REVIEW

Annals of Internal Medicine

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

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Background: Dyslipidemia may occur in younger adults (defined as persons aged 21 to 39 years) and is an important risk factor for cardiovascular disease. Screening might identify younger adults with asymptomatic dyslipidemia who may benefit from lipid-lowering therapies.

Purpose: To update the 2008 U.S. Preventive Services Task Force review on dyslipidemia screening in younger adults.

Data Sources: The Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and MEDLINE through May 2016, and reference lists.

Study Selection: Randomized, controlled trials; cohort studies; and case–control studies on screening for or treatment of asymptomatic dyslipidemia in adults aged 21 to 39 years.

Data Extraction: The plan was for 1 investigator to abstract data and a second to check their accuracy, and for 2 investigators to independently assess study quality; however, no studies met the inclusion criteria.

Data Synthesis: 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 (such as targeted screening of persons with a family history of hyperlipidemia vs. general screening) in younger adults.

Limitation: No direct relevant evidence.

Conclusion: Direct evidence on the benefits and harms of screening for or treatment of dyslipidemia in younger adults remains unavailable. Estimating the potential effects of screening for dyslipidemia in this population requires extrapolation from studies performed in older adults.

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Dyslipidemia affects about 53% of U.S. adults (105.3 million) (1). Although dyslipidemia becomes more prevalent with age, it also affects younger adults. About 36% of adults aged 20 to 29 years and 43% aged 30 to 39 years meet levels recommended by the National Cholesterol Education Program for all lipids (2). Dyslipidemia is associated with cardiovascular disease, the leading cause of death in the United States. In 2010, the prevalence of coronary heart disease (CHD) was 1.2% among those aged 18 to 44 years (3). The number of myocardial infarctions or fatal CHD events annually is estimated at 20 000 for men aged 35 to 44 and 5000 for women aged 35 to 44 years (4). In 2011, CHD caused 12% of deaths in persons aged 25 to 44 years (5).

Because of the asymptomatic nature of dyslipidemia before signs or symptoms of cardiovascular disease develop, its identification requires screening. Detecting dyslipidemia in younger adults might enable management strategies, including lifestyle modification or medications, to be implemented to reduce the risk for cardiovascular events. Screening may be particularly beneficial in identifying young adults with markedly elevated lipid levels due to unrecognized familial hypercholesterolemia.

In 2008, the U.S. Preventive Services Task Force (USPSTF) recommended lipid screening in men aged 20 to 35 years and women aged 20 to 45 years with CHD risk factors (B recommendation) (6). Although the USPSTF found no direct evidence regarding benefits or harms of lipid screening in these age groups, its recommendation was based on data showing that some younger adults with CHD risk factors have lipid levels sufficient to place them at high (>10%) 10-year cardiovascular risk and might benefit from lipid-lowering therapies. The USPSTF made no recommendation for or against lipid screening in men and women in these age groups without CHD risk factors (C recommendation) because of the low likelihood of identifying lipid levels high enough to justify treatment, thus resulting in small expected benefits. Recommendations from other groups vary regarding lipid screening in persons without CHD risk factors. Some guidelines recommend screening starting at age 20 years; others do not recommend screening until age 35 to 40 for men or 40 to 50 for women (7–10). In general, all guidelines recommend lipid testing in younger adults with CHD, CHD equivalents, or 1 or more CHD risk factors. The 2014 American College of Cardiology and American Heart Association guideline on assessing cardiovascular risk considers it "reasonable" to evaluate traditional cardiovascular risk factors, including lipids, every 4 to 6 years starting at age 20 (7).

The purpose of this report is to update previous USPSTF reviews (11–13) on screening for dyslipidemia in adults. It will be used by the USPSTF to update its 2008 recommendation (6). One difference between this update and earlier USPSTF reviews is that it focuses on screening in younger adults (defined as those aged 21 to 39 years). The USPSTF did not re-review evidence on screening for dyslipidemia in older adults because it already strongly recommends screening in men older

than 35 years and women older than 45 (A recommendation). In addition, the decision to initiate lipid-lowering therapy with statins is based on a global assessment of cardiovascular risk, not just lipid levels. Therefore, the USPSTF commissioned a separate evidence review on the use of statin therapy for cardiovascular disease prevention in adults aged 40 years or older (14). A separate USPSTF review addresses dyslipidemia screening in persons younger than 21 years (15).

