C of >159 mg/dL; (3) ≥1 biological parent with untreated LDL-C value ≥210 mg/dL not associated with a disorder known to elevate LDL-C; or (4) tendinous xanthomas not associated with a disorder known to elevate LDL-C. Clinical criteria for primary nonFH was an LDL-C >159 to <400 mg/dL and a clinical diagnosis of primary nonFH	Multinational Conducted across 29 sites in Canada, Colombia, France, Greece, Israel, Italy, Norway, The Netherlands, US	2009-2012	138
Fibrate	Wheeler, 1985 ¹²⁸	Children and adolescents aged	TC >269 mg/dL, heterozygous FH type IIa pattern on lipoprotein electrophoresis, and normal fasting TG (<	UK	NR	14

Table 29. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Study Characteristics, by Intervention (Key Question 4-5)

Intervention	Author, Year Quality	Brief Population Description*	FH Criteria	Country	Years of data collection	N
	Fair	4-15 years with FH	1.5 mmol/L), with either similar lipoprotein abnormalities in one of the parents, or where a parent had died of premature CHD, a similar lipid abnormality in another close relative			
PCSK9 inhibitor	Santos, 2020 ¹²⁹ Good	Patients 10-17 years with heterozygous FH who had received ≥4 wks of stable lipid-lowering therapy	Heterozygous FH diagnosed by genetic testing or applicable clinical diagnostic criteria (Simon Broome Register Group, the Dutch Lipid Clinic Network, or MEDPED)	Multinational Conducted across 47 sites in North America, Latin America, Europe, and the Asia-Pacific region	2016-2019	158
Combination drug therapy	van der Graaf, 2008 ¹³⁰ Fair	Male and postmenarchal female adolescents 10-17 years and Tanner stage ≥2	At least 1 of the following clinical criteria: Genotype-confirmed FH and LDL-C >159 mg/dl and <400 mg/dl; LDL-C >159 mg/dl and <400 mg/dl and at least 1 biological parent with genotype-confirmed FH and historical untreated LDL-C >159 mg/dl; LDL-C >159 mg/dl and <400 mg/dl and at least 1 biological parent with untreated LDL-C of at least 210 mg/dl in the absence of another condition associated with secondary elevated LDL-C; LDL-C >189 mg/dl and <400 mg/dl and a family history of hypercholesterolemia consistent with dominant autosomal transmission; LDL-C >159 mg/dl and <400 mg/dl and tendinous xanthomas, without another condition associated with secondary elevated LDL-C	Multinational	NR	248

*Defining adolescent as age 10-19 years based on WHO, however some have argued for broader definition²⁰¹

Abbreviations: CHD = coronary heart disease; FH= familial hypercholesterolemia; FH type IIa = familial hypercholesterolemia type IIa; FN = false negative; LDL-C = low-density lipoprotein-cholesterol; MEDPED = Make Early Diagnosis to Prevent Early Death Program; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NCEP = National Cholesterol Education Program; NR = not reported; PCSK9 = proprotein convertase subtilisin/kexin type 9; RCTs = randomized controlled trials; TC = total cholesterol; TG = triglycerides; UK = United Kingdom; US = Unites States

Table 30. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Population Characteristics, by Intervention (Key Question 4-5)

Intervention	Author, Year	Mean age, years (Age range)	% Female	Race & Ethnicity	% Smoking	% With Family Hx of CVD and Definition	Other BL Char	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
Bile acid sequestrant	Tonstad, 1996 ¹²⁵	8 (6-11)	39	NR	NR	NR	100% Tanner Stage 1	320	NR	46	76
	Tonstad, 1996b ¹²⁶	13 (10-16)	44	NR	NR	NR	Mean Tanner Stage: 2.6	306	245	43	87
	Stein, 2010 ¹²⁴	14 (10-17)	37	White: 87 Black: 3 Asian: 4 Native American: NR Latino: NR Other: 6	NR	NR	BMI, kg/m ² : 22.5 Statin therapy: 47%	265	199	47	Median: 95
Ezetimibe	Kusters, 2015 ¹²⁷	8 (6-11)	57	White: 80 Black: 1 Asian: 3 Native American: NR Latino: NR Multiracial: 15	NR	NR	NR	293	227	50	85
Fibrate	Wheeler, 1985 ¹²⁸	11 (4-15)	57	NR	NR	NR	NR	359	NR	39	89
PCSK9 inhibitor	Santos, 2020 ¹²⁹	14 (10-17)	56	White: 85 Black: NR Asian: NR Native American: NR Latino: NR Other: NR	NR	1 st degree family history of premature atherosclerotic CVD: 33	Overweight: ≥85 th percentile to <95 th percentile: 18% Obese: ≥95 th percentile: 16% Genetic diagnosis of FH: 66% Two or more risk	250	184	47	84*

Table 30. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Population Characteristics, by Intervention (Key Question 4-5)

Intervention	Author, Year	Mean age, years (Age range)	% Female	Race & Ethnicity	% Smoking	% With Family Hx of CVD and Definition	Other BL Char	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
							factors for atherosclerotic CVD: 11% Using high-intensity or moderate-intensity statins: 79% Taking ezetimibe (in addition to statins): 13%				
Combination drug therapy	van der Graaf, 2008 ¹³⁰	14 (10-17)	43	White: 82 Black: 2 Asian: 4 Native American: NR Latino: NR Other: 13	Cigarette smoking in previous month: 5	CHD in male first-degree relative <55 years old or CHD in female first-degree relative <65 years old: 39	NR	NR	222	NR	NR

*Calculated as a mean of IG and CG medians (this calculation was only made if sample sizes were >100)

†Median

‡Median (IQR) in IG: 70 (44–161) mg/dL; CG: 95 (30–159) mg/dL. Cannot calculate overall mean due to sample size

Abbreviations: BL = baseline; CHD = coronary heart disease; CVD = cardiovascular disease; FH= familial hypercholesterolemia; FN = false negative; HDL-C = high-density lipoprotein cholesterol; Hx = history; LDL-C = low-density lipoprotein-cholesterol; MEDPED = Make Early Diagnosis to Prevent Early Death Program; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NR = not reported; PCSK9 = proprotein convertase subtilisin/kexin type 9; RCTs = randomized controlled trials; TC = total cholesterol; TG = triglycerides

Table 31. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Intervention Characteristics, by Intervention (Key Question 4-5)

Intervention	Author, Year	IG	IG n	IG Brief Desc	Run-in Background diet/PA	Duration and Longest FU, wks	Tx goals	CG n	CG Descr
Bile acid sequestrant	Tonstad, 1996 ¹²⁵	IG1	36	Cholestyramine 8 mg/day	1-week buildup phase of 4 mg/day; 1 yr of a low-fat and low-cholesterol diet NCEP diet; dietitian reinforcing diet at each visit during randomized phase	52	NR	36	Placebo
	Tonstad, 1996b ¹²⁶	IG1	33	Colestipol 10 g QD or 5 g BID	6-week stabilization phase after discontinuation of any bile acid binding resins and dietary instructions. Diet containing ≤30% of energy from fat, <10% of energy from saturated fat, and <200 mg cholesterol/d	8	NR	33	Placebo
	Stein, 2010 ¹²⁴	IG1	64	Colesevelam 3.75 g/d	Step 1 diet during run-in period. NR	8	LDL-C <110 mg/dl	65	Placebo
		IG2	65	Colesevelam 1.875 g/d	Same as above	Same as above	LDL-C <110 mg/dl	65	Placebo
Ezetimibe	Kusters, 2015 ¹²⁷	IG1	93	Ezetimibe 10 mg/day	5 wk placebo run-in with Step 2 diet stabilization NR	12	NR	45	Placebo
Fibrate	Wheeler, 1985 ¹²⁸	IG1	14	Bezafibrate 10-20 mg/kg/day BID	NR	13	NR	14	Placebo
PCSK9 inhibitor	Santos, 2020 ¹²⁹	IG1	104	Evolocumab (420 mg) by monthly subcutaneous injections	4 wks stable lipid-lowering therapy Per inclusion criteria, all subjects on low-fat diet (not otherwise specified).	24	NR	53	Monthly subcutaneous injections of placebo using prefilled Al-Pen.
Combination drug therapy	van der Graaf, 2008 ¹³⁰	IG1	126	Simvastatin 10 – 40 mg/d simvastatin and ezetimibe 10-	NR	33	Acceptable LDL-C goal of <130	122	Simvastatin 10-, 20-, or 40-mg/d simvastatin

Table 31. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Intervention Characteristics, by Intervention (Key Question 4-5)

Intervention	Author, Year	IG	IG n	IG Brief Desc	Run-in Background diet/PA	Duration and Longest FU, wks	Tx goals	CG n	CG Descr
				mg/d			mg/dL; ideal goal of <110 mg/dL		and placebo for 6 weeks, followed by 27 weeks of simvastatin 40-mg/d and placebo.

Abbreviations: AI = auto-injector; BID = two times per day (Latin); CG = control group; Descr = Description; FH = familial hypercholesterolemia; FU = follow up; IG = intervention group; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; NCEP = National Cholesterol Education Program; NR = not reported; PA = physical activity; PCSK9 = proprotein convertase subtilisin/kexin type 9; QD = every day (Latin); RCTs = randomized controlled trials; TX = treatment; wks = weeks

Table 32. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Results for Mean Difference in Change in Total Cholesterol (mg/dL), by Intervention (Key Question 4)

Intervention type	Author, Year	Drug name	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Bile acid sequestrant	Stein, 2010 ¹²⁴	Colesevelam	3.75 g	8	63	65	-17.90 (-29.92 to -5.88)	4.20 (-6.30 to 14.70)	-22.10 (-38.03 to -6.17), 0.001*
			1.875 g	8	63	65	-6.40 (-16.77 to 3.97)	4.20 (-6.30 to 14.70)	-10.60 (-25.37 to 4.17), NSD*
	Tonstad, 1996 ¹²⁵	Cholestyramine	8 mg	52	36	36	Mean % Chg: -11.50 (-16.85 to -6.15)	Mean % Chg: 3.00 (-1.88 to 7.88)	MD in % Chg: -14.50 (-21.74 to -7.26), <0.001
	Tonstad, 1996b ¹²⁶	Colestipol	10 g	8	29	30	-45.20 (-65.80 to -24.60)	-4.60 (-22.57 to 13.37)	-40.60 (-67.88 to -13.32), ≤0.01
Ezetimibe	Kusters, 2015 ¹²⁷	Ezetimibe	10 mg	12	85	42	-59.00 (-68.40 to -49.60)	5.00 (-10.25 to 20.25)	-64.00 (-81.12 to -46.88), <0.001
Fibrate	Wheeler, 1985 ¹²⁸	Bezafibrate	10-20 mg	13	14	14	-57.90 (-84.65 to -31.15)	27.00 (-4.40 to 58.40)	-84.90 (-126.15 to -43.65), <0.0001
Combination drug therapy	van der Graaf, 2008 ¹³⁰	Simvastatin +ezetimibe	10-40 mg	33	126	120	-125.41 (-133.07 to -117.75)	-85.27 (-93.08 to -77.46)	-40.14 (-51.08 to -29.20), <0.01

* P-value is based on study's reported ANCOVA of least square mean % change with LOCF to handle missing data. The imputed MD in change (95% CI) as shown was not adjusted.

Abbreviations: ANCOVA = analysis of covariance; BL = baseline; CG = control group; Chg = change; CI = confidence interval; FU = follow up; IG = intervention group; LOCF = last observation carried forward; MD = mean difference; NSD = no significant difference; wks = weeks

Table 33. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Results for Mean Difference in Change in Low-Density Lipoprotein Cholesterol (mg/dL), by Intervention (Key Question 4)

Intervention	Author, Year	Drug name	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Bile acid sequestrant	Stein, 2010 ¹²⁴	Coesevelam	3.75 g	8	63	65	-24.10 (-35.94 to -12.26)	2.00 (-7.80 to 11.80)	-26.10 (-41.43 to -10.77), <0.001*
			1.875 g	8	63	65	-11.20 (-21.30 to -1.10)	2.00 (-7.80 to 11.80)	-13.20 (-27.27 to 0.87), <0.05*
	Tonstad, 1996 ¹²⁵	Cholestyramine	8 mg	52	22	26	Mean % Chg: -16.90 (-22.90 to -10.80)	Mean % Chg: 1.40 (-4.40 to 7.20)	MD in % Chg: -18.30 (-26.71 to -9.89), 0.0001
	Tonstad, 1996b ¹²⁶	Colestipol	10 g	8	29	30	-50.60 (-68.87 to -32.33)	-4.70 (-22.06 to 12.66)	-45.90 (-71.09 to -20.71), ≤0.01
Ezetimibe	Kusters, 2015 ¹²⁷	Ezetimibe	10 mg	12	85	42	-60.00 (-68.98 to -51.02)	3.00 (-11.97 to 17.97)	-63.00 (-79.54 to -46.46), <0.001
PCSK9 inhibitor	Santos, 2020 ¹²⁹	Evolocumab	420 mg (monthly injections)	24	104	53	-77.50 (-86.10 to -68.90)	-9.00 (-21.10 to 3.20)	-68.60 (-83.10 to -54.00), <0.001
Combination drug therapy	van der Graaf, 2008 ¹³⁰	Simvastatin +ezetimibe	10-40 mg	33	126	120	-122.16 (-129.53 to -114.79)	-84.67 (-92.17 to -77.17)	-37.49 (-48.01 to -26.97), <0.01

* P-value is based on study's reported ANCOVA of LSM % change with LOCF to handle missing data. The imputed MD in change (95% CI) as shown was not adjusted.

Abbreviations: BL = baseline; CG = control group; Chg = change; CI = confidence interval; FU = follow up; IG = intervention group; MD = mean difference; NSD = no significant difference; PCSK9 = proprotein convertase subtilisin/kexin type 9; wks = weeks

Table 34. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Results for Mean Difference in Change in High-Density Lipoprotein Cholesterol (mg/dL), by Intervention (Key Question 4)

Intervention	Author, Year	Drug	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Bile acid sequestrant	Stein, 2010 ¹²⁴	Colesevelam	3.75 g	8	63	65	3.60 (1.02 to 6.18)	0.70 (-1.52 to 2.92)	2.90 (-0.49 to 6.29), 0.008*
			1.875 g	8	63	65	1.80 (-1.36 to 4.96)	0.70 (-1.52 to 2.92)	1.10 (-2.75 to 4.95), NSD*
	Tonstad, 1996 ¹²⁵	Cholestyramine	8 mg	52	36	36	Mean % Chg: 13.40 (5.25 to 21.55)	Mean % Chg: 8.80 (0.15 to 17.45)	MD in % Chg: 4.60 (-7.43 to 16.63), NSD
	Tonstad, 1996b ¹²⁶	Colestipol	10 g	8	29	30	2.70 (-1.69 to 7.09)	2.40 (-0.59 to 5.39)	0.30 (-4.98 to 5.58),
Ezetimibe	Kusters, 2015 ¹²⁷	Ezetimibe	10 mg	12	85	42	1.00 (-1.16 to 3.16)	1.00 (-2.63 to 4.63)	0.00 (-3.99 to 3.99), 0.807
Fibrate	Wheeler, 1985 ¹²⁸	Bezafibrate	10-20 mg	13	14	14	10.00 (3.68 to 16.32)	3.40 (-1.65 to 8.45)	6.60 (-1.49 to 14.69), NR†
Combination drug therapy	van der Graaf, 2008 ¹³⁰	Simvastatin +ezetimibe	10-40 mg	33	126	120	1.39 (-0.26 to 3.04)	1.51 (-0.17 to 3.19)	-0.12 (-2.47 to 2.23), 0.58

* P-value is based on study's reported ANCOVA of LSM % change with LOCF to handle missing data. The imputed MD in change (95% CI) as shown was not adjusted.

†Study reported statistical significance between treatment and placebo periods (p<0.001) based on absolute values and not for MD in change from BL. The overall HDL-C was not significant during placebo period than in the period before the trial.

Abbreviations: BL = baseline; CG = control group; Chg = change; CI = confidence interval; FU = follow up; IG = intervention group; MD = mean difference; NR = not reported; NSD = no significant difference; wks = weeks

Table 35. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Results for Mean Difference in Change in Triglyceride Levels (mg/dL), by Intervention (Key Question 4)

Intervention	Author, Year	Drug name	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Bile acid sequestrant	Stein, 2010 ¹²⁴	Colesevelam	3.75 g	8	63	65	Mean % Chg: 17.40 (NR)	Mean % Chg: 12.30 (NR)	MD in % Chg: 5.10 (NR), 0.466
			1.875 g	8	63	65	18.50 (NR)	12.30 (NR)	6.40 (NR), NSD
	Tonstad, 1996 ¹²⁵	Cholestyramine	8 mg	52	36	36	NR	NR	NR, NSD*
	Tonstad, 1996b ¹²⁶	Colestipol	10 g	8	29	30	14.20 (-11.42 to 39.82)	-10.70 (-28.82 to 7.42)	24.90 (-6.31 to 56.11),
Ezetimibe	Kusters, 2015 ¹²⁷	Ezetimibe	10 mg	12	85	42	-2.00 (-9.67 to 5.67)	8.00 (-10.92 to 26.92)	-10.00 (-27.17 to 7.17), NSD†
Fibrate	Wheeler, 1985 ¹²⁸	Bezafibrate	10-20 mg	13	14	14	-29.20 (-44.44 to -13.96)	-11.50 (-26.10 to 3.10)	-17.70 (-38.80 to 3.40), NSD
Combination drug therapy	van der Graaf, 2008 ¹³⁰	Simvastatin +ezetimibe	10-40 mg	33	126	120	Med % Chg (SD): -20.0 (23.8)	Med % Chg (SD): -13.0 (39.0)	Med diff in Chg: -9.50 (NR), <0.01‡

* Mean triglyceride levels remained unchanged in both groups (mean, 80 to 89 mg/dL; SD, 35 to 53 mg/dl)

† Geometric mean % change based on log-transformed data using a constrained longitudinal data analysis model was statistically significant (p=0.021), but the p-value was NS based on prespecified multiplicity adjustment.

‡ SD of median was derived by IQR/1.075

Abbreviations: BL = baseline; CG = control group; Chg = change; CI = confidence interval; FU = follow up; g = gram; IG = intervention group; MD = mean difference; Med = median; mg = milligram; NR = not reported; NSD = no significant difference; SD = standard deviation

Table 36. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Results for Mean Difference in Change in Non-High-Density Lipoprotein Cholesterol (mg/dL), by Intervention (Key Question 4)

Intervention	Author, Year	Statin	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Bile acid sequestrant	Stein, 2010 ¹²⁴	Colesevelam	3.75 g	8	63	65	-21.40 (-33.72 to -9.08)	3.50 (-7.03 to 14.03)	-24.90 (-41.07 to -8.73), 0.0001*
			1.875 g	8	63	65	-7.70 (-17.88 to 2.48)	3.50 (-7.03 to 14.03)	-11.20 (-25.86 to 3.46), NSD*
Ezetimibe	Kusters, 2015 ¹²⁷	Ezetimibe	10 mg	12	85	42	-60.00 (-69.19 to -50.81)	5.00 (-11.05 to 21.05)	-65.00 (-82.25 to -47.75), <0.001
PCSK9 inhibitor	Wheeler, 1985 ¹²⁸	Evolocumab	420 mg (monthly injections)	24	104	53	Mean % Chg: -41.20 (-45.20 to -37.20)	Mean % Chg: -6.10 (-11.80 to 0.50)	MD in % Chg: -35.10 (-42.00 to -28.20), <0.001
Combination drug therapy	van der Graaf, 2008 ¹³⁰	Simvastatin +ezetimibe	10-40 mg	33	126	120	-126.78 (-134.52 to -119.04)	-86.84 (-94.76 to -78.92)	-39.94 (-51.01 to -28.87), <0.01

*P-value is based on study's reported ANCOVA of LSM % change with LOCF to handle missing data. The imputed MD in change (95% CI) as shown was not adjusted.

Abbreviations: BL = baseline; CG = control group; Chg = change; CI = confidence interval; FU = follow up; g = gram; IG = intervention group; MD = mean difference; Med = median; mg = milligram; NR = not reported; NSD = no significant difference; PCSK9 = proprotein convertase subtilisin/kexin type 9

Table 37. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Results for Proportion Achieving Low-Density Lipoprotein Cholesterol Goal (Absolute Risk Difference, %), by Intervention (Key Question 4)

Drug category	Author, year	Drug	Daily Dose	LDL-C Goal (mg/dL)	IG	IG N	CG N	IG n/N (%)	CG n/N (%)	% ARD (95% CI)
Bile acid sequestrant	Stein, 2010 ¹²⁴	Colesevelam	3.75 g	<110	8	63	65	5/63 (7.9)	0/65 (0.0)	7.94 (1.26 to 14.61)
		Colesevelam	1.875 g	<110	8	63	65	2/63 (3.2)	0/65 (0.0)	3.17 (-1.15 to 7.50)
PCSK9 inhibitor	Santos, 2020 ¹²⁹	Evolocumab	420 mg (monthly injections)	<130	24	96	44	71/96 (74.0)	10/44 (22.7)	51.23 (36.05 to 66.41)
				>50% reduction	24	96	44	43/96 (44.8)	1/44 (2.3)	42.52 (31.64 to 53.40)
				<100	24	96	44	60/96 (62.5)	1/44 (2.3)	60.23 (49.59 to 70.87)
Combination drug therapy	van der Graaf, 2008 ¹³⁰	Simvastatin and ezetimibe	10-40 mg	<110	33	126	120	79/126 (62.7)	32/120 (26.7)	36.03 (24.46 to 47.60)
				<130	33	126	120	97/126 (77.0)	64/120 (53.3)	23.65 (12.09 to 35.21)

Abbreviations: AAP = American Academy of Pediatrics; ARD = absolute risk difference; CG = control group; CI = confidence interval; g = gram; IG = intervention group; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; PCSK9 = proprotein convertase subtilisin/kexin type 9

Table 38. Familial Hypercholesterolemia: Behavioral Intervention Trials—Study Characteristics (Key Question 4)

Author, Year	Brief Population Desc	Condition criteria	Country	Yrs of data collection	N Rand
Kinnear, 2020 ¹³¹	Children and adolescents aged 10-18 years with FH	Genetic diagnosis of FH	US	2018-2019	21

Abbreviations: Desc = description; FH= familial hypercholesterolemia; Rand = randomized; US = United states; Yrs = years

Table 39. Familial Hypercholesterolemia: Behavioral Intervention Trials—Population Characteristics (Key Question 4)

Author, Year	Age, mean (range)	Female, %	Race/ethnicity, %	BMI	Smoking, %	Other BL Char	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
Kinnear, 2020 ¹³¹	14 (10-18)	50	White: 82 Black: 0 Asian: 18 Native American: 0 Latino: 0 Other: 0	Overweight: ≥91 st percentile: 18 Obese: ≥98 th percentile: 9	0	On lifestyle treatment only, n (%): 5 (23) On statin medication, n (%): 17 (77)	193	127	50	NR

Abbreviations: BL = baseline; BMI = body mass index; CVD = cardiovascular disease; FH= familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; NR = not reported; SES = socioeconomic status; TC = total cholesterol; TG = triglycerides

Table 40. Familial Hypercholesterolemia: Behavioral Intervention Trials—Intervention Characteristics (Key Question 4)

Author, Year	IG n	IG Brief Description	Behavioral intv approach	Intv setting Provider	CG Category	CG n	CG Description
Kinnear, 2020 ¹³¹	10	1 in-person 60-min individual session with dietitian and 4 email or telephone follow-up sessions over 12-weeks	Behavioral change techniques	Lipid clinic, home Dietitian	Waitlist	12	Waitlist to receive the intervention at the end of the 12-week study period and received usual care, which comprised an annual outpatient lipid clinic appointment.

Abbreviations: CG = control group; FH= familial hypercholesterolemia; IG = intervention group; Intv = intervention; min = minute

Table 41. Familial Hypercholesterolemia: Behavioral Intervention Trials—Results for Mean Difference in Change in Serum Lipid Levels (mg/dL) (Key Question 4)

Author, Year	Serum Lipid Outcome	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Kinnear, 2020 ¹³¹	TC	12	8	10	-7.70 (-56.09 to 40.69)	3.90 (-17.51 to 25.31)	-11.58 (-34.75 to 15.44),
	LDL-C	12	8	10	-11.50 (-48.59 to 25.59)	3.80 (-16.40 to 24.00)	-13.90 (-31.66 to 4.63),
	HDL-C	12	8	10	0.00 (-8.04 to 8.04)	3.90 (-3.18 to 10.98)	0.39 (-3.86 to 7.72),

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; FH= familial hypercholesterolemia; FU = follow up; HDL-C = high-density lipoprotein cholesterol; IG = intervention group; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol

Table 42: Familial Hypercholesterolemia: Supplement Intervention Trials—Study Characteristics (Key Questions 4-5)

Author, Year Quality	Study design	Condition criteria	Brief Population Desc	Country	N Rand
de Jongh, 2003 ¹³² Fair	Randomized crossover	Plasma LDL-C >95 th percentile for age and gender; documented family history of hyperlipidemia with LDL-C >95 th percentile for age and gender before treatment or a personal diagnosis of FH by detection of a mutation in the LDL-C receptor gene	Prepubertal heterozygous FH children between 5 and 12 years of age	Netherlands	41
Gylling, 1995 ¹³³ Fair	Randomized crossover	Primarily by DNA technique; no other details reported	Children and adolescents 2-15 years with heterozygous FH	Finland	14
Amundsen, 2002 ¹³⁴ Fair	Randomized crossover	All subjects had a mother or father with hypercholesterolemia and were diagnosed with “definite” or “possible” heterozygous FH. The diagnosis was confirmed by documentation of the presence of an FH mutation in 25 (of 41) of the children.	Children and adolescents aged 7-12 years with FH	Norway	41
Engler, 2005 ¹³⁵ Fair	Randomized crossover	LDL-C >130 mg/dl and a parent diagnosed with FH or familial combined hyperlipidemia (LDL-C >130 mg/dl and/or TG >150 mg/dl, and a parent with 1 of these phenotypes)	Children 8-21 years with FH or familial combined hypercholesterolemia	US	20

Abbreviations: DNA = deoxyribonucleic acid; FH= familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; Rand = randomized; TG = triglycerides; US = United States

Table 43. Familial Hypercholesterolemia: Supplement Intervention Trials—Population Characteristics (Key Questions 4-5)

Author, Year	Age, mean (range)	Female, %	Race/ethnicity, %	BMI	Smoking, %	Other BL Char	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
de Jongh, 2003 ¹³²	9 (5-12)	51	NR	NR	0	NR	282	219	48	65*
Gylling, 1995 ¹³³	9 (2-15)	50	NR	NR	NR	NR	297	NR	NR	77
Amundsen, 2002 ¹³⁴	10 (NR)	NR	NR	NR	NR	Reached menarche: 7.3%	271	208	53	50
Engler, 2005 ¹³⁵	NR (9-19)	45	NR	NR	0	NR	275	214	42	133

*Median

Abbreviations: BL = baseline; BMI = body mass index; CVD = cardiovascular disease; FH= familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; NR = not reported; SES = socioeconomic status; TC = total cholesterol; TG = triglycerides

Table 44. Familial Hypercholesterolemia: Supplement Intervention Trials—Intervention Characteristics (Key Questions 4-5)

Author, Year	IG n	Intervention	Daily dose	IG Brief Description	Run-in Background diet	CG Category	CG N	CG Description
de Jongh, 2003 ¹³²	41	plant sterols	15 g over 4 wks	Spreads containing 2.3 g of plant sterols (mainly sitosterol and campesterol) per 15 g spread for 4-wks	2 mo compliance with dietary instruction from trained nutritionist Low-saturated-fat, low-cholesterol diet (Step I)	Placebo	41	Control spread containing 5.4 g of fat (composed of 23.2% SFA, 25.5% MUFA and 50.8% PUFA) per 15 g of spread.
Gylling, 1995 ¹³³	14	rapeseed margarine + sitostanol ester	3 g over 6 wks	Rapeseed oil-rich margarine with sitostanol ester (3 g sitostanol) for 6 weeks	None; all families had been on low animal-fat, low cholesterol diet for years prior Low animal fat, low cholesterol diet rich in monoenic fatty acids	Placebo	14	Replacement of 24 g of normal daily fat intake by the same amount of a rapeseed oil-rich margarine without sitostanol ester.
Amundsen, 2002 ¹³⁴	41	plant sterols	20 g of spread (1.76 g plant sterol) over 8 wks	20 g of plant sterol esters-enriched spread per day (containing 1.76 g plant sterols) for 8 weeks. Spread contained 8.8% free plant sterols, of which 50% was sitosterol.	3 wk run-in of control spread in small tubs of 20 g. A compliance rate of 50% was required for the subjects to continue in the study. AHA Step I diet	Placebo	41	Control spread in small tubs of 20 g
Engler, 2005 ¹³⁵	20	DHA	1.2 g over 6 wks	Six capsules/day of DHA (1.2g) for 6 weeks	Washout and run-in before 2 nd intervention periods Nutrition counseling based on NCEP II diet and food guide pyramid	Placebo	20	6 capsules/day of corn/soy oil for 6 weeks

