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

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**Suggested Citation**

Structured Abstract

**Background:** This review updates prior reviews on screening for lipid disorders in adults, and will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2008 recommendation. Unlike prior USPSTF reviews, this one focuses on screening in younger adults, defined as adults ages 21 to 39 years, 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 through May 2016 and manually reviewed reference lists.

**Study Selection:** Two investigators independently reviewed the literature for studies on screening for and treatment of dyslipidemia in asymptomatic adults ages 21 to 39 years, 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 vs. 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 change 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 for or treatment of 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\textsuperscript{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.\textsuperscript{4}

In 2008, the USPSTF strongly recommended lipid screening in all men age 35 years and older and in women age 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 lipid levels, resulting in substantial absolute benefits.\textsuperscript{4} The USPSTF recommended screening in men ages 20 to 35 years and women ages 20 to 45 years with risk factors for CHD (B recommendation); due to the lower incidence of CHD events in these populations, screening results in lower expected benefits. The USPSTF made no recommendation for or against lipid screening in men ages 20 to 35 years or in women age 20 years 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 in this report as adults ages 21 to 39 years). 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 statin therapy 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 reduce lipid levels.\textsuperscript{5}

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

Condition Definition

Lipid disorders refer to abnormalities of cholesterol, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. The National Cholesterol Education Project (NCEP) Adult Treatment Panel III (ATP III) defined “optimal” LDL-C levels as less than 100 mg/dL and “high” as 160 mg/dL and greater; “desirable” total cholesterol (TC) levels as less than 200 mg/dL and “high” as 240 mg/dL and greater; “low” HDL-C levels as less than 40 mg/dL; and elevated triglycerides as greater than 150 mg/dL, although thresholds for treatment varied depending on the presence of risk factors for CVD.\textsuperscript{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. 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 data from 2003 to 2006, 13 percent of 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 ages 20 to 34 years. In 2003 to 2004, 64 percent of adults ages 20 to 29 years and 57 percent of adults ages 30 to 39 years met NCEP-recommended lipid levels.

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 of the same age. In 2010, the overall prevalence of CHD was 6.0 percent, and among persons ages 18 to 44 years, the age-adjusted prevalence was 1.2 percent. Prevalence of CHD varies by race/ethnicity, affecting 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. For young adults ages 20 to 39 years, the prevalence of CVD, including all diseases of the circulatory system and congenital CVD, was 14.9 percent in men and 8.7 percent in women.

CHD is the leading cause of death in the United States. 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. The number of myocardial infarctions or fatal CHD events is estimated at 20,000 annually for men ages 35 to 44 years and 5,000 annually for women ages 35 to 44 years. In 2011, CHD caused 12 percent of deaths in persons ages 25 to 44 years. Estimates based on Framingham Heart Study participants from 1971 to 1996 indicate that the lifetime risks (through age 80 years) of CHD for 40-year-old men with a TC level of 200, 200 to 239, and 240 mg/dL and greater 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 as 0.58 percent in those ages 18 to 29 years and 1.72 percent in those ages 30 to 39 years.

In 2010, heart disease was associated with 972 age-adjusted potential life-years lost per 100,000 persons younger than age 75 years. In 2008, heart disease and stroke accounted for nearly $300 billion in health care costs.

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. 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 1,400 mg per day. A total of 1,000 to 2,000 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). There are three classes of lipoproteins: LDL-C, HDL-C, and very low-density lipoprotein cholesterol (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. 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 such as 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 ages 18 to 30 years with nonoptimal levels of LDL-C (defined as ≥100 mg/dL) at baseline found an association between cumulative exposure to higher LDL-C or lower HDL-C levels and markers of atherosclerosis two decades later.