METHODS

Scope of the Review

Using established methods (16, 17), the USPSTF determined the scope, key questions, and analytic framework (Figure 1) used to guide this review. A standard protocol was developed and publicly posted on the USPSTF Web site before the review was carried out (www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan98/statin-use-in-adults-preventive-medication1).

Key questions are as follows:

1. What are the benefits of screening for dyslipidemia in asymptomatic adults aged 21 to 39 years on CHD- or cerebrovascular accident (CVA, or stroke)–related morbidity or mortality, or on all-cause mortality?

2. What are the harms of screening for dyslipidemia in asymptomatic adults aged 21 to 39 years?

3. What is the diagnostic yield of alternative screening strategies (for example, universal vs. risk-based screening) for asymptomatic dyslipidemia in adults aged 21 to 39 years?

4. What are the benefits of dyslipidemia treatment (such as drug or lifestyle interventions) in adults aged 21 to 39 years on CHD- or CVA-related morbidity or mortality, or on all-cause mortality?

5. What are the benefits of delayed versus immediate dyslipidemia treatment in adults aged 21 to 39 years on CHD- or CVA- related morbidity or mortality, or on all-cause mortality?

6. What are the harms of drug treatment of asymptomatic dyslipidemia in adults aged 21 to 39 years?

Detailed methods and data for this review, including search strategies and detailed inclusion criteria, are contained in the full USPSTF report (18). The full review also includes 2 contextual questions (not reviewed systematically): 1 on how intermediate outcomes are affected by drug treatment of dyslipidemia in younger adults and the other on how lipid levels change over time in younger adults.

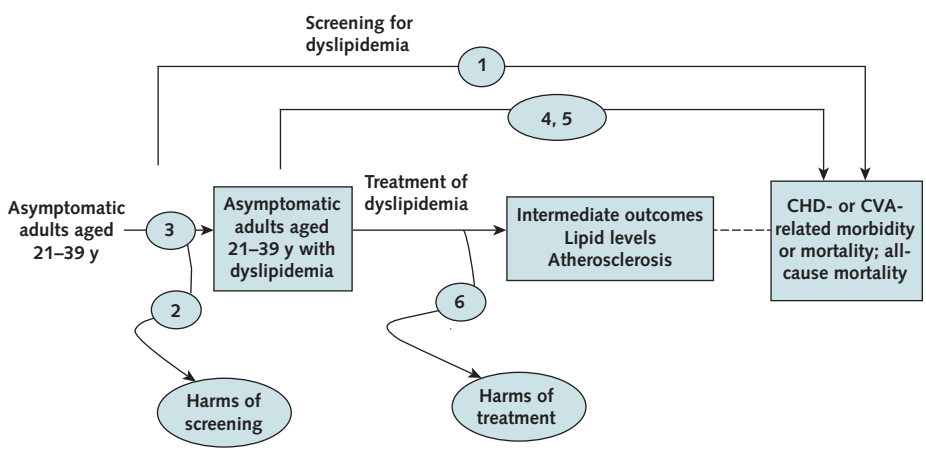
Data Sources and Searches

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through May 2016), Ovid MEDLINE (2008 through May 2016) (Appendix Table 1, available at www.annals.org), and reference lists. Searches were limited to English-language articles. We also searched ClinicalTrials.gov for ongoing studies.