Abbreviations: AHA = American Heart Association; CG = control group; DHA = docosahexaenoic acid; FH= familial hypercholesterolemia; g = gram; IG = intervention group; MUFA = monounsaturated fatty acid; NCEP = National Cholesterol Education Program; PUFA = polyunsaturated fatty acids; SAFA = saturated fatty acid; SE = standard error; wk/wks = week(s)

Table 45. Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in Total Cholesterol (mg/dL) (Key Question 4)

Author, Year	Supplement	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Amundsen, 2002 ¹³⁴	plant sterols	20 g of spread (1.76 g plant sterol)	8	38	38	-19.60 (-38.25 to -0.95)	0.80 (-20.32 to 21.92)	-20.46 (-36.14 to -8.64), 0.007
de Jongh, 2003 ¹³²	plant sterols	15 g	4*	41	41	-39.80 (-55.84 to -23.76)	-9.30 (-26.28 to 7.68)	-30.50 (-39.38 to -23.17), <0.001
Engler, 2005 ¹³⁵	DHA	1.2 g	6	20	20	10.00 (-28.16 to 48.16)	1.00 (-38.23 to 40.23)	9.00 (-45.72 to 63.72),
Gylling, 1995 ¹³³	rapeseed margarine + sistostanol ester	3 g	6	14	14	-33.60 (-59.68 to -7.52)	-2.30 (-27.75 to 23.15)	-31.30 (-67.74 to 5.14), NR

*Capillary lipid profile

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; DHA = docosahexaenoic acid; FH= familial hypercholesterolemia; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; wks = weeks

Table 46. Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in Low-Density Lipoprotein Cholesterol (mg/dL) (Key Question 4)

Author, Year	Supplement	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Amundsen, 2002 ¹³⁴	plant sterols	20 g of spread (1.76 g plant sterol)	8	38	38	-19.70 (-39.77 to 0.37)	3.10 (-19.00 to 25.20)	-22.39 (-34.46 to -6.47), 0.003
de Jongh, 2003 ¹³²	plant sterols	15 g	4*	41	41	-42.50 (-58.75 to -26.25)	-10.80 (-28.02 to 6.42)	-30.12 (-38.61 to -23.17), <0.001
Engler, 2005 ¹³⁵	DHA	1.2 g	6	20	20	12.00 (-26.37 to 50.37)	2.00 (-37.68 to 41.68)	10.00 (-45.19 to 65.19),
Gylling, 1995 ¹³³	rapeseed margarine + sistostanol ester	3 g	6	14	14	-38.30 (-63.75 to -12.85)	-6.60 (-31.41 to 18.21)	-31.70 (-67.24 to 3.84),

*Capillary lipid profile

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; DHA = docosahexaenoic acid; FH= familial hypercholesterolemia; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; wks = weeks

Table 47. Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in High-Density Lipoprotein Cholesterol (mg/dL)

Author, Year	Supplement	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Amundsen, 2002 ¹³⁴	plant sterols	20 g of spread (1.76 g plant sterol)	8	38	38	1.10 (-2.92 to 5.12)	0.00 (-4.07 to 4.07)	1.31 (-2.00 to 4.63), NSD
de Jongh, 2003 ¹³²	plant sterols	15 g	4*	41	41	2.30 (-11.03 to 15.63)	1.50 (-11.90 to 14.90)	0.77 (-2.32 to 3.86), 0.594
Engler, 2005 ¹³⁵	DHA	1.2 g	6	20	20	1.00 (-3.02 to 5.02)	2.00 (-1.51 to 5.51)	-1.00 (-6.33 to 4.33),
Gylling, 1995 ¹³³	rapeseed margarine + sistostanol ester	3 g	6	14	14	3.10 (-2.62 to 8.82)	1.10 (-4.19 to 6.39)	2.00 (-5.80 to 9.80),

*Capillary lipid profile

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; DHA = docosahexaenoic acid; FH= familial hypercholesterolemia; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; NSD = no significant difference; wks = weeks

Table 48. Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in Triglyceride Levels (mg/dL) (Key Question 4)

Author, Year	Supplement	Daily dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Amundsen, 2002 ¹³⁴	plant sterols	20 g of spread (1.76 g plant sterol)	8	38	38	-3.50 (-14.85 to 7.85)	-11.50 (-29.32 to 6.32)	8.41 (-12.98 to 29.79), NSD
de Jongh, 2003 ¹³²	plant sterols	15 g	4*	41	41	NR	NR	-4.43 (-17.70 to 7.97), 0.476
Engler, 2005 ¹³⁵	DHA	1.2 g	6	20	20	-19.00 (-47.58 to 9.58)	-17.00 (-46.59 to 12.59)	-2.00 (-43.13 to 39.13),
Gylling, 1995 ¹³³	rapeseed margarine + sistostanol ester	3 g	6	14	14	4.40 (-14.93 to 23.73)	14.20 (-6.27 to 34.67)	-9.80 (-37.95 to 18.35),

*Capillary lipid profile

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; DHA = docosahexaenoic acid; FH= familial hypercholesterolemia; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; wks = weeks

Table 49. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Study Characteristics (Key Question 4)

Author, Year Study name	Condition criteria	Brief Population Desc	Country	Yrs of data collection	N Rand
DISC Collaborative Research Group, 1995 ¹³⁷ Dietary Intervention Study in Children (DISC) Good	LDL-C $\geq 80^{\text{th}}$ and $< 98^{\text{th}}$ percentiles for age and sex	Children aged 7-10 years, Tanner stage 1, with LDL-C between $\geq 80^{\text{th}}$ (≥ 111.5 mg/dL for males and ≥ 117.5 mg/dL for females) and $< 98^{\text{th}}$ (< 164.5 mg/dL for males and females) for age and sex- specific percentiles	US	1988-1990	663
Shannon, 1994 ¹³⁶ Children’s Health Project (CHP) Fair	Initial screening TC > 176 mg/dL; subsequent mean fasting LDL-C for males between 107 to 164 mg/dL and for females between 112 to 164 mg/dL	Children aged 4-10 years with MFD	UK	1990-1992	271

Abbreviations: DISC = The Dietary Intervention Study in Children; HDL-C = high-density lipoprotein cholesterol; HMO = Health Maintenance Organization; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; Rand = randomized; TC = total cholesterol; UK = United Kingdom; US = United States; Yrs = years

Table 50. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Population Characteristics (Key Question 4)

Author, Year Study name	Age, mean (range)	Female, %	Race/ ethnicity, %	BMI	Smoking, %	Other BL Char	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
DISC Collaborative Research Group, 1995 ¹³⁷ Dietary Intervention Study in Children (DISC)	9 (7-10)	45	White: 86 Black: 8 Asian: 0 Native American: 0 Latino: 0 Other*: 5	NR	NR	Tanner stage 1: 100%	200	131	57	80
Shannon, 1994 ¹³⁶ Children’s Health Project	6 (4-10)	50	White: 87 Black: 10 Asian: 0 Native American: 0 Latino: 0 Other: 3	NR	NR	Weight z-score, mean: 0.14 Height z-score, mean: -0.06	NR	122	NR	NR

Other defined as other than Black or White race

Abbreviations: DISC = The Dietary Intervention Study in Children; HDL-C = high-density lipoprotein cholesterol; HMO = Health Maintenance Organization; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; TC = total cholesterol; UK = United Kingdom; US = United States

Table 51. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Intervention Characteristics (Key Question 4)

Author, year Study name	IG	IG n	IG brief description	Behavioral intv approach	Intv setting	Intv provider(s)	CG category	CG N	CG description
DISC Collaborative Research Group, 1995 ¹³⁷ Dietary Intervention Study in Children (DISC)	IG1	334	19 (min, NR) individual sessions with case manager; 31 (min, NR) group sessions with dietitian, behaviorists, and health educators for 7 years	Dietary	Academic medical center	Dietitian, Behaviorists, Health educators	Usual care	329	Parents or guardians informed that child's blood cholesterol level was high; no specific recommendations to see their physician were given.
Shannon, 1994 ¹³⁶ Children's Health Project	IG1	92	Ten audiotape storybooks (length NR), paper-pencil activities and manual with parent for 10 weeks	Dietary	Home	Parent	No intervention	89	Received no educational information or materials.
	IG2	90	One 45- to 60-minute counseling sessions with dietitian	Dietary	Academic medical center	Dietician	No intervention	89	Received no educational information or materials

Abbreviations: CG = control group; DISC = The Dietary Intervention Study in Children; IG = intervention group; Intv = Intervention MFD = multifactorial dyslipidemia; min = minute; NR = not reported

Table 52. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Results for Mean Difference in Change in Serum Lipid Levels (mg/dL) (Key Question 4)

Serum Lipid Outcome	Author, Year	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD (95% CI), p-value
TC	DISC Collaborative Research Group, 1995 ¹³⁷	IG1	156	334	329	-16.70 (-18.78 to -14.62)	-13.60 (-15.81 to -11.39)	-3.30 (-6.40 to -0.02), 0.04
			385	334	329	-20.60 (-23.05 to -18.15)	-19.90 (-22.65 to -17.15)	-1.10 (-5.00 to 2.80), 0.59
LDL-C	DISC Collaborative Research Group, 1995 ¹³⁷	IG1	156	334	329	-15.30 (-17.10 to -13.50)	-11.90 (-13.80 to -10.00)	-3.30 (-6.00 to -0.60), 0.02
			385	334	329	-16.50 (-18.11 to -14.89)	-14.60 (-16.90 to -12.30)	-1.90 (-4.68 to 0.88), 0.25
	Shannon, 1994 ¹³⁶	IG1	52	88	87	-5.79 (NR)	-5.02 (NR)	NR, NSD*
		IG2	52	86	87	-6.95 (NR)	-5.02 (NR)	NR, NSD*
HDL-C	DISC Collaborative Research Group, 1995 ¹³⁷	IG1	156	334	329	-4.40 (-5.54 to -3.26)	-4.40 (-5.60 to -3.20)	-0.20 (-1.20 to 0.90), 0.75
			385	334	329	-7.30 (-8.57 to -6.03)	-7.70 (-8.95 to -6.45)	0.30 (-1.00 to 1.70), 0.62
TG	DISC Collaborative Research Group, 1995 ¹³⁷	IG1	156	334	329	19.40 (14.99 to 23.81)	18.00 (13.59 to 22.41)	1.50 (-4.50 to 7.50), 0.62
			385	334	329	20.40 (15.22 to 25.58)	16.10 (11.46 to 20.74)	3.40 (-4.10 to 10.90), 0.3

* Significant within-group difference from baseline, (p<0.05)

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; DISC = The Dietary Intervention Study in Children; FU = follow up; HDL-C = high-density lipoprotein cholesterol; IG = intervention group; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; MD = mean difference; NR = not reported; NSD = no significant difference; TC = total cholesterol

Table 53. Multifactorial Dyslipidemia: Supplement Intervention Trials—Study Characteristics (Key Questions 4-5)

Author, Year Quality	Study design	Condition criteria	Brief Population Description	Country	Yrs of data collection	N Rand
Wong, 2013 ¹³⁸ Fair	RCT	Fasting serum LDL-C 135-193 mg/dL	Children and adolescents aged 8-18 years with elevated fasting serum LDL-C levels (135-193 mg/dL) and a positive first-degree family history of hypercholesterolemia or premature atherosclerotic cardiovascular disease	Canada	2009-2010	32
Gidding, 2014 ¹³⁹ Fair	Randomized crossover	Fasting TG \geq 150 mg/dL and $<$ 750 mg/dL on 2 separate occasions, and LDL-C $<$ 160 mg/dL	Adolescents 10-17 years with elevated TG (\geq 150 mg/dL and $<$ 750 mg/dL) and LDL-C $<$ 160 mg/dL	US	NR	42

Abbreviations: LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NR = not reported; Rand = randomized; RCT = randomized controlled trial; TG = triglycerides; US = United States; Yrs = years

Table 54. Multifactorial Dyslipidemia: Supplement Intervention Trials—Population Characteristics (Key Questions 4-5)

Author, Year	Age, mean (range)	Female, %	Race/ethnicity, %	BMI	Smoking, %	% With Family History of CVD and Definition	Other BL Char	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)
Wong, 2013 ¹³⁸	13 (8-18)	47	NR	NR	NR	100% with positive family history of 1 st - degree relatives with hypercholesterolemia or premature atherosclerotic CVD	HTN: 0% Compliant with STEP II diet): 100%	208	138	49	112
Gidding, 2014 ¹³⁹	14 (10-17)	31	White: 86 Black: 5 Asian: 0 Native American: 0 Latino: 7 Other: 2	Mean: 31 kg/m ²	0	NR	Tanner 4 or greater: 100%	194	112	39	272

Abbreviations: BL = baseline; BMI = body mass index; CVD = cardiovascular disease; FH= familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NR = not reported; TG = triglycerides

Table 55. Multifactorial Dyslipidemia: Supplement Intervention Trials—Intervention Characteristics (Key Questions 4-5)

Author, Year	IG n	Intervention	IG Brief Description	Run-in Background diet	CG Category	CG n	CG Description
Wong, 2013 ¹³⁸	16	flaxseed	30 g/day flaxseed supplement in muffins and breads baked with ground flaxseed for 4 weeks	None None, but compliance with the NCEP Step II diet for a minimum of 6 months prior to study enrollment was required. NR if this was enforced during study period.	Placebo	16	Identical muffins and bread, containing whole-wheat flour in place of flaxseed.
Gidding, 2014 ¹³⁹	NR	fish oil	Fish oil 4 g/day for 8 weeks	NR Patients were advised to maintain a stable diet and not alter baseline fish consumption. Any fish oil supplements were discontinued. Advice on a heart-healthy diet was provided.	Placebo	NR	Corn oil placebo

Abbreviations: CG = control group; g = gram; IG = intervention group; MFD = multifactorial dyslipidemia; NR = not reported; SD = standard deviation

Table 56. Multifactorial Dyslipidemia: Supplement Intervention Trials—Results for Mean Difference in Change in Serum Lipid Levels (mg/dL) (Key Question 4)

Serum Lipid Outcome	Author, Year	Supplement	Dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	Mean Diff in Change (95% CI), p-value
TC	Gidding, 2014 ¹³⁹	fish oil	4 g	8	NR	NR	-1.70 (-10.72 to 7.32)	-3.00 (-12.02 to 6.02)	NR, 0.83
	Wong, 2013 ¹³⁸	flaxseed	30 g	4	16	16	NR	NR	-8.51 (-21.66 to 4.25), 0.20
LDL-C	Gidding, 2014 ¹³⁹	fish oil	4 g	8	NR	NR	8.00 (1.53 to 14.47)	-0.02 (-6.49 to 6.45)	NR, 0.14
	Wong, 2013 ¹³⁸	flaxseed	30 g	4	16	16	NR	NR	-6.96 (-16.63 to 2.71), 0.15
HDL-C	Gidding, 2014 ¹³⁹	fish oil	4 g	8	NR	NR	2.00 (0.24 to 3.76)	1.70 (-0.06 to 3.46)	NR, 0.84
	Wong, 2013 ¹³⁸	flaxseed	30 g	4	16	16	NR	NR	-7.35 (-11.60 to -3.09), 0.001
TG	Gidding, 2014 ¹³⁹	fish oil	4 g	8	NR	NR	-52.00 (-83.36 to -20.64)	-16.00 (-45.40 to 13.40)	NR, 0.04*
	Wong, 2013 ¹³⁸	flaxseed	30 g	4	16	16	NR	NR	29.23 (4.43 to 53.24), 0.02

*IG significantly different as compared to BL (p <0.05)

Abbreviations: BL = baseline; CG = control group; CI = confidence interval; FU = follow up; g = gram; HDL-C = high-density lipoprotein cholesterol; IG = intervention group; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NR = not reported; TC = total cholesterol

Table 57. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Study Characteristics (Key Questions 4-5)

Author, Year Study name Quality	Study design	Brief Population Description	Country	Yrs of data collection	n Rand
Guardamagna, 2013 ¹⁴⁰ Fair	Randomized crossover	Hypercholesterolemic children and adolescents aged 6-15 years	Italy	2011-NR	36
Martino, 2005 ¹⁴⁵ Fair	RCT	Children and adolescents age ≤14 years with hypercholesterolemia	Italy	NR	51
Verduci, 2014 ¹⁴⁶ Good	RCT	Children 8-13 years with primary hyperlipidemia (defined as TC ≥200 mg/dL and LDL-C ≥130 mg/dL)	Italy	NR	36
Del Bo, 2019 ¹⁴¹ Fair	RCT	Children and adolescents 6-16 years with primary hyperlipidemia (according to international standards)	Italy	2015	36
Deon, 2018 ¹⁴² Fair	RCT	Children and adolescents with primary hyperlipidemia	Italy	2015	66
Dennison, 1993 ¹⁴³ Fair	Randomized crossover	Children 5-17 years with LDL-C levels >110 mg/dL after 3 months of dietary intervention	US	NR	25
Guardamagna, 2014 ¹⁴⁴ Fair	Randomized crossover	Hypercholesterolemic children ages 6-18 years with serum TC >90th percentile for age and sex	Italy	NR	38

Abbreviations: BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; mg/dL = milligrams per deciliter; NR = not reported; Rand = randomized; RCT = randomized control trial; TG = triglycerides; US = United States

Table 58. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Proportion of MFD and FH Participants in Included Trials (Key Questions 4-5)

Author, Year	FH, %	FH criteria	MFD, %	MFD criteria
Guardamagna, 2013 ¹⁴⁰	FH: 13.9 FCH: 52.8	FH: Criteria included children with LDL-C \geq 135 mg/dL, parental hypercholesterolemia with LDL-C \geq 190 mg/dL, tendon xanthomas and/ or CVD (phenotype IIA). FCH: Familial combined hyperlipidemia, defined as children showing TC and/or TG >90th age- and sex-specific percentile, at least one parent affected by isolated hypercholesterolemia, hypertriglyceridemia, or both (IIA, IV, or IIB phenotype, respectively) with concomitant individual and familial lipid phenotype variability	33.3	Undefined hypercholesterolemia: Children with LDL-C >90th percentile and a family history of hypercholesterolemia, but who did not fulfil the biochemical international criteria for inclusion in FH or FCH
Martino, 2005 ¹⁴⁵	FH: 47.5 FCH: 7.5	TC >95th percentile for age and sex, in two different determinations before enrollment FCH: 1st degree relative with high TG and/or TC >95th percentile for age and sex	45	PHC: TC >95th percentile for age and sex without clear family transmission
Verduci, 2014 ¹⁴⁶	FH: 69.4	'Suspected FH': according to the definition of the US National Lipid Association	30.6	NR, estimated based on suspected FH participants
Del Bo, 2019 ¹⁴¹	FH: 5.6 FCH: 25	FH: criteria not specified FCH: criteria not specified	69.4	PHC: criteria not specified
Deon, 2018 ¹⁴²	FH: NR	FH: diagnosed in presence of LDL-C \geq 95th percentile, parental LDL-C \geq 190 mg/dL, tendon xanthomas and/or cardiovascular disease (phenotype IIA) FCH: diagnosed in children with TC and/or TG >90th age- and sex-specific percentile, with at least one parent affected by hypercholesterolemia, hypertriglyceridemia, or both (IIA, IV, or IIB phenotype, respectively), with concomitant individual and familial lipid phenotype variability	NR	PHC: Children with LDL-C >90th percentile and a family history of dominant inherited hypercholesterolemia, but not fulfilling the biochemical international diagnostic criteria of FH or FCH
Dennison, 1993 ¹⁴³	FH: "Most"	FH: "familial form of hyperlipidemia", not otherwise specified	NR	Criteria not specified
Guardamagna, 2014 ¹⁴⁴	FH: 5.3 FCH: 60.5	FH: Children with LDL-C >95th percentile, parental hypercholesterolemia with LDL-C \geq 190 mg/dL,	34.2	Undefined hypercholesterolemia: LDL-C >90th percentile and a family history of

Table 58. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Proportion of MFD and FH Participants in Included Trials (Key Questions 4-5)

Author, Year	FH, %	FH criteria	MFD, %	MFD criteria
		tendon xanthomas, and/or cardiovascular disease (phenotype IIA) FCH: Children showing TC or triglycerides (TG), or both above the 90th age- and sex-specific percentile, at least one parent affected by isolated hypercholesterolemia, hypertriglycerolemia, or both (IIA, IV, or IIB phenotype, respectively) with concomitant individual and familial lipid phenotype variability		hypercholesterolemia, but who did not fulfill the biochemical international criteria for inclusion in FH or FCH

Abbreviations: BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; FCH = familial combined hypercholesterolemia; FH= familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; PHC = Polygenic hypercholesterolemia; TC = total cholesterol; TX = treatment; US = United States

Table 59. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Population Characteristics (Key Questions 4-5)

Author, Year	Age, mean (range)	Female, %	Race/ethnicity, %	BMI	Smoking, %	% w family Hx of CVD	Other BL Char	Mean Fasting TC (mg/dL)	Mean Fasting LDL-C (mg/dL)	Mean Fasting HDL-C (mg/dL)	Mean Fasting TG (mg/dL)	Non-HDL-C (mg/dL)
Guardamagna, 2013 ¹⁴⁰	11 (6-15)	20	NR	>85 th percentile: 0%	0	NR	On lipid-lowering tx (including functional foods) 3mo before trial: 0%	222	148	56	80	166
Martino, 2005 ¹⁴⁵	8 (≤14)	50	NR	NR	NR	100*	NR	NR	NR	NR	NR	NR
Verduci, 2014 ¹⁴⁶	10 (8-13)	47	NR	Normal weight according to IOBT: 100	NR	NR	Mean dietary saturated fats higher than recommended upper limit.	252	175	60	82	192
Del Bo, 2019 ¹⁴¹	12 (6-15)	36	NR	>85 th percentile: 0% "Borderline overweight" 22%	0	NR	Normal BP: 100%	209†	136†	57	88†	154†
Deon, 2018 ¹⁴²	12 (7-18)	47	NR	"Mild overweight" 8%	0	NR	Normal BP: 100%	216†	140†	60	Med: 68	157†
Dennison, 1993 ¹⁴³	11 (5-17)	45	NR	NR	NR	NR	NR	201	139	46	196	NR
Guardamagna, 2014 ¹⁴⁴	11 (6-15)	58	NR	>85 th percentile: 0%	0	NR	On lipid-lowering tx (including functional foods) 3mo before trial: 0%	223	147	56	99	NR

* Reporting familial history of premature CHD or at least one parent with TC ≥240 mg/dl

†Mean serum lipid levels exceeded the 90th age and sex related percentiles, with the exclusion of HDL-C values, which were in the normal range

Abbreviations: BL = baseline; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; Hx = history; IOTF: International Obesity Task Force; LDL-C = low-density lipoprotein cholesterol; Med = median; mg/dL = milligrams per deciliter; Mo = months; NR = not reported; TC = total cholesterol; TG = triglycerides; tx = treatment

Table 60. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Intervention Characteristics (Key Questions 4-5)

Author, Year	IG	IG n	Intervention	IG Brief Description	Run-in	Background diet	CG Category	CG n	CG Description
Guardamagna, 2013 ¹⁴⁰	IG1	36	glucomannan	8 week intervention of dietary supplement, oral gelatin capsules containing 500 mg glucomannan	4 wk run-in with dietary counseling	Continuation of run-in diet	Placebo	36	Placebo
Martino, 2005 ¹⁴⁵	IG1	NR	glucomannan	Glucomannan 2-3 d/day for 8 weeks	8-week run in with Step 1 diet period	Step I diet	Usual care	NR	Step 1 diet
Verduci, 2014 ¹⁴⁶	IG1	12	DHA+EPA	One 500 mg gel-capsule of DHA plus EPA alone per day over 16 weeks	8-wk	Step I guidance given to parent	Placebo	12	Wheat germ oil (58.5% linoleic acid, 7.1% linolenic acid and 12.8% oleic acid).
	IG2	12	DHA	One 500 mg gel-capsule of DHA alone per day over 16 weeks	8-wk	Step I guidance given to parent	Placebo	12	Wheat germ oil (58.5% linoleic acid, 7.1% linolenic acid and 12.8% oleic acid).
Del Bo, 2019 ¹⁴¹	IG1	18	hempseed oil	Four hempseed oil gel capsules/day (3g total) for 8 weeks	2 mo compliance with dietary instructions, provided by trained nutritionist	Subjects and family trained by nutritionist to adhere to diet based on CHLD1 guidelines	Usual care	18	Maintained usual diet based on CHLD1 guidelines throughout entire study period.
Deon, 2018 ¹⁴²	IG1	22	Hazelnut w skin	One daily 15-30 g portion of hazelnuts with skin for 8 weeks	3 mo run-in where pts should demonstrate a good dietary compliance	Recommendations given based on CHLD1 guidelines. Participants encouraged to maintain same dietary and lifestyle habits	Usual care	22	Advised to follow a nut-free diet for 8 wks

Table 60. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Intervention Characteristics (Key Questions 4-5)

Author, Year	IG	IG n	Intervention	IG Brief Description	Run-in	Background diet	CG Category	CG n	CG Description
	IG2	22	Hazelnut w/o skin	One daily 15-30 g portion of hazelnuts without skin for 8 weeks	3 mo run-in where pts should demonstrate a good dietary compliance	Recommendations given based on CHLD1 guidelines. Participants encouraged to maintain same dietary and lifestyle habits	Usual care	22	Advised to follow a nut-free diet for 8 wks
Dennison, 1993 ¹⁴³	IG1	25	psyllium fiber	Ready-to-eat cereals with water-soluble psyllium fiber (6 g/day) for 4-5 weeks	At least 3 mo of a low total fat, low saturated fat, low cholesterol diet	Continuation of low total fat, low saturated fat, low cholesterol diet.	Placebo	25	Two 28 g servings (1 ounce or 2/3 cup each) of control cereal which contained 5 g water-insoluble wheat fiber per serving; to be eaten for 4-5 weeks.
Guardamagna, 2014 ¹⁴⁴	IG1	38	Probiotic	One daily probiotic capsule for 12 weeks	4-wk diet run-in	Instructed by a trained dietitian not to change their standard low-saturated fat, low-cholesterol diet (Step I diet). Children and their families were instructed not to modify children's physical activity.	Placebo	38	Placebo

Abbreviations: CG = control group; CHLD1 = cardiovascular health integrated lifestyle diet; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FH= familial hypercholesterolemia; g = gram; IG = intervention group; MFD = multifactorial dyslipidemia; mo = month; w/ = with; wks = weeks; w/o = without

Table 61. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in Total Cholesterol (mg/dL) (Key Question 4)

Author, Year	Supplement	Dose	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Del Bo, 2019 ¹⁴¹	Hempseed oil	3 g	IG1	8	18	18	-4.50 (-13.60 to 4.60)	-6.20 (-19.70 to 7.20)	1.70 (-13.39 to 16.79), 0.824
Dennison, 1993 ¹⁴³	Psyllium fiber	6 g	IG1	5	20	20	2.70 (-4.86 to 10.27)	3.09 (-2.97 to 9.14)	-0.39 (-7.72 to 7.34), NSD
Deon, 2018 ¹⁴²	Hazelnut w skin	Varied (15-30 g)	IG1	8	22	18	-5.30 (-22.81 to 12.21)	-6.20 (-28.22 to 15.82)	0.90 (-26.86 to 28.66),
	Hazelnut w/o skin	Varied (15-30 g)	IG2	8	20	18	-9.30 (-32.98 to 14.38)	-6.20 (-28.22 to 15.82)	-3.10 (-35.65 to 29.45),
Guardamagna, 2013 ¹⁴⁰	Glucomannan	2 or 3 capsules BID	IG1	8	36	36	NR	NR	-10.80 (-18.50 to -3.10), 0.008
Guardamagna, 2014 ¹⁴⁴	Probiotic	NR	IG1	12	38	38	-10.90 (-19.06 to -2.74)	-7.50 (-15.89 to 0.89)	-3.40 (-15.10 to 8.30), NR*
Martino, 2005 ¹⁴⁵	Glucomannan	2-3 g (depending on age)	IG1	8	20	20	-44.10 (-60.73 to -27.47)	-28.20 (-44.24 to -12.16)	-15.90 (-39.00 to 7.20), .042†
Verduci, 2014 ¹⁴⁶	DHA+EPA	500 mg	IG1	16	12	12	-10.20 (-54.50 to 34.10)	-14.60 (-39.65 to 10.45)	4.40 (-46.50 to 55.30),
	DHA	500 mg	IG2	16	12	12	-12.10 (-45.22 to 21.02)	-14.60 (-39.65 to 10.45)	2.50 (-39.03 to 44.03),

*Study reported statistical significance between treatments (IG vs CG, p=0.0263) based on analysis of variance for repeated measures and the Greenhouse-Geisser correction on actual absolute values, not accounting for MD in change from BL

†Study reported statistical significance between treatments (IG vs CG, p=0.042) based on analysis of variance, testing equality of means and not accounting for mean differences from BL.