Persons with familial hypercholesterolemia may have dramatically high levels of LDL-C, which can lead to accelerated atherosclerosis and, if untreated, early cardiovascular death. 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 mutated copies of the LDL receptor gene have the homozygous form of familial hypercholesterolemia. This condition is rare, with a prevalence of about 1 in 1,000,000. The characteristic clinical presentation includes skin and tendon
xanthomas, TC levels of 500 to 1,000 mg/dL, and the onset in childhood of symptomatic coronary disease as well as aortic valve and proximal root disease. The heterozygous form of familial hypercholesterolemia is more common, with a prevalence of approximately 1 in 500 in the United States and United Kingdom. TC levels in persons with heterozygous familial hypercholesterolemia are less highly elevated than in those with 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. The estimated proportion of persons with familial hypercholesterolemia who would have an early-onset CHD event in the absence of recognition and treatment is 5 to 15 percent in men younger than age 35 years and 10 to 15 percent in women younger than age 45 years. Many patients with severe hypercholesterolemia do not have an identifiable genetic defect. 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-C, low HDL-C, high triglycerides) include physical inactivity, obesity, abdominal obesity, metabolic syndrome, hypertension, atherogenic diet (high in saturated fatty acids, cholesterol, and sodium), consumption of added dietary sugars, genetic factors (including family history of familial hypercholesterolemia), older age, male sex, and hypothyroidism. 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. Hyperlipidemia is also associated with HIV infection, renal transplant, and use of antipsychotic medications and protease inhibitors.

Dyslipidemia is a risk factor for CHD. Other modifiable risk factors for CHD include hypertension, smoking, thrombogenic/hemostatic state, diabetes, obesity, physical inactivity, and atherogenic diet. Nonmodifiable risk factors include age (≥45 years in men, ≥55 years in women), male sex, and family history of early-onset CHD.

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

In 2008, the USPSTF recommended screening with a fasting or nonfasting HDL-C level and either TC or a measure of LDL-C. 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...
persons at intermediate risk for CHD as high risk, although it found that evidence for C-reactive protein was promising. 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 that may be obtained in a fasting or nonfasting state. Although current recommendations generally recommend testing TC and LDL-C levels, they differ on the inclusion of other lipid components, the age at which to start testing, and the frequency of screening (see the “Recommendations of Other Groups” section).

Interventions/Treatment

Standard treatments for lipid disorders in adults include use of medications, diet, exercise, 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. LDL-C thresholds for initiation of lipid-lowering therapy following lifestyle intervention efforts varied from 130 mg/dL and greater to 190 mg/dL, depending on the assessed risk category (low: 10-year CVD event risk <10%; intermediate: 10% to 20%; high: >20%). Drug options for lipid reduction included statins, bile acid sequestrants, nicotinic acid, and fibrates, although statins were designated as the initial drug of choice given its proven efficacy for reducing LDL-C levels and evidence showing improved clinical outcomes. Statin or other lipid-lowering therapy was targeted to achieve LDL-C levels varying from less than 100 mg/dL to less than 160 mg/dL, depending on the risk category.

Updated guidelines issued in 2013 from the American College of Cardiology (ACC) and the AHA on lipid-lowering therapy differ from those of ATP III in a number of ways. In the new guidelines, statins are the recommended first-line lipid-lowering therapy to reduce CVD risk, as evidence on its effectiveness in improving clinical outcomes is strongest. Target populations for statin therapy were redefined as four groups: persons with clinical CVD, persons ages 40 to 75 years with diabetes and LDL-C levels of 70 to 189 mg/dL, persons with LDL-C levels of 190 mg/dL or greater, or persons ages 40 to 75 years with an estimated 10-year CVD risk of 7.5 percent or greater. For 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 a target LDL-C level, 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 guidelines also recommend the use of a newly developed global risk calculator to estimate risk.

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

**Current Clinical Practice in the United States**

A study based on 1996 to 2006 National Health and Nutrition Examination Survey data from 2,587 adults ages 20 to 45 years found overall lipid screening rates of less than 50 percent.42 Screening rates varied based on the presence of cardiovascular risk factors. Lipid testing rates were 68 percent in adults with CHD or CHD equivalents, 47 percent in those with two or more 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 a CHD equivalent was associated with increased likelihood of screening compared with presence of no risk factors (relative risk, 1.5 [95% confidence interval (CI), 1.1 to 2.2]). In addition, women were more likely to have undergone screening compared with men. Among women with CHD or a CHD equivalent, two or more risk factors, one risk factor, or no risk factors, screening rates were 69, 53, 52, and 49 percent, respectively; corresponding rates for men were 64, 38, 36, and 30 percent, respectively.4,43 A study based on a 2005 National Ambulatory Medical Care Survey found disparities in rates of lipid screening in adults age 20 years and older, 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 within the last 5 years for persons older than age 18 years (an increase 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 years and others not recommending screening until ages 35 to 40 years for men or 40 to 50 years for women. In general, guidelines recommend screening younger adults with CHD, CHD equivalents, or one or more CHD risk factors.

