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Screening for Dyslipidemia in Younger Adults: Systematic Review to Update the 2008 U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: This review updates prior reviews on screening for lipid disorders in adults, and will be used by the United States Preventive Services Task Force (USPSTF) to update their 2008 recommendation. Unlike prior USPSTF reviews, it focuses on screening in younger adults, defined as adults 21 to 39 years of age, as there is more uncertainty about the need to perform lipid screening in this population than in older adults.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE from 2008 to November 2015, and manually reviewed reference lists.

Study Selection: Two investigators independently reviewed the literature for studies on screening and treatment of asymptomatic adults ages 21 to 39 years for dyslipidemia, including randomized controlled trials, case-control studies, cohort studies, and good-quality systematic reviews.

Results: No study evaluated the effects of lipid screening versus no screening, treatment versus no treatment, or delayed versus earlier treatment on clinical outcomes in younger adults. In addition, no study evaluated the diagnostic yield of alternative screening strategies in younger adults (e.g., targeted screening of persons with a family history of hyperlipidemia versus general screening). Longitudinal studies suggest that lipid levels have a tendency to increase over time in younger adults, though no study evaluated how lipid levels changed according to different intervals between repeat testing or the proportion of patients who would move from one risk category to another.

Limitations: Lack of direct evidence in younger adults.

Conclusions: Direct evidence on benefits and harms of screening or treatment for dyslipidemia in younger adults remains unavailable.

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Chapter 1. Introduction

Purpose and Previous U.S. Preventive Services Task Force Recommendation

The purpose of this report is to update prior reviews[1-3] conducted for the U.S. Preventive Services Task Force (USPSTF) on screening for lipid disorders in adults. It will be used by the USPSTF to update its 2008 recommendation.[4]

In 2008, the USPSTF strongly recommended lipid screening in all men 35 years and older and in women 45 years and older at increased risk for coronary heart disease (CHD) (*A Recommendation*) based on good evidence that lipid-lowering drug therapy decreases the incidence of CHD events in persons with abnormal lipids, resulting in substantial absolute benefits.[4] The USPSTF recommended screening in men 20 to 35 years of age and women 20 to 45 years of age with risk factors for CHD (*B recommendation*) due to the lower incidence of CHD events in these populations, resulting in lower expected benefits. The USPSTF made no recommendation for or against lipid screening in men aged 20 to 35 or in women 20 and older not at increased risk (*C Recommendation)* due to small expected benefits.

A difference between this update and prior USPSTF reviews on lipid screening is that it focuses on screening in younger adults (defined for this report as adults 21 to 39 years of age). The USPSTF restricted the scope of this update to younger adults because in older adults, lipid levels are obtained as part of routine cardiovascular risk assessment, and the decision to initiate statins is often based on a global assessment of cardiovascular risk or presence of cardiovascular risk factors in addition to abnormal lipid levels. In younger adults, however, there is more uncertainty about the need to perform cardiovascular risk assessment, and lipid screening might identify those who would benefit from earlier interventions to lower lipid levels.[5]

A separate evidence review has been commissioned by the USPSTF on use of statins for prevention of cardiovascular disease (CVD) in adults 40 years of age and older.[6]

Condition Definition

Lipid disorders refer to abnormalities of cholesterol, including low-density lipoproteins (LDL-C), high-density lipoproteins (HDL-C), and triglycerides. The National Cholesterol Education Project (NCEP) Adult Treatment Panel III (ATP III) defined "optimal" LDL levels as <100 mg/dL and "high" as ≥160 mg/dL; "desirable" total cholesterol as <200 mg/dL and "high" as ≥240 mg/dL; "low" HDL-C as <40 mg/dL; and elevated triglycerides as >150 mg/dL; although thresholds for treatment varied depending on the presence of risk factors for cardiovascular disease.[7]

Prevalence and Burden of Disease/Illness

The prevalence of lipid disorders is high in the United States, with an estimated 53 percent (105.3 million) of adults affected.[8] Specifically, 27 percent of Americans (53.5 million) have high LDL-C, 23 percent (46.4 million) have low HDL-C, and 30 percent (58.9 million) have high triglycerides. According to National Health and Nutrition Examination Survey (NHANES) data from 2003 to 2006, 13 percent of those adults with high LDL-C, 22 percent of adults with high non-HDL-C, and 8 percent of adults with the combination of high LDL-C, low HDL-C, and high triglycerides were in the 20 to 34 year age group.[8] In 2003 to 2004, 64 percent of adults aged 20 to 29 and 57 percent of adults aged 30 to 39 met NCEP recommended levels for all lipids.[9]

Lipid disorders are associated with CHD, which may lead to sudden coronary death and myocardial infarction. Prevalence of CHD increases with age and is higher in men than in women at the same age.[10] In 2010, the overall prevalence of CHD was 6.0 percent, and among those aged 18 to 44 the age-adjusted prevalence was 1.2 percent.[10] Prevalence of CHD varies by race, with 11.6 percent of American Indians/Alaska Natives, 6.5 percent of blacks, 6.1 percent of Hispanics, 5.8 percent of whites, and 3.9 percent of Asian/Pacific Islanders affected. For young adults ages 20 to 39, the prevalence of CVD, including all diseases of the circulatory system as well as congenital CVD, was 14.9 percent in men and 8.7 percent in women.[11]

CHD is the leading cause of death in the United States.[12,13] In 2013, the American Heart Association (AHA) estimated that approximately 635,000 Americans would have a new myocardial infarction or CHD death and 280,000 would have a recurrent cardiovascular event, with an additional 150,000 persons having silent myocardial infarctions.[14] The number of myocardial infarctions or fatal CHD events is estimated at 20,000 annually for men aged 35 to 44 years and 5,000 annually for women aged 35 to 44 years.[14] In 2011, CHD caused 12 percent of deaths in persons aged 25 to 44 years.[13] Estimates based on Framingham Heart Study participants from 1971 to 1996 indicated that the lifetime risks (through age 80 years) of CHD for 40 year old men with a total cholesterol of 200, 200 to 239, and $\geq$240 mg/dL were 31, 43, and 57 percent, respectively, with 10-year cumulative risks of 3, 5, and 12 percent. For younger adults, data from the Chicago Heart Association study (from 1967 to 1973) with mortality followup in 2002, estimated 10-year CHD mortality in the highest risk decile of 0.58 percent in the 18 to 29 age group and 1.72 percent in the 30 to 39 age group.[15]

In 2010, heart disease was associated with 972 age-adjusted potential life-years lost per 100,000 persons under 75 years of age.[16,17] In 2008, heart disease and stroke accounted for nearly 300 billion dollars in health care costs.[18]

Etiology and Natural History

Cholesterol is a lipid that is present in all animal cells; it is vital to cell membrane structure and acts as a precursor to vitamin D, adrenal and gonadal steroid hormones and bile acids.[19] The body is able to absorb dietary cholesterol and also synthesize it *de novo*. In a typical Western diet, cholesterol intake is about 300 to 450 mg per day and endogenous cholesterol amounts to

800 to 1400 mg per day. A total of 1000 to 2000 mg of cholesterol can be absorbed by the small intestine. Plasma cholesterol levels depend on many factors including diet and genetics. In the general population, there is great variability in how cholesterol is synthesized and absorbed. Plasma cholesterol levels are the sum of intestinal cholesterol absorption and hepatic cholesterol synthesis balanced by net biliary excretion and cell use.

Cholesterol is transported in the body as particles of lipid and protein (lipoproteins).[7] There are three classes of lipoproteins: LDL-C, HDL-C, and very low density lipoproteins (VLDL-C). LDL-C makes up 60 to 70 percent of total serum cholesterol, HDL-C contributes 20 to 30 percent, and VLDL-C contributes 10 to 15 percent. LDL-C is the primary atherogenic lipoprotein and is the primary target of cholesterol-lowering therapy, although some forms of VLDL-C are precursors to LDL-C and promote atherosclerosis. HDL-C is inversely related to risk for CHD.

LDL-C is atherogenic when it accumulates in blood vessels, contributing to plaque formation. The fully developed plaque consists of a core of cholesterol, surrounded by a capsule of connective tissue.[20] The plaque core is surrounded by foam cells, which are macrophages containing intracytoplasmic cholesterol. These cells produce procoagulant and inflammatory cell mediators. Early stage plaque formation is not associated with structural damage to the endothelium, but later stage plaque formation leads to endothelial erosion that exposes the underlying connective tissue and allows platelets to adhere to the site, potentially leading to plaque smooth muscle cell growth through release of growth factor. Further endothelial erosion and disruption contribute to thrombus formation. As the thrombus builds, blood flow sends clumps of platelets into the distal small arteries as emboli and the thrombus may continue to grow until it occludes the artery, resulting in myocardial infarction, cerebrovascular accident (CVA), or another ischemic event. Endothelial erosion and disruption result from enhanced inflammatory activity within the plaque produced by smooth muscle cells and macrophages. Certain plaque characteristics like a large lipid core, high density of macrophages, and low density of smooth muscle cells in the cap are markers of plaques that are more likely to undergo thrombosis. The risk of a person with coronary artery disease having a future thrombogenic event is more associated with the presence and number of vulnerable plaques than the total number of plaques.

Exposure to nonoptimal lipid levels in young adulthood is associated with atherosclerotic changes later in life. One prospective cohort study of 2,824 persons age 18 to 30 years with nonoptimal levels of LDL–C (defined as $\geq$100 mg/dl) at baseline found an association between cumulative exposure to higher LDL or lower HDL levels and markers of atherosclerosis two decades later.[21]

People with familial hypercholesterolemia may have dramatically high levels of LDL-C, which can lead to accelerated atherosclerosis and, if untreated, early cardiovascular death.[22-24] Familial hypercholesterolemia is caused by mutations in the LDL receptor gene, which reduce the number of LDL–C receptors or prevent LDL-C from binding to these receptors, thereby reducing LDL-C removal from the blood. Patients with two mutant copies of the LDL receptor gene have the homozygous form of familial hypercholesterolemia. This condition is rare, with a prevalence of about 1:1,000,000.[25] The characteristic clinical presentation includes skin and tendon

xanthomoas, total cholesterol levels between 500 and 1,000 mg/dL, and the onset in childhood of symptomatic coronary disease as well as aortic valve and proximal root disease.[26,27] The heterozygous form of familial hypercholesterolemia is more common, with a prevalence of approximately 1:500 in the United States and United Kingdom. Total cholesterol levels in heterozygous familial hypercholesterolemia are less highly elevated than for homozygous familial hypercholesterolemia, averaging 325 to 450 mg/dL, but patients are also at increased risk for CHD and death in young adulthood due to prolonged exposure to high lipid levels that often starts in childhood.[23] The estimated proportion of persons with familial hypercholesterolemia who would have an early CHD event in the absence of recognition and treatment is 5 percent to 15 percent in men prior to 35 years of age, and 10 percent to 15 percent in women prior to 45 years of age.[28,29] Many patients with severe hypercholesterolemia do not have an identifiable genetic defect.[24] Evidence suggests that the clinical consequences of severe hypercholesterolemia are the same regardless of the underlying cause.

Risk Factors

Risk factors for dyslipidemia (high LDL, low HDL, high triglycerides) include physical inactivity, obesity, abdominal obesity, metabolic syndrome, hypertension, an atherogenic diet (high in saturated fatty acids, cholesterol, and sodium), consumption of added dietary sugars, genetic factors (including family history of familial hypercholesterolemia), increased age, male sex, and hypothyroidism.[7,8,30,31] Elevated triglycerides are associated with overweight and obesity, physical inactivity, smoking, excess alcohol intake, high carbohydrate diet, other diseases such as diabetes and nephritic syndrome, medications such as corticosteroids or estrogens, and genetic factors.[7] Hyperlipidemia is also associated with human immunodeficiency virus infection, renal transplant, and use of antipsychotic medications and protease inhibitors.[32-34]

Dyslipidemia is a risk factor for CHD.[7] Other modifiable risk factors for CHD include hypertension, smoking, thrombogenic/hemostatic state, diabetes, obesity, physical inactivity, and an atherogenic diet. Non-modifiable risk factors include age (male $\geq$45 years, female $\geq$55 years), male sex, and family history of early CHD.

Non-HDL-C (i.e., total cholesterol minus HDL-C) is a measure that includes all potentially atherogenic lipoprotein particles (LDL, VLDL, intermediate-density lipoprotein [IDL], and lipoprotein[a]), and it may be a more accurate predictor of CHD risk than LDL-C.[32,34,35] Apolipoprotein-B directly measures the total number of atherogenic particles, although it is unclear whether it adds to HDL-C and total cholesterol as a marker of CHD risk.[34,36-39] In addition, total and HDL-C are easier and less costly to measure. Other potential risk factors for CVD include alternative measures of lipid status such as total cholesterol-to-HDL ratio or other lipoprotein levels and non-lipid factors such as inflammatory markers (e.g., C-reactive protein,[40] homocysteine) and thrombogenic factors (e.g., fibrinogen, antithrombin III, factor V Leiden).[7]

In 2008, the USPSTF recommended screening with a fasting or nonfasting HDL, with either the total cholesterol or a measure of LDL.[4] In 2009, a USPSTF evidence review of nine emerging risk factors including C-reactive protein, leukocyte count, homocysteine levels, and lipoprotein levels found that evidence was insufficient to support the use of these risk factors to reclassify

intermediate-risk persons for CHD as high-risk, although it found that evidence for C-reactive protein was promising.[40] Clinical practice guidelines continue to predominantly focus on LDL-C as the primary lipid risk factor.

Rationale for Screening/Screening Strategies

Due to the asymptomatic nature of lipid disorders, screening is required for detection. Detection of younger adults with lipid disorders could enable implementation of management strategies such as lifestyle modification or medications that could prevent negative cardiovascular outcomes in persons at immediate risk for an event, or decrease risk of future events. Screening could be of particular benefit for identification of young adults with markedly elevated lipid levels due to unrecognized familial hypercholesterolemia.

Screening involves blood tests which may be obtained fasting or non-fasting. Although current recommendations generally recommend testing of total cholesterol and LDL-C, they differ on other lipid components to be tested, the age to start testing, and frequency of screening. (See Recommendations of Other Groups section below).

Interventions/Treatment

Standard treatments for lipid disorders in adults include use of medications, diet, and/or exercise interventions, or a combination of these interventions. Prior to 2013, treatment in the United States generally followed recommendations from the Third Report of the NCEP ATP III, which recommended global cardiovascular risk evaluation including measurement of lipids starting at age 20 years to guide decisions regarding use of lipid lowering therapy.[7] LDL-C thresholds for initiation of lipid lowering therapy following lifestyle intervention efforts varied from ≥130 to 190 mg/dL depending on the assessed risk category (defined as low, based on estimated risk of <10% for a CVD event after 10 years; intermediate, based on estimated 10% to 20% risk; or high, based on estimated risk >20%). Drug options for lipid lowering included statins, bile acid sequestrants, nicotinic acid, and fibrates, although statins were designated as the initial drug of choice given proven efficacy for lowering LDL-C and evidence showing improved clinical outcomes. Therapy with a statin or other lipid-lowering therapy was targeted to achieve goal LDL levels that varied from <100 to <160 mg/dL depending on the risk category.