Study Selection

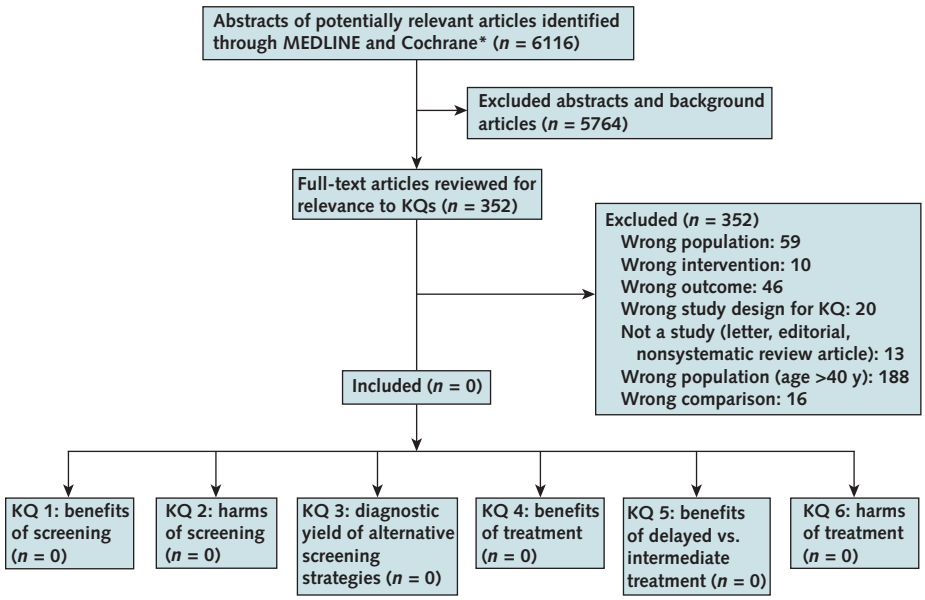
Two reviewers independently evaluated the literature on the basis of predefined criteria (Appendix Table 2, available at www.annals.org). Eligible studies were randomized trials, cohort studies, and case–control studies of lipid screening versus no screening, dyslipidemia treatment versus no treatment, and delayed versus immediate dyslipidemia treatment in asymptomatic adults aged 21 to 39 years that evaluated mortality, cardiovascular outcomes (CHD- or CVA-related morbidity or mortality), or harms of screening or treatment. Studies reporting the diagnostic yield (number of true positives per number tested) of lipid screening in adults aged 21 to 39 years also were eligible for inclusion. Studies enrolling older adults were also eligible if the results were reported separately for patients younger than 40 years or if the mean age of the population was less than 40 years. Regarding treatment, both drug therapy and lifestyle interventions (such as exercise and diet changes) were eligible for inclusion.

Figure 1. Analytic framework.



Numbers in circles correspond to the key question numbers. CHD = coronary heart disease; CVA = cerebrovascular accident (stroke).

Figure 2. Literature flow diagram.



KQ = key question.
* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

Studies of individuals with prior cardiovascular events were excluded. The literature selection is summarized in Figure 2.

Data Abstraction and Quality Rating

We planned for 1 investigator to abstract details about each article's study design, patient population, setting, screening method, treatment regimen, analysis, follow-up, and results; 1 investigator to review the data abstraction for accuracy; and 2 investigators to independently apply criteria developed by the USPSTF (16) to rate the quality of each study as good, fair, or poor (Appendix, available at www.annals.org), with discrepancies resolved through consensus. No studies, however, met the 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) by using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results among studies; and directness of evidence (16). No studies, however, met the inclusion criteria.

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Investigators worked with USPSTF members and AHRQ staff to develop and refine the scope, analytic framework, and key questions; resolve issues arising during the project; and finalize the report. The AHRQ had no role in the study selection, quality assessment, synthesis, or development of conclusions. It provided project oversight; reviewed the draft report; and distributed the draft for peer review, including to representatives of professional societies and federal agencies. The AHRQ performed a final review of the manuscript to ensure that the analysis met methodological standards.

RESULTS

Screening

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

Diagnostic Yield of Alternate Screening Strategies

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

Treatment

We identified no studies on benefits or harms of treatment versus no treatment regarding cardiovascular outcomes in adults aged 21 to 39 years. Although 4 trials of statins for primary prevention enrolled patients younger than 40 years, results were not reported separately for this subgroup, which made up a small part of the study populations (19–22). One cohort study evaluated the efficacy of statins in patients with familial hypercholesterolemia, but the mean age at enrollment was 44 years (23). We also identified no studies on benefits or harms of delayed versus immediate dyslipidemia treatment in adults aged 21 to 39 years.