The ATP III guidelines recommend screening all persons age 20 years and older every 5 years with LDL-C, HDL-C, TC, 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 age 20 years and older 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 do not specifically address lipid screening but recommend, “as reasonable,” assessment of traditional cardiovascular risk factors every 4 to 6 years starting at age 20 years (grade IIa recommendation). Although the Pooled Cohort Equations risk calculator developed by the ACC and AHA estimates lifetime risk of atherosclerotic CVD in persons age 20 years and older, the guidelines do not make any recommendation to apply the risk calculator to persons younger than age 40 years.

The American Diabetes Association recommends lipid screening in patients with diabetes 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).

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/m², family history of premature CVD and familial dyslipidemia, chronic inflammatory disease, chronic kidney disease). Assessment of lipid levels may be considered in men older than age 40 years and women older than age 50 years.

The Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias recommends screening in men older than age 40 years, postmenopausal women, women older than age 50 years, and patients with diabetes mellitus, hypertension, smoking, abdominal obesity, strong family history of premature CVD manifestations of hyperlipidemia (e.g., xanthelasma, xanthoma, or arcus corneae), or evidence of symptomatic or asymptomatic atherosclerosis, as well as any patient for whom “lifestyle changes are indicated.” This group further recommends use of the NCEP ATP III risk estimation algorithm, with LDL-C level and TC-to-HDL-C ratio as targets.

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

The American College of Physicians Web site refers to an inactive guideline from 1996 recommending screening in men older than age 35 years and women older than age 45 years for TC levels.
Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the USPSTF, the USPSTF and the Agency for Healthcare Research and Quality 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 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) of 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 of 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 (through May 2016) and Ovid MEDLINE (2008 through May 2016) for relevant studies and systematic reviews. Search strategies are available in Appendix A1. We also reviewed reference lists of relevant articles, and searched ClinicalTrials.gov for ongoing studies.
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). Eligible studies were randomized trials, cohort studies, and case-control studies of lipid screening versus no screening, treatment of dyslipidemia versus no treatment, and delayed versus immediate treatment of dyslipidemia in asymptomatic adults ages 21 to 39 years that evaluated mortality, cardiovascular outcomes (CHD- or CVA-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 ages 21 to 39 years were also included. Studies that enrolled older adults would be included if results were reported separately for the subgroup of patients younger than age 40 years or if the mean age of the population was younger than 40 years. Included interventions were drug and 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 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,” or “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; however, no studies met inclusion criteria.

External Review

The draft report was reviewed by content experts (Appendix A6), USPSTF members, Agency for Healthcare Research and Quality 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 the 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 the 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 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 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 the benefits of treatment versus no treatment in adults ages 21 to 39 years on cardiovascular outcomes.

Evidence

We identified no studies on the 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 age 40 years, 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.\textsuperscript{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 the 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 of Dyslipidemia in Asymptomatic Adults Ages 21 to 39 Years?**

We identified no studies on the harms of treatment of 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?**