Updated guidelines from the American College of Cardiology (ACC) and the AHA on lipid lowering therapy were issued at the end of 2013, and differ from ATP III in a number of ways. In the new guideline, statins are the recommended first-line lipid-lowering therapy to reduce CVD risk, as evidence on effectiveness of lipid lowering therapies at improving clinical outcomes is strongest for statins.[27] Target populations for statin therapy were re-defined as four groups: persons with clinical CVD, persons 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL, persons with LDL-C ≥190 mg/dL, or persons 40 to 75 years of age with an estimated 10-year risk of CVD of 7.5 percent or higher. In patients in the latter group who do not meet criteria for one of the other target populations, a clinician-patient risk discussion is recommended prior to initiation of statin therapy. Rather than managing statin therapy to achieve an LDL-C target,

the ACC/AHA recommends fixed dose statin therapy, with the intensity (based on the dose and potency of the statin used, and thus, the expected degree of LDL-C reduction) of therapy determined by the risk profile. The updated guideline also recommends the use of a newly developed global risk calculator to estimate risk.

In patients with familial hyperlipidemia, a guideline from the National Lipid Association recommends lifestyle modification, moderate to high potency statins as first-line drug therapy (alternative drugs or combination therapy is recommended in persons who cannot tolerate statins or do not meet LDL reduction of ≥50% from baseline), and LDL apheresis in high-risk patients who do not meet lipid targets on lifestyle and drugs.[41]

Current Clinical Practice in the United States

A study based on 1996 to 2006 NHANES data from 2,587 adults aged 20 to 45 years found overall lipid screening rates of <50 percent.[42] Screening rates varied based on the presence of cardiovascular risk factors. Lipid testing rates was 68 percent in those with CHD or CHD equivalents, 47 percent in those with ≥2 risk factors, 45 percent in those with one risk factor, and 42 percent in those with no known risk factors. The presence of CHD or CHD equivalent was associated with increased likelihood of screening compared with presence of no risk factors (relative risk 1.5; 95 percent confidence interval 1.1 to 2.2). In addition, women were more likely to have undergone screening compared with men. Among those with a CHD or CHD equivalent, two or more risk factors, one, or no risk factors, screening rates for women were 69 percent, 53 percent, 52 percent, and 49 percent, respectively; corresponding rates for men were 64 percent, 38 percent, 36 percent, and 30 percent, respectively.[4,43] A study based on a 2005 United States National Ambulatory Medical Care survey found disparities in rates of lipid screening in adults ≥20 years of age, with higher rates in whites (40%) versus blacks (33%) or Hispanics (39%).[44] Results were not reported separately for younger adults.

Healthy People 2020 has set a target screening rate of 82 percent screening rate within the last five years for age >18 years (increased from 75% in 2008).[45]

Recommendations of Other Groups

Recommendations for lipid screening in young adults without risk factors for CHD vary, with some guidelines recommending screening starting at age 20 and others not recommending screening until age 35 to 40 for men or 40 to 50 for women. In general, guidelines recommend screening younger adults with CHD, CHD equivalents, or one or more CHD risk factor.

The ATP III guideline recommends screening all persons ≥20 years old every 5 years with LDL-C, HDL-C, total cholesterol, and triglycerides.[7] It recommends that clinicians perform a lipoprotein analysis and risk factor evaluation to assign risk status as part of the first patient visit for adults ≥20 years and, depending on the results, initiate efforts to control risk factors with re-evaluation in 1 to 5 years or initiate lifestyle changes.[7]

The ACC and AHA guidelines of assessment of cardiovascular risk does not specifically address lipid screening, but recommends "as reasonable" assessment of traditional cardiovascular risk factors every 4 to 6 years starting at age 20 (grade IIa recommendation).[5] Although the Pooled Cohort Equations CV Risk Calculator developed by the ACC and AHA estimates lifetime risk of atherosclerotic cardiovascular disease in persons 20 years of age or older, the guideline does not make a recommendation to apply the Pooled Cohort Equations CV Risk Calculator in persons younger than 40 years of age.

The American Diabetes Association recommends lipid screening in patients with diabetes recommended at least annually, and every 2 years for adults with low-risk lipid values (LDL-C <100 mg/dL, HDL-C >50 mg/dL, and triglycerides <150 mg/dL).[46]

The Task Force for the Management Dyslipidaemias of the European Society of Cardiology and the European Atherosclerosis Society recommend risk-level based screening depending on various risk factors (e.g., diabetes, established CVD, hypertension, smoking, body mass index >30 kg/m^2, family history of premature CVD and familial dyslipidemia, chronic inflammatory disease, chronic kidney disease). Assessment of lipid levels may be considered in men >40 and women >50 years of age.[47]

The Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias recommend screening men over 40 years of age, postmenopausal women, or women over 50 years of age, patients with diabetes mellitus, hypertension, smoking or abdominal obesity, or a strong family history of premature cardiovascular disease manifestations of hyperlipidemia (e.g., xanthelasma, xanthoma or arcus corneae), or evidence of symptomatic or asymptomatic atherosclerosis, or any patient for whom "lifestyle changes are indicated." This group further recommends use of NCEP ATP-III risk estimation algorithm with LDL and total HDL ratio as targets.[48]

The American Academy of Family Physicians concurs with current USPSTF recommendations.[49]

The American College of Physicians lists an inactive guideline from 1996 recommending screening in men >35 years old and women >45 years old with total cholesterol levels.[50]

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF[51,52] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and Key Questions for this review. In conjunction with the USPSTF, investigators created an analytic framework with the Key Questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**).

Key Questions

1. What are the benefits of screening for dyslipidemia in asymptomatic adults ages 21 to 39 years on CHD- or CVA-related morbidity or mortality or all-cause mortality?
2. What are the harms of screening for dyslipidemia in asymptomatic adults ages 21 to 39 years?
3. What is the diagnostic yield of alternative screening strategies (e.g., universal screening versus risk-based screening) for dyslipidemia in asymptomatic adults ages 21 to 39 years?
4. What are the benefits of treatment (e.g., drug or lifestyle interventions) for dyslipidemia in adults ages 21 to 39 years on CHD- or CVA-related morbidity or mortality or all-cause mortality?
5. What are the benefits of delayed versus immediate treatment in adults ages 21 to 39 years with dyslipidemia on CHD- or CVA- related morbidity or mortality or all-cause mortality?
6. What are the harms of drug treatment for dyslipidemia in asymptomatic adults ages 21 to 39 years?

Two Contextual Questions were also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology. Rather, the approach to Contextual Questions is to focus on evidence from key, high-quality studies.

Contextual Questions

1. What are the benefits of drug treatment in adults ages 21 to 39 years on intermediate outcomes (e.g., lipid levels, atherosclerosis)?
2. How do lipid levels change over time in adults ages 21 to 39 years?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (to November 2015), and Ovid MEDLINE (2008 to November 2015) for relevant studies and systematic reviews. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. Studies were reviewed on the basis of inclusion and exclusion criteria developed for each Key Question (**Appendix A2**). Includable studies were randomized trials, cohort studies, and case-control studies of lipid screening versus no screening, treatment for dyslipidemia versus no treatment, and delayed versus immediate treatment for dyslipidemia in asymptomatic adults 21 to 39 years of age that evaluated mortality, cardiovascular outcomes (CHD or cerebrovascular disease-related morbidity or mortality), or harms of screening or treatment. Studies that reported the diagnostic yield (number of true positives per number tested) of lipid screening in adults 21 to 39 years of age were also includable. Studies that enrolled older adults would be included if results were reported separately for the subgroup of patients younger than 40 years of age or if the mean age of the population was <40 years. Included interventions were drug as well as lifestyle interventions (e.g., exercise and diet changes).

Effects of treatment on intermediate outcomes (such as changes in markers of atherosclerosis or lipid levels) were evaluated for one of the Contextual Questions. Studies of individuals with prior cardiovascular events were excluded. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We planned to have one investigator abstract details about each article's study design, patient population, setting, screening method, treatment regimen, analysis, followup, and results; a second investigator review data abstraction for accuracy; and two investigators independently apply criteria developed by the USPSTF[51] to rate the quality of each study as good, fair, or poor (**Appendix A5**) with discrepancies resolved through consensus; however, no studies met inclusion criteria.

Data Synthesis

We planned to assess the aggregate internal validity (quality) of the body of evidence for each key question ("good", "fair", "poor") using methods developed by the USPSTF, based on the number, quality and size of studies, consistency of results among studies, and directness of evidence;[51] however, no studies met inclusion criteria.

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, AHRQ Project Officers, and collaborative partners.

Chapter 3. Results

Key Question 1. What Are the Benefits of Screening for Dyslipidemia in Asymptomatic Adults Ages 21 to 39 Years on CHD- or CVA-Related Morbidity or Mortality or All-Cause Mortality?

We identified no studies on benefits of screening versus no screening for dyslipidemia in asymptomatic adults ages 21 to 39 years on cardiovascular outcomes.

Key Question 2. What Are the Harms of Screening for Dyslipidemia in Asymptomatic Adults Ages 21 to 39 Years?

We identified no studies on harms of screening versus no screening for dyslipidemia in asymptomatic adults ages 21 to 39 years that evaluated clinical outcomes.

Key Question 3. What Is the Diagnostic Yield of Alternative Screening Strategies (e.g., Universal vs. Risk-Based Screening) for Dyslipidemia in Asymptomatic Adults Ages 21 to 39 Years?

We identified no studies on the diagnostic yield of alternative screening strategies for dyslipidemia in asymptomatic adults ages 21 to 39 years.

Key Question 4. What Are the Benefits of Treatment (e.g., Drug or Lifestyle Interventions) in Adults Ages 21 to 39 Years on CHD- or CVA-Related Morbidity or Mortality or All-Cause Mortality?

Summary

We identified no studies on benefits of treatment versus no treatment in adults ages 21 to 39 years on cardiovascular outcomes.

Evidence

We identified no studies on benefits of treatment versus no treatment in adults ages 21 to 39 years on cardiovascular outcomes. Although four trials of statins for primary prevention enrolled patients younger than 40 years of age, results were not reported separately for this subgroup and

they comprised a small part of the population.[53-56] One cohort study evaluated efficacy of statins in patients with familial hypercholesterolemia, but the mean age at enrollment was 44 years.[57]

Key Question 5. What Are the Benefits of Delayed Versus Immediate Treatment in Adults Ages 21 to 39 Years With Dyslipidemia on CHD- or CVA-Related Morbidity or Mortality or All-Cause Mortality?

We identified no studies on benefit of delayed versus immediate treatment of dyslipidemia in adults ages 21 to 39 years.

Key Question 6. What Are the Harms of Drug Treatment for Dyslipidemia in Asymptomatic Adults Ages 21 to 39 Years?

We identified no studies on harms of treatment for dyslipidemia versus no treatment in adults ages 21 to 39 years.

Contextual Question 1. What Are the Benefits of Drug Treatment in Adults Ages 21 to 39 Years on Intermediate Outcomes (e.g., Lipid Levels, Atherosclerosis)?

We identified no randomized trials, cohort studies, or case-control studies on effects of drug treatment in adults ages 21 to 39 years on intermediate outcomes, such as lipid levels or atherosclerosis.

Contextual Question 2. How Do Lipid Levels Change Over Time in Adults Ages 21 to 39 Years?

Few longitudinal studies have assessed how lipid levels change over time in adults ages 21 to 39 years. In the Framingham Heart Study, the average biennial difference among serial cholesterol measurements among individuals <45 years at enrollment was 4.4 +/- 6.9 mg/dL in men and 7.5 +/- 7.2 mg/dL in women.[58] Including all adults, the rate of change was higher in persons with lower total cholesterol (6.7 +/- 5.6 mg/dL for men and 9.2 +/- 6.6 mg/dL for women with initial cholesterol <200 mg/dL versus 0.6 +/- 7.4 mg/dL for men and 3.7 +/- 11.2 mg/dL for women with initial cholesterol ≥240 mg/dL). Some evidence also suggests that young adults with low lipid levels often do not maintain them. The Coronary Artery Risk Development in Young Adults Study, which enrolled individuals in the United States 18 to 30 years of age, found that between 44 and 52 percent of those with total cholesterol levels below the 10th percentile remained below the same percentile 7 years later.[59]

Several European studies have also evaluated stability of lipid levels over time in young adults. In general, lipid levels in young adults increased over time, though the magnitude of change varied depending on baseline age and sex. In the Nijmegen (the Netherlands) Cohort Study, the increase over a period of 18 years was largest for younger men, with total cholesterol increasing an average of 20 percent in men 20 to 24 years of age at baseline and 9.1 percent in men 35 to 39 years of age at baseline.[60] In women the pattern was in the opposite direction, at 9.8 percent for those 20 to 24 years of age at baseline and 16 percent for those 35 to 39 years of age at baseline. The proportion with cholesterol levels of 251 mg/dL or higher increased from 3 percent in men 20 to 24 years of age and 6 percent in women 20 to 24 years of age at baseline to 26 percent and 16 percent, respectively, 18 years later; and from 23 percent in men and 12 percent in women 35 to 39 years of age to 36 percent and 43 percent after followup. In the Tromso (Norway) Study, the tracking coefficient (a measure of the tendency of individuals to maintain their rank or position in a group over time) for HDL-C in men 20 to 38 years of age ranged from 0.52 to 0.56 and for women ranged from 0.51 to 0.62.[61] The tracking coefficient was higher for total cholesterol, at 0.70 to 0.74 for men and 0.62 to 0.69 for women, and was lower for triglycerides, at 0.30 to 0.49 for men and 0.33 to 0.39 for women. Tracking was also higher for total cholesterol than triglycerides in younger adults in the Vorarlberg (Austria) Health Monitoring and Promotion Programme.[62] A Spanish study of military recruits 20 years of age found that after 15 years, cholesterol increased an average of 68 mg/dL, LDL cholesterol 58 mg/dL, and HDL cholesterol -5.2 mg/dL.[63]

Chapter 4. Discussion

Summary of Review Findings

As shown in **Table 1**, no study has evaluated the effects of screening versus no screening or treatment versus no treatment on clinical outcomes. In addition, no study evaluated the diagnostic yield of alternative screening strategies in younger adults (e.g., targeted screening of persons with a family history of hyperlipidemia versus general screening). Although some primary prevention trials have enrolled younger adults,[53-56] they comprised a small part of the population and results were not reported separately for this age group. In addition, because of the small numbers of cardiovascular events expected in this age group, even if the data were reported, the trials were probably underpowered to detect effects on clinical outcomes. Therefore, estimates of benefits of lipid-lowering therapies or lifestyle changes for dyslipidemia in younger adults require extrapolation from trials conducted in older populations. Even assuming that the relative benefits are the same for statins or other therapies in younger and older adults, the absolute benefits over the short-term (e.g., 5 to 10 years) would generally be lower in younger adults because of the lower incidence of CHD events. An exception may be young adults with familial hypercholesterolemia, who are at increased risk of CHD events at a younger age. However, the only study that compared effects of statins versus no statins for familial hypercholesterolemia enrolled persons with a mean age of 44 years and did not meet inclusion criteria.[57]

We also found no evidence on the incremental benefit of delayed versus earlier treatment. Earlier initiation of therapy might reduce risk of CHD events that occur later in life if the primary mechanism of lipid lowering therapy is regression of atherosclerosis. However, in trials of middle-aged and older populations, CHD event prevention appears to start within 1 to 2 years of statin initiation,[64] suggesting that long-term therapy started during early adulthood may not be required to experience benefits from treatment, which might be related in part to early plaque stabilization or other shorter-term effects.