Abbreviations: BL = baseline; BID = twice per day (latin); CG = control group; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; NSD = no significant difference; w/ = with; wks = weeks; w/o = without

Table 62. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in Low-Density Lipoprotein Cholesterol (mg/dL) (Key Question 4)

Author, Year	Supplement	Dose	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Del Bo, 2019 ¹⁴¹	Hempseed oil	3 g	IG1	8	18	18	-14.20 (-15.20 to -13.20)	-4.94 (-13.70 to 3.81)	NR, 0.156*
Dennison, 1993 ¹⁴³	Psyllium fiber	6 g	IG1	5	20	20	1.54 (-4.51 to 7.60)	-2.32 (-8.37 to 3.74)	3.86 (-4.63 to 12.36), NSD
Deon, 2018 ¹⁴²	Hazelnut w skin	Varied (15-30 g)	IG1	8	22	18	-9.20 (-28.22 to 9.82)	-4.80 (-25.73 to 16.13)	-4.40 (-32.69 to 23.89), NR†
	Hazelnut w/o skin	Varied (15-30 g)	IG2	8	20	18	-8.80 (-33.49 to 15.89)	-4.80 (-25.73 to 16.13)	-4.00 (-36.74 to 28.74), NR†
Guardamagna, 2013 ¹⁴⁰	Glucosamin	2 or 3 capsules BID	IG1	8	36	36	NR	NR	-10.10 (-17.40 to -2.90), 0.008
Guardamagna, 2014 ¹⁴⁴	Probiotic	NR	IG1	12	38	38	-11.90 (-19.35 to -4.45)	-8.10 (-16.34 to 0.14)	-3.80 (-14.90 to 7.30), NR‡
Martino, 2005 ¹⁴⁵	Glucosamin	2-3 g (depending on age)	IG1	8	20	20	-40.90 (-60.64 to -21.16)	-21.20 (-40.69 to -1.71)	-19.70 (-47.44 to 8.04), .026§
Verduci, 2014 ¹⁴⁶	DHA+EPA	500 mg	IG1	16	12	12	-9.70 (-53.74 to 34.34)	-9.10 (-36.37 to 18.17)	-0.60 (-52.40 to 51.20),
	DHA	500 mg	IG2	16	12	12	-9.30 (-43.90 to 25.30)	-9.10 (-36.37 to 18.17)	-0.20 (-44.25 to 43.85),

*Imputed CI of MD of change was based on imbalanced variances between the control (SD= 17.6) and the treatment (SD=2.0) and not accounting for the crossover trial design with small sample size (N=36).

† IG significantly different as compared to BL (p <0.05)

‡ Study reported statistical significance between treatments (IG vs CG, p=0.0017) based on analysis of variance for repeated measures and the Greenhouse-Geisser correction on actual absolute values, not accounting for MD in change from BL.

§ Study reported statistical significance between treatments (IG vs CG, p=0.026) based on analysis of variance, testing equality of means and not accounting for mean differences from BL.

Abbreviations: BL = baseline; BID = twice per day (latin); CG = control group; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; NSD = no significant difference; w/ = with; wks = weeks; w/o = without

Table 63. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in High-Density Lipoprotein Cholesterol (mg/dL) (Key Question 4)

Author, Year	Supplement	Dose	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Del Bo, 2019 ¹⁴¹	Hempseed oil	3 g	IG1	8	18	18	-1.94 (-5.34 to 1.46)	-2.56 (-6.49 to 1.37)	0.62 (-4.21 to 5.45), 0.806
Dennison, 1993 ¹⁴³	Psyllium fiber	6 g	IG1	5	20	20	-0.77 (-4.56 to 3.01)	-1.54 (-3.81 to 0.73)	1.16 (-1.93 to 3.86), NSD
Deon, 2018 ¹⁴²	Hazelnut w skin	Varied (15-30 g)	IG1	8	22	18	1.20 (-4.63 to 7.03)	0.10 (-6.25 to 6.45)	1.10 (-7.54 to 9.74),
	Hazelnut w/o skin	Varied (15-30 g)	IG2	8	20	18	1.40 (-5.86 to 8.66)	0.10 (-6.25 to 6.45)	1.30 (-8.44 to 11.04),
Guardamagna, 2013 ¹⁴⁰	Glucomannan	2-3 cap BID	IG1	8	36	36	NR	NR	0.40 (-2.10 to 2.90), 0.739
Guardamagna, 2014 ¹⁴⁴	Probiotic	NR	IG1	12	38	38	4.90 (0.61 to 9.19)	3.20 (-1.01 to 7.41)	1.70 (-4.32 to 7.72), NR*
Martino, 2005 ¹⁴⁵	Glucomannan	2-3 g (depending on age)	IG1	8	20	20	-5.80 (-12.35 to 0.75)	-3.90 (-10.43 to 2.63)	-1.90 (-11.15 to 7.35), NSD
Verduci, 2014 ¹⁴⁶	DHA+EPA	500 mg	IG1	16	12	12	1.30 (-3.13 to 5.73)	2.60 (-2.61 to 7.81)	-1.30 (-8.14 to 5.54),
	DHA	500 mg	IG2	16	12	12	4.80 (0.81 to 8.79)	2.60 (-2.61 to 7.81)	2.20 (-4.36 to 8.76),

*Study reported statistical significance between treatments (IG vs CG, p=0.0352) based on analysis of variance for repeated measures and the Greenhouse-Geisser correction on actual absolute values, not accounting for MD in change from BL.

Abbreviations: BL = baseline; BID = twice per day (latin); CG = control group; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; NSD = no significant difference; w/ = with; wks = weeks; w/o = without

Table 64. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in Triglyceride Levels (mg/dL) (Key Question 4)

Author, Year	Supplement	Dose	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Del Bo, 2019 ¹⁴¹	Hempseed oil	3 g	IG1	8	18	18	16.00 (-3.60 to 35.60)	-6.30 (-24.10 to 11.60)	22.30 (-2.33 to 46.93), 0.085
Dennison, 1993 ¹⁴³	psyllium fiber	6 g	IG1	5	20	20	21.24 (-9.98 to 52.46)	81.42 (36.32 to 126.52)	MD Chg: -60.18 (-115.93 to -3.54), <0.05
Deon, 2018 ¹⁴²	Hazelnut w skin	Varied (15-30 g)	IG1	8	22	18	NR	NR	NR, NR
	Hazelnut w/o skin	Varied (15-30 g)	IG2	8	20	18	NR	NR	NR, NR
Guardamagna, 2013 ¹⁴⁰	Glucosamin	2-3 cap BID	IG1	8	36	36	NR	NR	MD Chg: -3.80 (-17.40 to 9.80), 0.399
Guardamagna, 2014 ¹⁴⁴	Probiotic	NR	IG1	12	38	38	-19.50 (-36.76 to -2.24)	-17.60 (-35.06 to -0.14)	-1.90 (-26.45 to 22.65), NR*
Martino, 2005 ¹⁴⁵	Glucosamin	2-3 g (depending on age)	IG1	8	20	20	-9.80 (-31.81 to 12.21)	-15.10 (-30.72 to 0.52)	5.30 (-21.69 to 32.29),
Verduci, 2014 ¹⁴⁶	DHA+EPA	500 mg	IG1	16	12	12	-9.60 (-24.21 to 5.01)	-5.30 (-23.17 to 12.57)	-4.30 (-27.39 to 18.79),
	DHA	500 mg	IG2	16	12	12	-12.60 (-28.92 to 3.72)	-5.30 (-23.17 to 12.57)	-7.30 (-31.50 to 16.90),

*Study reported statistical significance between treatments (IG vs CG, p=0.0384) based on analysis of variance for repeated measures and the Greenhouse-Geisser correction on actual absolute values, not accounting for MD in change from BL.

Abbreviations: BL = baseline; BID = twice per day (latin); cap = capsule; CG = control group; Chg: change; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; NSD = no significant difference; w/ = with; wks = weeks; w/o = without

Table 65. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Supplement Intervention Trials—Results for Mean Difference in Change in Non-High-Density Lipoprotein Cholesterol (mg/dL) (Key Question 4)

Author, Year	Supplement	Dose	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Del Bo, 2019 ¹⁴¹	Hempseed oil	3 g	IG1	8	18	18	3.40 (-31.20 to 37.90)	-6.30 (-17.60 to 4.90)	9.70 (-24.05 to 43.45), 0.577
Deon, 2018 ¹⁴²	Hazelnut w skin	Varied (15-30 g)	IG1	8	22	18	-6.50 (-25.97 to 12.97)	-6.30 (-28.11 to 15.51)	-0.20 (-29.40 to 29.00),
	Hazelnut w/o skin	Varied (15-30 g)	IG2	8	20	18	-10.70 (-36.04 to 14.64)	-6.30 (-28.11 to 15.51)	-4.40 (-38.20 to 29.40), NR*
Guardamagna, 2013 ¹⁴⁰	glucomannan	2 -3 cap BID	IG1	8	36	36	NR	NR	-11.20 (-18.00 to -4.50), 0.002

* IG significantly different as compared to BL (p <0.05)

Abbreviations: BL = baseline; BID = twice per day (latin); cap = capsule; CG = control group; Chg: change; CI = confidence interval; FU = follow up; g = gram; IG = intervention group; MD = mean difference; NR = not reported; w/ = with; wks = weeks; w/o = without

Table 66. Familial Hypercholesterolemia: Characteristics of Statin Nonrandomized Studies of Interventions in Children and Adolescents With Familial Hypercholesterolemia or Multifactorial Dyslipidemia (Key Question 5)

Previous Include	Author, Year Study Name Quality	Study Aim	Lipid Criteria	Brief Population Description	Country	Years of data collection	Recruitment Setting and Methods	N
	Desai, 2019 ¹⁴⁸ Fair	To evaluate the hepatotoxicity of statins	FH/MFD not part of inclusion criteria; participants evaluated in lipid clinic	Patients ≤21 years evaluated in lipid clinic from September 1, 2010 to March 1, 2014 with ≥1 serum ALT measurement	US	2010-2014	Lipid clinic Patients ≤21 years evaluated in Preventive Cardiology Program	943
	Joyce, 2017 ¹⁴⁹ Fair	To evaluate the association between statin use and the risk of type 2 diabetes	FH/MFD not part of inclusion criteria; patients with a claim for "pure-hypercholesterolemia" (ICD-9 272.0) which includes heFH were part of a subgroup analysis	Youth aged 8-20 years with dyslipidemia and without type 2 diabetes	US	2003-2014	Commercial health insurance claims database	9393
X	Kusters, 2014 ¹⁴⁷ AfterTen Good	10-year observational followup after participation in an RCT of statin therapy in children and adolescents with FH	100% FH 1 parent with definite clinical or molecular diagnosis of FH; 2 fasting samples with LDL-C levels ≥155 mg/dL and TG levels <350 mg/dL after 3 months on fat-restricted diet	Children aged 8-18 years with FH who previously participated in 2-yr statin trial and non-FH siblings	Netherlands	1997-2011	Academic Participants of a statin RCT and their non-FH siblings	309

Abbreviations: FH/MFD = familial hypercholesterolemia/multifactorial dyslipidemia; heFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; NRSI = non-randomized studies of interventions; RCT = randomized controlled trial; TG = triglycerides

Table 67. Familial Hypercholesterolemia: Summary of Evidence

Intervention	Number of included studies K (n)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
<i>KQ1 (Screening Benefits)</i>						
Universal or Selective Screening	0		N/A		INSUFFICIENT	
<i>KQ2 (Yield)</i>						
Universal or Selective Screening	3 (N=395,465) New studies: 3	<p>Diagnostic yield: No studies reported true diagnostic yield as there were no screening studies with genetic testing</p> <p>Prevalence: Using thresholds of LDL-C ≥ 190 mg/dL or TC ≥ 270 mg/dL, FH prevalence was 0.20 to 0.42% (1:250 to 1:500)</p> <p>Targeted screening based on family history would miss a substantial proportion of cases.</p>	<p>Diagnostic yield: NA</p> <p>Prevalence: Reasonably consistent; reasonably precise</p>	No genetic or family history criteria; lipid values are used as a proxy for FH	<p>INSUFFICIENT for diagnostic yield</p> <p>LOW for prevalence</p>	US children and adolescents with most evidence for ages 10 or older; applicability to various recruitment settings and geographic locations
<i>KQ3 (Screening Harms)</i>						
Universal or Selective Screening	0		N/A		INSUFFICIENT	
<i>KQ4 (Treatment Benefit)</i>						
Statin	10 (n=1230) New studies: 1	<p>TC: k= 7, N=706, MD in change -82.1 mg/dL (95% CI - 101.1 to -63.2, I² 83.0%)</p> <p>LDL-C: k= 8, N=742, MD in change -81.3 mg/dL (95% CI, - 97.6 to -65.0, I² 81.6%)</p> <p>TC and LDL-C effects appear dose related.</p> <p>HDL-C: no difference</p>	Consistent; reasonably precise	<p>Heterogeneity of statin drugs and intensity</p> <p>Short-term followup: One 2-year trial but all other trials <6 months</p> <p>No health outcomes.</p> <p>Small sample sizes, ranging from 50 to 214</p>	MODERATE for benefit	Children and adolescents aged 6-18 years with FH defined using various diagnostic criteria

Table 67. Familial Hypercholesterolemia: Summary of Evidence

Intervention	Number of included studies K (n)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
		TG: mixed results cIMT: 1 trial (N=214) reported statistically significant mean difference in change favoring IG at 2 years				
Bile acid sequestrants	3 (n=332) New studies: 0	TC: MD in change -22.1 to -40.6 mg/dL LDL-C: MD in change -13.2 to -45.9 mg/dL TG: no difference HDL-C: mixed results Variation in effect by dose.	Reasonably consistent; reasonably precise	Different formulations of bile acid sequestrants Short duration 8 to 52 weeks No health outcomes.	LOW for benefit	Children and adolescents age 6-17 years with FH
Ezetimibe	1 (n=138) New studies: 0	TC: MD in change -64.0 mg/dL (95% CI, -81.1 to -46.9) LDL-C: MD in change -63.0 mg/dL (95% CI, -79.5 to -46.5) HDL-C and TG: No difference Non-HDL-C: MD in change -65.0 mg/dL (95% CI, -82.2 to -47.8)	Consistency NA; reasonably precise	Short duration 12 weeks No health outcomes.	LOW for benefit	Children 6-11 years with FH
Fibrate	1 (n=14) New studies: 1	TC: MD in change -84.9 mg/dL (95% CI, -126.2 to -43.6) HDL-C and TG: no difference	Consistency NA; imprecise	Very small trial size Short duration 13 weeks No health outcomes.	INSUFFICIENT	Children and adolescents 4-15 years with FH; This drug is not available in the U.S and is not FDA approved

Table 67. Familial Hypercholesterolemia: Summary of Evidence

Intervention	Number of included studies K (n)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
						in children. Currently, there are no fibrate drugs approved in children or adolescents.
PCSK9 inhibitor	1 (n=158) New studies: 1	LDL-C: MD in change -68.6 mg/dL (95% CI, -83.1 to -54.0) Non-HDL-C: MD in % change -35.1 (-412.0 to -28.2) cIMT: no difference	Consistency NA; reasonably precise	Short duration 24 weeks No health outcomes.	LOW for benefit	Children and adolescents age 10-17 with FH
Drug combination (simvastatin+ ezetimibe)	1 (n=248) New studies: 0	(Compared to single drug) TC: MD in change -40.1 mg/dL [95% CI, -51.1 to -29.2]) LDL-C: MD in change -37.5 mg/dL (95% CI, -48.0 to -27.0) TG: -9.5 median difference in % change, p<0.01 Non-HDL-C: MD in change -40.0 mg/dL (95% CI, -51.0 to -28.9)	Consistency NA; reasonably precise	Short duration 33 weeks No health outcomes.	LOW for benefit	Children and adolescents 10-17 years with FH
Behavioral counseling	1 (n=21) New studies: 1	Lipids: no difference Physical activity outcomes: overlapping CIs for IG v CG Dietary outcomes: mixed results	Consistency NA; imprecise	Very small trial Short duration 12 weeks No health outcomes.	INSUFFICIENT	Low intensity diet and PA intervention for 10–18-year-olds with FH
Supplement (Plant sterols, omega-3 fatty acid,	4 (n=116) New studies:4	Plant sterol spreads (k=2, n= 82): statistically significant MD in change TC -20.5 to -30.5 mg/dL and LDL-C -22.4 to -30.1 mg/dL	Plant sterols: Reasonably consistent; imprecise	1-2 trial for each intervention type Short duration 4 to 8 weeks	Plant sterols: LOW for benefit Omega 3 fatty acids: INSUFFICIENT	Long term adherence to food spread uncertain

Table 67. Familial Hypercholesterolemia: Summary of Evidence

Intervention	Number of included studies K (n)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
combination plant sterol/stanol and omega-3 fatty acid)		Omega-3 fatty acids (k=1, n=20): no statistically significant difference in TC or LDL-C Combination plant sterol/stanol and omega-3 fatty acid (k=1, n=14): no statistically significant difference in TC or LDL-C	Omega 3 fatty acid and combination plant sterol-omega 3 fatty acid: consistency NA, imprecise	No health outcomes.	Combination plant sterol-omega 3 fatty acid: INSUFFICIENT	
<i>KQ5 (Treatment Harms)</i>						
Statin	12 (n=1476 in trials, 10,336 in NRSI harms-only studies) New studies: 3 (1 RCT, 2 NRSI)	Transaminitis >3 times ULN: 0-4.5% (IG) vs 0-1.9% (CG) but largest trial (N=214) with 2-year followup reported no cases in the statin group and only 2 cases of AST >3 times ULN in the control group. In the 10-year observational followup of this trial, transaminitis at this threshold was similarly rare (ALT: 1 case of >3 times elevation in the statin group; AST: 1 case of >3 times ULN each in the statin and control group). CK ≥10x ULN: 0 in 2 trials and up to 4.5% (IG) vs 1.7% (CG) but one trial's 10-year observational followup reported no instances of elevated CK. 1 NRSI (n=943) reported ALT elevations of greater than 3 times the upper limit of normal with a frequency of 4.4 percent	Inconsistent; imprecise	Most trials were short term and small with few events leading to imprecise estimates Clinical importance of transient elevations in these lab values in unknown	LOW for reversible liver and musculoskeletal lab abnormalities INSUFFICIENT for new onset diabetes LOW for no growth or hormonal harms	Short term harms

Table 67. Familial Hypercholesterolemia: Summary of Evidence

Intervention	Number of included studies K (n)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
		<p>in the statin group and 1.5 percent in the control group over 3.5 years of observation</p> <p>1 NRSI (N=9393) showed no difference in new diabetes diagnoses over 9 years</p> <p>6 trials (n=931) and 1 NRSI (n=309) reported no significant differences between Tanner stages or other hormonal adverse events</p>				
Bile acid sequestrants	3 (n=332) New studies: 0	Similar rates of total adverse events in IG and CG	Relatively consistent, imprecise	Different formulations, few events Short 8-52 week duration	LOW for minimal harm	Children and adolescents age 6-17 years with FH
Ezetimibe	1 (n=138) New studies: 0	Similar rates of total adverse events in IG and CG	Consistency NA, imprecise	Single trial, short duration 12 weeks, few events	INSUFFICIENT	Children 6-11 years with FH
Fibrate	1 (n=14) New studies: 1	Transient ALT elevation: 1 event in IG Alkaline phosphatase elevation: 1 event in IG	Consistency NA, imprecise	Single trial, short duration 13 weeks, few events	INSUFFICIENT	Children and adolescents 4-15 years with FH
PCSK9 inhibitor	1 (n=158) New studies: 1	Similar rates of total adverse events in IG and CG	Consistency NA, imprecise	Single trial, short duration 24 week, few events	INSUFFICIENT	Children and adolescents age 10-17 with FH
Drug combination (simvastatin + ezetimibe)	1 (n=248) New studies: 0	Similar rates of total adverse events in IG and CG	Consistency NA, imprecise	High total AEs in both IG and CG Short 33 week duration	INSUFFICIENT	Children and adolescents 10-17 years with FH
Behavioral counseling	0					
Supplement (DHA, plant sterols)	3 (n=102) New studies: 3	All 3 trials reported that there were 0 adverse events	Consistency NA; imprecise	Small studies, short duration 6-16 weeks	INSUFFICIENT	Children and adolescents 6-18 years

* For our review-of-reviews method, we adopted the strength of the overall body of evidence assigned within the primary systematic review. In most cases, these grades were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group definitions which consider study limitations, consistency of effect,

Table 67. Familial Hypercholesterolemia: Summary of Evidence

imprecision, indirectness and publication bias. Where strength of evidence grades were not available, we adapted the EPC approach to assign an overall strength of evidence grade based on consensus discussions involving at least two reviewers.

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CG = control group; CI = confidence interval; cIMT = carotid intima-media thickness test; FH = familial hypercholesterolemia; IG = intervention group; KQ = key question; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; MD = mean difference; mg/dL = milligram per deciliter; NA = not applicable; Non-HDL-C = non-high-density-lipoprotein cholesterol; NR = not reported; NRSI = nonrandomized controlled study of intervention; RCT = randomized controlled trial; TC = total cholesterol; TG = triglycerides; ULN = upper limit of normal

Table 68. Multifactorial Dyslipidemia: Summary of Evidence

Intervention	Number of included studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
KQ1 (Screening Benefits)						
Universal or selective screening	0					
KQ2 (Yield)						
Universal or selective screening	5 (n=142,257) New studies: 5	<p>Diagnostic yield: No studies reported true diagnostic yield as there were no screening studies with confirmatory testing</p> <p>Prevalence: 1+ abnormal lipid value: 19.2% (NHANES, N=4,381)</p> <p>TC ≥200 mg/dL: 7.1% (NHANES) to 9.4% (PVHS) (3 studies, N=75,551)</p> <p>LDL-C ≥130 mg/dL: 6.4% (NHANES) to 7.4% (CARDIAC) (2 studies, N=56,824)</p> <p>HDL-C <40 mg/dL: 12.1% (NHANES) to 22.2% (PVHS) (4 studies, N=72, 320)</p> <p>TG ≥130 mg/dL: 10.2% (NHANES) (1 study, N=2,045)</p> <p>Non-HDL-C ≥145 mg/dL: 6.4% (NHANES) and 13.0% (PVHS) (2 studies, N=16,150)</p>	<p>Diagnostic yield: NA</p> <p>Prevalence: Consistent; reasonably precise for TC, LDL-C, but imprecise for other measures</p>	<p>No confirmatory testing</p> <p>NHANES represents only national sample and included most recent years of 2016; fasting and nonfasting samples</p> <p>Prevalence varies by population characteristics</p>	<p>INSUFFICIENT for diagnostic yield of screening tests</p> <p>MODERATE that abnormal lipid values are common</p>	<p>US children and adolescents age 6-19 years</p> <p>Overall prevalence lower in national dataset (NHANES) compared to other geographically focused recruitment settings</p>
KQ3 (Screening Harms)						
Universal or selective screening	0					
KQ4 (Treatment Benefits)						
Behavioral counseling	2 (n=934) New studies: 1	<p>One high-intensity dietary intervention (DISC) 7-year trial showed statistically significant reductions in TC, LDL-C (MD in change -3.3 mg/dL for TC and LDL-C) at 3 years that were not sustained at 7-year follow-up.</p> <p>One low intensity dietary 10-week intervention with up to 1-year followup: statistically</p>	Consistent, reasonably precise	Heterogeneous dietary interventions with variable intensity, duration and follow-up	LOW for no long-term benefit	Children ages 4-10 years

Table 68. Multifactorial Dyslipidemia: Summary of Evidence

Intervention	Number of included studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
		<p>significant reduction in LDL-C (MD in change -6.7 mg/dL) at 3 months not sustained at 1-year followup</p> <p>HDL-C and TG: no difference</p> <p>Both trials reported that interventions were associated with improved dietary intake outcomes which were attenuated at longer followup.</p>				
Supplement (flaxseed and fish oil)	2 (n=74) New studies: 1	<p>Flaxseed: no difference in TC or LDL-C but worsening of TG and HDL-C in IG, no differences in BMI or total caloric intake.</p> <p>Fish Oil: no difference in TC or LDL-C</p>	Consistency NA, imprecise	<p>Small studies with single study for each supplement.</p> <p>Short duration 4-8 weeks</p>	INSUFFICIENT	Children and adolescents 8-18 years
KQ5 (Treatment Harms)						
Behavioral counseling	2 (n=934) New studies: 1	No harmful effects identified in growth (BMI, weight, height), development (Tanner stage), nutritional (serum ferritin, red cell folate, zinc, albumin) or psychological (anxiety, depression, behavior) outcomes. One trial (DISC) reported better depression outcomes in the IG.	Consistent, reasonably precise	Heterogeneous dietary interventions with variable intensity, duration and follow-up	LOW for no harms	Children 6-11 years
Supplement (flaxseed and fish oil)	2 (n=74) New studies: 1	<p>Flaxseed trial (N= 32): no adverse events</p> <p>Fish oil trial (N=42): GI symptoms, fishy taste and frequent nose bleeds more common in intervention group</p>	Consistency NA, imprecise	<p>Single small trial for each supplement.</p> <p>Short duration 4-8 weeks</p>	INSUFFICIENT	Children and adolescents 8-18 years

* For our review-of-reviews method, we adopted the strength of the overall body of evidence assigned within the primary systematic review. In most cases, these grades were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group definitions which consider study limitations, consistency of effect, imprecision, indirectness and publication bias. Where strength of evidence grades were not available, we adapted the EPC approach to assign an overall strength of evidence grade based on consensus discussions involving at least two reviewers.

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; CG = control group; CI = confidence interval; cIMT = carotid intima-media thickness test; DISC = Dietary Intervention Study in Children; FH = familial hypercholesterolemia; IG = intervention group; KQ = key question; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; MD = mean difference; mg/dL = milligram per deciliter; NA = not applicable; NHANES = National Health and Nutrition Examination Survey; Non-HDL-C = non-high-density-lipoprotein cholesterol; NR = not reported; NRSI = nonrandomized controlled study of intervention; PVHS = The Poudre Valley Health System study; RCT = randomized controlled trial; TC = total cholesterol; TG = triglycerides; ULN = upper limit of normal

Table 69. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Summary of Evidence

Intervention	Number of included studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence*	Applicability
KQ1 (Screening Benefits)						
Universal and selective screening	0					
KQ2 (Yield)						
Universal and selective screening	See above tables for yield of FH and MFD					
KQ3 (Screening Harms)						
Universal and selective screening	0					
KQ4 (Treatment Benefits)						
Supplement (fiber, omega 3/6 fatty acids, hazelnut, probiotic)	7 (n=288) New studies: 7	Fiber: 1 trial (N= 36) of the glucomannan showed 10-11 mg/dL statistically significant improvement in TC, LDL-C; 2 other fiber trials showed no statistically significant improvements. One psyllium fiber trial showed 60.2 mg/dL reduction in TG, other fiber trials showed no difference. Omega 3/6 fatty acids: No difference in any lipid parameter Probiotics: No difference in any lipid parameter Hazelnuts: No difference in any lipid parameter	Inconsistent, imprecise	1 to 3 very small trials for each supplement type Short term trials 5-16 weeks No health outcomes.	INSUFFICIENT for any single supplement	Children and adolescents 5-18 years
KQ5 (Treatment Harms)						
Supplement (fiber, omega 3/6 fatty acids, probiotic)	5 (n=186) New studies: 5	2 trials reported 0 adverse events (1 fiber trial, 1 omega 3/6 trial) 2 fiber trials reported various GI side effects up to 5-22.2% and the probiotic trial reported few cases of abdominal pain (5.4% v 2.8%).	Consistent, imprecise	1 to 3 small trials for each supplement category Short term trials 5-16 weeks Few events	Fiber: LOW for GI side effects Other supplements: INSUFFICIENT	Children and adolescents 5-18 years

* For our review-of-reviews method, we adopted the strength of the overall body of evidence assigned within the primary systematic review. In most cases, these grades were based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group definitions which consider study limitations, consistency of effect,

Table 69. Multifactorial Dyslipidemia/Familial Hypercholesterolemia: Summary of Evidence

imprecision, indirectness and publication bias. Where strength of evidence grades were not available, we adapted the EPC approach to assign an overall strength of evidence grade based on consensus discussions involving at least two reviewers.

Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CG = control group; CI = confidence interval; FH = familial hypercholesterolemia; IG = intervention group; KQ = key question; LDL-C = low-density lipoprotein cholesterol; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; MD = mean difference; mg/dL = milligram per deciliter; NA = not applicable; Non-HDL-C = non-high-density-lipoprotein cholesterol; NR = not reported; NRSI = nonrandomized controlled study of intervention; RCT = randomized controlled trial; TC = total cholesterol; TG = triglycerides

Appendix A. Detailed Methods and Background

Search Strategies

Sources Searched: database and platform 5/16/22
MEDLINE via Ovid
Cochrane Central Register of Controlled Clinical Trials via Wiley

Search filters used:

RCT filter used is a modified version incorporating:

- Chris Cooper, Jo Varley-Campbell and Patrice Carter, Established search filters may miss studies when identifying randomized controlled trials, *Journal of Clinical Epidemiology*, 2019-08-01, Volume 112, Pages 12-19
- Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006; 94: 130-136. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1435857/>
- Box 6.4.b: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format, *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0, [updated March 2011]

MEDLINE via Ovid

Ovid MEDLINE(R) ALL <1946 to July 12, 2021>

1	Hyperlipidemias/	27553
2	Dyslipidemias/	12641
3	Hypercholesterolemia/	26292
4	Lipid Metabolism Disorders/	632
5	Hyperlipoproteinemias/	2580
6	Hypertriglyceridemia/	6187
7	Hyperlipoproteinemia Type II/	7011
8	Hyperlipidemia, Familial Combined/	756
9	Hypobetalipoproteinemias/	335
10	Abetalipoproteinemia/	588
11	hyperlipid?emi\$.ti,ab.	32411
12	dyslipid?emi\$.ti,ab.	37499
13	hypercholesterol?emi\$.ti,ab.	35886
14	hyperlipoprotein?emi\$.ti,ab.	4527
15	hypertriglycerid?emia\$.ti,ab.	13505
16	dysbetalipoprotein?emi\$.ti,ab.	227
17	hypobetalipoproteinemi\$.ti,ab.	350
18	abetalipoproteinemi\$.ti,ab.	392
19	(familial adj3 apolipoprotein).ti,ab.	258
20	heterozygous fh.ti,ab.	486
21	homozygous fh.ti,ab.	295
22	(lipid\$ adj2 disorder\$.ti,ab.	5134
23	or/1-22	144578
24	Cholesterol/bl	65354
25	Triglycerides/bl	50807

Appendix A. Detailed Methods and Background

26	Lipoproteins/bl	20785	
27	Cholesterol, HDL/	29233	
28	Cholesterol, LDL/	28735	
29	Apolipoprotein B-100/	2219	
30	Apolipoprotein B 100.ti,ab.	1240	
31	apob 100.ti,ab.	1136	
32	apo b 100.ti,ab.	615	
33	((high\$2 or elevated or abnormal\$2 or aberr\$) adj3 (cholesterol or lipid\$ or LDL\$ or lipoprotein\$)).ti,ab.	100165	
34	((low or lower\$3 or decreas\$ or deficien\$ or abnormal\$2 or aberr\$) adj3 HDL\$).ti,ab.	18662	
35	or/24-34	196986	
36	23 or 35	288584	
37	Mass screening/	108551	
38	screen\$.ti,ab.	815937	
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.	84891	
40	((fasting or nonfasting or non-fasting or preprandial or pre-prandial or postprandial or post-prandial) adj (lipid\$ or lipoprotein\$ or cholesterol)).ti,ab.	2973	
41	or/37-40	928086	
42	36 and 41	51528	
43	adolescent/ or young adult/ or child/ or child, preschool/ or infant/ or infant, newborn/	4107555	
44	(pediatric\$ or paediatric\$ or preterm\$ or newborn\$ or child\$ or infant\$ or infancy or neonat\$ or preschool\$ or young\$ or early years or adolescen\$ or teenage\$ or teens or preteen\$ or youth or young people or girl\$ or boy\$ or student\$ or juvenile\$ or minor or minors or baby or babies or school\$ or toddler*).ti,ab.	3584227	
45	limit 44 to ("in data review" or in process or publisher or "pubmed not medline")	427278	
46	43 or 45	4534833	
47	42 and 46	9834	
48	limit 47 to (english language and yr="2015 -Current")	3205	
49	remove duplicates from 48	3195	
50	36 or 39 or 40	333425	
51	"Sensitivity and Specificity"/	356654	
52	"Predictive Value of Tests"/	212465	
53	ROC Curve/	63662	
54	Receiver operat\$.ti,ab.	96033	
55	ROC curve\$.ti,ab.	40013	
56	sensitivit\$.ti,ab.	874685	
57	specificit\$.ti,ab.	518244	
58	predictive value.ti,ab.	99037	
59	accuracy.ti,ab.	444776	
60	False Negative Reactions/	18125	
61	False Positive Reactions/	28261	
62	Diagnostic Errors/	38618	
63	"Reproducibility of Results"/	420811	
64	Reference Values/	161821	
65	Reference Standards/	44064	
66	Observer Variation/	43705	

Appendix A. Detailed Methods and Background

67	Psychometrics/	79809	
68	Psychometric\$.ti,ab.	50874	
69	false positive\$.ti,ab.	62169	
70	false negative\$.ti,ab.	35163	
71	miss rate\$.ti,ab.	554	
72	error rate\$.ti,ab.	15558	
73	or/51-72	2432428	
74	50 and 73	32787	
75	46 and 74	4949	
76	limit 75 to (english language and yr="2015 -Current")	1671	
77	hydroxymethylglutaryl-coa reductase inhibitors/ or lovastatin/ or pravastatin/ or simvastatin/	39187	
78	Rosuvastatin Calcium/ or Atorvastatin/	8969	
79	hypolipidemic agents/	15509	
80	bezafibrate/ or fenofibrate/ or gemfibrozil/ or niacin/	15755	
81	anticholesteremic agents/ or cholestyramine resin/ or clofenapate/ or clofibrate/ or clofibric acid/ or colestipol/ or Colesevelam Hydrochloride/	23331	
82	probucol/	1392	
83	Ezetimibe/ or Ezetimibe, Simvastatin Drug Combination/	2275	
84	3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor\$.ti,ab.	1124	
85	hydroxymethylglutaryl coa reductase inhibitor\$.ti,ab.	95	
86	hydroxymethylglutaryl coa inhibitor\$.ti,ab.	2	
87	hydroxymethylglutaryl coenzyme a reductase.ti,ab.	452	
88	hydroxymethylglutaryl coenzyme a inhibitor\$.ti,ab.	8	
89	hmg coa reductase inhibitor\$.ti,ab.	4117	
90	hmg coa inhibitor\$.ti,ab.	80	
91	atorvastatin.ti,ab.	9052	
92	fluvastatin.ti,ab.	1916	
93	lovastatin.ti,ab.	3891	
94	pitavastatin.ti,ab.	965	
95	pravastatin.ti,ab.	4130	
96	rosuvastatin.ti,ab.	3720	
97	simvastatin.ti,ab.	9844	
98	hypolipidemic\$.ti,ab.	4975	
99	anticholesteremic\$.ti,ab.	37	
100	colestipol.ti,ab.	388	
101	colesevelam.ti,ab.	267	
102	cholestyramine.ti,ab.	2421	
103	Lomitapide.ti,ab.	182	
104	antilipidemic.ti,ab.	261	
105	statin\$.ti,ab.	45838	
106	lipid lower\$.ti,ab.	15952	
107	(treat\$ or therap\$ or medicat\$).ti.	2279609	
108	Ezetimibe.ti,ab.	3315	
109	(Pcsk9 or alirocumab or evolocumab or kexin type 9).ti,ab.	4190	
110	diet, carbohydrate-restricted/	1743	
111	diet, fat-restricted/	3800	
112	diet, mediterranean/	3987	

Appendix A. Detailed Methods and Background

113	diet, protein-restricted/	3021	
114	diet, reducing/	11270	
115	diet, vegetarian/	3353	
116	caloric restriction/	6509	
117	portion size/	558	
118	Food habits/	86673	
119	Diet Therapy/	10758	
120	Soybean Proteins/	5023	
121	exp Fatty Acids, Omega-3/	26264	
122	Phytosterols/	3590	
123	Dietary Fiber/	18003	
124	Dietary Protein/	38273	
125	Dietary Carbohydrates/	26325	
126	Dietary Fats/	48594	
127	Flax/ or Linseed Oil/	3159	
128	diet\$.ti,ab.	597673	
129	((reduce\$ or reduction\$ or manipulat\$ or restrict\$) adj3 (fat\$ or carbohydrate\$ or cholesterol)).ti,ab.	37176	
130	low fat.ti,ab.	11788	
131	lowfat.ti,ab.	53	
132	fiber.ti,ab.	163435	
133	omega 3.ti,ab.	16378	
134	n 3 polyunsaturated fatty acid\$.ti,ab.	4075	
135	n 3 fatty acid\$.ti,ab.	4925	
136	n 3 pufa.ti,ab.	3738	
137	(oily fish or fish oil).ti,ab.	9983	
138	soy\$ protein\$.ti,ab.	5079	
139	plant stanol\$.ti,ab.	244	
140	plant sterol\$.ti,ab.	1642	
141	phytosterol\$.ti,ab.	3023	
142	esters.ti,ab.	55517	
143	(flaxseed or flax seed or linseed).ti,ab.	3865	
144	Exercise/	120559	
145	Exercise therapy/	43645	
146	Motor activity/	98253	
147	Physical fitness/	28251	
148	Plyometric Exercise/	699	
149	Physical Conditioning, Human/	2675	
150	Running/	21021	
151	Jogging/	826	
152	Swimming/	18576	
153	Walking/	35572	
154	Resistance training/	10008	
155	(exercise or exercising or exercises).ti,ab.	303724	
156	physical fitness.ti,ab.	10175	
157	physical conditioning.ti,ab.	840	
158	physical activity.ti,ab.	118971	
159	(running or jog\$ or swim\$ or walk\$).ti,ab.	228166	

Appendix A. Detailed Methods and Background

160 (lifestyle\$ or life style\$).ti,ab. 121203
161 Hyperlipidemias/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention and Control, Therapy]
10829
162 Dyslipidemias/dh, dt, pc, th 5481
163 Hypercholesterolemia/dh, dt, pc, th 13039
164 Lipid Metabolism Disorders/dh, dt, pc, th 116
165 Hyperlipoproteinemias/dh, dt, pc, th 850
166 Hypertriglyceridemia/dh, dt, pc, th 2038
167 Hyperlipoproteinemia Type II/dh, dt, pc, th 3087
168 Hyperlipidemia, Familial Combined/dh, dt, pc, th 214
169 Hypobetalipoproteinemias/dh, dt, pc, th 19
170 Abetalipoproteinemia/dh, dt, pc, th 76
171 or/77-170 3929484
172 (randomized controlled trial or controlled clinical trial).pt. or clinical trials as topic.sh. or exp
Randomized Controlled Trials as Topic/ or (randomized or randomised or placebo or randomly or phase
iii or phase 3).ti,ab. or trial.ti. 1503222
173 (RCT or placebo or sham or dummy or single blind\$ or double blind\$ or allocated or allocation or
triple blind\$ or treble blind\$ or random\$).ti,ab. not medline.st. 219633
174 172 or 173 1579915
175 36 and 46 and 171 and 174 3049
176 limit 175 to (english language and yr="2015 -Current") 949
177 ae.fs. 1817933
178 "Drug-Related Side Effects and Adverse Reactions"/ 33927
179 Mortality/ 47028
180 Morbidity/ 31543
181 Death/ 18279
182 mo.fs. 607424
183 (harm or harms or harmful or harmed).ti,ab. 130556
184 (adverse adj (effect\$ or event\$ or outcome\$)).ti,ab. 367548
185 safety.ti,ab. 559414
186 overtreat\$.ti,ab. 5495
187 (death or deaths).ti,ab. 878026
188 drug-induced liver injury/ 30304
189 drug-induced liver injury, chronic/ 408
190 Liver Neoplasms/ci 5534
191 Liver/de 88609
192 Liver failure/ci 649
193 Liver failure, acute/ci 1231
194 (liver adj3 (injur\$ or dysfunction\$ or failure\$)).ti,ab. 64935
195 (Hepatic adj3 (injur\$ or dysfunction\$ or failure\$)).ti,ab. 25836
196 (transaminase adj3 (elevat\$ or abnormal\$ or dysfunction\$)).ti,ab. 2650
197 Liver enzyme\$.ti,ab. 17388
198 alanine transaminase.ti,ab. 5576
199 alanine aminotransferase.ti,ab. 28631
200 aspartate transaminase.ti,ab. 4589
201 aspartate aminotransferase.ti,ab. 22827
202 (AST or ALT).ti,ab. 42513
203 Muscular Diseases/ci 2914

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204	Myositis/	8629
205	Myositis.ti,ab.	10130
206	Dermatomyositis/	8251
207	Dermatomyositis.ti,ab.	9326
208	myositis ossificans.ti,ab.	1437
209	Rhabdomyolysis/	5735
210	rhabdomyolysis.ti,ab.	8314
211	myotoxicity.ti,ab.	833
212	myopathy.ti,ab.	21049
213	muscle enzyme\$.ti,ab.	1853
214	(creatine adj3 (high or elevat\$ or abnormal\$)).ti,ab.	3591
215	Myalgia/	2095
216	myalgia.ti,ab.	7666
217	(Pain\$3 or rash\$2 or (skin adj (disease\$1 or disorder\$1 or reaction\$1)) or pruritus or cellulitis or prurigo or paraesthesia or nose bleeding or headache\$1 or migraine\$1 or (stomach adj (ache\$1 or complain\$)) or ((GI or gastrointestinal or gastro-intestinal) adj symptom\$1) or nausea or vomit\$3 or constipat\$ or bloat\$ or gas or flatulen\$ or gastroenteritis or loose stool\$ or diarrh?ea or dyspep\$ or (sleep adj (disturbance\$ or disorder\$)) or (muscle\$ adj (ache\$ or tender\$ or complain\$ or spasm\$)) or proteinuria or weight gain or decreased appetite or intestinal obstruction or fatigue or pharyngitis or nasopharyngitis or accidental injur\$3 or fever or flu syndrome or infection\$ or influenza or toothache\$1).ti,ab.	3098492
218	or/177-217	6390168
219	36 and 46 and 171 and 218	4166
220	limit 219 to (english language and yr="2015 -Current")	1363
221	49 or 76 or 176 or 220	5621

Cochrane Central Register of Controlled Clinical Trials (CENTRAL) via Wiley

Date Run: 14/07/2021 05:08:44

ID Search Hits

- #1 (hyperlipid*emi*:ti,ab,kw or dyslipid*emi*:ti,ab,kw or hypercholesterol*emi*:ti,ab,kw or hyperlipoprotein*emi*:ti,ab,kw or hypertriglycerid*emi*:ti,ab,kw or dysbetalipoprotein*emi*:ti,ab,kw or hypobetalipoproteinemi*:ti,ab,kw or abetalipoproteinemi*:ti,ab,kw) 20646
- #2 (familial near/3 apolipoprotein):ti,ab,kw 4
- #3 "heterozygous fh":ti,ab,kw or "homozygous fh":ti,ab,kw 58
- #4 (lipid next disorder*):ti,ab,kw or (lipid near/3 dysfunction*):ti,ab,kw 196
- #5 (high* or elevated or abnormal* or aberr*):ti,ab,kw near/3 (cholesterol or lipid* or LDL* or lipoprotein*):ti,ab,kw 16503
- #6 (low* or decrease* or deficien* or abnormal* or aberr*):ti,ab,kw near/3 HDL*:ti,ab,kw 3036
- #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 18069
- #8 (fasting or nonfasting or non-fasting or preprandial or pre-prandial or postprandial or post-prandial):ti,ab,kw next (lipid* or lipoprotein* or cholesterol):ti,ab,kw 1311
- #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 42855

Appendix A. Detailed Methods and Background

#10 (p*ediatric* or newborn* or child* or infant* or infancy or neonat* or preschool* or "early years" or adolescen* or teenage* or teens or preteen* or youth or "young people" or girl* or boy* or juvenile* or minors or baby or babies or school* or toddler*):ti,ab,kw 316698
#11 #9 and #10 with Publication Year from 2015 to present, in Trials 1631
#12 #11 NOT conference:pt 1392
#13 #12 NOT (clinicaltrials or trialsearch):so 953

Appendix A Table 1. Inclusion and Exclusion Criteria

	Inclusion criteria	Exclusion criteria
Condition	FH or multifactorial dyslipidemia* as defined by the studies	
Population	All KQs: Asymptomatic children and adolescents ≤20 years of age at time of screening or treatment initiation KQs 4,5 (Treatment Benefits and Harms): Treatment studies can have populations identified in any manner (including cascade screening)	KQs 1,2,3: Children and adolescents with any of the following: <ul style="list-style-type: none"> • Known dyslipidemia • Diagnosis associated with secondary dyslipidemia† • Established family history of FH KQs 4,5: <ul style="list-style-type: none"> • Diagnosis associated with secondary dyslipidemia* • Homozygous FH
Interventions	KQs 1,2,3 (Screening Benefits, Yield, and Harms): <ul style="list-style-type: none"> • Universal or selective screening using serum lipid panel (fasting or nonfasting lipid measurement, including one or more of the following: TC, LDL-C, HDL-C, non-HDL-C, TG) KQs 4,5 (Treatment Benefits and Harms): <ul style="list-style-type: none"> • Lipid-lowering medications • Behavioral interventions to promote healthy diet and physical activity • Dietary supplements 	KQs 1,2,3: <ul style="list-style-type: none"> • Genetic screening alone • Cascade screening KQs 4,5 in FH population: <ul style="list-style-type: none"> • Apheresis • Revascularization
Comparators	KQs 1,3 (Screening Benefits and Harms): <ul style="list-style-type: none"> • No screening or usual care KQ2: No comparator or any confirmatory test KQs 4,5 (Treatment Benefits and Harms): <ul style="list-style-type: none"> • No treatment or usual care 	
Outcomes	KQs 1,4 (Screening and Treatment Benefits): <ul style="list-style-type: none"> • Health outcomes: <ul style="list-style-type: none"> ○ MI ○ Ischemic stroke ○ CVD mortality ○ All-cause mortality • Intermediate outcomes: <ul style="list-style-type: none"> ○ Serum lipid concentrations (TC, LDL-C, HDL-C, and non-HDL-C, TG) ○ Atherosclerosis markers (carotid intima-media thickness, calcium score, pathological findings) ○ BMI • Behavioral Intermediate outcomes: <ul style="list-style-type: none"> ○ Physical activity, sedentary behavior, 	KQs 1,4: <ul style="list-style-type: none"> • Other serum markers (e.g., apolipoprotein A1, C-reactive protein)

Appendix A Table 1. Inclusion and Exclusion Criteria

	<p>dietary intake (for behavioral counseling interventions only)</p> <p>KQ2 (Yield):</p> <ul style="list-style-type: none"> • Screen positivity • PPV <p>KQ3 (Screening Harms):</p> <ul style="list-style-type: none"> • Psychosocial effects • Overdiagnosis • False positives/negatives <p>KQ5 (Treatment Harms): All harms from:</p> <ul style="list-style-type: none"> • Lipid-lowering medications (e.g., AEs, long-term safety, overtreatment) • Lifestyle modifications (e.g., nutritional, psychosocial) 	
Setting	<p>KQs 1,3-5: Primary care or referable from primary care</p> <p>KQ2 (Yield): Primary care or referable from primary care, population-based or community settings</p>	All KQs: Settings not generalizable to primary care
Study design	<p>KQ 1 (Screening Benefits): RCTs, CCTs</p> <p>KQs 3,5 (Yield, Screening and Treatment Harms): RCTs, CCTs, cohort studies, observational studies</p> <p>KQ2 (Yield): Recent large cohorts</p> <p>KQ4 (Treatment Benefits): RCTs</p>	KQ4: Comparative effectiveness studies
Country	<p>Studies that take place in countries categorized as “Very High” on the 2019 Human Development Index (as defined by the United Nations Development Programme) (published 2020).</p> <p>KQ2 (Yield): U.S. only</p>	Primary studies that are conducted in countries that are not categorized as “Very High” on the Human Development Index.
Publication language	English	Any language other than English
Quality rating	Fair – or good-quality studies	Poor quality studies, according to design- specific USPSTF criteria

* Multifactorial dyslipidemia defined as dyslipidemia not due to familial hypercholesterolemia

†Secondary causes of dyslipidemia include: renal (chronic renal disease, hemolytic uremic syndrome, nephrotic syndrome); infectious (acute viral or bacterial infections, HIV, hepatitis); hepatic (obstructive liver disease, cholestasis, biliary cirrhosis, Alagille syndrome); inflammatory (systemic lupus erythematosus, juvenile rheumatoid arthritis); storage (glycogen storage disease, Gaucher disease, cystine storage disease, Tay-Sachs disease, Niemann-Pick disease); and other (Kawasaki disease, anorexia nervosa, cancer, previous solid organ transplant, progeria, idiopathic hypercalcemia, Klinefelter syndrome, Werner syndrome, polycystic ovary syndrome, type 1 or 2 diabetes).

Abbreviations: AE = adverse event; BMI = body mass index; CCT = controlled clinical trials; CVD = cardiovascular disease; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein

Appendix A Table 1. Inclusion and Exclusion Criteria

cholesterol; KQs = Key Questions; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PPV = positive predictive value; RCT = randomized controlled trial; TC = total cholesterol; TG = triglycerides; U.S. = United States; USPSTF = United States Preventive Services Task Force

Appendix A Table 2. Study-Design Quality Rating Criteria

Study Design	Adapted Quality Criteria
Randomized clinical trials*, adapted from U.S. Preventive Services Task Force Manual ¹	<p>Bias arising in the randomization process or due to confounding</p> <ul style="list-style-type: none"> • Valid random assignment/random sequence generation method used • Allocation concealed • Balance in baseline characteristics <p>Bias in selecting participants into the study</p> <ul style="list-style-type: none"> • CCT only: No evidence of biased selection of sample <p>Bias due to departures from intended interventions</p> <ul style="list-style-type: none"> • Fidelity to the intervention protocol • Low risk of contamination between groups • Participants were analyzed as originally allocated <p>Bias from missing data</p> <ul style="list-style-type: none"> • No, or minimal, post-randomization exclusions • Outcome data are reasonably complete and comparable between groups • Reasons for missing data are similar across groups • Missing data are unlikely to bias results <p>Bias in measurement of outcomes</p> <ul style="list-style-type: none"> • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups • No evidence of biased use of inferential statistics <p>Bias in reporting results selectively</p> <p>No evidence that the measures, analyses, or subgroup analyses are selectively reported</p>
Nonrandomized studies of interventions*, adapted from ROBINS-I ²	<p>Bias arising in the randomization process or due to confounding</p> <ul style="list-style-type: none"> • Balance in baseline characteristics • No baseline confounding • No time-varying confounding • No evidence of biased selection of sample • Start of followup and start of intervention coincide <p>Bias in classifying interventions</p> <ul style="list-style-type: none"> • Participant intervention status is clearly and explicitly defined and measured • Classification of intervention status is unaffected by knowledge of the outcome or risk of the outcome. <p>Bias due to departures from intended interventions</p> <ul style="list-style-type: none"> • Participants were analyzed as originally allocated/assigned <p>Bias from missing data</p> <ul style="list-style-type: none"> • Outcome data are reasonably complete and comparable between groups • Confounding variables that are controlled for in analysis are reasonably complete • Reasons for missing data are similar across groups • Missing data are unlikely to bias results <p>Bias in measurement of outcomes</p> <ul style="list-style-type: none"> • Blinding of outcome assessors • Outcomes are measured using consistent and appropriate procedures and instruments across treatment groups <p>Bias in reporting results selectively</p> <p>No evidence that the measures, analyses, or subgroup analyses are selectively reported</p>
Cross-sectional studies assessed for Yield (KQ2)*, adapted from U.S. Preventive Services Task Force Manual ¹	<p>Bias arising due to confounding</p> <ul style="list-style-type: none"> • Evidence of biased sample selection or does the cohort represent a screening-eligible population • Differences between those participating in the study and not <p>Bias from missing data</p> <ul style="list-style-type: none"> • Extent of missing data • Outcomes measured using consistent and appropriate procedures across groups <p>Bias in reporting results selectively</p> <ul style="list-style-type: none"> • Evidence of selective reporting

*Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using *a priori* quality criteria

Appendix A Table 2. Study-Design Quality Rating Criteria

are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer.