We identified no randomized trials, cohort studies, or case-control studies on the 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 persons younger than age 45 years at enrollment was 4.4 ± 6.9 mg/dL in men and 7.5 ± 7.2 mg/dL in women.\textsuperscript{58} Including all adults, the rate of change was higher in persons with lower TC levels (6.7 ± 5.6 mg/dL in men and 9.2 ± 6.6 mg/dL in women with initial TC levels <200 mg/dL vs. 0.6 ± 7.4 mg/dL in men and 3.7 ± 11.2 mg/dL in women with initial TC levels ≥240 mg/dL). Some evidence also suggests that young adults with low lipid levels often do not maintain them as they age. The Coronary Artery Risk Development in Young Adults Study, which enrolled persons in the United States ages 18 to 30 years, found that between 44 and 52 percent of those with TC levels below the 10th percentile remained below the same percentile 7 years later.\textsuperscript{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 Cohort Study (the Netherlands), the increase over a period of 18 years was largest for younger men, with TC levels increasing an average of 20 percent in men ages 20 to 24 years at baseline and 9.1 percent in men ages 35 to 39 years at baseline. In women, the pattern was in the opposite direction, at 9.8 percent in those ages 20 to 24 years at baseline and 16 percent in those ages 35 to 39 years at baseline. The proportion with TC levels of 251 mg/dL or greater increased from 3 to 26 percent in men ages 20 to 24 years at baseline and from 6 to 16 percent in women ages 20 to 24 years at baseline after 18 years; TC levels increased from 23 percent in men and 12 percent in women ages 35 to 39 years to 36 and 43 percent, respectively, after followup. In the Tromsø Study (Norway), the tracking coefficient (a measure of the tendency of individuals to maintain their rank or position in a group over time) for HDL-C levels in men ages 20 to 38 years ranged from 0.52 to 0.56, and for women ranged from 0.51 to 0.62. The tracking coefficient was higher for TC levels (0.70 to 0.74 in men and 0.62 to 0.69 in women) and was lower for triglycerides (0.30 to 0.49 in men and 0.33 to 0.39 in women). Tracking coefficients were also higher for TC levels than triglycerides in younger adults in the Vorarlberg Health Monitoring and Promotion Programme (Austria). A Spanish study of military recruits age 20 years found that after 15 years, TC levels increased an average of 68 mg/dL, LDL-C levels by 58 mg/dL, and HDL-C levels by -5.2 mg/dL.
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 has evaluated the diagnostic yield of alternative screening strategies in younger adults (e.g., targeted screening of persons with a family history of hyperlipidemia vs. general screening). Although some primary prevention trials have enrolled younger adults, 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 the treatment of 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 in 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 the treatment of familial hypercholesterolemia enrolled persons with a mean age of 44 years and did not meet inclusion criteria.

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, prevention of CHD events appears to start within 1 to 2 years of statin initiation, 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, which also found no direct evidence on the benefits or harms of screening or subsequent treatment in younger adults. Although persons with familial hypercholesterolemia are at increased risk for early-onset cardiovascular events, a factor limiting the potential benefits of screening for 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 before age 40 years.

Longitudinal studies suggest that lipid levels have a tendency to increase over time in younger adults, although no study has evaluated how lipid levels change 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 use of statins in middle-aged and older adults appears to be relatively safe, the long-term adverse effects of statin therapy (e.g., risk of developing diabetes) started in younger adulthood and lasting 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 for or treatment of dyslipidemia.

Future Research

Research is needed to understand the effects of screening for and treatment of dyslipidemia in younger adults. As very large, long-term trials would be required to evaluate screening in younger adults in the general population and may not be feasible, initial screening trials might target persons with a family history of familial hypercholesterolemia or early-onset 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. 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 the harms associated with very long-term statin therapy.