Our findings are in accordance with prior USPSTF reviews,[1,3] which also found no direct evidence on benefits or harms of screening or subsequent treatment in younger adults. Although individuals with familial hypercholesterolemia are at increased risk for early cardiovascular events, a factor limiting potential benefits for screening from this condition is that familial hypercholesterolemia is a low prevalence condition (estimated at 1 in 500 persons), and that even among this population the majority (85% to 90%) do not experience a CHD event prior to 40 years of age.[28,29]

Longitudinal studies suggest that lipid levels have a tendency to increase over time in younger adults,[58,60] although no study evaluated how lipid levels changed according to different intervals between repeat testing, or the proportion of patients who would move from one risk category to another.

Limitations

The major limitation of this review is the lack of direct evidence in younger adults.

Emerging Issues/Next Steps

Statins have become the mainstay of lipid-lowering therapy. Although statins in middle-aged and older adults appear to be relatively safe, long-term adverse effects of statins (e.g., risk of developing diabetes) started in younger adulthood and taken for decades have not been well studied.

Relevance for Priority Populations

No evidence was identified for priority populations on the benefits and harms of screening or treatment for dyslipidemia

Future Research

Research is needed to understand effects of screening and treatment for dyslipidemia in younger adults. As very large, long-term trials would be required to evaluate screening of younger adults in the general population and may not be feasible, initial screening trials might target individuals with a family history of familial hypercholesterolemia or early CHD and initial treatment trials might target persons with highly elevated lipid levels (e.g., due to familial hypercholesterolemia). A recently established registry of persons with familial hyperlipidemia could be useful for understanding effects of treatment.[65] Trials of delayed versus immediate lipid lowering therapy in younger adults found to have dyslipidemia would also be helpful for understanding the effectiveness of earlier treatment, and studies are needed to understand harms associated with very long-term statin therapy.

Conclusions

Direct evidence on benefits and harms of screening or treatment for dyslipidemia in younger adults remains unavailable.

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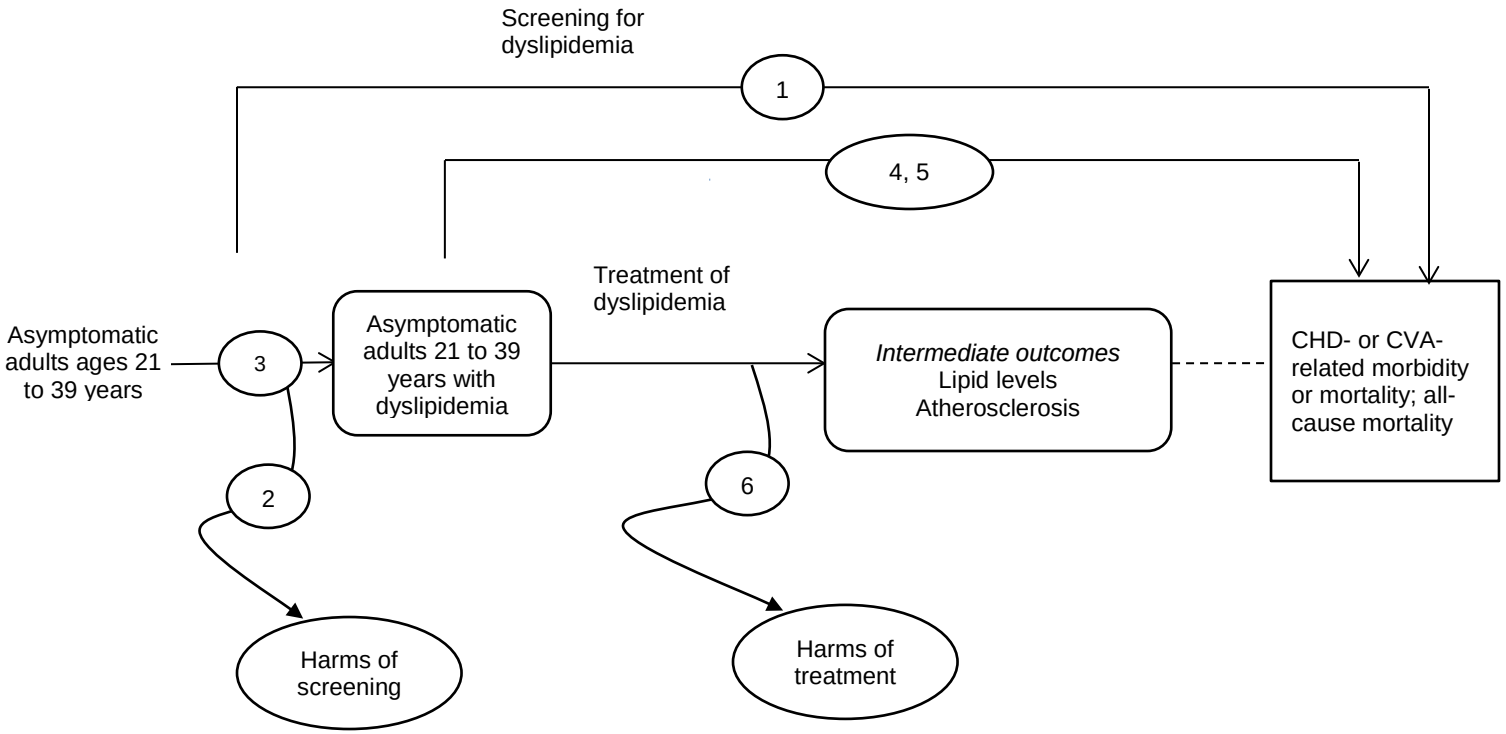
Figure 1. Analytic Framework



Note: Numbers correspond to the Key Questions.

Abbreviations: CHD = coronary heart disease; CVA = cerebrovascular accident (stroke).

Table 1. Summary of Evidence

Main findings from prior USPSTF reports*	Number and type of studies identified for update	Limitations	Consistency	Applicability	Summary of findings	Overall quality†
Key Question 1. What are the benefits of screening for dyslipidemia in asymptomatic adults ages 21 to 39 years on CHD- or CVA-related morbidity or mortality or all-cause mortality?						
No studies	No studies	-	-	-	-	-
Key Question 2. What are the harms of screening for dyslipidemia in asymptomatic adults ages 21 to 39 years?						
No studies	No studies	-	-	-	-	-
Key Question 3. What is the diagnostic yield of alternative screening strategies (e.g., universal vs. risk-based screening) for dyslipidemia in asymptomatic adults ages 21 to 39 years?						
No studies	No studies	-	-	-	-	-
Key Question 4. What are the benefits of treatment (e.g., drug or lifestyle interventions) for dyslipidemia in adults ages 21 to 39 years on CHD- or CVA-related morbidity or mortality or all-cause mortality?						
No studies	No studies	-	-	-	Although four trials of statins for primary prevention enrolled patients younger than 40 years of age, results were not reported separately for this subgroup and they comprised a small part of the population. One cohort study evaluated efficacy of statins in patients with familial hypercholesterolemia but the mean age at enrollment was 44 years.	-
Key Question 5. What are the benefits of delayed versus immediate treatment in adults ages 21 to 39 years with dyslipidemia on CHD- or CVA-related morbidity or mortality or all-cause mortality?						
No studies	No studies	-	-	-	-	-
Key Question 6. What are the harms of drug treatment for dyslipidemia in asymptomatic adults ages 21 to 39 years?						
No studies	No studies	-	-	-	-	-

* A difference between this update and prior USPSTF reviews on lipid screening is that this review focuses on screening in younger adults (defined as adults 21 to 39 years of age).

† "Overall quality" is based on new evidence plus previously reviewed evidence.

Abbreviations: CHD= coronary heart disease; CVA= cerebrovascular accident (stroke).

Appendix A1. Search Strategies

Screening

Database: Ovid MEDLINE(R) without Revisions

1 exp Dyslipidemias/
2 Cholesterol/bl
3 Mass Screening/
4 (1 or 2) and 3
5 limit 4 to yr="2008 - 2015"
6 limit 5 to humans
7 limit 6 to English language
8 limit 6 to abstracts
9 7 or 8

Treatment

Randomized Controlled Trials and Controlled Observational Studies

Database: Ovid MEDLINE(R) without Revisions

1 exp Dyslipidemias/
2 Cholesterol, HDL/bl
3 Cholesterol, LDL/bl
4 Lipids/bl
5 Triglycerides/bl
6 or/2-5
7 Cardiovascular Diseases/pc
8 or/1-7
9 Hypolipidemic Agents/
10 Anticholesteremic Agents/
11 Hydroxymethylglutaryl-CoA Reductase Inhibitors/
12 (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin).mp.
13 (lipitor or lescol or mevacor or livalo or pravachol or crestor or zocor).mp.
14 Gemfibrozil/
15 Fenofibrate/
16 Niacin/
17 or/9-16
18 Diet/ or Diet, Reducing/
19 Exercise Therapy/
20 Weight Loss/
21 (diet or exercise or lifestyle).ti,ab.
22 or/18-21
23 8 and (17 or 22)
24 23 and (random$ or control$ or cohort).ti,ab.
25 24 not (child$ or pediatric$ or adolescen$ or teen$).mp.
26 limit 25 to (English language and humans)
27 limit 26 to yr="2008 - 2015"

Database: Cochrane Central Register of Controlled Trials

1 exp Dyslipidemias/
2 Cholesterol, HDL/bl
3 Cholesterol, LDL/bl
4 Lipids/bl
5 Triglycerides/bl
6 or/2-5
7 Cardiovascular Diseases/pc
8 or/1-7

Appendix A1. Search Strategies

9 Hypolipidemic Agents/
10 Anticholesteremic Agents/
11 Hydroxymethylglutaryl-CoA Reductase Inhibitors/
12 (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin).mp.
13 (lipitor or lescol or mevacor or livalo or pravachol or crestor or zocor).mp.
14 Gemfibrozil/
15 Fenofibrate/
16 Niacin/
17 or/9-16
18 Diet/ or Diet, Reducing/
19 Exercise Therapy/
20 Weight Loss/
21 (diet or exercise or lifestyle).ti,ab.
22 or/18-21
23 8 and (17 or 22)
24 limit 23 to yr="2008 - 2015"

Systematic Reviews

Database: Ovid MEDLINE(R) without Revisions
1 exp Dyslipidemias/
2 Cholesterol, HDL/bl
3 Cholesterol, LDL/bl
4 Lipids/bl
5 Triglycerides/bl
6 or/2-5
7 Cardiovascular Diseases/pc
8 or/1-7
9 Hypolipidemic Agents/
10 Anticholesteremic Agents/
11 Hydroxymethylglutaryl-CoA Reductase Inhibitors/
12 (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin).mp.
13 (lipitor or lescol or mevacor or livalo or pravachol or crestor or zocor).mp.
14 Gemfibrozil/
15 Fenofibrate/
16 Niacin/
17 or/9-16
18 Diet/ or Diet, Reducing/
19 Exercise Therapy/
20 Weight Loss/
21 (diet or exercise or lifestyle).ti,ab.
22 or/18-21
23 8 and (17 or 22)
24 limit 23 to evidence based medicine reviews
25 limit 24 to (English language and humans)
26 limit 25 to yr="2008 - 2015"

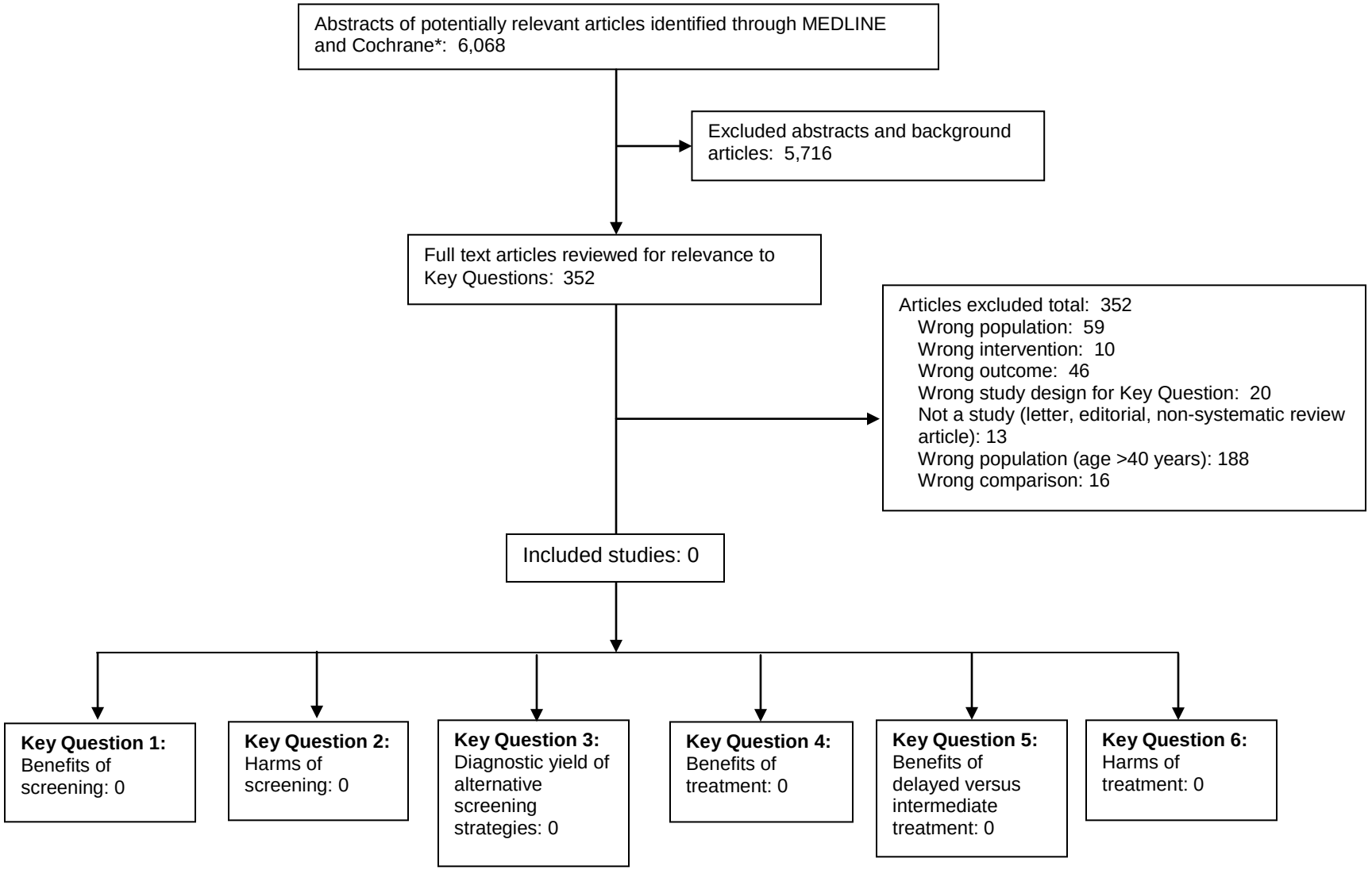
Database: Cochrane Database of Systematic Reviews
1 (lipid$ or cholesterol).ti,ab.
2 1 not (child$ or pediatric$ or adolescen$ or teen$).mp.
3 limit 2 to full systematic reviews