Abbreviations: KQ = Key Question; ROBINS-I = Risk of Bias in Nonrandomised Studies - of Interventions; U.S. = United States

Appendix A Table 3. Treatment Recommendations of Other Organizations in Pediatric Populations

Organization, Year	Year published	Diet and Lifestyle	Medication
<p>American Heart Association Scientific Statement on cardiovascular risk reduction in high-risk pediatric patients³</p>	<p>2019</p>	<p>With elevated LDL-C</p> <ul style="list-style-type: none"> • If high-risk, consider simultaneous lifestyle modification and treatment with statin • If moderate risk, consider lifestyle modification for 3 mo (with addition of statin if LDL-C remains elevated) • If at risk, consider lifestyle modification for 6 mo (with addition of statin if LDL-C remains elevated) <p>With elevated triglycerides</p> <ul style="list-style-type: none"> • Provide lifestyle change counseling and repeat measures in 1-2 weeks • If still abnormal, obtain diagnostic evaluation and initiate management • Base treatment on TG level: <ul style="list-style-type: none"> ○ If TG 130-400 mg/dL and non-HDL-C < 145 mg/dL, treat with lifestyle modifications and repeat measures in 3 months and then periodically <ul style="list-style-type: none"> ▪ If TG 400-999 mg/dL, or triglycerides 130-400 mg/dL and non-HDL-C ≥ 145 mg/dL, treat based on risk category with goal of triglycerides < 150 mg/dL and non-HDL-C < 145 mg/dL. If high-risk, consider simultaneous lifestyle modification and pharmacotherapy ▪ If moderate-risk, consider lifestyle modification for 3 months (with addition of pharmacotherapy if goal not reached) ▪ If at-risk, consider lifestyle modification for 6 months (with addition of pharmacotherapy if goal not reached) <p>If TG >1,000 mg/dL confirmed with repeat testing, treat simultaneously with lifestyle</p>	<p>Recommended for high-risk, moderate-risk, and at-risk children*</p> <p>With elevated LDL-C</p> <ul style="list-style-type: none"> • If high risk, LDL-C goal <100 mg/dL • If mod-risk or at-risk, LDL-C goal <130 mg/dL • Statins first-line; if goals not met then add cholesterol absorption inhibitors • For homozygous familial hypercholesterolemia: additional treatments (LDL apheresis and proprotein convertase subtilisin kexin 9 [PCSK9] inhibitors) <p>With elevated triglycerides</p> <ul style="list-style-type: none"> • Goal TG < 150 mg/dL and non-HDL < 145 mg/dL • options include: <ul style="list-style-type: none"> ○ fenofibrate with consideration of potential hepatic and muscle effects and drug interactions ○ omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) 4 g/day) ○ statin if elevated non-HDL or apolipoprotein B

Appendix A Table 3. Treatment Recommendations of Other Organizations in Pediatric Populations

Organization, Year	Year published	Diet and Lifestyle	Medication
		modifications and omega-3 fatty acids or medications	
American Heart Association Scientific Statement ⁴ on Added Sugars and Cardiovascular Disease Risk in Children	2019	On added sugars and CVD risk in children: For all children, limit intake of sugar-sweetened beverages to ≤one 8-ounce beverage/week For children aged 2-18 years, consume ≤ 25 g (100 cal or approximately 6 teaspoons) of added sugar per day For children <2 years old, avoid added sugars	-
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol ⁵	2018	In children and adolescents with lipid disorders related to obesity: <ul style="list-style-type: none"> Intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity In children and adolescent with lipid abnormalities: lifestyle counseling is beneficial for lowering LDL-C	Children and adolescents >10 years of age with an LDL-C persistently above 190 mg/dL or above 160 mg/dL with a clinical presentation consistent with FH and who do not adequately respond to lifestyle change after 3-6mo: Initiate statin therapy
American Associate of Clinical Endocrinologists ⁶	2017	-	Offer pharmacotherapy for children > 10 years old who do not sufficiently respond to lifestyle modifications, especially if: <ul style="list-style-type: none"> LDL-C ≥ 190 mg/dL LDL-C ≥ 160 mg/dL and ≥ 2 CV risk factors after vigorous lifestyle intervention Family history of premature (before age 55 years) atherosclerotic CVD Overweight, obesity, or other elements of insulin resistance syndrome Further details on followup and monitoring are provided
National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents ⁷	2012	Recommended first step: Cardiovascular Health Integrated Lifestyle Diet (CHILD 1 Diet);† but if triglyceride levels ≥ 500 mg/dL or low-density lipoprotein cholesterol (LDL-C) ≥ 250 mg/dL child should also be referred immediately to lipid specialist.	Age 0-10 years: <ul style="list-style-type: none"> Pharmacologic treatment (under care of lipid specialist) limited to children with: <ul style="list-style-type: none"> Homozygous FH with LDL-C ≥ 400 mg/dL Primary hypertriglyceridemia with TGs ≥ 500 mg/dL High-risk condition Evidence CVD

Appendix A Table 3. Treatment Recommendations of Other Organizations in Pediatric Populations

Organization, Year	Year published	Diet and Lifestyle	Medication
		<p>If CHILD 1 diet† and lifestyle mgmt. do not achieve therapeutic goals after 3 months, lipid parameter-specific dietary changes recommended</p> <p>Consider CHILD 2-LDL diet† for elevated LDL cholesterol in pts aged 2-21 years</p> <p>Age 11-21 years with elevated LDL-C levels (using average of 2 measures 2 weeks to 3 months apart):</p> <ul style="list-style-type: none"> • Detailed family history and risk factor assessment required before starting drug therapy • If LDL-C ≥ 250 mg/dL consult lipid specialist • If LDL-C 130mg/dL to <250 mg/dL, or HDL-C ≥ 145mf/dL <ul style="list-style-type: none"> ○ Refer to dietitian for medical nutrition therapy with CHILD 1 diet, then CHILD 2-LDL diet for 6 months, then repeat fasting lipid profile ○ If LDL-C <130mg/dL, continue CHILD 2-LDL diet and reevaluate in 12 months ○ If LDL-C 130-189mg/dL, negative family history, and no other risk factors or risk conditions <ul style="list-style-type: none"> ▪ Continue CHILD 2-LDL diet and reevaluate every 6 months ▪ Drug therapy not generally indicated, but treatment with bile acid sequestrants might be considered in consultation with lipid specialist <p>Consider CHILD 2-triglyceride (TG) diet† for elevated TGs (or non-high-density lipoprotein cholesterol) for pts aged 2-21 years</p>	<ul style="list-style-type: none"> ○ Postcardiac transplantation • Statins may be considered in children aged 8-9 years with average LCL-C ≥ 190 mg/dL after CHILD 2-LDL diet if positive family history, ≥ 1 high-level risk factor, or ≥ 2 moderate-level risk factors <p>Age 11-21 years with elevated LDL-C levels (using average of 2 measures 2 weeks to 3 months apart): Consider starting statin therapy if</p> <ul style="list-style-type: none"> ▪ LDL-C 130-159 mg/dL and either ≥ 2 high-level risk factors or 1 high-level and ≥ 2 ▪ LDL-C 160-189 mg/dL and any of positive family history, ≥ 1 high-level risk factors, or ≥ 2 moderate-level risk factors ▪ LDL-C ≥ 190 mg/dL <p>Children > 10 years old with non-HDL-C ≥145 mg/dL after LDL-C goal achieved may be considered (with lipid specialist) for additional treatment with statins, fibrates, or niacin</p> <p>Children on statin therapy should be counseled and carefully monitored</p>

Appendix A Table 3. Treatment Recommendations of Other Organizations in Pediatric Populations

Organization, Year	Year published	Diet and Lifestyle	Medication
		<p>Age 11-21 years with elevated TG levels (using average of 2 measure 2 weeks to 3 months apart):</p> <ul style="list-style-type: none"> • Detailed family history and risk factor assessment required before starting drug therapy • In child with obesity, nutrition therapy should include calorie restriction and increased activity beyond that recommended for all children • If TG \geq100 mg/dL in child <10 years old or \geq 130 md/dL in child aged 10-19 years but <500 mg/dL <ul style="list-style-type: none"> ○ Refer to dietitian for medical nutrition therapy with CHILD 1 diet, then CHILD 2-TG diet for 6 months, then repeat fasting lipid profile <ul style="list-style-type: none"> ▪ If TG < 100 mg/dL in child < 10 years old or < 130 mg/dL in child aged 10-19 years, continue CHILD 2-TG diet and reevaluate every 6-12 months ▪ If TG > 100 mg/dL in child < 10 years old or > 130 mg/dL in child aged 10-19 years, reconsult dietitian for intensified CHILD 2-TG counseling ▪ If TG 200-499 mg/dL and non-HDL-C \geq 145 mg/dL, consider fish oil and/or consultation with lipid specialist ▪ If TG \geq500 mg/dL, consult lipid specialist ○ If average fasting TG levels \geq500 mg/dL OR any single TG level \geq1000 mg/dL related to primary hypertriglyceridemia, start CHILD 2-TG diet (and consider fish oil, fibrate, or niacin to prevent pancreatitis) 	

Appendix A Table 3. Treatment Recommendations of Other Organizations in Pediatric Populations

Organization, Year	Year published	Diet and Lifestyle	Medication
		Physical activity recommendations: 1 hour/day of moderate-to-vigorous physical activity with vigorous physical activity 3 days/week and limiting leisure screen time to < 2 hours/day	
National Lipid Association ⁸	2011	-	<p>Both children and adults with LDL cholesterol ≥ 190 mg/dL [or non-HDL-C ≥ 220 mg/dL] after lifestyle changes will require drug therapy</p> <p>Statins are preferred for initial pharmacologic treatment in children after initiation of diet and physical activity management.</p> <p>Consideration should be given to starting treatment at ≥ 8. In special cases, such as those with homozygous FH, treatment might need to be initiated at earlier ages.</p> <p>Further details on management issues in pediatrics are provided</p>

*High risk = Homozygous FH, type-2 diabetes, end-stage renal disease, type-1 diabetes, Kawasaki disease with persistent aneurysms, solid-organ transplant vasculopathy, childhood cancer survivor (stem cell recipient)

Moderate risk = Severe obesity (BMI $>95^{\text{th}}$ percentile), heterozygous FH, confirmed HTN, coarctation, Lp(a), predialysis CKD, AS, childhood cancer survivor (chest radiation)

At risk = Obesity, insulin resistance with comorbidities (dyslipidemia, NAFLD, PCOS), white-coat HTN, HCM and other cardiomyopathies, pulmonary HTN, chronic inflammatory conditions (JIA, SLE, IBD, HIV), s/p coronary (cardiotoxic chemotherapy only), Kawasaki disease with regressed aneurysms ($z_{\text{Max}} \geq 5$)

†Full details of CHILD 1 and CHILD-2 diets can be found in the full recommendation report.

Abbreviations: AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA = American Academy of Physician Assistants; ABC = Association of Black Cardiologists; ACC = American College of Cardiology; ACPM = American College of Preventive Medicine; ADA = American Diabetes Association; AGS = American Geriatrics Society; AHA = American Heart Association; APhA = American Pharmacists Association; ASPC = American Society for Preventive Cardiology; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; ; CV = cardiovascular; CVD = cardiovascular disease; DNA = deoxyribonucleic acid; FH = familial hypercholesterolemia; g/day = grams per day; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; mg/dL = milligrams per deciliter; NLA = National Lipid Association; PCNA = Preventive Cardiovascular Nurses Association; PCSK9 = proprotein convertase subtilisin/kexin type 9; TG = triglycerides

Appendix A Table 4. NCEP Step I and II Dietary Therapy of High Cholesterol⁹

Nutrient	Step I Diet, recommended intake	Step II Diet, recommended intake
Total Fat	<30% of total calories	<30% of total calories
<ul style="list-style-type: none"> • Saturated fatty acids 	<10% of total calories	<7% of total calories
<ul style="list-style-type: none"> • Polyunsaturated fatty acids 	Up to 10% of total calories	Up to 10% of total calories
<ul style="list-style-type: none"> • Monounsaturated fatty acids 	10-15% of total calories	10-15% of total calories
Carbohydrates	50-60% of total calories	50-60% of total calories
Protein	10-20% of total calories	10-20% of total calories
Cholesterol	<300 mg/d	<200 mg/d
Total calories	To achieve and maintain desirable weight	To achieve and maintain desirable weight

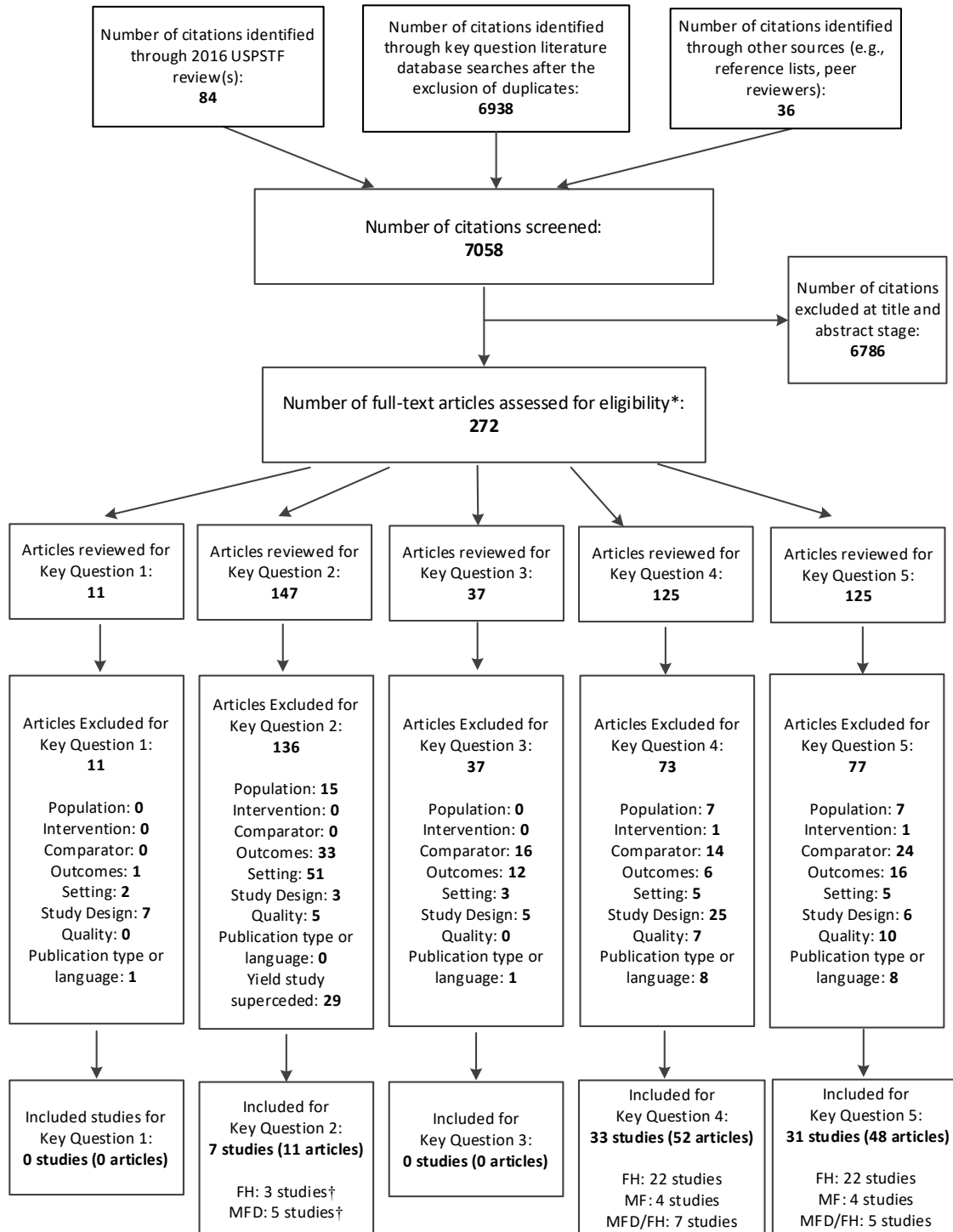
Abbreviations: mg/d = milligrams per day; NCEP = National Cholesterol Education Program

Appendix A Table 5. FDA-Approved Drugs in Pediatric Populations¹⁰⁻¹³

Drug Class	Drug (No of included studies)	Ages, years	Indication	Dose (mg/day)
Statins	Atorvastatin (1)	10-17	Heterozygous FH	10-20
	Fluvastatin (0)	10-16	Heterozygous FH	20-80
	Lovastatin (2)	10-17	Heterozygous FH	10-40
	Pitavastatin (1)	≥8	Heterozygous FH	2-4
	Pravastatin (2)	8-18	Heterozygous FH	20-40
	Rosuvastatin (1)	8-17	Heterozygous FH	5-20
	Simvastatin (3)	10-17	Heterozygous FH	10-40
Bile acid sequestrants	Colesevelam (1)	10-17	Heterozygous FH	1.875-3.75 g/day
Ezetimibe	Ezetimibe (1)	≥10	Heterozygous FH	10
PCSK9 Inhibitor	Evolocumab (1)	≥10	Heterozygous FH	420 mg in monthly injections

Abbreviations: FDA = U.S. Food & Drug Administration; FH= familial hypercholesterolemia; g = gram; mg/dL = milligram per deciliter; PCSK9 = proprotein convertase subtilisin/kexin type 9

Appendix B Figure 1. Literature Flow Diagram



* Studies may appear in more than one Key Question

† One study reports both FH and MFD populations

Appendix C. Included Studies List

Included studies List, by Key Question (KQ)

Ancillary publication(s) indented under primary article

KQs 1 and 3: Included studies for screening benefits and harms

No included studies

KQ 2: Included studies for screening yield, by condition

Familial Hypercholesterolemia

de Ferranti SD, Rodday AM, Mendelson MM, et al. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation*. 2016;133(11):1067-72. <https://doi.org/10.161/CIRCULATIONAHA.115.018791>.

Elliott E, Lilly C, Murphy E, et al. The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project: An 18 Year Review. *Curr Pediatr Rev*. 2017;13(4):265-76. PMID: 29345596. <https://doi.org/10.2174/1573400514666180117093652>

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. doi: 10.1542/peds.2009-546. Epub 10 Jul 12.

Jackson CL, Keeton JZ, Eason SJ, et al. Identifying Familial Hypercholesterolemia Using a Blood Donor Screening Program With More Than 1 Million Volunteer Donors. *JAMA Cardiol*. 2019;4(7):685-9. PMID: 31116347. <https://dx.doi.org/10.1001/jamacardio.2019.1518>

Multifactorial dyslipidemia

Bauer KW, Marcus MD, El ghormli L, et al. Cardio-metabolic risk screening among adolescents: understanding the utility of body mass index, waist circumference and waist to height ratio. *Pediatr Obes*. 2015;10(5):329-37. PMID: 25515620. <https://dx.doi.org/10.1111/ijpo.267>

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Nguyen D, Kit B, Carroll M. Abnormal Cholesterol Among Children and Adolescents in the United States, 2011-2014. *NCHS data brief.* 2015(228):1-8.

Reina SA, Llabre MM, Vidot DC, et al. Metabolic Syndrome in Hispanic Youth: Results from the Hispanic Community Children's Health Study/Study of Latino Youth. *Metab.* 2017;15(8):400-6. PMID: 28829223. <https://dx.doi.org/10.1089/met.2017.0054>

KQs 4-5: Included studies for treatment benefit and harms, by condition

Familial Hypercholesterolemia

Amundsen AL, Ose L, Nenseter MS, et al. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia. *Am J Clin Nutr.* 2002;76(2):338-44. PMID: 12145004. <https://doi.org/10.1093/ajcn/76.2.338>

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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. [https://doi.org/10.1016/s0735-1097\(02\)02593-7](https://doi.org/10.1016/s0735-1097(02)02593-7)

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Multifactorial dyslipidemia/FH

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Dennison BA, Levine DM. Randomized, double-blind, placebo-controlled, two-period crossover clinical trial of psyllium fiber in children with hypercholesterolemia. J Pediatr. 1993;123(1):24-9. PMID: 8391569. [https://doi.org/10.1016/s0022-3476\(05\)81532-x](https://doi.org/10.1016/s0022-3476(05)81532-x)

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Guardamagna O, Abello F, Cagliero P, et al. Could dyslipidemic children benefit from glucomannan intake? Nutrition. 2013;29(7-8):1060-5. <https://doi.org/10.1016/j.nut.2013.02.010>

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Martino F, Martino E, Morrone F, et al. Effect of dietary supplementation with glucomannan on plasma total cholesterol and low density lipoprotein cholesterol in hypercholesterolemic children. Nutr Metab Cardiovasc Dis. 2005;15(3):174-80. PMID: 15955465. <https://doi.org/10.1016/j.numecd.2004.04.004>

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. 2014;65(3):375-9. <https://doi.org/10.3109/09637486.2013.858239>

Appendix D. Excluded Studies List

Reason for Exclusion*
E1. Aim/relevant
E2. Population
E3. Intervention
E4. Comparator
E5. Outcomes (no relevant outcomes)
E6. Setting
E6a. Not conducted in US (KQ2-specific)
E7. Design
E8. Non-Very High HDI Country
E9. Non-English
E10. Poor quality
E11. Ongoing study, no outcomes published
E12. Conference abstract only
E13. Yield study that is out for size or recency (KQ2-specific)
E13a. Yield study with sub-analyses that are not relevant for review
E13b. Yield study where data is captured in another overlapping cohort or publication

*Assigned at full-text phase

Abbreviations: E = exclude; HDI = Human Development Index; KQ = key question, US = United States

- Abello, F, Cagliero, P, et al. Lycopene supplementation in children affected by primary dyslipidaemia: Effects on lipid profile and oxidative stress. *High Blood Press Cardiovasc Prev.* 2(94): . 2012. <https://dx.doi.org/>. **KQ4E12, KQ5E12**
- Abul-Husn, NS, Manickam, K, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science.* 354(6319): aaf7000. doi: 10.1126/science.aaf7000.. 2016. <https://dx.doi.org/>. **KQ2E5**
- Ademi, Z, Martin, AC. Universal screening of children for familial hypercholesterolaemia: Value for money?. *Atherosclerosis.* 275(): 384-386. 2018. <https://dx.doi.org/><https://dx.doi.org/10.1016/j.atherosclerosis.2018.06.874>. **KQ1E7, KQ3E7**
- Akcan, N, Obaid, M, et al. Evidence in obese children: contribution of tri-ponderal mass index or body mass index to dyslipidemia, obesity-inflammation, and insulin sensitivity. *Journal of Pediatric Endocrinology & Metabolism.* 33(2): 223-231. 2020. <https://dx.doi.org/><https://dx.doi.org/10.1515/jpem-2019-0106>. **KQ2E6a**
- Albaum, JM, Carsley, S, et al. Persistent High Non-High-Density Lipoprotein Cholesterol in Early Childhood: A Latent Class Growth Model Analysis. *J Pediatr.* 191(): 152-157. 2017. <https://dx.doi.org/><https://dx.doi.org/10.1016/j.jpeds.2017.08.079>. **KQ2E6a**
- Alemzadeh, R, Kichler, J. Comparison of Apolipoprotein (ApoB/ApoA-1) and Lipoprotein (Total Cholesterol/HDL) Ratios in Obese Adolescents. *Metab Syndr Relat Disord.* 16(1): 40-45. 2018. <https://dx.doi.org/><https://dx.doi.org/10.1089/met.2017.0135>. **KQ2E5**
- Alias-Hernandez, I, Galera-Martinez, R, et al. Insulinaemia and insulin resistance in Caucasian general paediatric population aged 2 to 10 years: Associated risk factors. *Pediatr Diabetes.* 19(1): 45-52. 2018. <https://dx.doi.org/><https://dx.doi.org/10.1111/pedi.12533>. **KQ2E6a**
- Allen-Tice, C, Steinberger, J, et al. Pediatric cholesterol screening practices in 9- to 11-year-olds in a large midwestern primary care setting. *J Clin Lipidol.* 14(2): 224-230. 2020. <https://dx.doi.org/><https://dx.doi.org/10.1016/j.jacl.2020.01.013>. **KQ2E10**
- Anderson, LN, Maguire, JL, et al. Duration of Fasting, Serum Lipids, and

Appendix D. Excluded Studies List

- Metabolic Profile in Early Childhood. *J Pediatr.* 180(): 47-52.e1. 2017. <https://dx.doi.org/https://dx.doi.org/10.1016/j.jpeds.2016.09.005>. **KQ2E6a**
10. Antwi, J, Lavin, R, et al. Perception of and risk factors for type 2 diabetes among students attending an upstate New York college: a pilot study. *Diabetol Metab Syndr.* 12(): 25. 2020. <https://dx.doi.org/https://dx.doi.org/10.1186/s13098-020-00535-1>. **KQ2E2**
11. Araujo, MB, Pacce, MS. A 10-year experience using combined lipid-lowering pharmacotherapy in children and adolescents. *Journal of Pediatric Endocrinology & Metabolism.* 29(11): 1285-1291. 2016. <https://dx.doi.org/https://dx.doi.org/10.1515/jpem-2016-0117>. **KQ4E7, KQ5E4**
12. Attilakos, A, Zerva, O, et al. Effect of phytosterols on serum lipids of children with hypercholesterolemia. *J Inherit Metab Dis.* 41 Suppl 1(): S43. 2018. <https://dx.doi.org/>. **KQ4E12, KQ5E12**
13. Balder, JW, Lansberg, PJ, et al. Pediatric lipid reference values in the general population: The Dutch lifelines cohort study. *J Clin Lipidol.* 12(5): 1208-1216. 2018. <https://dx.doi.org/https://dx.doi.org/10.1016/j.jacl.2018.05.011>. **KQ2E6a, KQ3E4**
14. Baran, J, Weres, A, et al. Blood lipid profile and body composition in a pediatric population with different levels of physical activity. *Lipids Health Dis.* 17(1): 171. 2018. <https://dx.doi.org/https://dx.doi.org/10.1186/s12944-018-0817-2>. **KQ2E6a**
15. Barreiro-Ribeiro, F, Vasques, AC, et al. Hypertriglyceridemic Waist Phenotype Indicates Insulin Resistance in Adolescents According to the Clamp Technique in the BRAMS Study. *Childhood Obesity.* 12(6): 446-454. 2016. <https://dx.doi.org/>. **KQ2E8, KQ3E8**
16. Behiry, EG, El Nady, NM, et al. Evaluation of TG-HDL Ratio Instead of HOMA Ratio as Insulin Resistance Marker in Overweight and Children with Obesity. *Endocr Metab Immune Disord Drug Targets.* 19(5): 676-682. 2019. <https://dx.doi.org/https://dx.doi.org/10.2174/1871530319666190121123535>. **KQ2E6a**
17. Blakeley, Ce, Van, Rompay Mi, et al. Relationship between muscle strength and dyslipidemia, serum 25(OH)D, and weight status among diverse schoolchildren: a cross-sectional analysis. *BMC Pediatr.* 18(1) (no pagination): . 2018. <https://dx.doi.org/10.1186/s12887-018-0998-x>. **KQ2E13**
18. Blumenfeld, Olivares Ja, San, Mauro Martín I, et al. Low-fat, fermented milk enriched with plant sterols, a strategy to reduce hypertriglyceridemia in children, a double-blind, randomized placebo-controlled trial. *Nutr Hosp.* 32(3): 1056-1060. 2015. <https://dx.doi.org/10.3305/nh.2015.32.3.9319>. **KQ4E9, KQ5E9**
19. Borresen, EC, Jenkins-Puccetti, N, et al. A Pilot Randomized Controlled Clinical Trial to Assess Tolerance and Efficacy of Navy Bean and Rice Bran Supplementation for Lowering Cholesterol in Children. *Lobal Pediatric Health.* 4(): 2333794X17694231. 2017. <https://dx.doi.org/https://dx.doi.org/10.1177/2333794X17694231>. **KQ4E10, KQ5E10**
20. Braamskamp, MJ, Hutten, BA, et al. Early initiation of statin treatment in children with familial hypercholesterolaemia. *Curr Opin Lipidol.* 26(3): 236-9. 2015. <https://dx.doi.org/https://dx.doi.org/10.1097/MOL.000000000000177>. **KQ1E7, KQ2E7, KQ3E7, KQ4E7, KQ5E7**
21. Braamskamp, Mjam, Langslet, G, et al. Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). *Circulation.* 136(4): 359-366. 2017. PMID: 28592434. <https://dx.doi.org/https://dx.doi.org/10.11>

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- 61/CIRCULATIONAHA.116.025158. **KQ4E7, KQ5E5**
22. Braamskamp, Mjam, Langslet, G, et al. Efficacy and safety of rosuvastatin therapy in children and adolescents with familial hypercholesterolemia: Results from the CHARON study. *J Clin Lipidol.* 9(6): 741-750. 2015. PMID: 26687694. <https://dx.doi.org/10.1016/j.jacl.2015.07.011>. **KQ4E4, KQ5E4**
23. Bridges, KG, Jarrett, T, et al. Use of the triglyceride to HDL cholesterol ratio for assessing insulin sensitivity in overweight and obese children in rural Appalachia. *Journal of Pediatric Endocrinology & Metabolism.* 29(2): 153-6. 2016. <https://dx.doi.org/https://dx.doi.org/10.1515/jpem-2015-0158>. **KQ2E13**
24. Bucholz, EM, Gooding, HC, et al. Awareness of Cardiovascular Risk Factors in U.S. Young Adults Aged 18-39 Years. *Am J Prev Med.* 54(4): e67-e77. 2018. <https://dx.doi.org/https://dx.doi.org/10.1016/j.amepre.2018.01.022>. **KQ2E2**
25. Bugge, A, Moller, S, et al. Associations between waist circumference, metabolic risk and executive function in adolescents: A cross-sectional mediation analysis. *PLoS ONE [Electronic Resource].* 13(6): e0199281. 2018. <https://dx.doi.org/https://dx.doi.org/10.1371/journal.pone.0199281>. **KQ2E6a**
26. Buonomo, PS, Macchiaiolo, M, et al. Statin-associated myopathy in pediatric settings: Myth or fact?. *J Pediatr.* 191(): 279. 2017. <https://dx.doi.org/https://dx.doi.org/10.1016/j.jpeds.2017.08.056>. **KQ4E5, KQ5E7**
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28. Cagliero, P, Abello, F, et al. Effects of bifidobacterium supplementation on plasma lipid profile in dyslipidemic children. *High Blood Press Cardiovasc Prev.* 20(2): 93-114. 2013. <https://dx.doi.org/>. **KQ4E12, KQ5E12**
29. Cagliero, P, Marini, E, et al. The effects of probiotics supplementation on antioxidant activity in children affected by primary hyperlipidemia. *High Blood Press Cardiovasc Prev.* 21(2): 151-169. 2014. <https://dx.doi.org/>. **KQ4E12, KQ5E12**
30. Carreau, V, Girardet, JP, et al. Long-term follow-up of statin treatment in a cohort of children with familial hypercholesterolemia: efficacy and tolerability. *Paediatr Drugs.* 13(4): 267-75. 2011. PMID: 21692550. <https://dx.doi.org/10.2165/11591650-000000000-00000>. **KQ4E4, KQ5E4**
31. Carson, V, Tremblay, MS, et al. Compositional analyses of the associations between sedentary time, different intensities of physical activity, and cardiometabolic biomarkers among children and youth from the United States. *PLoS ONE [Electronic Resource].* 14(7): e0220009. 2019. <https://dx.doi.org/https://dx.doi.org/10.1371/journal.pone.0220009>. **KQ2E5**
32. Cayres, SU, de Lira, FS, et al. The mediating role of physical inactivity on the relationship between inflammation and artery thickness in prepubertal adolescents. *J Pediatr.* 166(4): 924-9. 2015. <https://dx.doi.org/https://dx.doi.org/10.1016/j.jpeds.2014.12.057>. **KQ2E6a**
33. Centers for Disease Control Prevention, . Prevalence of abnormal lipid levels among youths --- United States, 1999-2006. *MMWR Morb Mortal Wkly Rep.* 59(2): 29-33. 2010. PMID: 20094024. <https://dx.doi.org/>. **KQ2E13**
34. Cesa, CC, Barbiero, SM, et al. Effectiveness of physical exercise to reduce cardiovascular risk factors in youths: a randomized clinical trial. *J Clin Med Res.* 7(5): 348-55. 2015. <https://dx.doi.org/https://dx.doi.org/10.14740/jocmr1700w>. **KQ1E8, KQ2E8, KQ3E8, KQ4E8, KQ5E8**