DISCUSSION

No study evaluated the effects of screening versus no screening or treatment versus no treatment on clinical outcomes in younger adults. In addition, no study evaluated the diagnostic yield of alternative screening strategies in younger adults (for example, targeted screening of persons with a family history of hyperlipidemia vs. general screening). Although some primary prevention trials enrolled younger adults (19–22), they made up 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 available, the trials were probably underpowered to detect effects on clinical outcomes. Therefore, estimating the benefits of lipid-lowering therapies or lifestyle changes for dyslipidemia in younger adults requires extrapolation from trials conducted in older populations. Even if one assumes that the relative benefits of statins or other therapies are the same in younger and older adults, the absolute benefits over the short term (for example, 5 to 10 years) generally would be lower in younger adults because of the lower incidence of CHD events in this group. An exception may be young adults with familial hypercholesterolemia, who are at increased risk for CHD events at a younger age. However, the only study comparing the effects of statins versus no statins for familial hypercholesterolemia enrolled persons with a mean age of 44 years and did not meet inclusion criteria (23).

We also found no evidence regarding the incremental benefit of early versus delayed treatment on clinical outcomes. Earlier initiation of therapy might reduce the risk for CHD events that occur later in life if the primary mechanism of lipid-lowering therapy is atherosclerosis regression. However, in trials of middle-aged and older populations, CHD event prevention appeared to start within 1 to 2 years of statin initiation (24), suggesting that long-term therapy started during early adulthood may not be required to experience treatment benefits related to early plaque stabilization or other, shorter-term effects. Although statins in middle-aged and older adults appear to be relatively safe and short-term adverse events generally resolve with discontinuation of therapy, long-term adverse effects of statins started in younger adulthood and taken for decades (such as the risk for diabetes and associated sequelae) have not been well-studied. As detailed in the full report, we also found no evidence regarding the effects of drug treatment of dyslipidemia on intermediate outcomes in younger adults (18).

Regarding screening in younger adults, another area of uncertainty is how frequently to test. We found little evidence to inform screening intervals in this population. As detailed in the full report, longitudinal studies suggest that lipid levels tend to increase over time in younger adults (25, 26); however, no study evaluated how lipid levels change according to different intervals between repeated testing or the proportion of patients who would move from one risk category to another over time.

The main limitation of this review is the lack of evidence in younger adults, the population of interest. Our findings are in accordance with prior USPSTF reviews (11, 13), which also found no direct evidence regarding benefits or harms of screening or subsequent treatment in this population. Although individuals with familial hypercholesterolemia are at increased risk for early cardiovascular events, a factor limiting potential benefits of screening for this condition is that this is a low-prevalence condition (estimated at 1 in 500 persons) and that even among this population, most (85% to 90%) do not experience a CHD event before the age 40 years (27, 28).

In conclusion, direct evidence regarding benefits and harms of dyslipidemia screening or treatment in younger adults remains unavailable. Because 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 should consider targeting individuals with a family history of hypercholesterolemia or early CHD, and initial treatment trials might target persons with very elevated lipid levels (such as those resulting from familial hypercholesterolemia), to increase statistical power. Trials of delayed versus immediate lipid-lowering therapy for younger adults with dyslipidemia also would be helpful for understanding the effectiveness of earlier treatment, and studies are needed to understand harms associated with very long-term statin therapy.

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Disclaimer: The investigators are solely responsible for the content and the decision to submit the manuscript for publication. The views expressed here do not represent and should not be construed to represent a determination or policy of the AHRQ or the U.S. Department of Health and Human Services.

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Reproducible Research Statement: *Study protocol:* Available at www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan98/statin-use-in-adults-preventive-medication1. *Statistical code:* Not applicable. *Data set:* Full report available at www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/statin-use-in-adults-preventive-medication1?ds=1&s=statin.