Appendix A2. Inclusion and Exclusion Criteria per Key Question

	Include	Exclude
Population	**KQs 1-3:** Asymptomatic adults ages 21 to 39 years **KQs 4-6:** Adults ages 21 to 39 years with dyslipidemia	**KQs 1-3:** Adults with known dyslipidemia (primary or secondary) or prior CVD events **KQs 4-6:** Adults with prior CVD events
Diseases	Dyslipidemia (as defined according to clinical practice guidelines, levels above the 90th percentile for lipid components positively associated with CHD risk, or other specified criteria)	Lipid levels not meeting thresholds for dyslipidemia
Screening Interventions	Lipid panel (fasting or nonfasting lipid measurement: total or LDL cholesterol alone or in combination with HDL cholesterol, with or without measurement of other lipid markers)	• Screening with family history only • Genetic screening only
Screening Comparator	No screening or usual care delivered in a universal or selective screening strategy	Other comparators not listed as included
Treatment Interventions	Drug (e.g., statins) and lifestyle interventions (e.g., exercise and diet changes)	Other types of treatments not listed as included
Treatment Comparator	No treatment or usual care	Other comparators not listed
Outcomes	**KQs 1, 4, 5:** CHD- and/or CVA-related morbidity or mortality; all-cause mortality **KQ 2:** Harms associated with the screening process (e.g., false-positives, false-negatives, psychosocial consequences such as anxiety, overdiagnosis, and others as identified in the literature) **KQ 3:** Diagnostic yield (true positives/number screened) **KQ 6:** Harms associated with drug treatment (e.g., myopathy, rhabdomyolysis, myalgia, cognitive loss, diabetes, elevations in liver function tests or creatine phosphokinase levels, and others as identified in the literature)	**KQs 1, 4, 5:** Outcomes not listed as included **KQ 2:** Adverse outcomes not associated with screening **KQ 3:** Outcomes not listed as included **KQ 6:** Other adverse outcomes not associated with drug treatment
Study Design	Randomized controlled trials, cohort studies, case-control studies, high-quality systematic reviews	Other study designs
Settings	• Publication date of 2008 to present; studies included in prior USPSTF reports • Primary care or primary care–relevant	Settings not generalizable to primary care; studies outside the stated timeframe

Abbreviations: CHD=coronary heart disease, CVA=cerebrovascular accident; CVD=cardiovascular disease, HDL=high density lipoprotein, KQ=Key Question; LDL=low density lipoprotein; USPSTF=United States Preventive Services Task Force.

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

Appendix A4. Excluded Studies With Reasons for Exclusion

Key to Exclusion Codes

Code 3	Wrong population
Code 4	Wrong intervention
Code 5	Wrong outcome
Code 6	Wrong study design for Key Question
Code 7	Not a study (letter, editorial, non-systematic review article)
Code 9	Wrong population: age >40 years
Code 13	Wrong comparison

The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251(3):351-64.
Exclusion code: 3

Clinical Guideline, Part 1: Guidelines for Using Serum Cholesterol, High-Density Lipoprotein Cholesterol, and Triglyceride Levels as Screening Tests for Preventing Coronary Heart Disease in Adults. Ann Intern Med. 1996;124(5):515-7.
Exclusion code: 9

MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. Eur Heart J. 1999;20(10):725-41.
Exclusion code: 9

Abourbih S, Filion KB, Joseph L, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009;122(10):962.e1-8.
Exclusion code: 4

Accord Study Group, Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus.[Erratum appears in N Engl J Med. 2010 May 6;362(18):1748]. N Engl J Med. 2010;362(17):1563-74.
Exclusion code: 9

Adams SP, Tsang M, Wright JM. Lipid lowering efficacy of atorvastatin. Cochrane Database Syst Rev. 2012;12:CD008226.
Exclusion code: 5

Adamsson V, Reumark A, Fredriksson IB, et al. Effects of a healthy Nordic diet on cardiovascular risk factors in hypercholesterolaemic subjects: a randomized controlled trial (NORDIET). J Intern Med. 2011;269(2):150-9.
Exclusion code: 9

Ai M, Otokozawa S, Asztalos BF, et al. Effects of maximal doses of atorvastatin versus rosuvastatin on small dense low-density lipoprotein cholesterol levels. Am J Cardiol. 2008;101(3):315-8.
Exclusion code: 9

Alberton M, Wu P, Druyts E, et al. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM. 2012;105(2):145-57.
Exclusion code: 4

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007.
Exclusion code: 9

Alsheikh-Ali AA, Trikalinos TA, Kent DM, et al. Statins, low-density lipoprotein cholesterol, and risk of cancer. J Am Coll Cardiol. 2008;52(14):1141-7.
Exclusion code: 9

Amarenco P, Benavente O, Goldstein LB, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009;40(4):1405-9.
Exclusion code: 9

Amarenco P, Bogousslavsky J, Callahan Ar, et al. High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. N Engl J Med. 2006;355(6):549-59.
Exclusion code: 9

Amarenco P, Goldstein LB, Callahan A, 3rd, et al. Baseline blood pressure, low- and high-density lipoproteins, and triglycerides and the risk of vascular events in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Atherosclerosis. 2009;204(2):515-20.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Amarenco P, Goldstein LB, Messig M, et al. Relative and cumulative effects of lipid and blood pressure control in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial. Stroke. 2009;40(7):2486-92.
Exclusion code: 9

Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet neurol. 2009;8(5):453-63.
Exclusion code: 9

Angermayr L, Melchart D, Linde K. Multifactorial lifestyle interventions in the primary and secondary prevention of cardiovascular disease and type 2 diabetes mellitus--a systematic review of randomized controlled trials. Ann Behav Med. 2010;40(1):49-64.
Exclusion code: 9

Ara R, Tumur I, Pandor A, et al. Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation. Health Technol Assess. 2008;12(21):iii, xi-xiii, 1-212.
Exclusion code: 7

Ashen MD, Foody JM. Evidence-based guidelines for cardiovascular risk reduction: the safety and efficacy of high-dose statin therapy. J Cardiovasc Nurs. 2009;24(6):429-38.
Exclusion code: 6

Asselbergs FW, Diercks GFH, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110(18):2809-16.
Exclusion code: 6

Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. Circulation. 2002;105(3):310-5.
Exclusion code: 3

Assmann G, Schulte H, Funke H, et al. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J. 1998;19 Suppl M:M8-14.
Exclusion code: 3

Aung MN, Yuasa M, Moolphate S, et al. Reducing salt intake for prevention of cardiovascular diseases in high-risk patients by advanced health education intervention (RESIP-CVD study), Northern Thailand: study protocol for a cluster randomized trial. Trials. 2012;13:158.
Exclusion code: 6

Azzarito C, Boiardi L, Vergoni W, et al. Testicular function in hypercholesterolemic male patients during prolonged simvastatin treatment. Horm Metab Res. 1996;28(4):193-8.
Exclusion code: 3

Badheka AO, Rathod A, Kizilbash MA, et al. Impact of lipid-lowering therapy on outcomes in atrial fibrillation. Am J Cardiol. 2010;105(12):1768-72.
Exclusion code: 9

Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181-92.
Exclusion code: 9

Baik I, Cho NH, Kim SH, et al. Dietary information improves cardiovascular disease risk prediction models. Eur J Clin Nutr. 2013;67(1):25-30.
Exclusion code: 9

Barylski M, Nikfar S, Mikhailidis DP, et al. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy--a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacol Res. 2013;72:35-44.
Exclusion code: 9

Bazzano LA, Thompson AM, Tees MT, et al. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2011;21(2):94-103.
Exclusion code: 3

Beishuizen ED, van de Ree MA, Jukema JW, et al. Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. Diabetes Care. 2004;27(12):2887-92.
Exclusion code: 5

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Berard E, Bongard V, Dallongeville J, et al. Cancer mortality according to lipid-lowering drugs and lipoproteins in a general population. Curr Med Res Opin. 2011;27(10):1963-71.
Exclusion code: 6

Bertoni AG, Bonds DE, Chen H, et al. Impact of a multifaceted intervention on cholesterol management in primary care practices: guideline adherence for heart health randomized trial. Arch Intern Med. 2009;169(7):678-86.
Exclusion code: 5

Blankstein R, Budoff MJ, Shaw LJ, et al. Predictors of coronary heart disease events among asymptomatic persons with low low-density lipoprotein cholesterol MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2011;58(4):364-74.
Exclusion code: 9

Boumendil E, Tubert-Bitter P. Depression-induced absenteeism in relation to antihyperlipidemic treatment: a study using GAZEL cohort data. Epidemiology. 1995;6(3):322-5.
Exclusion code: 9

Broekhuizen K, van Poppel MNM, Koppes LL, et al. No significant improvement of cardiovascular disease risk indicators by a lifestyle intervention in people with familial hypercholesterolemia compared to usual care: results of a randomised controlled trial. BMC Res Notes. 2012;5:181.
Exclusion code: 5

Broekhuizen K, van Poppel MNM, Koppes LLJ, et al. A tailored lifestyle intervention to reduce the cardiovascular disease risk of individuals with Familial Hypercholesterolemia (FH): design of the PRO-FIT randomised controlled trial. BMC Public Health. 2010;10:69.
Exclusion code: 5

Bruckert E, Giral P, Paillard F, et al. Effect of an educational program (PEGASE) on cardiovascular risk in hypercholesterolaemic patients. Cardiovasc Drugs Ther. 2008;22(6):495-505.
Exclusion code: 9

Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ. 2009;338:b2376.
Exclusion code: 9

Bulbulia R, Armitage J. Does the benefit from statin therapy extend beyond 5 years? Curr Atheroscler Rep. 2013;15(2):297.
Exclusion code: 6

Burgess DC, Hunt D, Li L, et al. Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Eur Heart J. 2010;31(1):92-9.
Exclusion code: 9

Burillo E, Andres EM, Mateo-Gallego R, et al. High-density lipoprotein cholesterol increase and non-cardiovascular mortality: a meta-analysis. Heart. 2010;96(17):1345-51.
Exclusion code: 6

Chan DKY, O'Rourke F, Shen Q, et al. Meta-analysis of the cardiovascular benefits of intensive lipid lowering with statins. Acta Neurol Scand. 2011;124(3):188-95.
Exclusion code: 9

Chan KL, Teo K, Dumesnil JG, et al. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation. 2010;121(2):306-14.
Exclusion code: 5

Chen YH, Feng B, Chen ZW. Statins for primary prevention of cardiovascular and cerebrovascular events in diabetic patients without established cardiovascular diseases: a meta-analysis. Exp Clin Endocrinol Diabetes. 2012;120(2):116-20.
Exclusion code: 9

Cholesterol Treatment Trialists Collaborators, Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371(9607):117-25.
Exclusion code: 9

Chu PH, Chen WJ, Chiang CW, et al. Rhabdomyolysis, acute renal failure and hepatopathy induced by lovastatin monotherapy. Jpn Heart J. 1997;38(4):541-5.
Exclusion code: 3

Appendix A4. Excluded Studies With Reasons for Exclusion

Claes N, Jacobs N, Clays E, et al. Comparing the effectiveness of two cardiovascular prevention programmes for highly educated professionals in general practice: a randomised clinical trial. BMC Cardiovasc Disord. 2013;13:38.
Exclusion code: 4

Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364(9435):685-96.
Exclusion code: 6

Colhoun HM, Betteridge DJ, Durrington PN, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009;54(5):810-9.
Exclusion code: 9

Collier DJ, Poulter NR, Dahlof B, et al. Impact of atorvastatin among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm. J Hypertens. 2011;29(3):592-9.
Exclusion code: 9

Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361(9374):2005-16.
Exclusion code: 9

Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.
Exclusion code: 9

Contermans J, Smit JW, Bar PR, et al. A comparison of the effects of simvastatin and pravastatin monotherapy on muscle histology and permeability in hypercholesterolaemic patients. Br J Clin Pharmacol. 1995;39(2):135-41.
Exclusion code: 13

Cooney M-T, Dudina A, Whincup P, et al. Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. Eur J Cardiovasc Prev Rehabil. 2009;16(5):541-9.
Exclusion code: 9

Cushman M, McClure LA, Lakoski SG, et al. Eligibility for statin therapy by the JUPITER trial criteria and subsequent mortality. Am J Cardiol. 2010;105(1):77-81.
Exclusion code: 9

Cutler N, Sramek J, Veroff A, et al. Effects of treatment with simvastatin and pravastatin on cognitive function in patients with hypercholesterolaemia. Br J Clin Pharmacol. 1995;39(3):333-6.
Exclusion code: 3

D'Agostino RB, Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.
Exclusion code: 9

Dansky HM, Bloomfield D, Gibbons P, et al. Efficacy and safety after cessation of treatment with the cholesteryl ester transfer protein inhibitor anacetrapib (MK-0859) in patients with primary hypercholesterolemia or mixed hyperlipidemia. Am Heart J. 2011;162(4):708-16.
Exclusion code: 9

Davidson MH, Rooney MW, Drucker J, et al. Efficacy and tolerability of atorvastatin/fenofibrate fixed-dose combination tablet compared with atorvastatin and fenofibrate monotherapies in patients with dyslipidemia: a 12-week, multicenter, double-blind, randomized, parallel-group study. Clin Ther. 2009;31(12):2824-38.
Exclusion code: 9

de Jong A, Plat J, Lutjohann D, et al. Effects of long-term plant sterol or stanol ester consumption on lipid and lipoprotein metabolism in subjects on statin treatment.[Erratum appears in Br J Nutr. 2009 Dec;102(11):1701-2]. Br J Nutr. 2008;100(5):937-41.
Exclusion code: 9

De Lorenzo F. UK screening plans. Lancet. 2008;372(9637):447-8.
Exclusion code: 7

de Vries FM, Denig P, Pouwels KB, et al. Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta-analysis. Drugs. 2012;72(18):2365-73.
Exclusion code: 9

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DeGorter MK, Tirona RG, Schwarz UI, et al. Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. Circulation. 2013;Cardiovascular Genetics. 6(4):400-8.
Exclusion code: 5

Delahoy PJ, Magliano DJ, Webb K, et al. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther. 2009;31(2):236-44.
Exclusion code: 5

Delluc A, Malecot J-M, Kerspern H, et al. Lipid parameters, lipid lowering drugs and the risk of venous thromboembolism. Atherosclerosis. 2012;220(1):184-8.
Exclusion code: 9

Devaraj S, Hirany S, Jialal I. Ratio of remnant-like particle cholesterol to serum total triglycerides is a reliable screening test for type III dyslipidaemia. Ann Clin Biochem. 2000;37(Pt 6):790-1.
Exclusion code: 6

Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302(18):1993-2000.
Exclusion code: 9

Diercks DB, Kirk JD, Turnipseed SD, et al. Cholesterol screening in an ED-based chest pain unit. Am J Emerg Med. 2002;20(6):510-2.
Exclusion code: 9

Dunkley AJ, Charles K, Gray LJ, et al. Effectiveness of interventions for reducing diabetes and cardiovascular disease risk in people with metabolic syndrome: systematic review and mixed treatment comparison meta-analysis. Diabetes Obes Metab. 2012;14(7):616-25.
Exclusion code: 9

Durand G, Tsismenakis AJ, Jahnke SA, et al. Firefighters' physical activity: relation to fitness and cardiovascular disease risk. Med Sci Sports Exerc. 2011;43(9):1752-9.
Exclusion code: 6