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35. Chahal, N, McCrindle, B, et al. A 4-week randomized clinical trial of flaxseed supplementation in children with hypercholesterolemia. *Can J Cardiol.* (5): S339. 2011. <https://dx.doi.org/>. **KQ4E12, KQ5E12**
36. Chahal, N, Rush, J, et al. Dyslipidemia management in overweight or obese adolescents: A mixed-methods clinical trial of motivational interviewing. *SAGE Open Medicine.* 5(5): 2050312117707152. 2017. <https://dx.doi.org/><https://dx.doi.org/10.1177/2050312117707152>. **KQ4E4, KQ5E4**
37. Chen, E, Miller, Ge, et al. Unsupportive parenting moderates the effects of family psychosocial intervention on metabolic syndrome in African American youth. *Int J Obes (Lond).* 42(4): 634-640. 2018. <https://dx.doi.org/10.1038/ijo.2017.246>. **KQ2E5, KQ4E5, KQ5E5**
38. Choi, YS, Klaric, JS, et al. Prediction of Insulin Resistance with Anthropometric and Clinical Laboratory Measures in Nondiabetic Teenagers. *Metab Syndr Relat Disord.* 17(1): 37-45. 2019. <https://dx.doi.org/><https://dx.doi.org/10.1089/met.2018.0072>. **KQ2E5**
39. Christensen, JJ, Ulven, SM, et al. Comprehensive lipid and metabolite profiling of children with and without familial hypercholesterolemia: A cross-sectional study. *Atherosclerosis.* 266(1): 48-57. 2017. <https://dx.doi.org/><https://dx.doi.org/10.1016/j.atherosclerosis.2017.09.021>. **KQ2E6a, KQ3E5**
40. Clarke, JT, Cullen-Dean, G, et al. Increased incidence of epistaxis in adolescents with familial hypercholesterolemia treated with fish oil. *J Pediatr.* 116(1): 139-41. 1990. [https://dx.doi.org/10.1016/s0022-3476\(05\)81666-x](https://dx.doi.org/10.1016/s0022-3476(05)81666-x). **KQ4E7, KQ5E4**
41. Corriveau, N, Eagle, T, et al. Sustained Benefit Over Four-Year Follow-Up of Michigan's Project Healthy Schools. *Am J Public Health.* 105(12): e19-25. 2015. <https://dx.doi.org/><https://dx.doi.org/10.2105/AJPH.2015.302835>. **KQ2E5**
42. Cottrell, L, John, C, 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.* 2013:732579.(doi): 10.1155/2013/732579. Epub 2013 Jun 5. 2013. PMID: 23840946. <https://dx.doi.org/>. **KQ2E13b**
43. Cottrell, L, Lilly, C, et al. Chronic disease risk screening: characteristics of parents who participate in screening with their children. *West Virginia Medical Journal.* 111(1): 26-31. 2015. <https://dx.doi.org/>. **KQ2E5**
44. Croyle, RT, Sun, YC, et al. Psychological minimization of cholesterol test results: moderators of appraisal in college students and community residents. *Health Psychol.* 12(6): 503-7. 1993. PMID: 8293735. <https://dx.doi.org/10.1037//0278-6133.12.6.503>. **KQ3E4**
45. Daniels, S, Caprio, S, et al. PCSK9 inhibition with alirocumab in pediatric patients with heterozygous familial hypercholesterolemia: The ODYSSEY KIDS study. *J Clin Lipidol.* 14(3): 322-330.e5. 2020. <https://dx.doi.org/><https://dx.doi.org/10.1016/j.jacl.2020.03.001>. **KQ4E7, KQ5E4**
46. Davidson, MH, Dugan, LD, et al. A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. *Am J Clin Nutr.* 63(1): 96-102. 1996. PMID: 8604676. <https://dx.doi.org/10.1093/ajcn/63.1.96>. **KQ4E10, KQ5E10**
47. Davidson, MH, Dugan, LD, et al. A psyllium-enriched cereal for the treatment of hypercholesterolemia in children: a controlled, double-blind, crossover study. *Am J Clin Nutr.* 63(1): 96-102. 1996. PMID: 8604676. <https://dx.doi.org/10.1093/ajcn/63.1.96>. **KQ4E10, KQ5E10**
48. de Ferranti, SD, Shrader, P, et al. Children with Heterozygous Familial Hypercholesterolemia in the United

Appendix D. Excluded Studies List

- States: Data from the Cascade Screening for Awareness and Detection-FH Registry. *J Pediatr.* 229(): 70-77. 2021. <https://dx.doi.org/https://dx.doi.org/10.1016/j.jpeds.2020.09.042>. **KQ2E5, KQ3E5, KQ4E7, KQ5E5**
49. Deeb, A, Attia, S, et al. Dyslipidemia and Fatty Liver Disease in Overweight and Obese Children. *J Obes.* 2018(): 8626818. 2018. <https://dx.doi.org/https://dx.doi.org/10.1155/2018/8626818>. **KQ2E6a**
50. Dhuper, S, Bayoumi, NS, et al. Ethnic Differences in Lipid Profiles of Overweight, Obese, and Severely Obese Children and Adolescents 6-19 Years of Age. *Childhood Obesity.* 13(3): 236-241. 2017. <https://dx.doi.org/https://dx.doi.org/10.1089/chi.2016.0208>. **KQ2E5**
51. Dickey, W, Arday, DR, et al. Outpatient evaluation, recognition, and initial management of pediatric overweight and obesity in U.S. military medical treatment facilities. *J Am Assoc Nurse Pract.* 29(2): 85-93. 2017. <https://dx.doi.org/https://dx.doi.org/10.1002/2327-6924.12398>. **KQ2E5**
52. Dong, B, Arnold, LW, et al. Ethnic differences in cardiometabolic risk among adolescents across the waist-height ratio spectrum: National Health and Nutrition Examination Surveys (NHANES). *Int J Cardiol.* 222(): 622-628. 2016. <https://dx.doi.org/https://dx.doi.org/10.1016/j.ijcard.2016.07.169>. **KQ2E13b**
53. Doshi, N, Perrin, EM, et al. Short-term change in body mass index in overweight adolescents following cholesterol screening. *Arch Pediatr Adolesc Med.* 163(9): 812-7. 2009. PMID: 19736334. <https://dx.doi.org/10.1001/archpediatrics.2009.152>. **KQ1E7, KQ3E5**
54. Douglas, MB, Birrer, RB, et al. Obese children should be screened for hypercholesterolemia. *J Health Care Poor Underserved.* 7(1): 24-35. 1996. <https://dx.doi.org/10.1353/hpu.2010.0012>. **KQ2E13**
55. Draijer, LG, Bosch, AM, et al. Screening for lysosomal acid lipase deficiency: A retrospective data mining study and evaluation of screening criteria. *Atherosclerosis.* 278(): 174-179. 2018. <https://dx.doi.org/https://dx.doi.org/10.1016/j.atherosclerosis.2018.09.023>. **KQ2E6a, KQ3E5**
56. Ducobu, J, Brasseur, D, et al. Simvastatin use in children. *Lancet.* 339(8807): 1488. 1992. PMID: 1351171. [https://dx.doi.org/10.1016/0140-6736\(92\)92092-t](https://dx.doi.org/10.1016/0140-6736(92)92092-t). **KQ4E7, KQ5E4**
57. Elmaogullari, S, Demirel, F, et al. Risk factors that affect metabolic health status in obese children. *Journal of Pediatric Endocrinology & Metabolism.* 30(1): 49-55. 2017. <https://dx.doi.org/https://dx.doi.org/10.1515/jpem-2016-0128>. **KQ2E6a**
58. Faigel, HC. Screening college students for hypercholesterolemia. *J Am Coll Health.* 40(6): 272-5. 1992. <https://dx.doi.org/10.1080/07448481.1992.9936292>. **KQ2E13**
59. Fich M, Krzysko-Pieczka, I, et al. FKBP5 polymorphism is associated with insulin resistance in children and adolescents with obesity. *Obes Res Clin Pract.* 12(Suppl 2): 62-70. 2018. <https://dx.doi.org/https://dx.doi.org/10.1016/j.orcp.2016.11.007>. **KQ2E6a**
60. Florentin, M, Elisaf, MS, et al. L-Carnitine/Simvastatin Reduces Lipoprotein (a) Levels Compared with Simvastatin Monotherapy: A Randomized Double-Blind Placebo-Controlled Study. *Lipids.* 52(1): 1-9. 2017. <https://dx.doi.org/https://dx.doi.org/10.1007/s11745-016-4216-z>. **KQ4E2, KQ5E2**
61. Fonseca, MJ, Oliveira, A, et al. Association of Pubertal Development With Adiposity and Cardiometabolic Health in Girls and Boys-Findings From the Generation XXI Birth Cohort. *J Adolesc Health.* 65(4): 558-563. 2019. <https://dx.doi.org/https://dx.doi.org/10.1016/j.jadohealth.2019.05.014>. **KQ2E6a**
62. Ford, ES, Li, C, et al. Concentrations of low-density lipoprotein cholesterol and

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- total cholesterol among children and adolescents in the United States. *Circulation*. 119(8): 1108-15. 2009. PMID: 19221218. <https://dx.doi.org/10.1161/CIRCULATIONAHA.108.816769>. **KQ2E13**
63. Fritz, J, Lopez-Ridaura, R, et al. The association of Native American genetic ancestry and high-density lipoprotein cholesterol: A representative study of a highly admixed population. *Am J Hum Biol*. 32(6): e23426. 2020. <https://dx.doi.org/https://dx.doi.org/10.1002/ajhb.23426>. **KQ2E6a**
64. Futema, M, Cooper, JA, et al. Screening for familial hypercholesterolaemia in childhood: Avon Longitudinal Study of Parents and Children (ALSPAC). *Atherosclerosis*. 260(): 47-55. 2017. <https://dx.doi.org/https://dx.doi.org/10.1016/j.atherosclerosis.2017.03.007>. **KQ2E6a, KQ3E4**
65. Gagliano, NJ, Emans, SJ, et al. Cholesterol screening in the adolescent. *J Adolesc Health*. 14(2): 104-8. 1993. [https://dx.doi.org/10.1016/1054-139x\(93\)90093-5](https://dx.doi.org/10.1016/1054-139x(93)90093-5). **KQ2E13**
66. Gagné, C, Kusters, M, et al. Efficacy and Safety of Ezetimibe Monotherapy in 6-10 Year Old Children with Heterozygous Familial or Nonfamilial Hypercholesterolemia. *J Clin Lipidol*. 7(3): 257-258. 2013. <https://dx.doi.org/>. **KQ4E12, KQ5E12**
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68. Garcia, RE, Moodie, DS. Routine cholesterol surveillance in childhood. *Pediatrics*. 84(5): 751-5. 1989. PMID: 2640549. <https://dx.doi.org/>. **KQ2E13**
69. Garoufi, A, Drakatos, A, et al. Comparing calculated LDL-C with directly measured LDL-C in healthy and in dyslipidemic children. *Clin Biochem*. 50(1-2): 16-22. 2017. <https://dx.doi.org/https://dx.doi.org/10.1016/j.clinbiochem.2016.05.026>. **KQ2E6a, KQ3E5**
70. Giardi EV, Paul, TK, et al. Cardiovascular Disease Risk Among Young Urban Women. *Journal of Women's Health*. 25(11): 1139-1146. 2016. <https://dx.doi.org/>. **KQ2E2**
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Appendix E Table 1. Familial Hypercholesterolemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	FH Condition Criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
NHANES, 1999-2012 ¹⁴	NHANES participants 12 to 19 years of age between years 1999-2012	Pregnancy	LDL-C \geq 190 mg/dL	NHANES combines in-home interviews with mobile examinations and laboratory tests. Height and weight were measured with a digital scale and stadiometer in the NHANES mobile examination center. Lipid profiles were measured from morning peripheral blood draws. Serum total cholesterol and triglycerides were measured enzymatically; high-density lipoprotein cholesterol was measured by direct immunoassay or by precipitation. LDL-C was calculated by the Friedewald equation if the triglycerides level was \leq 400 mg/dL. 97.6% of participants with LDL-C reported fasting for \geq 8 hours.	LDL-C \geq 190 mg/dL	Community	NR
Blood donors ¹⁵	Age 16 years or older voluntarily donated blood to	Donors missing data for age or TC	To classify FH, the Make Early Diagnosis to Prevent Early Death	Deidentified data were obtained from the Carter BloodCare database. Demographic data, including age at the	Make Early Diagnosis to Prevent Early Death (MEDPED) criteria for FH:	Blood donation center	

Appendix E Table 1. Familial Hypercholesterolemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	FH Condition Criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
	Carter BloodCare between January 2002 and December 2016		(MEDPED) criteria were used, with TC thresholds of 270, 290, 340, and 360 mg/dL for donors younger than 20 years, 20 to 29 years, 30 to 39 years, and 40 years or older, respectively. For repeated donors, the maximum TC value was used for FH classification.	time of donation, sex, and race/ethnicity, were routinely collected, and TC was measured for each donation. Nonfasting TC was measured from 2002 through 2009 using the Abbott Aeroset System (Abbott Laboratories) and from 2010 through 2016 using the Beckman Coulter AU680 Chemistry Analyzer (Beckman Coulter Diagnostics). Both assays have a total coefficient of variation of less than 3%	TC \geq 270 mg/dL for donors younger than 20 years. For repeated donors, the maximum TC value was used for FH classification.		
CARDIAC ¹⁶	Fifth grade children enrolled in schools in West Virginia.	NR	Significant likelihood of FH: LDL \geq 190 mg/dL Suggests a genetic etiology, such as FH: LDL-C \geq 160mg/dL	Lipid screening including TC, LDL, HDL, and TG. BMI and blood pressure were also assessed, and children were screened for acanthosis nigricans to assess for prediabetes. Use of fasting lipid profile (instead of fingerstick) started in Year 5 (2002-2003) and changed from fasting	LDL \geq 130 mg/dL and HDL $<$ 40 mg/dL for MF	School	38.6% of eligible 5th graders participated in the screening program.

Appendix E Table 1. Familial Hypercholesterolemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	FH Condition Criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
				<p>to non-fasting lipid profile started 2nd semester of Year 15 (2012-2013). Children with LDL >130 mg/dL and HDL <40 mg/dL were considered with abnormal lipid values. Children with ≥190 mg/dL and a strong family history of premature heart disease were considered to have a significant likelihood of FH. Students received all assessments at one screening period at the beginning of the school day and a health report with findings was sent home to the participant's family 4-6 weeks after screening. Results and recommendations are also shared with the primary care physician if authorized by the parent/guardian on the consent form, as well as school nurses for appropriate follow-up and recording. A personal phone call is</p>			

Appendix E Table 1. Familial Hypercholesterolemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	FH Condition Criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
				<p>made to each parent and parent-identified physician if the child's results show triglycerides are >500 mg/dL, glucose is >125 mg/dL, systolic blood pressure is > 175 mm Hg, and LDL cholesterol is > 190 mg/dL. In addition, the parents of participating children receive a voucher to get their fasting lipid profile measured at no cost at a commercial reference laboratory. The CARDIAC Project identified and referred for treatment children and relatives with familial hypercholesterolemia (FH).</p>			

Abbreviations: CARDIAC = Coronary Artery Risk Detection in Appalachian Communities; FH = familial hypercholesterolemia; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MEDPED = Make Early Diagnosis to Prevent Early Death Program; MF = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; mm Hg = millimeters of mercury; NHANES = National Health and Nutrition Examination Survey; NR = not reported; TC = total cholesterol; TG = triglycerides

Appendix E Table 2. Multifactorial Dyslipidemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
NHANES ¹⁷	<p>Youths aged 6 to 19 years who attended an examination during any NHANES cycle from 1999-2000 to 2015-2016.</p> <p>Data from 1999-2000 through 2015-2016 to include all 9 continuous NHANES data cycles (vs earlier intermittent cycles). Included all available NHANES cycles for total cholesterol (1999-2016), triglycerides and LDL cholesterol (1999-2014), and apolipoprotein B (2005-2014). For HDL and non-HDL cholesterol, we included data from 2007-2016 only because NHANES documentation indicates that differing assay</p>	Friedewald LDL-C set to missing if TG >400 mg/dL	Data from the National Health and Nutrition Examination Survey (NHANES), which uses a complex, multistage probability sampling design to select a representative sample of the civilian noninstitutionalized US population. NHANES combines in-home interviews with mobile examinations and laboratory tests, including HDL and total cholesterol in youths aged 6 to 19 years and fasting triglycerides and apolipoprotein B in a subset of adolescents aged 12 to 19 years. Written informed consent, assent, or both was obtained from all participants.	<p>"Adverse cut points: TC ≥ 200 mg/dL HDL-C <40 mg/dL Non-HDL-C ≥145 mg/dL LDL-C ≥130 mg/dL TG ≥130 mg/dL</p>	Mobile clinical setting	Overall response rate was 81% (range, 65%-86% across cycles)

Appendix E Table 2. Multifactorial Dyslipidemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
	<p>methods and laboratories before 2007 caused bias within the HDL cholesterol values</p>					
<p>Study of Latinos (SOL) Youth study¹⁸</p>	<p>Eligible participants ages 8–16 whose parents/legal guardians participated in the Hispanic Community Health Study/ Study of Latinos (HCHS/SOL) were recruited to participate in the SOL Youth study.</p>	<p>All 8–9-year olds were excluded due to International Diabetes Federation (IDF) age cutpoints</p>	<p>Youth and parent participants underwent a 3.5-hr examination, during which biospecimens, anthropometric measures, blood pressure, fitness level, dietary intake, and physical activity were assessed. Psychosocial characteristics were also assessed by questionnaire in the participant’s preferred language (Spanish or English). Blood specimens (HDL, triglycerides, fasting glucose, and insulin) were taken after an overnight fast, stored at -70C, and shipped to the central laboratory for processing the specimen collection. HDL and triglycerides were measured in serum on a</p>	<p>Fasting. Multiple reported for Trig and HDL thresholds--> NCEP ATP III, mg/Dl: Trig ≥110; HDL <40 WHO, mg/Dl: Trig ≥150; HDL <35 IDF (ages 10+) mg/dL: Trig ≥150; HDL <50 (those 10-15), <40 (Ages 16+)</p>	<p>NR</p>	<p>NR</p>

Appendix E Table 2. Multifactorial Dyslipidemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
			Roche/Modular P Chemistry Analyzer (Roche Diagnostics Corporation, Indianapolis, IN) using a direct magnesium/dextran sulfate method (HDL) and glycerol blanking enzymatic method (triglycerides).			
HEALTHY study ¹⁹	Middle schools with student populations at increased risk for type 2 diabetes, i.e., with at least 50% of students eligible for free or reduced-price lunch or belonging to a racial or ethnic minority group; Sixth-grade students who participated in each school were invited to health screenings in the fall of 2006; and with complete measurements	Students with incomplete measurements	HEALTHY study, a 3-year cluster randomized controlled trial to prevent the development of risk factors for type 2 diabetes in a high risk group of middle school-aged children. Blood was drawn from fasted students to assess metabolic (glucose, insulin) and cardiovascular (total cholesterol, low density lipoprotein (LDL), HDL, triglycerides) risk factors, and analyzed by the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle.	Abnormal lipid levels were defined by the “high” cut points as described by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents Summary Report: [total cholesterol \geq 200 mg/dL, LDL \geq 130 mg/dL, triglycerides \geq 130 mg/dL, and HDL \leq 40 mg/dL]. Variables indicating an accumulation of elevated risk factors (\geq 1, \geq 2, and \geq 3), out of	School	57.6% of eligible students participated

Appendix E Table 2. Multifactorial Dyslipidemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
				the 7 possible risk factors, were also created.		
The Poudre Valley Health System (PVHS), Healthy Hearts Club 5885	4th grade students who participated in the Poudre Valley Health Systems, Healthy Hearts Club in Northern Colorado from 1992-2013	Data were not collected in 1997 or 1999 due to lack of funding	The Poudre Valley Health System (PVHS), Healthy Hearts Club provided cardiovascular screening data among 4th grade students in six Northern Colorado school districts. Each school who participated did so a maximum of one time per school year; schools who participated varied from year to year throughout the six school districts. Data were collected cross-sectionally every year, except 1997 and 1999 (due to lack of funding), beginning in 1992 through 2013. Objective measures of non-fasting total and high-density lipoprotein cholesterol (HDL-C), blood pressure and body mass index were calculated. Surveys were filled out by the parent and/or legal guardian and included questions about diet and physical activity of	Nonfasting lipids: Acceptable TC < 170 mg/dL; borderline TC ≥ 170–199 mg/dL and TC ≥ 200 mg/dL; Low HDL-C < 40 mg/dL and high non-HDL-C as ≥ 145 mg/dL	School	NR

Appendix E Table 2. Multifactorial Dyslipidemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Cohort	Inclusion criteria	Exclusion criteria	Detailed description of screening	Threshold definition for positive screen	Screening setting	Acceptability
			<p>the child as well as CVD risk factors among family members. Cholesterol was determined using venipuncture to obtain samples through 2000 and then the Cholestech LDX Finger Stick Test was used beginning in 2001. Collection of samples was done with the Cholestech LDX capillary tubes. Both total and HDL-C cassettes were used for analysis. Cholesterol values were non-fasting and one sample was obtained for each child.</p>			
CARDIAC ¹⁶	Fifth grade children enrolled in schools in West Virginia.	NR	<p>"NHANES is a cross-sectional, national, stratified, multistage probability survey conducted in 2-year waves with randomly selected noninstitutionalized US civilians. NHANES oversampled racial/ethnic minority groups as well as those at or below 130% of the federal poverty level.</p>	LDL ≥130 mg/dL and HDL <40 mg/dL for MF	School	38.6% of eligible 5th graders participated in the screening program.

Appendix E Table 2. Multifactorial Dyslipidemia: Additional Study Characteristics for US Cohorts Included for Key Question 2

Abbreviations: CVD = cardiovascular disease; HDL = high-density lipoprotein cholesterol; LDL = low density lipoprotein; LDL-C = low density lipoprotein-cholesterol; MF = multifactorial dyslipidemia; mg/dL = milligrams per deciliter; NCEP = National Cholesterol Education Program; NHANES = National Health and Nutrition Examination Survey; NR = not reported; TC = total cholesterol; TG = triglycerides; Trig = triglycerides; US = United States; WHO = World Health Organization

Appendix E Table 3. Familial Hypercholesterolemia: Behavioral Intervention Trials—Results for Mean Difference in Change for Additional Outcomes

Author, Year	Outcome	Outcome descr	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Kinnear, 2020 ²⁰	Meeting dietary goals	Consuming 2 g/d plant stanols or sterols	IG1	0	10	12	IG n/N (%): 0/10 (0.0)	IG n/N (%): 0/12 (0.0)	NR
	Meeting dietary goals	Consuming 2 g/d plant stanols or sterols	IG1	12	10	10	IG n/N (%): 9/10 (90.0)	IG n/N (%): 0/10 (0.0)	NR
	PUFA	% total energy daily intake, poly-unsaturated fatty acids	IG1	12	9	10	0.00 (-0.83 to 0.83)	0.70 (-0.14 to 1.54)	-0.60 (-1.90 to 0.70), NR
	MUFA	% total energy daily intake, mono-unsaturated fatty acids	IG1	12	9	10	-2.20 (-4.52 to 0.12)	0.90 (-0.55 to 2.35)	-3.20 (-5.30 to -1.01), NR
	SFA	% total energy daily intake	IG1	12	9	10	-2.30 (-3.84 to -0.76)	0.00 (-1.80 to 1.80)	-1.80 (-4.30 to 0.80), NR
	Total fat	% total energy daily intake	IG1	12	9	10	-4.70 (-8.53 to -0.87)	1.00 (-2.11 to 4.11)	-5.30 (-8.90 to -1.50), NR
	Fiber	g/day	IG1	12	9	10	4.20 (0.35 to 8.05)	0.90 (-2.61 to 4.41)	5.20 (-0.70 to 10.90), NR
	Fruit and vegetable	portions/day	IG1	12	9	10	1.00 (0.04 to 1.96)	-0.20 (-0.86 to 0.46)	2.20 (1.20 to 3.20), NR
	Cholesterol intake	mg/day	IG1	12	9	10	-32.50 (-74.65 to 9.65)	-37.40 (-95.23 to 20.43)	-24.10 (-100.90 to 52.70), NR
	BMI	z-score	IG1	12	10	12	Med Chg (Range): -0.2 (-0.4 to 0.1)	Med Chg (Range): 0.1 (-0.3 to 0.3)	NR, NR
	Body fat	%	IG1	12	6	6	Med Chg (Range): -0.1 (-1.0 to 0.9)	Med Chg (Range):	NR, NR

Appendix E Table 3. Familial Hypercholesterolemia: Behavioral Intervention Trials—Results for Mean Difference in Change for Additional Outcomes

Author, Year	Outcome	Outcome descr	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
								0.2 (-1.4 to 0.3)	
	Sedentary behavior	min/day (accelerometer measured)	IG1	12	9	10	Med Chg (Range): 14 (-41 to 105)	Med Chg (Range): 81 (10 to 160)	NR, NR
	MVPA	min/day, moderate and vigorous physical activity (accelerometer measured)	IG1	12	10	10	Med Chg (Range): -4.2 (-14.3 to 2.4)	Med Chg (Range): -5.9 (-19.1 to 12.4)	NR, NR

Abbreviations: BL = base line; BMI = body mass index; CG = control group; Chg = change; CI = confidence interval; FU = follow up; g = gram IG = intervention group; MD = mean difference; Med = median; MUFA = monounsaturated fatty acid; MVPA = moderate to vigorous physical activity; n/N = number of people experiencing an event/total number of participants; NR = not reported; PUFA = polyunsaturated fatty acids; SFA = saturated fatty acid; wks = weeks

Appendix E Table 4. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Detailed Intervention Descriptions

Author, Year Study name	Detailed Intervention Description
<p>DISC Collaborative Research Group, 1995²¹</p> <p>Dietary Intervention Study in Children (DISC)</p>	<p>6 weekly and then 5 biweekly group sessions augmented by two individual visits of children with their family members were held in the first 6 months. In the second 6 months, four group sessions and two individual sessions were held. During the second and third years, group and individual maintenance sessions were held four to six times each year with monthly telephone contacts between sessions.</p> <p>Group sessions were based on a combination of instructional approaches, cooperative learning experiences, and problem-solving activities that stressed behavior modification approaches to help maintain adherence. Intervention strategies were based on social learning theory and social action theory. The intervention program was family oriented.</p> <p>The primary goal of the intervention was adherence to a diet providing 28% of energy from total fat, less than 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75 mg/4200 kJ (1000 kcal) per day of cholesterol (not to exceed 150 mg/d). The diet was designed to meet age- and sex-specific recommended dietary allowances for energy, protein, and micronutrients.</p> <p>All participants were given educational publications on heart-healthy eating available to the public.</p> <p>At 3 years, cases exceeding cut points for clinical monitoring were reviewed to assess whether physician referral was warranted. If so, the parent or guardian was given the results with a referral letter to take to their regular physician.</p>
<p>Shannon, 1994²²</p> <p>Children's Health Project</p>	<p>Dietary messages consistent with NCEP step 1 diet; no physical activity messages included. Based on social cognitive theory included ten talking book lessons (audiotape stories and accompanying picture books) and follow-up paper-pencil activities for children along with a manual for parents. A story and accompanying activities are completed at home each week by the child and family for a ten-week period.</p> <p>Dietary messages consistent with NCEP step 1 diet; no physical activity messages included. Children and at least one parent (usually the mother) in the Counseling group attended a 45- to 60-minute counseling session with a pediatric registered dietitian. Take home print materials were provided and study dietitian was available via telephone to answer questions.</p>

Abbreviations: kJ = kilojoule (calorie); mg/d = milligrams per day; NCEP = National Cholesterol Education Program

Appendix E Table 5. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Results for Mean Difference in Change in Behavioral Outcomes

Outcome	Outcome descr	Author, Year	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD (95% CI), p-value
Cholesterol intake	mg/1000 kcal	DISC Collaborative Research Group, 1995 ²¹	IG1	156	328	325	-22.70 (-28.49 to -16.91)	-1.00 (-6.83 to 4.83)	-18.10 (-25.70 to -10.40), <0.001
				385	328	325	-18.70 (-24.63 to -12.77)	-10.90 (-17.51 to -4.29)	-7.80 (-16.66 to 1.06), NSD
Cholesterol intake	mg	Shannon, 1994 ²²	IG1	13	88	87	-23.30 (-43.68 to -2.92)	6.60 (-12.61 to 25.81)	MD in Chg: -29.90 (-57.90 to -1.90), NR*
				IG2	13	86	87	-24.40 (-44.00 to -4.80)	6.60 (-12.61 to 25.81)
PUFA	% of energy (% kcal)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	328	325	-0.20 (-0.39 to -0.01)	-0.10 (-0.30 to 0.10)	-0.30 (-0.60 to -0.04), 0.03
MUFA	% of energy (% kcal)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	328	325	-1.80 (-2.07 to -1.53)	-0.40 (-0.65 to -0.15)	-1.60 (-1.90 to -1.20), <0.001
SFA	% of energy (% kcal)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	328	325	-2.30 (-2.60 to -2.00)	-0.40 (-0.67 to -0.13)	-2.10 (-2.50 to -1.70), <0.001
				385	328	325	-2.30 (-2.61 to -1.99)	-1.40 (-1.80 to -1.00)	-0.90 (-1.40 to -0.40), <0.001
SFA	g	Shannon, 1994 ²²	IG1	13	88	87	-2.20 (-3.96 to -0.44)	1.60 (0.03 to 3.17)	MD in Chg: -3.80 (-6.15 to -1.45), <0.05
				IG2	13	86	87	-2.60 (-4.17 to -1.03)	1.60 (0.03 to 3.17)
Total fat	% of energy (% kcal)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	328	325	-4.80 (-5.43 to -4.17)	-1.00 (-1.55 to -0.45)	-4.20 (-5.10 to -3.40), <0.001
				385	328	325	-4.90 (-5.46 to -4.34)	-3.40 (-4.15 to -2.65)	-1.50 (-2.43 to -0.57), <0.001

Appendix E Table 5. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Results for Mean Difference in Change in Behavioral Outcomes

Outcome	Outcome descr	Author, Year	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD (95% CI), p-value
	% calories	Shannon, 1994 ²²	IG1	52	88	87	-1.60 (-2.97 to -0.23)	-0.30 (-1.51 to 0.91)	MD in Chg: -1.30 (-3.12 to 0.52), NR†
			IG2	52	86	87	-2.60 (-3.93 to -1.27)	-0.30 (-1.51 to 0.91)	MD in Chg: -2.30 (-4.09 to -0.51), NR
BMI	kg/m ²	DISC Collaborative Research Group, 1995 ²¹	IG1	156	334	329	2.40 (2.08 to 2.72)	2.50 (2.15 to 2.85)	-0.04 (-0.30 to 0.20), 0.83
				385	334	329	5.40 (5.02 to 5.78)	5.40 (4.98 to 5.82)	-0.10 (-0.50 to 0.40), 0.39
Height	cm	DISC Collaborative Research Group, 1995 ²¹	IG1	156	334	329	20.00 (19.17 to 20.83)	19.60 (18.70 to 20.50)	0.60 (-0.02 to 1.20), 0.97
				385	334	329	34.60 (33.69 to 35.51)	34.90 (33.94 to 35.86)	-0.30 (-1.00 to 0.40), 0.20
Height	z-score	Shannon, 1994 ²²	IG1	52	88	87	0.05 (-0.15 to 0.25)	-0.01 (-0.21 to 0.19)	MD in change: 0.06 (-0.23 to 0.35),
			IG2	52	86	87	0.12 (-0.11 to 0.35)	-0.01 (-0.21 to 0.19)	MD in change: 0.13 (-0.17 to 0.43),
Weight	kg	DISC Collaborative Research Group, 1995 ²¹	IG1	156	334	329	16.20 (15.15 to 17.25)	16.40 (15.25 to 17.55)	0.30 (-0.50 to 1.00), 0.49
Weight	z-score	Shannon, 1994 ²²	IG1	52	88	87	0.05 (-0.18 to 0.28)	0.03 (-0.19 to 0.25)	MD in change: 0.02 (-0.30 to 0.34),
			IG2	52	86	87	0.07 (-0.16 to 0.30)	0.03 (-0.19 to 0.25)	MD in change: 0.04 (-0.28 to 0.36),

* The imputed MD in change from BL (95% CI) are unadjusted compared to the study's adjusted p-value of NSD.