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References

1. **Tóth 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;6:325-30. [PMID: 22836069] doi:10.1016/j.jacl.2012.05.002
2. **Ghandehari H, Kamal-Bahl S, Wong ND.** Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003-2004. Am Heart J. 2008;156:112-9. [PMID: 18585505] doi:10.1016/j.ahj.2008.03.005
3. **Centers for Disease Control and Prevention (CDC).** Prevalence of coronary heart disease–United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011;60:1377-81. [PMID: 21993341]
4. **Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics–2013 update: a report from the American Heart Association. Circulation. 2013;127:e6-245. [PMID: 23239837] doi:10.1161/CIR.0b013e31828124ad
5. **Miniño AM.** Death in the United States, 2011. NCHS Data Brief no 115. Hyattsville, MD: National Center for Health Statistics; 2013.
6. **U.S. Preventive Services Task Force.** Lipid disorders in adults (cholesterol, dyslipidemia): screening. 2008. Accessed at www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lipid-disorders-in-adults-cholesterol-dyslipidemia-screening on 8 June 2016.
7. **Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines.** 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2935-59. [PMID: 24239921] doi:10.1016/j.jacc.2013.11.005
8. **National Diabetes Education Initiative.** Diabetes management guidelines: American Diabetes Association (ADA) 2016 guidelines. 2013. Accessed at www.ndei.org/ADA-diabetes-management-guidelines-diagnosis-A1C-testing.aspx on 8 June 2016.
9. **Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al; European Association for Cardiovascular Prevention & Rehabilitation.** ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769-818. [PMID: 21712404] doi:10.1093/eurheartj/ehr158
10. **Genest J, Frohlich J, Fodor G, McPherson R; Working Group on Hypercholesterolemia and Other Dyslipidemias.** Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. CMAJ. 2003;169:921-4. [PMID: 14581310]
11. **Helfand M, Carson S.** Screening for Lipid Disorders in Adults: Selective Update of 2001 U.S. Preventive Services Task Force Review. AHRQ publication no. 08-05114-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2008. Accessed at www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lipid-disorders-in-adults-cholesterol-dyslipidemia-screening?ds=1&s=dyslipidemia on June 8, 2016.
12. **Pignone MP, Phillips CJ, Atkins D, Teutsch SM, Mulrow CD, Lohr KN.** Screening and treating adults for lipid disorders. Am J Prev Med. 2001;20:77-89. [PMID: 11306236]
13. **Pignone MP, Phillips CJ, Lannon CM, Mulrow CD, Teutsch SM, Lohr KN, et al.** Screening for Lipid Disorders. AHRQ publication no. 01-S004. Rockville, MD: Agency for Healthcare Research and Quality; 2001. Accessed at www.ahrq.gov/downloads/pub/prevent/pdfser/lipidser.pdf on June 8, 2016.
14. **Chou R, Dana T, Blazina I, Daeges M, Bougatsos C, Jeanne T.** Statins for Prevention of Cardiovascular Disease in Adults: Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis no. 139. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
15. **Lozano P, Henrikson NB, Morrison CC, Dunn J, Nguyen M, Blasi P, et al.** Draft evidence review: lipid screening in childhood for detection of multifactorial dyslipidemia: a systematic review for the U.S. Preventive Services Task Force. 2015. Accessed at www.uspreventiveservicestaskforce.org/Page/Document/draft-evidence-review-screening-for-multifactorial-dyslipide/lipid-disorders-in-children-screening1 on 8 June 2016.
16. **U.S. Preventive Services Task Force.** Procedure manual. 2016. Accessed at www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes on 8 June 2016.
17. **Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al; Methods Work Group, Third US Preventive Services Task Force.** Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. [PMID: 11306229]
18. **Chou R, Dana T, Blazina I, Daeges M, Bougatsos C, Jeanne T.** Screening for Dyslipidemia in Younger Adults: A Systematic Review to Update the 2008 U.S. Preventive Services Task Force Recommendation. Evidence Synthesis no. 138. AHRQ publication no. 14-05206-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2016.
19. **Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al; Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators.** Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110:2809-16. [PMID: 15492322]
20. **Chan KL, Teo K, Dumesnil JG, Ni A, Tam J; ASTRONOMER Investigators.** 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;121:306-14. [PMID: 20048204] doi:10.1161/CIRCULATIONAHA.109.900027
21. **Beishuizen ED, van de Ree MA, Jukema JW, Tamsma JT, van der Vijver JC, Meinders AE, 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;27:2887-92. [PMID: 15562202]
22. **Muldoon MF, Ryan CM, Sereika SM, Flory JD, Manuck SB.** Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. Am J Med. 2004;117:823-9. [PMID: 15589485]
23. **Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al.** Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ. 2008;337:a2423. [PMID: 19001495] doi:10.1136/bmj.a2423
24. **Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) Collaborators.** Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267-78. [PMID: 16214597]
25. **Kreger BE, Odell PM, D'Agostino RB, Wilson PF.** Long-term intraindividual cholesterol variability: natural course and adverse impact on morbidity and mortality–the Framingham Study. Am Heart J. 1994;127:1607-14. [PMID: 8197990]
26. **Bakx JC, van den Hoogen HJ, Deurenberg P, van Doremalen J, van den Bosch WJ.** Changes in serum total cholesterol levels over 18 years in a cohort of men and women: The Nijmegen Cohort Study. Prev Med. 2000;30:138-45. [PMID: 10656841]
27. **Slack J.** Risks of ischaemic heart-disease in familial hyperlipoproteinaemic states. Lancet. 1969;2:1380-2. [PMID: 4188273]
28. **Stone NJ, Levy RI, Fredrickson DS, Verter J.** Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. Circulation. 1974;49:476-88. [PMID: 4813182]