Eaton CB, Parker DR, Borkan J, et al. Translating cholesterol guidelines into primary care practice: a multimodal cluster randomized trial.[Erratum appears in Ann Fam Med. 2012 Mar-Apr;10(2):179]. Ann Fam Med. 2011;9(6):528-37.
Exclusion code: 9

Ebrahimpour P, Fakhrzadeh H, Heshmat R, et al. Serum uric acid levels and risk of metabolic syndrome in healthy adults. Endocr Pract. 2008;14(3):298-304.
Exclusion code: 3

Edo A, Adediran OS. Dyslipidaemia among Nigerian oil workers with type 2 diabetes mellitus. West Afr J Med. 2011;30(3):206-9.
Exclusion code: 4

Edwards JB, Tudiver F. Women's preventive screening in rural health clinics. Women Health Iss. 2008;18(3):155-66.
Exclusion code: 5

Egede R, Jensen LO, Hansen HS, et al. Effect of intensive lipid-lowering treatment compared to moderate lipid-lowering treatment with rosuvastatin on endothelial function in high risk patients. Int J Cardiol. 2012;158(3):376-9.
Exclusion code: 9

Egert S, Bosy-Westphal A, Seiberl J, et al. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. Br J Nutr. 2009;102(7):1065-74.
Exclusion code: 4

Einvik G, Ekeberg O, Lavik JG, et al. The influence of long-term awareness of hyperlipidemia and of 3 years of dietary counseling on depression, anxiety, and quality of life. J Psychosom Res. 2010;68(6):567-72.
Exclusion code: 9

Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, et al. Effect of probiotic yogurt containing Lactobacillus acidophilus and Bifidobacterium lactis on lipid profile in individuals with type 2 diabetes mellitus. J Dairy Sci. 2011;94(7):3288-94.
Exclusion code: 9

Elbarasi EA, Goodman SG, Yan RT, et al. Management of risk factors among ambulatory patients at high cardiovascular risk in Canada: a follow-up study. Can J Cardiol. 2013;29(12):1586-92.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Eliasson B, Moller-Goede D, Eeg-Olofsson K, et al. Lowering of postprandial lipids in individuals with type 2 diabetes treated with alogliptin and/or pioglitazone: a randomised double-blind placebo-controlled study. Diabetologia. 2012;55(4):915-25.
Exclusion code: 9

Elis A, Pereg D, Tirosh A, et al. Family history of cardiovascular disease does not predict risk-reducing behavior. Eur J Cardiovasc Prev Rehabil. 2008;15(3):325-8.
Exclusion code: 6

Enger C, Gately R, Ming EE, et al. Pharmacoepidemiology safety study of fibrate and statin concomitant therapy. Am J Cardiol. 2010;106(11):1594-601.
Exclusion code: 6

Enright KA, Krzyzanowska MK. Control of cardiovascular risk factors among adult cancer survivors: a population-based survey. Cancer Causes Control. 2010;21(11):1867-74.
Exclusion code: 5

Eriksson M, Budinski D, Hounslow N. Long-term efficacy of pitavastatin versus simvastatin. Adv Ther. 2011;28(9):799-810.
Exclusion code: 9

Eriksson M, Budinski D, Hounslow N. Comparative efficacy of pitavastatin and simvastatin in high-risk patients: a randomized controlled trial. Adv Ther. 2011;28(9):811-23.
Exclusion code: 9

Ersoy C, Kiyici S, Budak F, et al. The effect of metformin treatment on VEGF and PAI-1 levels in obese type 2 diabetic patients. Diabetes Res Clin Pract. 2008;81(1):56-60.
Exclusion code: 9

Estoppey D, Paccaud F, Vollenweider P, et al. Trends in self-reported prevalence and management of hypertension, hypercholesterolemia and diabetes in Swiss adults, 1997-2007. BMC Public Health. 2011;11:114.
Exclusion code: 6

Everett BM, Glynn RJ, MacFadyen JG, et al. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Circulation. 2010;121(1):143-50.
Exclusion code: 9

Faatoese AF, Pitama SG, Gillies TW, et al. Community screening for cardiovascular risk factors and levels of treatment in a rural Maori cohort. Aust N Z J Public Health. 2011;35(6):517-23.
Exclusion code: 5

Faergeman O, Hill L, Windler E, et al. Efficacy and tolerability of rosuvastatin and atorvastatin when force-titrated in patients with primary hypercholesterolemia: results from the ECLIPSE study. Cardiology. 2008;111(4):219-28.
Exclusion code: 9

Faghihimani E, Adibi P, Amini M. Dyslipidaemia and its management in diabetic patients in an academic centre in Iran. Endokrynol Pol. 2009;60(5):353-6.
Exclusion code: 6

Fallon KE. The clinical utility of screening of biochemical parameters in elite athletes: analysis of 100 cases. BJSM online. 2008;42(5):334-7.
Exclusion code: 5

Farmer JA. Simvastatin with or without ezetimibe in familial hypercholesterolemia (the ENHANCE trial). Curr Atheroscler Rep. 2009;11(2):81-2.
Exclusion code: 3

Farnier M, Averna M, Missault L, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high-risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy - The IN-CROSS study. Int J Clin Pract. 2009;63(4):547-59.
Exclusion code: 9

Farnier M, Ducobu J, Bryniarski L. Long-term safety and efficacy of fenofibrate/pravastatin combination therapy in high risk patients with mixed hyperlipidemia not controlled by pravastatin monotherapy. Curr Med Res Opin. 2011;27(11):2165-73.
Exclusion code: 4

Farnier M, Marcereuil D, De Niet S, et al. Safety of a fixed-dose combination of fenofibrate/pravastatin 160 mg/40 mg in patients with mixed hyperlipidaemia: a pooled analysis from a database of clinical trials. Clin Drug Invest. 2012;32(4):281-91.
Exclusion code: 9

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Farnier M, Perevozskaya I, Taggart WV, et al. VAP II analysis of lipoprotein subclasses in mixed hyperlipidemic patients on treatment with ezetimibe/simvastatin and fenofibrate. J Lipid Res. 2008;49(12):2641-7.
Exclusion code: 5

Fazio S, Guyton JR, Polis AB, et al. Long-term safety and efficacy of triple combination ezetimibe/simvastatin plus extended-release niacin in patients with hyperlipidemia. Am J Cardiol. 2010;105(4):487-94.
Exclusion code: 9

Felix-Redondo FJ, Fernandez-Berges D, Grau M, et al. Prevalence and clinical characteristics of peripheral arterial disease in the study population Hermex. Rev Esp Cardiol (Engl). 2012;65(8):726-33.
Exclusion code: 6

Feresu SA, Zhang W, Puumala SE, et al. The frequency and distribution of cardiovascular disease risk factors among Nebraska women enrolled in the WISEWOMAN screening program. J Womens Health (Larchmt). 2008;17(4):607-17.
Exclusion code: 9

Filip RS, Panasiuk L, Haratym-Maj A, et al. Serum lipid profile and metabolic syndrome occurrence among obese rural women from Lublin Region (Eastern Poland). Ann Agric Environ Med. 2006;13(1):77-80.
Exclusion code: 9

Firmann M, Marques-Vidal P, Paccaud F, et al. Prevalence, treatment and control of dyslipidaemia in Switzerland: still a long way to go. Eur J Cardiovasc Prev Rehabil. 2010;17(6):682-7.
Exclusion code: 9

Fitzgerald KC, Chiuve SE, Buring JE, et al. Comparison of associations of adherence to a Dietary Approaches to Stop Hypertension (DASH)-style diet with risks of cardiovascular disease and venous thromboembolism. J Thromb Haemost. 2012;10(2):189-98.
Exclusion code: 9

Flack JM, Victor R, Watson K, et al. Improved attainment of blood pressure and cholesterol goals using single-pill amlodipine/atorvastatin in African Americans: the CAPABLE trial. Mayo Clin Proc. 2008;83(1):35-45.
Exclusion code: 9

Florentin M, Liberopoulos EN, Moutzouri E, et al. The effect of simvastatin alone versus simvastatin plus ezetimibe on the concentration of small dense low-density lipoprotein cholesterol in subjects with primary hypercholesterolemia. Curr Med Res Opin. 2011;27(3):685-92.
Exclusion code: 9

Fonseca FAH, Izar MCO. Primary prevention of vascular events in patients with high levels of C-reactive protein: the JUPITER study. Expert Rev Cardiovasc Ther. 2009;7(9):1041-56.
Exclusion code: 9

Fontbonne A, Diouf I, Baccara-Dinet M, et al. Effects of 1-year treatment with metformin on metabolic and cardiovascular risk factors in non-diabetic upper-body obese subjects with mild glucose anomalies: a post-hoc analysis of the BIGPRO1 trial. Diabetes Metab. 2009;35(5):385-91.
Exclusion code: 9

Foody JM, Joyce AT, Rudolph AE, et al. Cardiovascular outcomes among patients newly initiating atorvastatin or simvastatin therapy: a large database analysis of managed care plans in the United States. Clin Ther. 2008;30(1):195-205.
Exclusion code: 9

Foucan L, Hanley J, Deloumeaux J, et al. Body mass index (BMI) and waist circumference (WC) as screening tools for cardiovascular risk factors in Guadeloupean women. J Clin Epidemiol. 2002;55(10):990-6.
Exclusion code: 6

Fouchier SW, Defesche JC, Kastelein JJP, et al. Familial defective apolipoprotein B versus familial hypercholesterolemia: an assessment of risk. Semin. 2004;4(3):259-64.
Exclusion code: 13

Frantz ID, Jr., Dawson EA, Ashman PL, et al. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. Arteriosclerosis. 1989;9(1):129-35.
Exclusion code: 3

Friedman HS, Rajagopalan S, Barnes JP, et al. Combination therapy with ezetimibe/simvastatin versus statin monotherapy for low-density lipoprotein cholesterol reduction and goal attainment in a real-world clinical setting. Clin Ther. 2011;33(2):212-24.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Gaede P, Lund-Andersen H, Parving H-H, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358(6):580-91.
Exclusion code: 9

Gasevic D, Frohlich J, Mancini GBJ, et al. The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort. Metabolism. 2012;61(4):583-9.
Exclusion code: 9

Ge C-J, Lu S-Z, Chen Y-D, et al. Synergistic effect of amlodipine and atorvastatin on blood pressure, left ventricular remodeling, and C-reactive protein in hypertensive patients with primary hypercholesterolemia. Heart Vessels. 2008;23(2):91-5.
Exclusion code: 9

Geng Q, Ren J, Chen H, et al. Adverse events of statin-fenofibric acid versus statin monotherapy: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2013;29(3):181-8.
Exclusion code: 13

Geng Q, Ren J, Chen H, et al. Adverse events following statin-fenofibrate therapy versus statin alone: a meta-analysis of randomized controlled trials. Clin Exp Pharmacol Physiol. 2013;40(3):219-26.
Exclusion code: 13

Genser B, Grammer TB, Stojakovic T, et al. Effect of HMG CoA reductase inhibitors on low-density lipoprotein cholesterol and C-reactive protein: systematic review and meta-analysis. Int J Clin Pharmacol Ther. 2008;46(10):497-510.
Exclusion code: 5

Genuth S, Ismail-Beigi F. Clinical implications of the ACCORD trial. J Clin Endocrinol Metab. 2012;97(1):41-8.
Exclusion code: 9

Gheith O, Sheashaa H, Abdelsalam M, et al. Efficacy and safety of Monascus purpureus Went rice in children and young adults with secondary hyperlipidemia: a preliminary report. Eur J Intern Med. 2009;20(3):e57-61.
Exclusion code: 5

Giraldez RR, Giugliano RP, Mohanavelu S, et al. Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis. J Am Coll Cardiol. 2008;52(11):914-20.
Exclusion code: 9

Glynn RJ, Danielson E, Fonseca FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009;360(18):1851-61.
Exclusion code: 9

Glynn RJ, MacFadyen JG, Ridker PM. Tracking of high-sensitivity C-reactive protein after an initially elevated concentration: the JUPITER Study. Clin Chem. 2009;55(2):305-12.
Exclusion code: 9

Goldberg AC, Bays HE, Ballantyne CM, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol. 2009;103(4):515-22.
Exclusion code: 5

Goldberg AC, Bittner V, Pepine CJ, et al. Efficacy of fenofibric acid plus statins on multiple lipid parameters and its safety in women with mixed dyslipidemia. Am J Cardiol. 2011;107(6):898-905.
Exclusion code: 9

Goldberg RB, Rosenson RS, Hernandez-Triana E, et al. Colesevelam improved lipoprotein particle subclasses in patients with prediabetes and primary hyperlipidaemia. Diab Vasc Dis Res. 2013;10(3):256-62.
Exclusion code: 5

Goldberg RB, Sabharwal AK. Fish oil in the treatment of dyslipidemia. Curr Opin Endocrionl Diabetes Obes. 2008;15(2):167-74.
Exclusion code: 7

Goldstein MR, Mascitelli L, Pezzetta F, et al. Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology. 2009;72(13):1190-1.
Exclusion code: 7

Golomb BA, Dimsdale JE, White HL, et al. Reduction in blood pressure with statins: results from the UCSD Statin Study, a randomized trial. Arch Intern Med. 2008;168(7):721-7.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Gomez-Huelgas R, Mancera-Romero J, Bernal-Lopez MR, et al. Prevalence of cardiovascular risk factors in an urban adult population from southern Spain. IMAP Study. Int J Clin Pract. 2011;65(1):35-40.
Exclusion code: 5

Grau M, Subirana I, Elosua R, et al. Why should population attributable fractions be periodically recalculated? An example from cardiovascular risk estimation in southern Europe. Prev Med. 2010;51(1):78-84.
Exclusion code: 6

Gray J, Edwards SJ, Lip GYH. Comparison of sequential rosuvastatin doses in hypercholesterolaemia: a meta-analysis of randomised controlled trials. Curr Med Res Opin. 2010;26(3):537-47.
Exclusion code: 5

Grover S, Coupal L, Kouache M, et al. Estimating the benefits of patient and physician adherence to cardiovascular prevention guidelines: the MyHealthCheckup Survey. Can J Cardiol. 2011;27(2):159-66.
Exclusion code: 9

Grover SA, Dorais M, Paradis G, et al. Lipid screening to prevent coronary artery disease: a quantitative evaluation of evolving guidelines. CMAJ. 2000;163(10):1263-9.
Exclusion code: 9

Grover SA, Levinton C, Paquet S. Identifying adults at low risk for significant hyperlipidemia: a validated clinical index. J Clin Epidemiol. 1999;52(1):49-55.
Exclusion code: 6

Grundy SM, Vega GL, Tomassini JE, et al. Comparisons of apolipoprotein B levels estimated by immunoassay, nuclear magnetic resonance, vertical auto profile, and non-high-density lipoprotein cholesterol in subjects with hypertriglyceridemia (SAFARI Trial). Am J Cardiol. 2011;108(1):40-6.
Exclusion code: 7

Gu Y, Warren J, Walker N, et al. Gender differences in cardiovascular disease risk management for Pacific Islanders in primary care. Qual Prim Care. 2013;21(5):275-85.
Exclusion code: 5

Guibert R, Leduc N, Fournier P, et al. What factors determine whether individuals found to have hypercholesterolaemia at mass screening accept advice to visit their physician. Public Health. 1999;113(3):105-10.
Exclusion code: 3