† The imputed MD in change from BL (95% CI) are unadjusted compared to the study's adjusted p-value of <0.05.

Abbreviations: BL = base line; CG = control group; Chg = change; CI = confidence interval; FU = follow up; g = grams; IG = intervention group; MD = mean difference; NR = not reported; NSD = no significant difference; wks = weeks

Appendix E Table 6. Multifactorial Dyslipidemia: Supplement Intervention Trials—Results for Mean Difference in Change in Non-Lipid Outcomes

Outcome	Author, Year	Supplement	Dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
BMI z-score	Wong, 2013 ²³	flaxseed	30 g	4	16	16	NR	NR	0.00 (-0.15 to 0.15), 0.30
Total caloric intake	Wong, 2013 ²³	flaxseed	30 g	4	16	16	NR	NR	MD in % Chg: (95% CI): 8 (-17, 33) P=0.52

Abbreviations: BL = baseline; BMI = body mass index; CG = control group; Chg = change; CI = confidence interval; FU = followup; IG = intervention group; MD = mean difference; NR = not reported; wks = weeks

Appendix E Table 7. Multifactorial Dyslipidemia/FH: Supplement Intervention Trials—Results for Mean Difference in Change in BMI

Author, Year	Supplement	Dose	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD in Change (95% CI), p-value
Del Bo, 2019 ²⁴	Hempseed oil	3 g	8	18	18	-0.03 (-0.39 to 0.33)	-0.05 (-0.29 to 0.19)	0.02 (-0.38 to 0.42), 0.907

Abbreviations: BL = baseline; BMI = body mass index; CG = control group; CI = confidence interval; FH = familial hypercholesterolemia; FU = followup; IG = intervention group; MD = mean difference; wks = weeks

Appendix E Table 8. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Total Adverse Events

Author, year	Statin	Daily Dose, mg/d	Statin intensity	FU	IG N	CG N	IG n/N (%)	CG n/N (%)
Avis, 2010 ²⁵	Rosuvastatin	20	H	12	44	46	24/44 (54.5)	25/46 (54.3)
		10	M	12	44	46	28/44 (63.6)	25/46 (54.3)
		5	M	12	42	46	21/42 (50.0)	25/46 (54.3)
Clauss, 2005 ²⁶	Lovastatin	20-40	L-M	24	35	19	23/35 (65.7)	13/19 (68.4)
de Jongh, 2002b ²⁷	Simvastatin	10-40	L-M	28	28	22	0/28 (0.0)	0/22 (0.0)
Knipscheer, 1996 ²⁸	Pravastatin	20	L	12	18	18	1/18 (5.6)*	9/18 (50)*
		10	L	12	18	18	6/18 (33.3)*	9/18 (50)*
		5	L	12	18	18	3/18 (16/7)*	9/18 (50)*
McCrintle, 2003 ²⁹	Atorvastatin	10-20	L-M	26	140	47	88/140 (62.9)	29/47 (61.7)
Stein, 1999 ³⁰	Lovastatin	10-40	L-M	48	67	65	47/67 (70.1)	48/65 (73.8)
Wiegman, 2004 ³¹ †	Pravastatin	20-40	L-M	104	104	107	4/104 (3.8)*	5/107 (4.7)*

*Number of events, not people. Percentages calculated assuming number of people.

†Abnormal elevations in lab values

Abbreviations: CG = control group; FU = followup; H = high intensity; IG = intervention group; L = low intensity; M = moderate intensity; mg/d = milligrams per day; n/N = number of participants experiencing an event/total number of participants

Appendix E Table 9. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Withdrawals Due to Adverse Events

Author, year Quality	Statin	Daily Dose, mg/d	Statin intensity	FU	IG N	CG N	IG n/N (%)	CG n/N (%)
Avis, 2010 ²⁵	Rosuvastatin	20	H	12	44	46	0/44 (0.0)	1/46 (2.2)
		10	M	12	44	46	0/44 (0.0)	1/46 (2.2)
		5	M	12	42	46	1/42 (2.4)	1/46 (2.2)
Braamskamp, 2015 ³²	Pitavastatin	4	M	12	26	27	1/26 (3.8)	0/27 (0.0)
		2	M	12	27	27	1/27 (3.7)	0/27 (0.0)
		1	L	12	26	27	0/26 (0.0)	0/27 (0.0)
Clauss, 2005 ²⁶	Lovastatin	20-40	L-M	24	35	19	0/35 (0.0)	0/19 (0.0)
de Jongh, 2002a ³³	Simvastatin	10-40	L-M	48	106	69	1/106 (0.9)	0/69 (0.0)
de Jongh, 2002b ²⁷	Simvastatin	10-40	L-M	28	28	22	0/28 (0.0)	0/22 (0.0)
Knipscheer, 1996 ²⁸	Pravastatin	20	L	12	18	18	0/18 (0.0)	0/18 (0.0)
		10	L	12	18	18	0/18 (0.0)	0/18 (0.0)
		5	L	12	18	18	0/18 (0.0)	0/18 (0.0)
Kusters, 2014 ³⁴	Pravastatin	20-40		520	194	83	3/194 (1.5)	0/83 (0.0)
McCordle, 2003 ²⁹	Atorvastatin	10-20	L-M	26	140	47	1/140 (0.7)	0/47 (0.0)
Stein, 1999 ³⁰	Lovastatin	10-40	L-M	48	67	65	1/67 (1.5)	2/65 (3.1)
Wiegman, 2004 ³¹	Pravastatin	20-40	L-M	104	104	107	0/104 (0.0)	0/107 (0.0)

Abbreviations: CG = control group; FU = followup; H = high intensity; IG = intervention group; L = low intensity; M = moderate intensity; mg/d = milligrams per day; n/N = number of participants experiencing an event/total number of participants

Appendix E Table 10. Familial Hypercholesterolemia: Statin Intervention Trials—Liver-Related Adverse Events

Outcome	Outcome Descr	Author, year	Statin	Daily Dose (mg)	FU	IG N	CG N	IG n/N (%)	CG n/N (%)
ALT	>ULN (reference range 5-35 U/L)	Braamskamp, 2015 ³²	Pitavastatin	4	12	26	27	1/26 (3.8)	1/27 (3.7)
				2	12	27	27	2/27 (7.4)	1/27 (3.7)
				1	12	26	27	2/26 (7.7)	1/27 (3.7)
	>2 ULN (reference range 5-35 U/L)	Braamskamp, 2015 ³²	Pitavastatin	4	12	26	27	0/26 (0.0)	0/27 (0.0)
				2	12	27	27	0/27 (0.0)	0/27 (0.0)
				1	12	26	27	0/26 (0.0)	0/27 (0.0)
	>3-fold ULN	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	1/86 (1.2)	0/58 (0.0)
	>ULN (reference range <26 U/L)	Knipscheer, 1996 ²⁸	Pravastatin	20	12	17	18	0/17 (0.0)	1/18 (5.6)
				10	12	16	18	3/16 (18.8)	1/18 (5.6)
				5	12	18	18	1/18 (5.6)	1/18 (5.6)
	>3x ULN	Kusters, 2014 ³⁴	Pravastatin	20-40	520	194	83	1/194 (0.5)	0/83 (0.0)
>3x ULN	McCrintle, 2003 ²⁹	Atorvastatin	10-20	26	140*	47*	1/140 (0.7)	0/47 (0.0)	
>3x ULN (ULN, <25)	Stein, 1999 ³⁰	Lovastatin	10-40	48	61	49	0/61 (0.0)	0/49 (0.0)	
>3x ULN	Wiegman, 2004 ³¹	Pravastatin	20-40	104	104	107	0/0 (0.0)	0/0 (0.0)	
AST	>ULN (reference range 0-40 U/L)	Braamskamp, 2015 ³²	Pitavastatin	4	12	26	27	1/26 (3.8)	0/27 (0.0)
				2	12	27	27	6/27 (22.2)	0/27 (0.0)
				1	12	26	27	5/26 (19.2)	0/27 (0.0)
	>2x ULN (reference range 0-40 U/L)	Braamskamp, 2015 ³²	Pitavastatin	4	12	26	27	1/26 (3.8)	0/27 (0.0)
				2	12	27	27	0/27 (0.0)	0/27 (0.0)
				1	12	26	27	0/26 (0.0)	0/27 (0.0)
	>3x ULN	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	1/86 (1.2)	0/58 (0.0)
	>ULN (reference range <30 U/L)	Knipscheer, 1996 ²⁸	Pravastatin	20	12	18	18	0/18 (0.0)	0/18 (0.0)
				10	12	18	18	1/18 (5.6)	0/18 (0.0)
				5	12	18	18	0/18 (0.0)	0/18 (0.0)
	>3x ULN	Kusters, 2014 ³⁴	Pravastatin	20-40	520	194	83	1/194 (0.5)	1/83 (1.2)

Appendix E Table 10. Familial Hypercholesterolemia: Statin Intervention Trials—Liver-Related Adverse Events

Outcome	Outcome Descr	Author, year	Statin	Daily Dose (mg)	FU	IG N	CG N	IG n/N (%)	CG n/N (%)
	>3x ULN	McCrinkle, 2003 ²⁹	Atorvastatin	10-20	26	140*	47*	2/140 (1.4)	0/47 (0.0)
	>3x ULN (ULN, <22)	Stein, 1999 ³⁰	Lovastatin	10-40	48	61	49	0/61 (0.0)	0/49 (0.0)
	>3x ULN	Wiegman, 2004 ³¹	Pravastatin	20-40	104	104	107	0/104 (0.0)†	2/107 (1.9)†
Abnormal alkaline phosphatase	20-80 U/L	Knipscheer, 1996 ²⁸	Pravastatin	20	12	18	18	0/18 (0.0)	0/18 (0.0)
				10	12	18	18	0/18 (0.0)	0/18 (0.0)
				5	12	18	18	0/18 (0.0)	0/18 (0.0)
Abnormal bilirubin	Total bilirubin <17 micromol/L	Knipscheer, 1996 ²⁸	Pravastatin	20	12	18	17	0/18 (0.0)	0/17 (0.0)
				10	12	18	17	1/18 (5.6)	0/17 (0.0)
				5	12	16	17	0/16 (0.0)	0/17 (0.0)
Transaminase elevation ≥3x ULN	ALT and/or AST ≥3x ULN	Avis, 2010 ²⁵	Rosuvastatin	20	12	44	46	2/44 (4.5)	0/46 (0.0)
				10	12	44	46	1/44 (2.3)	0/46 (0.0)
				5	12	42	46	0/42 (0.0)	0/46 (0.0)
	ALT and/or AST ≥3x ULN (single or consecutive)	Clauss, 2005 ²⁶	Lovastatin	20-40	24	35	19	0/35 (0.0)	0/19 (0.0)
Clinically relevant statin-related hepatotoxic events	Not further defined	Desai, 2019 ³⁵	Statin	NR	182	208	735	0/208 (0.0)	0/735 (0.0)

*Estimated n: the denominator is “among pts with normal liver function tests at baseline” thus, the full IG and CG are likely not the N analyzed

†Number of events, not people. Percentages calculated assuming number of people.

NOTE: The ALT measurement is the unit of analysis because participants switch groups if a statin was initiated

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CG = control group; FU = followup; IG = intervention group; n/N = number of participants experiencing an event/total number of participants; U/L = units/liter; ULN = upper limit of normal

Appendix E Table 11. Familial Hypercholesterolemia: Nonrandomized Studies of Statin Interventions—Additional Liver-Related Adverse Event Outcomes

Author, Year	Weeks	Outcome Notes	IG N ALT measures*	CG N ALT measures*	IG event (event rate)	CG Event (event rate)	Between Grp
Desai, 2019 ³⁵	182	ALT ≥5x ULN (ULN of ≥26 for males and ≥22 for females)	1,789	915	21 (1.1)	5 (0.5)	NR
		ALT 1- <3x ULN (ULN of ≥26 for males and ≥22 for females)	1,789	915	581 (32.5)	237 (25.9)	NR
		ALT 3- <5x ULN (ULN of ≥26 for males and ≥22 for females)	1,789	915	57 (3.2)	9 (1.0)	NR
		ALT ≥3 ULN (ULN of ≥26 for males and ≥22 for females)	1,789	915	78 (4.4)	14 (1.5)	NR

NOTE: The ALT measurement is the unit of analysis because participants switch groups if a statin was initiated

Abbreviations: ALT = alanine transaminase; CG = control group; Grp = group; IG = intervention group; NR = not reported ULN = upper limit of normal

Appendix E Table 12. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Abnormal Creatine Kinase

Outcome Definition	Author, Year	Statin	Dose, mg/d	FU, wks	IG N	CG N	IG n/N (%)	CG n/N (%)
>ULN (reference range <120 U/L)	Knipscheer, 1996 ²⁸	Pravastatin	20	12	13	14	8/13 (61.5)	8/14 (57.1)
			10	12	13	14	11/13 (84.6)	8/14 (57.1)
			5	12	11	14	6/11 (54.5)	8/14 (57.1)
>ULN (reference range 25-300 U/L)	Braamskamp, 2015 ³² PASCAL	Pitavastatin	4	12	26	27	3/26 (11.5)	0/27 (0.0)
			2	12	27	27	2/27 (7.4)	0/27 (0.0)
			1	12	26	27	4/26 (15.4)	0/27 (0.0)
>4x ULN	Wiegman, 2004 ³¹	Pravastatin	20-40	104	104	107	4/104 (3.8)*	3/107 (2.8)*
>5x ULN (reference range 25-300 U/L)	Braamskamp, 2015 ³² PASCAL	Pitavastatin	4	12	26	27	0/26 (0.0)	0/27 (0.0)
			2	12	27	27	0/27 (0.0)	0/27 (0.0)
			1	12	26	27	0/26 (0.0)	0/27 (0.0)
>5x ULN (ULN, <120)	Stein, 1999 ³⁰	Lovastatin	10-40	48	61	49	3/61 (4.9)	1/49 (2.0)
5 to 10x ULN	Clauss, 2015 ²⁶	Lovastatin	20-40	24	35	19	3/61 (4.9)	1/49 (2.0)
>10x ULN	Stein, 1999 ³⁰	Lovastatin	10-40	48	61	49	0/61 (0.0)	0/49 (0.0)
	Avis, 2010 ²⁵	Rosuvastatin	20	12	44	46	2/44 (4.5)	0/46 (0.0)
			10	12	44	46	2/44 (4.5)	0/46 (0.0)
			5	12	42	46	0/42 (0.0)	0/46 (0.0)
	Clauss, 2005 ²⁶	Lovastatin	20-40	24	35	19	0/61 (0.0)	0/49 (0.0)
	Kusters, 2014 ³⁴ AfterTen	Pravastatin	20-40	520	194	83	0/194 (0.0)	2/83 (2.4)
>10x ULN with or without muscular symptoms; 5-10x increase with symptoms	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	1/86 (1.2)	1/58 (1.7)

* Number of events, not people. Percentages calculated assuming number of people.

Abbreviations: CG = control group; FU = followup; IG = intervention group; mg/d = milligrams per day; n/N = number of participants experiencing an event/total number of participants; U/L = units/liter; ULN = upper limit of normal; wks = weeks

Appendix E Table 13. Familial Hypercholesterolemia: Statin Intervention Trials—Musculoskeletal Adverse Events

Outcome	Author, Year	FU, wks	IG N	CG N	IG n/N (%)	CG n/N (%)
Arthropathy	Stein, 1999 ³⁰	48	67	65	1/67 (1.5)	2/65 (3.1)
Rhabdomyolysis	Kusters, 2014 ³⁴ AfterTen	520	194	83	0/194 (0.0)	0/83 (0.0)
Myalgia	Braamskamp, 2015 ³² PASCAL	12	26	27	1/26 (3.8)	0/27 (0.0)
		12	27	27	0/27 (0.0)	0/27 (0.0)
		12	26	27	0/26 (0.0)	0/27 (0.0)
	Knipscheer, 1996 ²⁸	12	18	18	0/18 (0)	1/18 (5.6)
		12	18	18	0/18 (0)	1/18 (5.6)
		12	18	18	0/18 (0)	1/18 (5.6)
	Stein, 1999 ³⁰	48	67	65	3/67 (4.5)	4/65 (6.2)
	Avis, 2010 ²⁵ PLUTO	12	44	46	2/44 (4.5)	0/46 (0.0)
		12	44	46	1/44 (2.3)	0/46 (0.0)
		12	42	46	1/42 (2.4)	0/46 (0.0)
	de Jongh, 2002a ³³	48	86	58	1/86 (1.2)	1/58 (1.7)

Abbreviations: CG = control group; FU = followup; IG = intervention group; n/N = number of participants experiencing an event/total number of participants; wks = weeks

Appendix E Table 14. Familial Hypercholesterolemia: Statin Intervention Trials—Results for Difference in Tanner Stage

Author, Year	Group description	FU, wks	IG n analyzed	CG n analyzed	IG n/N (%)	CG n/N (%)	Reported between-group p-value
Stein, 1999 ³⁰	All participants	48	61	49	NR	NR	0.33
McCordle, 2003 ²⁹	All participants	26	140	47	39/140 (28)*	15/47 (31)*	0.7
Wiegman, 2004 ³¹	All participants	104	104	107	63/104 (61)	68/107 (64)	0.66
	Females	104	55	56	36/55 (65)	34/56 (61)	0.61
	Males	104	49	51	27/49 (55)*	34/51 (67)*	0.24
de Jongh, 2002a ³³	All participants	48	83	56	21/83 (25)	16/56 (29)	0.699
	Males	48	45	30	12/45 (27)	11/30 (37)	0.445
	Females	48	38	26	9/38 (24)*	5/26 (19)*	0.765

*Proportion with an increase in Tanner stage at followup

Abbreviations: CG = control group; FU = followup; IG = intervention group; n/N = number of participants experiencing an event/total number of participants; NR = not reported; wks = weeks

Appendix E Table 15. Familial Hypercholesterolemia: Statin Intervention Trials—Hormonal Adverse Events

Outcome	Author, Year	Group descr	FU, wks	IG N	CG N	IG n/N (%)	CG n/N (%)	Reported between-group p-value
Abnormal ACTH 5-55 ng/L	Knipscheer, 1996 ²⁸	All	12	18	18	0/18 (0.0)	0/18 (0.0)	1.000
			12	18	18	0/18 (0.0)	0/18 (0.0)	1.000
			12	18	18	0/18 (0.0)	0/18 (0.0)	1.000*
Abnormal cortisol Free, 0.22-0.65 micromole/L (9 h)	Knipscheer, 1996 ²⁸	All	12	18	18	3/18 (16.7)	2/18 (11.1)	0.387
			12	18	18	5/18 (27.8)	2/18 (11.1)	0.387
			12	18	18	2/18 (11.1)	2/18 (11.1)	0.387
Abnormal DHEAS level >17 micromole/L	Kusters, 2014 ³⁴ AfterTen	All	520	88	62	1/88 (1.1)	10/62 (16.1)	NR
Abnormal follicle-stimulating hormone levels >10 U/L	Kusters, 2014 ³⁴ AfterTen	All	520	88	62	2/88 (2.3)	5/62 (8.1)	NR
Abnormal TSH 0.4-4.0 mU/L	Knipscheer, 1996 ²⁸	All	12	18	18	0/18 (0.0)	0/18 (0.0)	0.239
			12	18	18	2/18 (11.1)	0/18 (0.0)	0.239
			12	18	18	0/18 (0.0)	0/18 (0.0)	0.239*
Gynecomastia	Stein, 1999 ³⁰	All	48	67	65	1/67 (1.5)	1/65 (1.5)	>0.99
Hyperandrogenism	Kusters, 2014 ³⁴ AfterTen	Female	520	20	16	0/20 (0.0)	0/16 (0.0)	NR
Involuntary childlessness	Kusters, 2014 ³⁴ AfterTen	Female	520	20	16	0/20 (0.0)	0/16 (0.0)	0.03
Irregular menstrual cycle	Kusters, 2014 ³⁴ AfterTen	Female	520	20	16	0/20 (0.0)	0/16 (0.0)	NR
Menstrual disorder	Clauss, 2005 ²⁶	All	24	35	19	2/35 (5.7)	1/19 (5.3)	NR
Menstrual disorder Considered by the investigator to be possibly, probably or definitely a result of treatment	Clauss, 2005 ²⁶	All	24	35	19	0/35 (0.0)	1/19 (5.3)	NR

*p-value is assumed to be all treatment groups vs placebo

Abbreviations: ACTH = Adrenocorticotrophic Hormone; CG = control group; FU = followup; IG = intervention group; ng/L = nanogram/liter; n/N = number of participants experiencing an event/total number of participants; NR = not reported; TSH = thyroid stimulating hormone; U/L = units/liter; wks = weeks

Appendix E Table 16. Familial Hypercholesterolemia: Statin Intervention Trials—Gastrointestinal Adverse Events

Outcome	Author, year Quality	Statin	Daily Dose, mg	Intensity	FU	IG N	CG N	IG n/N (%)	CG n/N (%)
Abdominal pain	Clauss, 2005 ²⁶	Lovastatin	20-40	L-M	24	35	19	3/35 (8.6)	0/19 (0.0)
	de Jongh, 2002a ³³	Simvastatin	10-40	L-M	48	86	58	1/86 (1.2)	0/58 (0.0)
	Knipscheer, 1996 ²⁸	Pravastatin	20	L	12	18	18	1/18 (5.6)	1/18 (5.6)
			10	L	12	18	18	1/18 (5.6)	1/18 (5.6)
			5	L	12	18	18	0/18 (0)	1/18 (5.6)
	McCrinkle, 2003 ²⁹	Atorvastatin	10-20	L-M	26	140	47	6/140 (4.3)	3/47 (6.4)
Stein, 1999 ³⁰	Lovastatin	10-40	L-M	48	67	65	7/67 (10.4)	6/65 (9.2)	
Constipation	de Jongh, 2002a ³³	Simvastatin	10-40	L-M	48	86	58	0/86 (0.0)	0/58 (0.0)
Diarrhea	Clauss, 2005 ²⁶	Lovastatin	20-40	L-M	24	35	19	2/35 (5.7)	0/19 (0.0)
	Knipscheer, 1996 ²⁸	Pravastatin	20	L	12	18	18	0/18 (0)	1/18 (5.6)
			10	L	12	18	18	0/18 (0)	1/18 (5.6)
			5	L	12	18	18	0/18 (0)	1/18 (5.6)
Stein, 1999 ³⁰	Lovastatin	10-40	L-M	48	67	65	1/67 (1.5)	4/65 (6.2)	
Flatulence	de Jongh, 2002a [#272]	Simvastatin	10-40	L-M	48	86	58	0/86 (0.0)	0/58 (0.0)
Dyspepsia	Knipscheer, 1996 ²⁸	Pravastatin	20	L	12	18	18	0/18 (0)	1/18 (5.6)
			10	L	12	18	18	0/18 (0)	1/18 (5.6)
			5	L	12	18	18	0/18 (0)	1/18 (5.6)
Gastroenteritis	Stein, 1999 ³⁰	Lovastatin	10-40	L-M	48	67	65	5/67 (7.5)	2/65 (3.1)
Nausea/vomiting	Avis, 2010 ²⁵	Rosuvastatin	20	H	12	44	46	2/44 (4.5)	2/46 (4.3)
			10	M	12	44	46	0/44 (0.0)	2/46 (4.3)
			5	M	12	42	46	2/42 (4.8)	2/46 (4.3)
	Clauss, 2005 ²⁶	Lovastatin	20-40	L-M	24	35	19	1/35 (2.9)	1/19 (5.3)
	Knipscheer, 1996 ²⁸	Pravastatin	20	L	12	18	18	1/18 (5.6)	2/18 (11.1)
			10	L	12	18	18	0/18 (0.0)	2/18 (11.1)
5			L	12	18	18	2/18 (11.1)*	2/18 (11.1)*	

Appendix E Table 16. Familial Hypercholesterolemia: Statin Intervention Trials—Gastrointestinal Adverse Events

*Number of events, not people. Percentages calculated assuming number of people.

Abbreviations: CG = control group; FU = followup; H = high intensity; IG = intervention group; L = low intensity; M = moderate intensity; mg = milligram ;
n/N = number of participants experiencing an event/total number of participants

Appendix E Table 17. Familial Hypercholesterolemia: Statin Intervention Trials—Dermatologic Adverse Events

Outcome	Author, Year	Statin	Daily Dose, mg	Timepoint, wks	IG N	CG N	IG n/N (%)	CG n/N (%)
Rash	Knipscheer, 1996 ²⁸	Pravastatin	20	12	18	18	0/18 (0.0)	0/18 (0.0)
			10	12	18	18	0/18 (0.0)	0/18 (0.0)
			5	12	18	18	1/18 (5.6)*	0/18 (0.0)*
Skin disease (Not otherwise specified)	Stein, 1999 ³⁰	Lovastatin	10-40	48	67	65	6/67 (9.0)	7/65 (10.8)
Cold sore	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	0/86 (0.0)	1/58 (1.7)
Pruritus	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	0/86 (0.0)	0/58 (0.0)

*Number of events, not people. Percentages calculated assuming number of people.