Conclusions

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


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

<table>
<thead>
<tr>
<th>Main findings from prior USPSTF reports*</th>
<th>Number and type of studies identified for update</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of findings</th>
<th>Overall quality†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>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 all-cause mortality?</strong></td>
<td>No studies</td>
<td>No studies</td>
<td>-</td>
<td>-</td>
<td>No studies</td>
<td>-</td>
</tr>
<tr>
<td><strong>Key Question 2. What are the harms of screening for dyslipidemia in asymptomatic adults ages 21 to 39 years?</strong></td>
<td>No studies</td>
<td>No studies</td>
<td>-</td>
<td>-</td>
<td>No studies</td>
<td>-</td>
</tr>
<tr>
<td><strong>Key Question 3. What is the diagnostic yield of alternative screening strategies for dyslipidemia in asymptomatic adults ages 21 to 39 years?</strong></td>
<td>No studies</td>
<td>No studies</td>
<td>-</td>
<td>-</td>
<td>No studies</td>
<td>-</td>
</tr>
<tr>
<td><strong>Key Question 4. What are the benefits of treatment of dyslipidemia in adults ages 21 to 39 years on CHD- or CVA-related morbidity or mortality or all-cause mortality?</strong></td>
<td>No studies</td>
<td>No studies</td>
<td>-</td>
<td>-</td>
<td>No studies</td>
<td>-</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Although 4 trials of statins for primary prevention enrolled patients age &lt;40 years, 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.</td>
<td>-</td>
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<tr>
<td><strong>Key Question 5. What are the benefits of delayed vs. immediate treatment in adults ages 21 to 39 years with dyslipidemia on CHD- or CVA-related morbidity or mortality or all-cause mortality?</strong></td>
<td>No studies</td>
<td>No studies</td>
<td>-</td>
<td>-</td>
<td>No studies</td>
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</tr>
<tr>
<td><strong>Key Question 6. What are the harms of drug treatment of dyslipidemia in asymptomatic adults ages 21 to 39 years?</strong></td>
<td>No studies</td>
<td>No studies</td>
<td>-</td>
<td>-</td>
<td>No studies</td>
<td>-</td>
</tr>
</tbody>
</table>

* 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 ages 21 to 39 years).

† “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 and Cochrane Central Register of Controlled Trials
1  exp Dyslipidemias/
2  Cholesterol/bl
3  Mass Screening/
4  (1 or 2) and 3
5  limit 4 to yr="2008 - 2016"
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 - 2016"

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 - 2016"

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 - 2016"

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
<table>
<thead>
<tr>
<th></th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>KQs 1–3: Asymptomatic adults ages 21 to 39 years</td>
<td>KQs 1–3: Adults with known dyslipidemia (primary or secondary) or prior CVD events</td>
</tr>
<tr>
<td></td>
<td>KQs 4–6: Adults ages 21 to 39 years with dyslipidemia</td>
<td>KQs 4–6: Adults with prior CVD events</td>
</tr>
<tr>
<td><strong>Diseases</strong></td>
<td>Dyslipidemia (as defined according to clinical practice guidelines, lipid levels &gt;90th percentile for lipid components positively associated with CHD risk, or other specified criteria)</td>
<td>Lipid levels not meeting thresholds for dyslipidemia</td>
</tr>
<tr>
<td><strong>Screening Interventions</strong></td>
<td>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)</td>
<td>• Screening with family history only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Genetic screening only</td>
</tr>
<tr>
<td><strong>Screening Comparator</strong></td>
<td>No screening or usual care delivered in a universal or selective screening strategy</td>
<td>Other comparators not listed as included</td>
</tr>
<tr>
<td><strong>Treatment Interventions</strong></td>
<td>Drug (e.g., statins) and lifestyle interventions (e.g., exercise and diet changes)</td>
<td>Other types of treatments not listed as included</td>
</tr>
<tr>
<td><strong>Treatment Comparator</strong></td>
<td>No treatment or usual care</td>
<td>Other comparators not listed</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>KQs 1, 4, 5: CHD- and/or CVA-related morbidity or mortality; all-cause mortality</td>
<td>KQs 1, 4, 5: Outcomes not listed as included</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td>KQ 2: Adverse outcomes not associated with screening</td>
</tr>
<tr>
<td></td>
<td>KQ 3: Diagnostic yield (true positives/number screened)</td>
<td>KQ 3: Outcomes not listed as included</td>
</tr>
<tr>
<td></td>
<td>KQ 6: Harms associated with drug treatment (e.g., myopathy, rhabdomyolysis, myalgia, cognitive loss, diabetes, elevations in liver enzyme or creatine phosphokinase levels, and others as identified in the literature)</td>
<td>KQ 6: Other adverse outcomes not associated with drug treatment</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Randomized, controlled trials; cohort studies; case-control studies; high-quality systematic reviews</td>
<td>Other study designs</td>
</tr>
<tr>
<td><strong>Settings</strong></td>
<td>• Publication date of 2008 to present; studies included in prior USPSTF reports</td>
<td>Settings not generalizable to primary care; studies outside the stated timeframe</td>
</tr>
<tr>
<td></td>
<td>• Primary care or primary care–relevant settings</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CHD=coronary heart disease, CVA=cerebrovascular accident (stroke); CVD=cardiovascular disease, HDL=high-density lipoprotein, KQ=key question; LDL=low-density lipoprotein; USPSTF=U.S. Preventive Services Task Force.
Appendix A3. Literature Flow Diagram