Gumprecht J, Gosho M, Budinski D, et al. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes Obes Metab. 2011;13(11):1047-55.
Exclusion code: 9

Guo J, Meng F, Ma N, et al. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol. 2012;110(9):1296-301.
Exclusion code: 9

Guo Z, Liu XM, Zhang QX, et al. Influence of consumption of probiotics on the plasma lipid profile: a meta-analysis of randomised controlled trials. Nutr Metab Cardiovasc Dis. 2011;21(11):844-50.
Exclusion code: 5

Gutierrez J, Ramirez G, Rundek T, et al. Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis. Arch Intern Med. 2012;172(12):909-19.
Exclusion code: 9

Guyton JR, Brown BG, Fazio S, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in patients with type IIa or type IIb hyperlipidemia. J Am Coll Cardiol. 2008;51(16):1564-72.
Exclusion code: 9

Haag MDM, Hofman A, Koudstaal PJ, et al. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam Study. J Neurol Neurosurg Psychiatry. 2009;80(1):13-7.
Exclusion code: 9

Haglin L, Lundstrom S, Kaati G, et al. All-cause mortality of patients with dyslipidemia up to 19 years after a multidisciplinary lifestyle modification programme: a randomized trial. Eur J Cardiovasc Prev Rehabil. 2011;18(1):79-85.
Exclusion code: 3

Appendix A4. Excluded Studies With Reasons for Exclusion

Halbert SC, French B, Gordon RY, et al. Tolerability of red yeast rice (2,400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. Am J Cardiology. 2010;105(2):198-204.
Exclusion code: 9

Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(7):496-507.
Exclusion code: 5

Hellenius ML, de Faire U, Berglund B, et al. Diet and exercise are equally effective in reducing risk for cardiovascular disease. Results of a randomized controlled study in men with slightly to moderately raised cardiovascular risk factors. Atherosclerosis. 1993;103(1):81-91.
Exclusion code: 9

Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197.
Exclusion code: 6

Hoffmann MM, Marz W, Genser B, et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and cardiovascular risk and efficacy of atorvastatin among subjects with diabetes on dialysis: the 4D study. Atherosclerosis. 2011;219(2):659-62.
Exclusion code: 9

Hooper L, Summerbell CD, Thompson R, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev. 2011(7):CD002137.
Exclusion code: 13

Hooper L, Summerbell CD, Thompson R, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database Syst Rev. 2012;5:CD002137.
Exclusion code: 13

Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. Eur Heart J. 2013;34(24):1807-17.
Exclusion code: 9

Hsia J, MacFadyen JG, Monyak J, et al. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol. 2011;57(16):1666-75.
Exclusion code: 9

Iseki K, Tozawa M, Ikemiya Y, et al. Relationship between dyslipidemia and the risk of developing end-stage renal disease in a screened cohort. Clin Exp Nephrol. 2005;9(1):46-52.
Exclusion code: 5

Itakura H, Kita T, Mabuchi H, et al. Relationship between coronary events and serum cholesterol during 10 years of low-dose simvastatin therapy: long-term efficacy and safety in Japanese patients with hypercholesterolemia in the Japan Lipid Intervention Trial (J-LIT) Extension 10 Study, a prospective large-scale observational cohort study. Circ J. 2008;72(8):1218-24.
Exclusion code: 9

Ito MK. Dyslipidemia: management using optimal lipid-lowering therapy. Ann Pharmacother. 2012;46(10):1368-81.
Exclusion code: 7

Jorgensen T, Ladelund S, Borch-Johnsen K, et al. Screening for risk of cardiovascular disease is not associated with mental distress: the Inter99 study. Prev Med. 2009;48(3):242-6.
Exclusion code: 13

Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ. 2008;178(5):576-84.
Exclusion code: 9

Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet. 2010;375(9729):1875-84.
Exclusion code: 13

Kadoglou NPE, Sailer N, Moumtzouoglou A, et al. Aggressive lipid-lowering is more effective than moderate lipid-lowering treatment in carotid plaque stabilization. J Vasc Surg. 2010;51(1):114-21.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Karlson BW, Nicholls SJ, Lundman P, et al. Achievement of 2011 European low-density lipoprotein cholesterol (LDL-C) goals of either <70 mg/dl or > 50% reduction in high-risk patients: results from VOYAGER. Atherosclerosis. 2013;228(1):265-9.
Exclusion code: 9

Keenan JM. Wax-matrix extended-release niacin vs inositol hexanicotinate: a comparison of wax-matrix, extended-release niacin to inositol hexanicotinate "no-flush" niacin in persons with mild to moderate dyslipidemia. J Clin Lipidol. 2013;7(1):14-23.
Exclusion code: 3

Kelishadi R, Ardalan G, Gheiratmand R, et al. Is family history of premature cardiovascular diseases appropriate for detection of dyslipidemic children in population-based preventive medicine programs? CASPIAN study. Pediatr Cardiol. 2006;27(6):729-36.
Exclusion code: 9

Kesse-Guyot E, Touvier M, Henegar A, et al. Higher adherence to French dietary guidelines and chronic diseases in the prospective SU.VI.MAX cohort. Eur J Clin Nutr. 2011;65(8):887-94.
Exclusion code: 6

Khemasuwan D, Divietro ML, Tangdhanakanond K, et al. Statins decrease the occurrence of venous thromboembolism in patients with cancer. Am J Med. 2010;123(1):60-5.
Exclusion code: 9

Kim C, Kerr EA, Bernstein SJ, et al. Gender disparities in lipid management: the presence of disparities depends on the quality measure. Am J Manag Care. 2006;12(3):133-6.
Exclusion code: 13

Kizer JR, Madias C, Wilner B, et al. Relation of different measures of low-density lipoprotein cholesterol to risk of coronary artery disease and death in a meta-regression analysis of large-scale trials of statin therapy. Am J Cardiol. 2010;105(9):1289-96.
Exclusion code: 13

Kojima S, Sakamoto T, Ogawa H, et al. Standard-dose statin therapy provides incremental clinical benefits in normocholesterolemic diabetic patients. Circ J. 2010;74(4):779-85.
Exclusion code: 9

Kokkinos PF, Faselis C, Myers J, et al. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. Lancet. 2013;381(9864):394-9.
Exclusion code: 9

Kostis JB, Breazna A, Deedwania PC, et al. The benefits of intensive lipid lowering in patients with stable coronary heart disease with normal or high systolic blood pressure: an analysis of the Treating to New Targets (TNT) study. J Clin Hypertens (Greenwich). 2008;10(5):367-76.
Exclusion code: 9

Kostis WJ, Cheng JQ, Dobrzynski JM, et al. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol. 2012;59(6):572-82.
Exclusion code: 9

Krane V, Winkler K, Drechsler C, et al. Association of LDL cholesterol and inflammation with cardiovascular events and mortality in hemodialysis patients with type 2 diabetes mellitus. Am J Kidney Dis. 2009;54(5):902-11.
Exclusion code: 9

Kruger P, Bailey M, Bellomo R, et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med. 2013;187(7):743-50.
Exclusion code: 9

Kruse LG, Ogletree RL, Jr. Omega-3 fatty acids and cardiovascular risk. J Miss State Med Assoc. 2013;54(6):156-7.
Exclusion code: 3

Ku E, Campese V. Is lipid management effective for all stages of CKD? Blood Purif. 2013;35(1-3):26-30.
Exclusion code: 7

Kushiro T, Mizuno K, Nakaya N, et al. Pravastatin for cardiovascular event primary prevention in patients with mild-to-moderate hypertension in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. Hypertension. 2009;53(2):135-41.
Exclusion code: 9

Kushiro T, Mizuno K, Nakaya N, et al. Blood pressure control status and effects of pravastatin on cardiovascular events occurrence in patients with dyslipidaemia. J Hum Hypertens. 2012;26(6):388-95.
Exclusion code: 9

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Labreuche J, Deplanque D, Touboul P-J, et al. Association between change in plasma triglyceride levels and risk of stroke and carotid atherosclerosis: systematic review and meta-regression analysis. Atherosclerosis. 2010;212(1):9-15.
Exclusion code: 5

Lafeber M, Spiering W, van der Graaf Y, et al. The combined use of aspirin, a statin, and blood pressure-lowering agents (polypill components) and the risk of vascular morbidity and mortality in patients with coronary artery disease. Am Heart J. 2013;166(2):282-9.e1.
Exclusion code: 9

Lagiou P, Sandin S, Lof M, et al. Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study. BMJ. 2012;344:e4026.
Exclusion code: 3

Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. J Am Coll Cardiol. 2013;61(4):440-6.
Exclusion code: 9

Lee M, Saver JL, Towfighi A, et al. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. Atherosclerosis. 2011;217(2):492-8.
Exclusion code: 5

Leuschen J, Mortensen EM, Frei CR, et al. Association of statin use with cataracts: a propensity score-matched analysis. JAMA Ophthalmol. 2013;131(11):1427-34.
Exclusion code: 9

Li TY, Brennan AM, Wedick NM, et al. Regular consumption of nuts is associated with a lower risk of cardiovascular disease in women with type 2 diabetes. J Nutr. 2009;139(7):1333-8.
Exclusion code: 9

Lindblad B, Borner G, Gottsater A. Factors associated with development of large abdominal aortic aneurysm in middle-aged men. Eur J Vasc Endovasc Surg. 2005;30(4):346-52.
Exclusion code: 5

Liu ZL, Li GQ, Bensoussan A, et al. Chinese herbal medicines for hypertriglyceridaemia. Cochrane Database Syst Rev. 2013;6:CD009560.
Exclusion code: 3

Livschitz S, Sharabi Y, Yushin J, et al. Limited clinical value of exercise stress test for the screening of coronary artery disease in young, asymptomatic adult men. Am J Cardiol. 2000;86(4):462-4.
Exclusion code: 9

Look ARG, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013;369(2):145-54.
Exclusion code: 9

Ma T, Tien L, Fang C-L, et al. Statins and new-onset diabetes: a retrospective longitudinal cohort study. Clin Ther. 2012;34(9):1977-83.
Exclusion code: 9

Maharjan N, Bedi U, Arora R, et al. Impact of statins on cardiovascular outcomes in renal transplant recipients: a systematic review. Am J Ther. 2011;18(3):e48-54.
Exclusion code: 3

Margolis KL, Dunn K, Simpson LM, et al. Coronary heart disease in moderately hypercholesterolemic, hypertensive black and non-black patients randomized to pravastatin versus usual care: the antihypertensive and lipid lowering to prevent heart attack trial (ALLHAT-LLT). Am Heart J. 2009;158(6):948-55.
Exclusion code: 9

Marks D, Thorogood M, Neil SM, et al. Cascade screening for familial hypercholesterolaemia: implications of a pilot study for national screening programmes. J Med Screen. 2006;13(3):156-9.
Exclusion code: 6

Marks D, Wonderling D, Thorogood M, et al. Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2000;4(29):1-123.
Exclusion code: 3

Martinez-Gonzalez MA, Garcia-Lopez M, Bes-Rastrollo M, et al. Mediterranean diet and the incidence of cardiovascular disease: a Spanish cohort. Nutr Metab Cardiovasc Dis. 2011;21(4):237-44.
Exclusion code: 3

McGrath ER, Glynn LG, Murphy AW, et al. Preventing cardiovascular disease in primary care: role of a national risk factor management program. Am Heart J. 2012;163(4):714-9.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Meuwese MC, de Groot E, Duivenvoorden R, et al. ACAT inhibition and progression of carotid atherosclerosis in patients with familial hypercholesterolemia: the CAPTIVATE randomized trial. JAMA. 2009;301(11):1131-9.
Exclusion code: 9

Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.
Exclusion code: 13

Mills EJ, O'Regan C, Eyawo O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. Eur Heart J. 2011;32(11):1409-15.
Exclusion code: 9

Mills EJ, Rachlis B, Wu P, et al. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008;52(22):1769-81.
Exclusion code: 9

Mills EJ, Wu P, Chong G, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM. 2011;104(2):109-24.
Exclusion code: 9

Mizuno K, Nakaya N, Ohashi Y, et al. Usefulness of pravastatin in primary prevention of cardiovascular events in women: analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA study). Circulation. 2008;117(4):494-502.
Exclusion code: 9

Mizuno K, Nakaya N, Teramoto T, et al. Usefulness of LDL-C-related parameters to predict cardiovascular risk and effect of pravastatin in mild-to-moderate hypercholesterolemia.[Erratum appears in J Atheroscler Thromb. 2012;19(9):881]. J Atheroscler Thromb. 2012;19(2):176-85.
Exclusion code: 9

Mora S, Glynn RJ, Boekholdt SM, et al. On-treatment non-high-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and lipid ratios in relation to residual vascular risk after treatment with potent statin therapy: JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). J Am Coll Cardiol. 2012;59(17):1521-8.
Exclusion code: 9

Mora S, Glynn RJ, Hsia J, et al. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. Circulation. 2010;121(9):1069-77.
Exclusion code: 9

Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. Circulation. 2013;128(11):1189-97.
Exclusion code: 9

Mora S, Musunuru K, Blumenthal RS. The clinical utility of high-sensitivity C-reactive protein in cardiovascular disease and the potential implication of JUPITER on current practice guidelines. Clin Chem. 2009;55(2):219-28.
Exclusion code: 7

Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation. 2012;125(16):1979-87.
Exclusion code: 9

Mori Y, Kuriyama G, Tanaka T, et al. Usefulness of aggressive lipid-lowering therapy with rosuvastatin in hypercholesterolemic patients with concomitant type 2 diabetes. Endocrine. 2009;36(3):412-8.
Exclusion code: 9

Morishita R, Itakura H, Nakaya N, et al. Risk factors for cardiovascular events in Japanese patients treated with fluvastatin from the long-term event monitoring (LEM) study. Curr Vasc Pharmacol. 2012;10(2):178-86.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Motsko SP, Russmann S, Ming EE, et al. Effectiveness of rosuvastatin compared to other statins for the prevention of cardiovascular events-a cohort study in 395 039 patients from clinical practice. Pharmacoepidemiol Drug Saf. 2009;18(12):1214-22.
Exclusion code: 13

Muldoon MF, Ryan CM, Sereika SM, et al. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. Am J Med. 2004;117(11):823-9.
Exclusion code: 9

Murphy AW, Cupples ME, Smith SM, et al. Effect of tailored practice and patient care plans on secondary prevention of heart disease in general practice: cluster randomised controlled trial. BMJ. 4220;339
Exclusion code: 3

Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circulation. 2013;Cardiovascular Quality & Outcomes. 6(4):390-9.
Exclusion code: 9

Naci H, Brugts JJ, Fleurence R, et al. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. Eur J Prev Cardiolog. 2013;20(4):641-57.
Exclusion code: 13

Nakamura H, Mizuno K, Ohashi Y, et al. Pravastatin and cardiovascular risk in moderate chronic kidney disease. Atherosclerosis. 2009;206(2):512-7.
Exclusion code: 9

Nakamura Y, Ueshima H, Okamura T, et al. A Japanese diet and 19-year mortality: national integrated project for prospective observation of non-communicable diseases and its trends in the aged, 1980. Br J Nutr. 2009;101(11):1696-705.
Exclusion code: 9