Abbreviations: CG = control group; IG = intervention group; mg = milligram; n/N = number of participants experiencing an event/total number of participants; wks = weeks

Appendix E Table 18. Familial Hypercholesterolemia: Statin Intervention Trials—Other Adverse Events

Outcome	Author, Year	Statin	Daily dose, mg	FU, wks	IG N	CG N	IG n/N (%)	CG n/N (%)
Accidental injury	McCrinkle, 2003 ²⁹	Atorvastatin	10-20	26	140	47	13/140 (9.3)	2/47 (4.3)
Chest pain	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	0/86 (0.0)	0/58 (0.0)
Clinically important ECG findings	Braamskamp, 2015 ³² PASCAL	Pitavastatin	4	12	26	27	0/26 (0.0)	0/27 (0.0)
			2	12	27	27	0/27 (0.0)	0/27 (0.0)
			1	12	26	27	0/26 (0.0)	0/27 (0.0)
Clinically important vital sign findings	Braamskamp, 2015 ³² PASCAL	Pitavastatin	4	12	26	27	0/26 (0.0)	0/27 (0.0)
			2	12	27	27	0/27 (0.0)	0/27 (0.0)
			1	12	26	27	0/26 (0.0)	0/27 (0.0)
ENT infection	Stein, 1999 ³⁰	Lovastatin	10-40	48	67	65	7/67 (10.4)	6/65 (9.2)
Fatigue	Knipscheer, 1996 ²⁸	Pravastatin	20	12	18	18	0/18 (0.0)	0/18 (0.0)
			10	12	18	18	0/18 (0.0)	0/18 (0.0)
			5	12	18	18	0/18 (0.0)*	0/18 (0.0)*
Fever	McCrinkle, 2003 ²⁹	Atorvastatin	10-20	26	140	47	2/140 (1.4)	3/47 (6.4)
Headache	Knipscheer, 1996 ²⁸	Pravastatin	20	12	18	18	0/18 (0.0)	0/18 (0.0)
			10	12	18	18	3/18 (16.7)	0/18 (0.0)
			5	12	18	18	0/18 (0.0)*	0/18 (0.0)*
	McCrinkle, 2003 ²⁹	Atorvastatin	10-20	26	140	47	13/140 (9.3)	3/47 (6.4)
	Avis, 2010 ²⁵ PLUTO	Rosuvastatin	20	12	44	46	9/44 (20.5)	9/46 (19.6)
			10	12	44	46	7/44 (15.9)	9/46 (19.6)
			5	12	42	46	6/42 (14.3)	9/46 (19.6)
	Clauss, 2005 ²⁶	Lovastatin	20-40	24	35	19	7/35 (20.0)	4/19 (21.1)
de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	2/86 (2.3)	0/58 (0.0)	
Infection (not otherwise specified)	McCrinkle, 2003 ²⁹	Atorvastatin	10-20	26	140	47	27/140 (19.3)	7/47 (14.9)
Influenza	McCrinkle, 2003 ²⁹	Atorvastatin	10-20	26	140	47	9/140 (6.4)	6/47 (12.8)
	Avis, 2010 ²⁵ PLUTO	Rosuvastatin	20	12	44	46	0/44 (0.0)	4/46 (8.7)
			10	12	44	46	2/44 (4.5)	4/46 (8.7)

Appendix E Table 18. Familial Hypercholesterolemia: Statin Intervention Trials—Other Adverse Events

Outcome	Author, Year	Statin	Daily dose, mg	FU, wks	IG N	CG N	IG n/N (%)	CG n/N (%)
			5	12	42	46	2/42 (4.8)	4/46 (8.7)
	Clauss, 2005 ²⁶	Lovastatin	20-40	24	35	19	4/35 (11.4)	0/19 (0.0)
Lymphadenopathy	Stein, 1999 ³⁰	Lovastatin	10-40	48	67	65	2/67 (3.0)	0/65 (0.0)
Nasopharyngitis	Avis, 2010 ²⁵ PLUTO	Rosuvastatin	20	12	44	46	7/44 (15.9)	5/46 (10.9)
			10	12	44	46	7/44 (15.9)	5/46 (10.9)
			5	12	42	46	3/42 (7.1)	5/46 (10.9)
New-onset diabetes†	Joyce, 2017 ³⁶	Statin	NR	520	869	8524	17/869 (2.0)	146/8524 (1.7)
Pharyngitis	McC Crindle, 2003 ²⁹	Atorvastatin	10-20	26	140	47	9/140 (6.4)	3/47 (6.4)
	Clauss, 2005 ²⁶ 271	Lovastatin	20-40	24	35	19	6/35 (17.1)	2/19 (10.5)
Pyrexia and generalized rash	Braamskamp, 2015 ³² PASCAL	Pitavastatin	4	12	26	27	1/26 (3.8)	0/27 (0.0)
			2	12	27	27	0/27 (0.0)	0/27 (0.0)
			1	12	26	27	0/26 (0.0)	0/27 (0.0)
Respiratory tract infection	Stein, 1999 ³⁰	Lovastatin	10-40	48	67	65	32/67 (47.8)	29/65 (44.6)
Upper respiratory tract infection	Clauss, 2005 ²⁶	Lovastatin	20-40	24	35	19	10/35 (28.6)	9/19 (47.4)
Sleep disorder	Stein, 1999 ³⁰	Lovastatin	10-40	48	67	65	1/67 (1.5)	0/65 (0.0)
	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	0/86 (0.0)	0/58 (0.0)
Streptococcal pharyngitis	Clauss, 2005 ²⁶	Lovastatin	20-40	24	35	19	4/35 (11.4)	0/19 (0.0)
Weight gain	de Jongh, 2002a ³³	Simvastatin	10-40	48	86	58	1/86 (1.2)	0/58 (0.0)

* Number of events, not people. Percentages calculated assuming number of people.

† New diagnosis for T2DM was identified if any of the following were observed: 1) 2 outpatient claims in a 24-month period, at least one of which was for T2DM due to evidence that T2DM can be mistakenly coded or difficult to distinguish from type I in pediatric populations, 2) An inpatient claim with a primary diagnosis of T2DM; 3) a single outpatient claim for T2DM and a dispensing for an oral hypoglycemic or insulin preparation within 120 days; 4) two prescriptions for an oral hypoglycemic or insulin preparation and a claim for a diabetes-related procedure within one year

Abbreviations: CG = control group; FU = followup; IG = intervention group; mg = milligram; n/N = number of participants experiencing an event/total number of participants; wks = weeks

Appendix E Table 19. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Total Adverse Events

Outcome	Intervention	Author, year Quality	Drug	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
Total AE	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	4/64 (6.3)	7/65 (10.8)
				1.875 g	8	65	65	7/65 (10.8)	7/65 (10.8)
	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	56/92 (60.9)	25/45 (55.6)
	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	64/104 (61.5)	34/53 (64.2)
Withdrawal due to AE	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	1/64 (1.6)	0/65 (0.0)
				1.875 g	8	65	65	3/65 (4.6)	0/65 (0.0)
		Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	36	36	14/36 (38.9)	10/36 (27.8)
	Tonstad, 1996b ⁴¹	Colestipol	10 g	8	33	33	0/33 (0.0)	0/33 (0.0)	
	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	122	118	2/122 (1.6)	1/118 (0.8)
	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	3/92 (3.3)	0/45 (0.0)
	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	1/104 (1.0)	0/53 (0.0)

Abbreviations: AE = adverse event; CG = control group; FU = followup; IG = intervention group; mg = milligram; n/N = number of participants experiencing an event/total number of participants; PCSK9 = proprotein convertase subtilisin/kexin type 9; wks = weeks

Appendix E Table 20. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Gastrointestinal Adverse Events

Outcome	Intervention	Author, year Quality	Drug/Suppl	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
Abdominal pain	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	1/64 (1.6)	0/65 (0.0)
				1.875 g	8	65	65	1/65 (1.5)	0/65 (0.0)
	Combination drug therapy	Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	26	2/22 (9.1)	3/26 (11.5)
		van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	6/126 (4.8)	3/122 (2.5)
		Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	4/92 (4.3)	5/45 (11.1)
Appendectomy	bile acid sequestrant	Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	26	0/22 (0.0)	1/26 (3.8)
Constipation	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	3/104 (2.9)	0/53 (0.0)
Diarrhea	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	2/64 (3.1)	1/65 (1.5)
				1.875 g	8	65	65	0/65 (0.0)	1/65 (1.5)
	Combination drug therapy	Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	26	2/22 (9.1)	0/26 (0.0)
		van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	9/126 (7.1)	3/122 (2.5)
		Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	1/92 (1.1)	4/45 (8.9)
Gastroenteritis	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	1/64 (1.6)	0/65 (0.0)
				1.875 g	8	65	65	1/65 (1.5)	0/65 (0.0)
	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	5/104 (4.8)	4/53 (7.5)
Intestinal obstruction	bile acid sequestrant	Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	26	1/22 (4.5)	0/26 (0.0)
Nausea/vomiting	bile acid sequestrant	Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	26	3/22 (13.6)	1/26 (3.8)
Nausea	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	8/126 (6.3)	4/122 (3.3)
	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	0/64 (0.0)	1/65 (1.5)
				1.875 g	8	65	65	2/65 (3.1)	1/65 (1.5)

Appendix E Table 20. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Gastrointestinal Adverse Events

Outcome	Intervention	Author, year Quality	Drug/Suppl	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
Pharyngolaryngeal pain	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	0/64 (0.0)	0/65 (0.0)
Vomiting	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	1/64 (1.6)	1/65 (1.5)
				1.875 g	8	65	65	2/65 (3.1)	1/65 (1.5)
	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	5/126 (4.0)	6/122 (4.9)

Abbreviations: CG = control group; FU = followup; IG = intervention group; mg = milligram; n/N = number of participants experiencing an event/total number of participants; wks = weeks

Appendix E Table 21. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Liver-Related Adverse Events

Outcome Category	Outcome description	Intervention	Author, year	Drug	Daily Dose, mg	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
ALT	>3x ULN	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10	12	92	45	1/92 (1.1)	0/45 (0.0)
		PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	0/104 (0.0)	0/53 (0.0)
	Elevated NOS	fibrate	Wheeler, 1985 ⁴³	Bezafibrate	10-20	13	14	14	1/14 (7.1)	0/14 (0.0)
		Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40	33	126	122	6/126 (4.8)	3/122 (2.5)
AST	≥3x ULN, consecutive	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10	12	92	45	0/92 (0.0)	0/45 (0.0)
Abnormal alkaline phosphatase	-	fibrate	Wheeler, 1985 ⁴³	Bezafibrate	10-20	13	14	14	1/14 (7.1)	0/14 (0.0)
Abnormal liver function	-	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10	12	92	45	1/92 (1.1)	0/45 (0.0)

NOTE: The ALT measurement is the unit of analysis because participants switch groups if a statin was initiated

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CG = control group; FU = followup; IG = intervention group; mg = milligram; n/N = number of participants experiencing an event/total number of participants; NOS = not otherwise specified; PCSK9 = proprotein convertase subtilisin/kexin type 9; ULN = upper limit of normal; wks = weeks

Appendix E Table 22. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Musculoskeletal Adverse Events

Outcome Category	Outcome descr	Intervention	Author, year	Drug	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
Abnormal CK	>5x ULN	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injection)	24	104	53	0/104 (0.0)	0/53 (0.0)
		ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	0/92 (0.0)	0/45 (0.0)
	≥10x ULN with or without clinical muscle symptoms	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	0/92 (0.0)	0/45 (0.0)
Myalgia	-	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40	33	126	122	7/126 (5.6)	1/122 (0.8)
	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	0/64 (0.0)	0/65 (0.0)
					1.875 g	8	65	65	2/65 (3.1)	0/65 (0.0)
Pain in extremity	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	0/64 (0.0)	0/65 (0.0)
					1.875 g	8	65	65	2/65 (3.1)	0/65 (0.0)
Rhabdomyolysis /myopathy	-	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	0/92 (0.0)	0/45 (0.0)

Abbreviations: ALT = alanine transaminase; CG = control group; CK = creatine kinase; FU = followup; IG = intervention group; mg = milligram; n/N = number of participants experiencing an event/total number of participants; PCSK9 = proprotein convertase subtilisin/kexin type 9; ULN = upper limit of normal; wks = weeks

Appendix E Table 23. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Additional Dichotomous Harms Outcome

Outcome Category	Outcome	Intervention	Author, year	Drug	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
Cough	-	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	4/126 (3.2)	8/122 (6.6)
Creatinine phosphokinase increase	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	1/64 (1.6)	0/65 (0.0)
					1.875 g	8	65	65	2/65 (3.1)	0/65 (0.0)
Dermatologic	Skin and subcutaneous tissue disorders	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	5/92 (5.4)	3/45 (6.7)
	Acne	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	4/126 (3.2)	9/122 (7.4)
Dizziness	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	2/64 (3.1)	0/65 (0.0)
					1.875 g	8	65	65	0/65 (0.0)	0/65 (0.0)
ENT infection	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	1/64 (1.6)	0/65 (0.0)
					1.875 g	8	65	65	1/65 (1.5)	0/65 (0.0)
Fatigue	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	2/64 (3.1)	1/65 (1.5)
					1.875 g	8	65	65	3/65 (4.6)	1/65 (1.5)
Fever	Pyrexia	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	3/104 (2.9)	3/53 (5.7)
	Fever	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	4/92 (4.3)	2/45 (4.4)
Folate deficiency	<230 nmol/L	bile acid sequestrant	Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	26	1/22 (4.5)	0/26 (0.0)
Growth	as assessed by measurement	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	NR*	NR*

Appendix E Table 23. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Additional Dichotomous Harms Outcome

Outcome Category	Outcome	Intervention	Author, year	Drug	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
	of height and weight.									
Headache	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	2/64 (3.1)	2/65 (3.1)
					1.875 g	8	65	65	3/65 (4.6)	2/65 (3.1)
			Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	26	1/22 (4.5)	0/26 (0.0)
	-	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	4/92 (4.3)	6/45 (13.3)
	-	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg	24	104	53	11/104 (10.6)	1/53 (1.9)
	-	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	16/126 (12.7)	16/122 (13.1)
Hormonal	Difference in change in Tanner stage	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg	24	104	53	NSD between groups	NSD between groups
	Sexual maturation	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	NSD between groups	NSD between groups
Influenza-like illness	-	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	3/104 (2.9)	0/53 (0.0)
Influenza	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	2/64 (3.1)	0/65 (0.0)
					1.875 g	8	65	65	0/65 (0.0)	0/65 (0.0)
		ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	5/92 (5.4)	3/45 (6.7)
		PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	6/104 (5.8)	2/53 (3.8)
		Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	8/126 (6.3)	12/122 (9.8)

Appendix E Table 23. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Additional Dichotomous Harms Outcome

Outcome Category	Outcome	Intervention	Author, year	Drug	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
Hypersensitivity	-	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	7/92 (7.6)	4/45 (8.9)
Height	0 to <10% change	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	111/126 (88.1)	106/122 (86.9)
Injection-site reaction	-	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	1/104 (1.0)	0/53 (0.0)
Nasopharyngitis	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	4/64 (6.3)	3/65 (4.6)
					1.875 g	8	65	65	4/65 (6.2)	3/65 (4.6)
		ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	10/92 (10.9)	5/45 (11.1)
		PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	12/104 (11.5)	6/53 (11.3)
		Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	27/126 (21.4)	27/122 (22.1)
New-onset diabetes	-	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	0/104 (0.0)	0/53 (0.0)
Oropharyngeal pain	-	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	7/104 (6.7)	0/53 (0.0)
Pancreatitis	-	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	0/92 (0.0)	0/45 (0.0)
Pharyngolaryngeal pain	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g/d	8	64	65	0/64 (0.0)	0/65 (0.0)
					1.875 g/d	8	65	65	2/65 (3.1)	0/65 (0.0)
		Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	6/126 (4.8)	3/122 (2.5)
Respiratory tract infection	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	1/64 (1.6)	3/65 (4.6)

Appendix E Table 23. Familial Hypercholesterolemia: Non-Statin Drug Intervention Trials—Additional Dichotomous Harms Outcome

Outcome Category	Outcome	Intervention	Author, year	Drug	Daily Dose	FU (wks)	IG N	CG N	IG, n/N (%)	CG, n/N (%)
					1.875 g	8	65	65	1/65 (1.5)	3/65 (4.6)
	Upper RTI	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	7/92 (7.6)	1/45 (2.2)
	Upper RTI	PCSK9 inhibitor	Santos, 2020 ³⁹	Evolocumab	420 mg (monthly injections)	24	104	53	6/104 (5.8)	1/53 (1.9)
Respiratory, thoracic, and mediastinal disorders	-	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	7/92 (7.6)	4/45 (8.9)
Rhinitis	-	bile acid sequestrant	Stein, 2010 ³⁷	Colesevelam	3.75 g	8	64	65	0/64 (0.0)	0/65 (0.0)
					1.875 g	8	65	65	3/65 (4.6)	0/65 (0.0)
Sinusitis	-	Combination drug therapy	van der Graaf, 2008 ⁴²	Simvastatin and ezetimibe	10-40 mg	33	126	122	6/126 (4.8)	5/122 (4.1)
Tonsillitis	-	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	4/92 (4.3)	1/45 (2.2)
Vitamin D	Subnormal levels <30 nmol/L	bile acid sequestrant	Tonstad, 1996 ⁴⁰	Cholestyramine	8 mg	52	22	23	3/22 (13.6)	0/23 (0.0)
Other	Cholecystitis/cholelithiasis	ezetimibe	Kusters, 2015 ³⁸	Ezetimibe	10 mg	12	92	45	0/92 (0.0)	0/45 (0.0)

*Reported that there were no clinically significant adverse effects on growth

Abbreviations: CG = control group; FU = followup; g = gram; IG = intervention group; mg = milligram; nmol/L = nanomole; n/N = number of participants experiencing an event/total number of participants; NOS = not otherwise specified; NR = not reported; NSD = no significant difference; PCSK9 = proprotein convertase subtilisin/kexin type 9; RTI = respiratory tract infection; wks = weeks

Appendix E Table 24. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Additional Dichotomous Harms Outcomes

Author, Year	Outcome category	Outcome	Outcome descr	FU, wks	IG n	CG n	IG, n/N (%)	CG, n/N (%)	Between-group
DISC Collaborative Research Group, 1995 [#287]	Psychosocial effects	Anxiety	score >45 State-trait Anxiety Inventory for Children, (STAIC)	156	289	271	4/289 (1.4)	10/271 (3.7)	OR: 0.40 (0.12 to 1.36); p=0.143
		Suicidal ideation	From the Child Depression Inventory	156	289	271	1/289 (0.3)	0/271 (0.0)	NR
		Suicidal ideation	From the Child Depression Inventory	0	334	329	3/334 (0.9)	0/329 (0.0)	NR
		Self-harm, suicide attempt, or suicide talk	Mother respondent from the Child Behavior Checklist that it was "somewhat or sometimes true"	156	203	196	6/203 (3.0)	5/196 (2.6)	NR
		Self-harm, suicide attempt, or suicide talk	Mother respondent from Child Behavior Checklist	0	203	196	0/203 (0.0)	0/196 (0.0)	NR
		Depression	score ≥14, Child Depression Inventory, (CDI)	156	289	271	6/289 (2.1)	18/271 (6.6)	OR: 0.24 (0.09 to 0.65); p=0.005
		Depression	score ≥14, Child Depression Inventory, (CDI)	0	289	271	26/289 (9.0)	16/271 (5.9)	

Appendix E Table 24. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Additional Dichotomous Harms Outcomes

Author, Year	Outcome category	Outcome	Outcome descr	FU, wks	IG n	CG n	IG, n/N (%)	CG, n/N (%)	Between-group
		Behavior problem	score >63, Child Behavior Problems and Competencies (CBCL)	0	203	196	8/203 (3.9)	14/196 (7.1)	
		Anxiety	score >45, State-trait Anxiety Inventory for Children, (STAIC)	0	289	271	14/289 (4.8)	11/271 (4.1)	
		Behavior problem	score >63, Child Behavior Problems and Competencies (CBCL)	156	203	196	12/203 (5.9)	14/196 (7.1)	OR: 0.93 (0.34 to 2.52); p=0.881
	hormone	Difference in change in Tanner stage		312	295	285	NR	NR	NSD
	Other	Requiring referral for evaluation of low serum ferritin		156	NR	NR	3/NR	1/NR	NR
		Requiring further evaluation for growth	Monitoring for slow growth using 3%tile or less of height velocity as the cut point	156	NR	NR	19/NR	28/NR	NR
		Adverse effects on height		385	294	283	0/294 (0.0)	0/283 (0.0)	NR

Appendix E Table 24. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Additional Dichotomous Harms Outcomes

Author, Year	Outcome category	Outcome	Outcome descr	FU, wks	IG n	CG n	IG, n/N (%)	CG, n/N (%)	Between-group
		Adverse effects on ferritin		385	287	270	0/287 (0.0)	0/270 (0.0)	NR

Abbreviations: CG = control group; FU = followup; IG = intervention group; n/N = number of participants experiencing an event/total number of participants; NR = not reported; NSD = no significant difference; OR = odd ratio; wks = weeks

Appendix E Table 25. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Additional Continuous Harms Outcomes

Outcome	Author, Year	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD (95% CI), p-value
Serum Ferritin (mg/mL)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	321	321	-6.70 (-8.85 to -4.55)	-5.10 (-7.69 to -2.51)	-2.10 (-4.90 to 0.80), 0.08
Serum retinol (µmol/L)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	322	319	0.10 (0.07 to 0.13)	0.07 (0.00 to 0.14)	0.02 (-0.02 to 0.07), 0.29*
Serum zinc (µmol/L)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	319	316	-0.60 (-0.95 to -0.25)	-0.30 (-0.53 to -0.07)	-0.14 (-0.50 to 0.20), 0.43†
Albumin (g/L)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	334	329	-1.50 (-1.78 to -1.22)	-1.60 (-1.89 to -1.31)	-0.05 (-0.40 to 0.30), 0.79†
Red cell folate (nmol/L)	DISC Collaborative Research Group, 1995 ²¹	IG1	156	311	308	32.00 (0.65 to 63.35)	10.00 (-21.73 to 41.73)	30.50 (-7.30 to 68.40), 0.11†
Serum Ferritin mg/mL	DISC Collaborative Research Group, 1995 ²¹	IG1	385	321	321	3.80 (0.85 to 6.75)	5.10 (1.68 to 8.52)	-2.90 (-7.20 to 1.40), 0.10
Behavioral problem (Conners Parent Rating Scale, 48-item scale on which parents rated the extent of problem behavior symptoms)	Shannon, 1994 ²²	IG1	52	NR‡	NR‡	-1.60 (NR)	-2.40 (NR)	NR, NR
		IG2	52	NR‡	NR‡	-1.80 (NR)	-2.40 (NR)	NR, NR
Health beliefs 5-item measure designed for	Shannon, 1994 ²²	IG1	52	NR‡	NR‡	0.00 (NR)	-0.10 (NR)	NR, NSD
		IG2	52	NR‡	NR‡	-0.20 (NR)	-0.10 (NR)	NR, NSD

Appendix E Table 25. Multifactorial Dyslipidemia: Behavioral Intervention Trials—Additional Continuous Harms Outcomes

Outcome	Author, Year	Group	FU, wks	IG n	CG n	IG Mean Change from BL (95% CI)	CG Mean Change from BL (95% CI)	MD (95% CI), p-value
this study; higher scores signify perceptions of better health								

*At last visit (avg 7.4 yrs), MD=0.07 $\mu\text{mol/L}$, p=0.02.

† Reported no differences between IG vs CG at the last visit (avg. 7 yrs) - data not provided.

‡ Total N calculated as 40% of 189 = 75-76 children, ages 4-6 years per study

Abbreviations: BL = base line; CG = control group; CI = confidence interval; FU = follow up; g/L = grams per Liter; IG = intervention group; $\mu\text{mol/L}$ = micromole per liter; MD = mean difference; mg/mL milligrams per milliliter; NR = not reported; NSD = no significant difference; wks = weeks

Appendix E Table 26. Multifactorial Dyslipidemia: Supplement Intervention Trials—Additional Dichotomous Harms Outcomes

Outcome	Author, Year	Intervention	FU, wks	IG n	CG n	IG n/N (%)	CG n/N (%)
Total AE	Wong, 2013 ²³	Flaxseed, 30g/d	4	16	16	0/16 (0.0)	0/16 (0.0)
WD due to AE	Wong, 2013 ²³	Flaxseed, 30 g/d	4	16	16	0/16 (0.0)	0/16 (0.0)
	Gidding, 2014 ⁴⁴	Fish oil, 4 g/d	8	NR	NR	0/NR (0.0)	0/NR (0.0)

Abbreviations: AE = adverse events; CG = control group; FU = follow up; g/d = grams per day; IG = intervention group n/N = number of participants experiencing an event/total number of participants; WD = withdrawal; wks = weeks

Appendix E Table 27. Multifactorial Dyslipidemia/FH: Supplement Intervention Trials—Additional Dichotomous Harms Outcomes

Outcome	Outcome Descr	Author, Year	Intv	FU, wks	IG n	CG n	IG n/N (%)	CG n/N (%)
Serious drug-related AE	-	Guardamagna, 2014 ⁴⁵	Probiotic	12	37	36	0/37 (0.0)	0/36 (0.0)
Total AE	-	Martino, 2005 ⁴⁶	Glucomannan 2-3 g (depending on age)	8	NR	NR	0/NR (NR)	0/NR (NR)
Total AE	-	Verduci, 2014 ⁴⁷	DHA+EPA 500 mg	16	12	12	0/12 (0.0)	0/12 (0.0)
			DHA 500 mg	16	12	12	0/12 (0.0)	0/12 (0.0)
WD due to AE	-	Guardamagna, 2014 ⁴⁵	Probiotic	8	18	18	0/18 (0.0)	0/18 (0.0)
GI	Diarrhea	Dennison, 1993 ⁴⁸	psyllium fiber 6g	5	20	20	0/20 (0.0)	1/20 (5.0)
	Abdominal pain	Guardamagna, 2014 ⁴⁵	Probiotic	12	37	36	2/37 (5.4)	1/36 (2.8)
	Flatulence, abdominal discomfort, and increased stool frequency	Guardamagna, 2013 ⁴⁹	Glucomannan 2-3 capsules based on weight	8	18	18	4/18 (22.2)	0/18 (0.0)
Other	Increased satiety	Guardamagna, 2013 ⁴⁹	Glucomannan 2-3 capsules based on weight	8	18	18	2/18 (11.1)	0/18 (0.0)

Abbreviations: AE = adverse events; CG = control group; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FH = familial hypercholesterolemia; FU = follow up; GI = gastrointestinal; IG = intervention group; n/N = number of participants experiencing an event/total number of participants; WD = withdrawal; wks = weeks

Appendix F. Ongoing Studies

Condition	Trial title	Trial number	Location	N	Duration (yrs)	Intervention	Relevant endpoints	Estimated completion date
FH Case Finding	Improved Diagnosis of Familial Hypercholesterolemia Across the Northland (ID-FH)	NCT05238519	US (Minnesota, Wisconsin, North Dakota)	200	6 months	Participants with suspected FH (2-75 yrs) are randomized to usual care or motivational interview designed to promote communication of risk to family members	Cascade screening of 1 st degree family members; Proportion of participants with LDL-C <100; Absolute change in LDL-C; Proportion of participants w self-reported genetic testing	Feb 2025
FH Registry	CASCADE FH Registry (CASCade SCReening for Awareness and DETection of Familial Hypercholesterolemia Registry)	NCT01960244	US	5000	3	National, multi-center registry to track therapy, clinical outcomes, and patient-reported outcomes over time	Number of identified FH patients, reaching optimal level of disease management; target treatment levels for LDL-C	Dec 2025
FH Tx	A Randomized, Double-Blind, Placebo-Controlled Study Followed by an Open Label Treatment Period to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Heterozygous Familial Hypercholesterolemia	NCT03510884	France	150	NR	Alirocumab (one of 4 doses)	Percent change in TC, LDL-C, HDL-C, and TG; AEs	Jul 2022 (Active, not recruiting)

Appendix F. Ongoing Studies

Condition	Trial title	Trial number	Location	N	Duration (yrs)	Intervention	Relevant endpoints	Estimated completion date
FH Tx	Study to Evaluate Efficacy and Safety of Inclisiran in Adolescents With Heterozygous Familial Hypercholesterolemia (ORION-16)	NCT04652726	Multinational (includes US)	150		1 year double-blind inclisiran (300mg) versus placebo / 1 year open-label inclisiran (300mg)	Percent change in LDL-C	Dec 2024 (recruiting)
MFD Tx	Omega-3 Fatty Acid Dietary Intervention for Dyslipidemia of Obesity in Children 10 to <18 Years of Age: O3DI Study	NCT05025943	US	40	NR	Standard lifestyle intervention + omega-3 fatty acid enriched diet	Change in serum TG	Aug 2022 (recruiting)

Abbreviations: AE = adverse events; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MFD = multifactorial dyslipidemia; NR = not reported; TC = total cholesterol; TG = triglycerides; Tx = treatment; US = United States; yrs = years

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