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Appendix: Criteria for Assessing Internal Validity of Individual Studies

The Methods Work Group for the U.S. Preventive Services Task Force (USPSTF) developed a set of criteria by which the internal validity of individual studies could be evaluated (16). At its September 1999 meeting, the USPSTF accepted the criteria, as well as the associated definitions of quality categories, that relate to internal validity.

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 most directly address the question under investigation and that are applicable to the population at issue. Thus, studies of any design that used outdated technology or 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 might be reasonable disagreement about this step. The following criteria are meant for studies that pass this initial filter.

Presented here is a set of minimal criteria for each study design followed by a general definition of 3 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, may be made. In general, a good study is one that meets all criteria. A fair study is one that does not meet (or it is unclear whether it meets) at least 1 criterion but has no known "fatal flaw." Poor studies have at least 1 fatal flaw.

Systematic Reviews

Criteria

Comprehensiveness of sources considered or the search strategy used

Standard appraisal of included studies

Validity of conclusions

Recency and relevance are especially important for systematic reviews

Definition of Ratings From Aforementioned 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 randomized, controlled trials (RCTs): adequate randomization, including first concealment and whether potential confounders were distributed equally among groups

Initial assembly of comparable 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, crossovers, adherence, and 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

Consideration of all important outcomes

Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs

Definition of Ratings From Aforementioned Criteria

Good: Meets all criteria. Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%); 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 is paid to confounders in the analysis. In addition, for RCTs, intention-to-treat analysis is used.

Fair: Studies are graded as fair if any or all of the following problems occur, but without the fatal flaws noted in the "poor" category: Generally comparable groups are assembled initially, but some question remains as to 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 are graded as poor if any of the following fatal flaws exist: 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 and 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 From Aforementioned Criteria

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

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

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

Appendix Table 1. Search Strategies

Screening

Databases: Ovid MEDLINE 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 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
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 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

Continued

Appendix Table 2. Inclusion and Exclusion Criteria per KQ

Include	Exclude
Population	
KQs 1-3: Asymptomatic adults aged 21 to 39 y	KQs 1-3: Adults with known dyslipidemia (primary or secondary) or prior CVD events
KQs 4-6: Adults aged 21 to 39 y with dyslipidemia	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	KQs 1, 4, 5: Outcomes not listed as included
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 2: Adverse outcomes not associated with screening
KQ 3: Diagnostic yield (true positives/number screened)	KQ 3: Outcomes not listed as included
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)	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 time frame

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.