Nakaya N, Mizuno K, Ohashi Y, et al. Low-dose pravastatin and age-related differences in risk factors for cardiovascular disease in hypercholesterolaemic Japanese: analysis of the management of elevated cholesterol in the primary prevention group of adult Japanese (MEGA study). Drugs Aging. 2011;28(9):681-92.
Exclusion code: 9

Navaneethan SD, Nigwekar SU, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for dialysis patients. Cochrane Database Syst Rev. 2009(3):CD004289.
Exclusion code: 3

Navaneethan SD, Pansini F, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2009(2):CD007784.
Exclusion code: 3

Navaneethan SD, Perkovic V, Johnson DW, et al. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev. 2009(2):CD005019.
Exclusion code: 3

Navigator Study Group, Holman RR, Haffner SM, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events.[Erratum appears in N Engl J Med. 2010 May 6;362(18):1748]. N Engl J Med. 2010;362(16):1463-76.
Exclusion code: 9

Newman CB, Szarek M, Colhoun HM, et al. The safety and tolerability of atorvastatin 10 mg in the Collaborative Atorvastatin Diabetes Study (CARDS). Diab Vasc Dis Res. 2008;5(3):177-83.
Exclusion code: 9

Norby GE, Holme I, Fellstrom B, et al. Effect of fluvastatin on cardiac outcomes in kidney transplant patients with systemic lupus erythematosus: a randomized placebo-controlled study. Arthritis Rheum. 2009;60(4):1060-4.
Exclusion code: 3

Ong HT, Cheah JS. Statin alternatives or just placebo: an objective review of omega-3, red yeast rice and garlic in cardiovascular therapeutics. Chin Med J. 2008;121(16):1588-94.
Exclusion code: 3

Oren A, Vos LE, Uiterwaal CSPM, et al. The Atherosclerosis Risk in Young Adults (ARYA) study: rationale and design. Eur J Epidemiol. 2003;18(7):715-27.
Exclusion code: 5

Owen CG, Carey IM, Shah S, et al. Hypotensive medication, statins, and the risk of glaucoma. Invest Ophthalmol Vis Sci. 2010;51(7):3524-30.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Palmer SC, Craig JC, Navaneethan SD, et al. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med. 2012;157(4):263-75.
Exclusion code: 3

Pan A, Chen M, Chowdhury R, et al. alpha-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr. 2012;96(6):1262-73.
Exclusion code: 9

Parish S, Offer A, Clarke R, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. Circulation. 2012;125(20):2469-78.
Exclusion code: 9

Peters BJM, Maitland-van der Zee A-H, Stricker BHC, et al. Effectiveness of statins in the reduction of the risk of myocardial infarction is modified by the GNB3 C825T variant. Pharmacogenet Genomics. 2008;18(7):631-6.
Exclusion code: 9

Peters BJM, Pett H, Klungel OH, et al. Genetic variability within the cholesterol lowering pathway and the effectiveness of statins in reducing the risk of MI. Atherosclerosis. 2011;217(2):458-64.
Exclusion code: 9

Petretta M, Costanzo P, Perrone-Filardi P, et al. Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. Int J Cardiol. 2010;138(1):25-31.
Exclusion code: 9

Preiss D, Tikkanen MJ, Welsh P, et al. Lipid-modifying therapies and risk of pancreatitis: a meta-analysis. JAMA. 2012;308(8):804-11.
Exclusion code: 9

Price HC, Coleman RL, Stevens RJ, et al. Impact of using a non-diabetes-specific risk calculator on eligibility for statin therapy in type 2 diabetes. Diabetologia. 2009;52(3):394-7.
Exclusion code: 9

Rahilly-Tierney CR, Lawler EV, Scranton RE, et al. Cardiovascular benefit of magnitude of low-density lipoprotein cholesterol reduction: a comparison of subgroups by age. Circulation. 2009;120(15):1491-7.
Exclusion code: 9

Rahimi K, Majoni W, Merhi A, et al. Effect of statins on ventricular tachyarrhythmia, cardiac arrest, and sudden cardiac death: a meta-analysis of published and unpublished evidence from randomized trials. Eur Heart J. 2012;33(13):1571-81.
Exclusion code: 9

Rahman M, Baimbridge C, Davis BR, et al. Pravastatin and cardiovascular outcomes stratified by baseline eGFR in the lipid- lowering component of ALLHAT. Clin Nephrol. 2013;80(4):235-48.
Exclusion code: 9

Razzolini R, Tarantini G, Ossena G, et al. Non-cardiovascular mortality, low-density lipoprotein cholesterol and statins: a meta-regression analysis. Cardiology. 2008;109(2):110-6.
Exclusion code: 13

Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207.
Exclusion code: 9

Robins SJ, Collins D, Nelson JJ, et al. Cardiovascular events with increased lipoprotein-associated phospholipase A(2) and low high-density lipoprotein-cholesterol: the Veterans Affairs HDL Intervention Trial. Arterioscler Thromb Vasc Biol. 2008;28(6):1172-8.
Exclusion code: 9

Rodondi N, Auer R, de Bosset Sulzer V, et al. Atherosclerosis screening by noninvasive imaging for cardiovascular prevention: a systematic review. J Gen Intern Med. 2012;27(2):220-31.
Exclusion code: 4

Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008;200(1):135-40.
Exclusion code: 9

Scott R, O'Brien R, Fulcher G, et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care. 2009;32(3):493-8.
Exclusion code: 3

Appendix A4. Excluded Studies With Reasons for Exclusion

Sheng X, Murphy MJ, MacDonald TM, et al. Effect of statins on total cholesterol concentrations and cardiovascular outcomes in patients with diabetes mellitus: a population-based cohort study. Eur J Clin Pharmacol. 2012;68(8):1201-8.
Exclusion code: 9

Sialvera TE, Pounis GD, Koutelidakis AE, et al. Phytosterols supplementation decreases plasma small and dense LDL levels in metabolic syndrome patients on a westernized type diet. Nutr Metab Cardiovasc Dis. 2012;22(10):843-8.
Exclusion code: 5

Silva H, Hernandez-Hernandez R, Vinueza R, et al. Cardiovascular risk awareness, treatment, and control in urban Latin America. Am J Ther. 2010;17(2):159-66.
Exclusion code: 5

Silverberg MJ, Leyden W, Hurley L, et al. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection.[Summary for patients in Ann Intern Med. 2009 Mar 3;150(5):I38; PMID: 19258553]. Ann Intern Med. 2009;150(5):301-13.
Exclusion code: 9

Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet. 2002;360(9344):1455-61.
Exclusion code: 9

Sjouke B, Langslet G, Ceska R, et al. Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. Lancet Diabetes Endocrinol. 2014;2(6):455-63. PMID: 24731671.
Exclusion code: 9

Snehalatha C, Mary S, Joshi VV, et al. Beneficial effects of strategies for primary prevention of diabetes on cardiovascular risk factors: results of the Indian Diabetes Prevention Programme. Diab Vasc Dis Res. 2008;5(1):25-9.
Exclusion code: 9

Sofi F, Whittaker A, Cesari F, et al. Characterization of Khorasan wheat (Kamut) and impact of a replacement diet on cardiovascular risk factors: cross-over dietary intervention study. Eur J Clin Nutr. 2013;67(2):190-5.
Exclusion code: 9

Song S, Lee JE, Song WO, et al. Carbohydrate intake and refined-grain consumption are associated with metabolic syndrome in the Korean adult population. J Acad Nutr Diet. 2014;114(1):54-62.
Exclusion code: 3

Song SH, Gray TA. Early-onset type 2 diabetes: higher burden of atherogenic apolipoprotein particles during statin treatment. QJM. 2012;105(10):973-80.
Exclusion code: 5

Sood A, Arora R. Vitamin D deficiency and its correlations with increased cardiovascular incidences. Am J Ther. 2010;17(4):e105-9.
Exclusion code: 7

Soran H, Durrington P. Rosuvastatin: efficacy, safety and clinical effectiveness. Expert Opin Pharmacother. 2008;9(12):2145-60.
Exclusion code: 7

Sorensen SV, Frick KD, Wade A, et al. Model-based simulation to explore the cost-effectiveness of following practice guidelines for triglyceride and low-density lipoprotein cholesterol control among patients with diabetes mellitus and mixed dyslipidemia. Clin Ther. 2009;31(4):862-79.
Exclusion code: 9

Soriguer F, Rojo-Martinez G, Goday A, et al. Olive oil has a beneficial effect on impaired glucose regulation and other cardiometabolic risk factors. Di@bet.es study. Eur J Clin Nutr. 2013;67(9):911-6.
Exclusion code: 5

Soveri I, Abedini S, Holdaas H, et al. Metabolic syndrome and cardiovascular risk in renal transplant recipients: effects of statin treatment. Clin Transplant. 2009;23(6):914-20.
Exclusion code: 3

Stefanick ML, Mackey S, Sheehan M, et al. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. N Engl J Med. 1998;339(1):12-20.
Exclusion code: 9

Steg PG, Verdier J-C, Carre F, et al. A randomised trial of three counselling strategies for lifestyle changes in patients with hypercholesterolemia treated with ezetimibe on top of statin therapy (TWICE). Arch Cardiovasc Dis. 2008;101(11-12):723-35.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Stein EA, Ballantyne CM, Windler E, et al. Efficacy and tolerability of fluvastatin XL 80 mg alone, ezetimibe alone, and the combination of fluvastatin XL 80 mg with ezetimibe in patients with a history of muscle-related side effects with other statins. Am J Cardiol. 2008;101(4):490-6.
Exclusion code: 3

Stein EA, Bays H, O'Brien D, et al. Lapaquistat acetate: development of a squalene synthase inhibitor for the treatment of hypercholesterolemia. Circulation. 2011;123(18):1974-85.
Exclusion code: 3

Stein EA, Vidt DG, Shepherd J, et al. Renal safety of intensive cholesterol-lowering treatment with rosuvastatin: a retrospective analysis of renal adverse events among 40,600 participants in the rosuvastatin clinical development program. Atherosclerosis. 2012;221(2):471-7.
Exclusion code: 3

Strippoli GFM, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. BMJ. 2008;336(7645):645-51.
Exclusion code: 4

Strony J, Yang B, Hanson ME, et al. Long-term safety and tolerability of ezetimibe coadministered with simvastatin in hypercholesterolemic patients: a randomized, 12-month double-blind extension study. Curr Med Res Opin. 2008;24(11):3149-57.
Exclusion code: 3

Sudhop T, Reber M, Tribble D, et al. Changes in cholesterol absorption and cholesterol synthesis caused by ezetimibe and/or simvastatin in men. J Lipid Res. 2009;50(10):2117-23.
Exclusion code: 3

Suh HS, Hay JW, Johnson KA, et al. Comparative effectiveness of statin plus fibrate combination therapy and statin monotherapy in patients with type 2 diabetes: use of propensity-score and instrumental variable methods to adjust for treatment-selection bias. Pharmacoepidemiol Drug Saf. 2012;21(5):470-84.
Exclusion code: 4

Sullivan MD, Katon WJ, Lovato LC, et al. Association of depression with accelerated cognitive decline among patients with type 2 diabetes in the ACCORD-MIND trial. JAMA Psychiatry. 2013;70(10):1041-7.
Exclusion code: 3

Sutton D, Davey T, Venkatraman G, et al. Can a functional food exert a cholesterol lowering effect in renal transplant patients? J Ren Care. 2009;35(1):42-7.
Exclusion code: 3

Suzuki T, Oba K, Igari Y, et al. Effects of bile-acid-binding resin (colestimide) on blood glucose and visceral fat in Japanese patients with type 2 diabetes mellitus and hypercholesterolemia: an open-label, randomized, case-control, crossover study. J Diabetes Complications. 2012;26(1):34-9.
Exclusion code: 3

Sviridov D, Hoang A, Ooi E, et al. Indices of reverse cholesterol transport in subjects with metabolic syndrome after treatment with rosuvastatin. Atherosclerosis. 2008;197(2):732-9.
Exclusion code: 9

Szkodzinski J, Romanowski W, Hudzik B, et al. Effect of HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors on the concentration of insulin-like growth factor-1 (IGF-1) in hypercholesterolemic patients.[Erratum appears in Pharmacol Rep. 2009 Sep-Oct;61(5):952]. Pharmacol Rep. 2009;61(4):654-64.
Exclusion code: 5

Tabuchi M, Kitayama J, Nagawa H. Hyperglycemia and hypertriglyceridemia may associate with the adenoma-carcinoma transition in colorectal epithelial cells. J Gastroenterol Hepatol. 2008;23(6):985-7.
Exclusion code: 5

Tahaineh L, Albsoul-Younes A, Al-Ashqar E, et al. The role of clinical pharmacist on lipid control in dyslipidemic patients in North of Jordan. Int J Clin Pharm. 2011;33(2):229-36.
Exclusion code: 9

Takagi H, Umemoto T. Atorvastatin decreases lipoprotein(a): a meta-analysis of randomized trials. Int J Cardiol. 2012;154(2):183-6.
Exclusion code: 5

Takahashi O, Glasziou PP, Perera R, et al. Lipid re-screening: what is the best measure and interval? Heart. 2010;96(6):448-52.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Takeshita M, Katsuragi Y, Kusuhara M, et al. Phytosterols dissolved in diacylglycerol oil reinforce the cholesterol-lowering effect of low-dose pravastatin treatment. Nutr Metab Cardiovasc Dis. 2008;18(7):483-91. PMID: 17964767.
Exclusion code: 5

Talati R, Sobieraj DM, Makanji SS, et al. The comparative efficacy of plant sterols and stanols on serum lipids: a systematic review and meta-analysis. J Am Diet Assoc. 2010;110(5):719-26.
Exclusion code: 5

Talavera J-O, Martinez G, Cervantes J-L, et al. A double-blind, double-dummy, randomized, placebo-controlled trial to evaluate the effect of statin therapy on triglyceride levels in Mexican hypertriglyceridemic patients. Curr Med Res Opin. 2013;29(4):379-86.
Exclusion code: 9

Talirevic E, Jelena S. Quercetin in the treatment of dyslipidemia. Med Arh. 2012;66(2):87-8. PMID: 22486135.
Exclusion code: 5

Tanumihardjo SA, Valentine AR, Zhang Z, et al. Strategies to increase vegetable or reduce energy and fat intake induce weight loss in adults. Exp Biol Med (Maywood). 2009;234(5):542-52.
Exclusion code: 3

Tapsell L, Batterham M, Huang XF, et al. Short term effects of energy restriction and dietary fat sub-type on weight loss and disease risk factors. Nutr Metab Cardiovasc Dis. 2010;20(5):317-25.
Exclusion code: 5

Taskinen MR, Barter PJ, Ehnholm C, et al. Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes. Diabetologia. 2010;53(9):1846-55.
Exclusion code: 9

Taskinen M-R, Sullivan DR, Ehnholm C, et al. Relationships of HDL cholesterol, ApoA-I, and ApoA-II with homocysteine and creatinine in patients with type 2 diabetes treated with fenofibrate. Arterioscler Thromb Vasc Biol. 2009;29(6):950-5.
Exclusion code: 3

Tatsuno I, Saito Y, Kudou K, et al. Efficacy and safety of TAK-085 compared with eicosapentaenoic acid in Japanese subjects with hypertriglyceridemia undergoing lifestyle modification: the omega-3 fatty acids randomized double-blind (ORD) study. J Clin Lipidol. 2013;7(3):199-207.
Exclusion code: 9

Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.
Exclusion code: 3

Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2011(1):CD004816.
Exclusion code: 3

Taylor JR, Dietrich E, Powell JG. New and emerging pharmacologic therapies for type 2 diabetes, dyslipidemia, and obesity. Clin Ther. 2013;35(1):A3-17.
Exclusion code: 3

Tehrani S, Mobarrez F, Antovic A, et al. Atorvastatin has antithrombotic effects in patients with type 1 diabetes and dyslipidemia. Thromb Res. 2010;126(3):e225-31.
Exclusion code: 9

Tekin A, Tekin G, Sezgin AT, et al. Short- and long-term effect of simvastatin therapy on the heterogeneity of cardiac repolarization in diabetic patients. Pharmacol Res. 2008;57(5):393-7.
Exclusion code: 9

Teng K-T, Voon P-T, Cheng H-M, et al. Effects of partially hydrogenated, semi-saturated, and high oleate vegetable oils on inflammatory markers and lipids. Lipids. 2010;45(5):385-92. PMID: 20437207.
Exclusion code: 3

Teramoto T. The clinical impact of pitavastatin: comparative studies with other statins on LDL-C and HDL-C. Expert Opin Pharmacother. 2012;13(6):859-65.
Exclusion code: 7

Teramoto T, Kitagawa Y, Daida H, et al. APPROACH-J study: design, rationale, and baseline data of the affirmation primary prevention with pravastatin in reduction of occlusive atherosclerotic complications in hypercholesterolemia--Japan study. J Atheroscler Thromb. 2011;18(12):1054-61.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Teramoto T, Shirai K, Daida H, et al. Effects of bezafibrate on lipid and glucose metabolism in dyslipidemic patients with diabetes: the J-BENEFIT study. Cardiovascular Diabetology. 2012;11:29. PMID: 22439599.
Exclusion code: 9

Teramoto T, Shirakawa M, Kikuchi M, et al. Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib in Japanese patients with dyslipidemia. Atherosclerosis. 2013;230(1):52-60.
Exclusion code: 13

Tey SL, Brown RC, Chisholm AW, et al. Effects of different forms of hazelnuts on blood lipids and alpha-tocopherol concentrations in mildly hypercholesterolemic individuals. Eur J Clin Nutr. 2011;65(1):117-24.
Exclusion code: 5

Thakkar RB, Kashyap ML, Lewin AJ, et al. Acetylsalicylic acid reduces niacin extended-release-induced flushing in patients with dyslipidemia. Am J Cardiovasc Drugs. 2009;9(2):69-79.
Exclusion code: 5

Thakur G, Mitra A, Pal K, et al. Effect of flaxseed gum on reduction of blood glucose and cholesterol in type 2 diabetic patients. Int J Food Sci Nutr. 2009;60 Suppl 6:126-36. PMID: 19548163.
Exclusion code: 9

Theytaz F, Noguchi Y, Egli L, et al. Effects of supplementation with essential amino acids on intrahepatic lipid concentrations during fructose overfeeding in humans. Am J Clin Nutr. 2012;96(5):1008-16. PMID: 23034968.
Exclusion code: 3

Thomas GS, Cromwell WC, Ali S, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2013;62(23):2178-84.
Exclusion code: 9

Thongtang N, Ai M, Otokozawa S, et al. Effects of maximal atorvastatin and rosuvastatin treatment on markers of glucose homeostasis and inflammation. Am J Cardiol. 2011;107(3):387-92.
Exclusion code: 9

Tiessen AH, Smit AJ, Broer J, et al. Which patient and treatment factors are related to successful cardiovascular risk score reduction in general practice? Results from a randomized controlled trial. BMC Fam Pract. 2013;14:123.
Exclusion code: 9

Tomasik T, Jozwiak J, Windak A, et al. Prevention of coronary heart disease in primary medical care in Poland: results from the LIPIDOGRAM study. Eur J Cardiovasc Prev Rehabil. 2011;18(2):287-96. PMID: 21450675.
Exclusion code: 9

Tonkin AM, Chen L. Effects of combination lipid therapy in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Circulation. 2010;122(8):850-2.
Exclusion code: 9

Toth PP, Potter D, Ming EE. Prevalence of lipid abnormalities in the United States: the National Health and Nutrition Examination Survey 2003-2006. J Clin Lipidol. 2012;6(4):325-30.
Exclusion code: 3

Turfaner N, Uzun H, Balci H, et al. Ezetimibe therapy and its influence on oxidative stress and fibrinolytic activity. South Med J. 2010;103(5):428-33. PMID: 20375933.
Exclusion code: 9

Tyerman PF, Tyerman GV. Another way of screening for familial hypercholesterolaemia. BMJ. 2002;325(7359):340.
Exclusion code: 7

Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, et al. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. Lancet. 2001;357(9251):165-8.
Exclusion code: 5

Ur E, Langer A, Rabkin SW, et al. Achieving cholesterol targets by individualizing starting doses of statin according to baseline low-density lipoprotein cholesterol and coronary artery disease risk category: the CANadians Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (CanACTFAST) study. C Journal Cardiol. 2010;26(2):80-6.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Valente AM, Newburger JW, Lauer RM. Hyperlipidemia in children and adolescents. Am Heart J. 2001;142(3):433-9.
Exclusion code: 3

van de Woestijne AP, van der Graaf Y, Liem A-H, et al. Low high-density lipoprotein cholesterol is not a risk factor for recurrent vascular events in patients with vascular disease on intensive lipid-lowering medication. J Am Coll Cardiol. 2013;62(20):1834-41.
Exclusion code: 9

van Duijnhoven FJB, Bueno-De-Mesquita HB, Calligaro M, et al. Blood lipid and lipoprotein concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition. Gut. 2011;60(8):1094-102.
Exclusion code: 9

Van Gaal L, Pi-Sunyer X, Despres J-P, et al. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. Diabetes Care. 2008;31 Suppl 2:S229-40.
Exclusion code: 3

van Wyk JT, van Wijk MAM, Sturkenboom MCJM, et al. Electronic alerts versus on-demand decision support to improve dyslipidemia treatment: a cluster randomized controlled trial. Circulation. 2008;117(3):371-8.
Exclusion code: 9

van Zuilen AD, Bots ML, Dulger A, et al. Multifactorial intervention with nurse practitioners does not change cardiovascular outcomes in patients with chronic kidney disease. Kidney Int. 2012;82(6):710-7.
Exclusion code: 9

Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ. 2008;337:a2423.
Exclusion code: 3

Versmissen J, Oosterveer DM, Yazdanpanah M, et al. A frequent variant in the ABCA1 gene is associated with increased coronary heart disease risk and a better response to statin treatment in familial hypercholesterolemia patients. Eur Heart J. 2011;32(4):469-75.
Exclusion code: 3

Vimalananda VG, Miller DR, Palnati M, et al. Gender disparities in lipid-lowering therapy among veterans with diabetes. Women Health Iss. 2011;21(4 Suppl):S176-81.
Exclusion code: 9

Visser ME, Wagener G, Baker BF, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J. 2012;33(9):1142-9.
Exclusion code: 9

Vladimirova-Kitova LG, Deneva TI, Nikolov FP. Effect of moderate and high dose simvastatin on adhesion molecules in severe hypercholesterolemia after targeting the LDL-cholesterol--a randomised, placebo-controlled study. Folia Med (Plovdiv). 2011;53(2):13-21.
Exclusion code: 9

Vlassara H, Uribarri J, Cai W, et al. Effects of sevelamer on HbA1c, inflammation, and advanced glycation end products in diabetic kidney disease. Clin J Am Soc Nephrol. 2012;7(6):934-42.
Exclusion code: 9

Vuksan V, Jenkins AL, Rogovik AL, et al. Viscosity rather than quantity of dietary fibre predicts cholesterol-lowering effect in healthy individuals. Br J Nutr. 2011;106(9):1349-52.
Exclusion code: 3

Wallach-Kildemoes H, Diderichsen F, Krasnik A, et al. Is the high-risk strategy to prevent cardiovascular disease equitable? A pharmacoepidemiological cohort study. BMC Public Health. 2012;12:610.
Exclusion code: 3

Walsh JA, 3rd, Ilkhanoff L, Soliman EZ, et al. Natural history of the early repolarization pattern in a biracial cohort: CARDIA (Coronary Artery Risk Development in Young Adults) Study. J Am Coll Cardiol. 2013;61(8):863-9.
Exclusion code: 5

Wang C-J, Li Y-Q, Wang L, et al. Development and evaluation of a simple and effective prediction approach for identifying those at high risk of dyslipidemia in rural adult residents. PLoS ONE. 2012;7(8):e43834.
Exclusion code: 5

Appendix A4. Excluded Studies With Reasons for Exclusion

Wang JS, Carson EC, Lapane KL, et al. The effect of physician office visits on CHD risk factor modification as part of a worksite cholesterol screening program. Prev Med. 1999;28(3):221-8.
Exclusion code: 4

Wang W, Ma L, Zhang Y, et al. The combination of amlodipine and angiotensin receptor blocker or diuretics in high-risk hypertensive patients: rationale, design and baseline characteristics. J Hum Hypertens. 2011;25(4):271-7.
Exclusion code: 9

Wani TA, Samad A, Tandon M, et al. The effects of rosuvastatin on the serum cortisol, serum lipid, and serum mevalonic acid levels in the healthy Indian male population. AAPS PharmSciTech. 2010;11(1):425-32. PMID: 20300897.
Exclusion code: 3

Webber LS, Srinivasan SR, Wattigney WA, et al. Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. Am J Epidemiol. 1991;133(9):884-99. PMID: 2028978.
Exclusion code: 3

West AM, Anderson JD, Meyer CH, et al. The effect of ezetimibe on peripheral arterial atherosclerosis depends upon statin use at baseline. Atherosclerosis. 2011;218(1):156-62.
Exclusion code: 9

Westerink J, Deanfield JE, Imholz BP, et al. High-dose statin monotherapy versus low-dose statin/ezetimibe combination on fasting and postprandial lipids and endothelial function in obese patients with the metabolic syndrome: The PANACEA study. Atherosclerosis. 2013;227(1):118-24.
Exclusion code: 9

Wierzbicki AS, Pendleton S, McMahon Z, et al. Rimonabant improves cholesterol, insulin resistance and markers of non-alcoholic fatty liver in morbidly obese patients: a retrospective cohort study. Int J Clin Pract. 2011;65(6):713-5.
Exclusion code: 7

Wiesbauer F, Heinze G, Mitterbauer C, et al. Statin use is associated with prolonged survival of renal transplant recipients. J Am Soc Nephrol. 2008;19(11):2211-8.
Exclusion code: 3

Williams B, Lacy PS, Cruickshank JK, et al. Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation-Lipid-Lowering Arm (CAFE-LLA) Study. Circulation. 2009;119(1):53-61.
Exclusion code: 9

Winters P, Tancredi D, Fiscella K. The role of usual source of care in cholesterol treatment. J Am Board Fam Med. 2010;23(2):179-85.
Exclusion code: 5

Wong ND, Chuang J, Wong K, et al. Residual dyslipidemia among United States adults treated with lipid modifying therapy (data from National Health and Nutrition Examination Survey 2009-2010). Am J Cardiol. 2013;112(3):373-9.
Exclusion code: 9

Wood DA, Kotseva K, Connolly S, et al. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. Lancet. 2008;371(9629):1999-2012.
Exclusion code: 3

Woods MN, Wanke CA, Ling P-R, et al. Effect of a dietary intervention and n-3 fatty acid supplementation on measures of serum lipid and insulin sensitivity in persons with HIV. Am J Clin Nutr. 2009;90(6):1566-78.
Exclusion code: 9

Wright WL. The management of type 2 diabetes mellitus: a novel approach for addressing glycemic and lipid control with colesevelam HCl. Adv Nurse Pract. 2009;17(11):suppl 1-16.
Exclusion code: 3

Wu H, Pan A, Yu Z, et al. Lifestyle counseling and supplementation with flaxseed or walnuts influence the management of metabolic syndrome. J Nutr. 2010;140(11):1937-42.
Exclusion code: 3

Yokote K, Shimano H, Urashima M, et al. Efficacy and safety of pitavastatin in Japanese patients with hypercholesterolemia: LIVES study and subanalysis. Expert Rev Cardiovasc Ther. 2011;9(5):555-62.
Exclusion code: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Zamorano J, Erdine S, Lopez AP, et al. Design and rationale of a real-life study to compare treatment strategies for cardiovascular risk factors: the CRUCIAL study. Postgrad Med. 2010;122(2):7-15.
Exclusion code: 5

Zamorano J, Erdine S, Pavia A, et al. Proactive multiple cardiovascular risk factor management compared with usual care in patients with hypertension and additional risk factors: the CRUCIAL trial. Curr Med Res Opin. 2011;27(4):821-33.
Exclusion code: 9

Zhang B, Miura S-i, Yanagi D, et al. Reduction of charge-modified LDL by statin therapy in patients with CHD or CHD risk factors and elevated LDL-C levels: the SPECIAL Study. Atherosclerosis. 2008;201(2):353-9.
Exclusion code: 9

Zhao X-Q, Krasuski RA, Baer J, et al. Effects of combination lipid therapy on coronary stenosis progression and clinical cardiovascular events in coronary disease patients with metabolic syndrome: a combined analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces Regression Study (AFREGS). Am J Cardiol. 2009;104(11):1457-64.
Exclusion code: 9

Zheng J, Huang T, Yu Y, et al. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. Public Health Nutr. 2012;15(4):725-37.
Exclusion code: 13

Zhu F-S, Liu S, Chen X-M, et al. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. World J Gastroenterol. 2008;14(41):6395-400.
Exclusion code: 5

Zoppini G, Targher G, Chonchol M, et al. Higher HDL cholesterol levels are associated with a lower incidence of chronic kidney disease in patients with type 2 diabetes. Nutr Metab Cardiovasc Dis. 2009;19(8):580-6.
Exclusion code: 9

Criteria for Assessing Internal Validity of Individual Studies

The Methods Work Group for the US Preventive Services Task Force (USPSTF) developed a set of criteria by which the internal validity of individual studies could be evaluated. The USPSTF accepted the criteria, and the associated definitions of quality categories, that relate to internal validity at its September 1999 meeting.

This appendix describes the criteria relating to internal validity and the procedures that topic teams follow for all updates and new assessments in making these judgments.

All topic teams use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technology or that use technology that is not feasible for primary care practice may be filtered out before the abstraction stage, depending on the topic and the decisions of the topic team. The teams justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter. Presented below are a set of minimal criteria for each study design and then a general definition of three categories: "good," "fair," and "poor," based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

Systematic Reviews

Criteria:
Comprehensiveness of sources considered/search strategy used.
Standard appraisal of included studies.
Validity of conclusions.
Recency and relevance are especially important for systematic reviews.

Definition of ratings from above criteria:
Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.
Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.
Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.

  - For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
- Important differential loss to follow-up or overall high loss to follow-up.
- Measurements: equal, reliable, and valid (includes masking of outcome assessment).
- Clear definition of interventions.
- All important outcomes considered.
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Definition of ratings based on above criteria:

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

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

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

Case-Control Studies

Criteria:

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

Definition of ratings based on criteria above:

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

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

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

Source: U.S. Preventive Services Task Force. Procedure Manual. Available at: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm.

Appendix A6. Reviewers of the Draft Report

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