Abstracts of potentially relevant articles identified through MEDLINE and Cochrane*: 6,116

Excluded abstracts and background articles: 5,764

Full-text articles reviewed for relevance to Key Questions: 352

Articles excluded total: 352
Wrong population: 59
Wrong intervention: 10
Wrong outcome: 46
Wrong study design for Key Question: 20
Not a study (letter, editorial, nonsystematic review article): 13
Wrong population (age >40 years): 188
Wrong comparison: 16

Included studies: 0

Key Question 1: Benefits of screening: 0

Key Question 3: Diagnostic yield of alternative screening strategies: 0

Key Question 4: Benefits of treatment: 0

Key Question 5: Benefits of delayed vs. intermediate treatment: 0

Key Question 6: Harms of treatment: 0

*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

<table>
<thead>
<tr>
<th>Code</th>
<th>Reason</th>
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</thead>
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<tr>
<td>3</td>
<td>Wrong population</td>
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<tr>
<td>4</td>
<td>Wrong intervention</td>
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<td>5</td>
<td>Wrong outcome</td>
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<tr>
<td>6</td>
<td>Wrong study design for Key Question</td>
</tr>
<tr>
<td>7</td>
<td>Not a study (letter, editorial, nonsystematic review article)</td>
</tr>
<tr>
<td>9</td>
<td>Wrong population (age &gt;40 years)</td>
</tr>
<tr>
<td>13</td>
<td>Wrong comparison</td>
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</table>


Appendix A4. Excluded Studies With Reasons for Exclusion

Exclusion code: 9

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Exclusion code: 9

Exclusion code: 7

Exclusion code: 6

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Exclusion code: 3

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Exclusion code: 6
Appendix A4. Excluded Studies With Reasons for Exclusion

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Appendix A4. Excluded Studies With Reasons for Exclusion


Appendix A4. Excluded Studies With Reasons for Exclusion


Appendix A4. Excluded Studies With Reasons for Exclusion

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Exclusion code: 6

Exclusion code: 13

Exclusion code: 3

Exclusion code: 9

Exclusion code: 9
Appendix A4. Excluded Studies With Reasons for Exclusion

Exclusion code: 9

Ge CJ, Lu SZ, Chen YD, 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

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Appendix A4. Excluded Studies With Reasons for Exclusion

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Appendix A4. Excluded Studies With Reasons for Exclusion

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Appendix A4. Excluded Studies With Reasons for Exclusion

Exclusion code: 13

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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

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Appendix A4. Excluded Studies With Reasons for Exclusion


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Appendix A4. Excluded Studies With Reasons for Exclusion

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Appendix A4. Excluded Studies With Reasons for Exclusion

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Appendix A4. Excluded Studies With Reasons for Exclusion

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Appendix A4. Excluded Studies With Reasons for Exclusion

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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

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Exclusion code: 9

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

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Exclusion code: 9

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Appendix A4. Excluded Studies With Reasons for Exclusion


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Exclusion code: 9


Exclusion code: 3


Exclusion code: 9


Exclusion code: 3


Exclusion code: 9


Exclusion code: 9


Exclusion code: 5


Exclusion code: 9


Exclusion code: 9

Zhao XQ, 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
Appendix A4. Excluded Studies With Reasons for Exclusion

Exclusion code: 13

Exclusion code: 5

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.
Appendix A5. U.S. Preventive Services Quality Rating Criteria

- 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 or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.
Appendix A5. U.S. Preventive Services Quality Rating Criteria

*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.

Appendix A6. Reviewers of the Draft Report

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