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Screening for Elevated Blood Lead Levels in Pregnant Women: A Systematic Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: In 2006, the U.S. Preventive Services Task Force (USPSTF) recommended against routine screening for elevated blood lead levels (BLLs) in asymptomatic pregnant women (D recommendation).

Purpose: To synthesize evidence on the effects of screening, testing, and treatment for elevated BLLs in pregnant women, to update a 2006 USPSTF systematic review.

Data Sources: Cochrane CENTRAL and Cochrane Database of Systematic Reviews (through June 2018) and Ovid MEDLINE (1946 to June 2018), reference lists, and surveillance through December 5, 2018.

Study Selection: English-language trials and observational studies of screening effectiveness, test accuracy, and benefits and harms of screening and interventions in asymptomatic pregnant women.

Data Extraction: One investigator abstracted details about study design, patient population, setting, screening method, followup, and results. Two investigators independently applied prespecified criteria to rate study quality using methods developed by the USPSTF. Discrepancies were resolved through consensus.

Data Synthesis: No studies directly evaluated clinical benefits and harms of screening pregnant women for elevated BLLs versus no screening, or how effectiveness of screening varies according to the gestational age at which screening is performed. One fair-quality study (N=314) evaluated the diagnostic accuracy of using a version of the Centers for Disease Control and Prevention screening questionnaire for lead exposure in children, modified for identifying pregnant women with elevated BLLs. The study used four out of five questions from the questionnaire and found a sensitivity of 75.7 percent and specificity of 46.2 percent. The most predictive single item was living in a home built before 1960. One fair-quality randomized, controlled trial from Mexico found that calcium supplementation in healthy pregnant women (N=670; mean baseline BLL, ~4 µg/dL) was associated with a reduction in serum lead levels compared with placebo (difference, 11%; p=0.004). No studies reported health outcomes or harms associated with interventions to reduce BLLs in asymptomatic pregnant women.

Limitations: Limited to English-language articles; quality and applicability of studies were limited due to flawed study design, poor reporting of statistical outcomes, and loss to followup. Two studies addressed the Key Questions, with no evidence on effects of screening or interventions for elevated BLLs in pregnant women on health outcomes.

Conclusions: Evidence on the benefits and harms of screening pregnant women for elevated BLLs is extremely limited, with no evidence on effects of screening or interventions for elevated BLLs in pregnant women on health outcomes.

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Chapter 1. Introduction and Background

Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2006 recommendation on screening for elevated blood lead levels (BLLs) in pregnancy. This update focuses on studies published since the prior USPSTF systematic review[1] of this topic and may include studies also included in the prior review.

In 2006, the USPSTF recommended against routine screening for elevated BLLs in asymptomatic pregnant women (D recommendation). The USPSTF found no studies that examined the effectiveness or harms of screening or interventions among pregnant women but did discuss a variety of potential harms similar to those among children. Given the low prevalence of elevated BLLs in asymptomatic pregnant women, the small amount of potential benefit was not thought to outweigh the potential harms of screening and intervention in this group.

Condition Background

Condition Definition

Elevated BLL is defined as greater than 5 µg/dL, according to the Centers for Disease Control and Prevention (CDC).[2] Although no safe level of lead exposure exists, this is the level at which further clinical monitoring or treatment is recommended for pregnant women.[2] This reference range value was based on the 98th percentile of the National Health and Nutrition Examination Survey (NHANES) blood lead distribution in women of childbearing age.[3]

Prevalence and Burden of Disease/Illness

Lead causes a number of adverse health effects, primarily affecting the central nervous, hematopoietic, hepatic, and renal systems.[4] Manifestations are variable, but there is a general correlation between higher BLLs and the presence of symptoms. Acute toxicity resulting from intense lead exposure over a short duration is very uncommon and primarily associated with occupational exposure.[4] Clinical symptoms of acute lead exposure include muscle pain, fatigue, abdominal pain, headache, vomiting, seizures, and coma.[4] Adults with lower level, chronic, or recurrent exposures may be asymptomatic or present with vague nonspecific symptoms (e.g., myalgia, fatigue, difficulty concentrating, and insomnia).[4]

Many potential health effects of lead exposure are irreversible. Compared with other organ systems, the nervous system is the most sensitive and chief target for lead-induced toxicity.[4] More severe manifestations occur at very high exposures and include delirium, lack of coordination, convulsions, paralysis, coma, and ataxia. Lead exposure can lead to anemia by directly affecting the synthesis of hemoglobin (by inhibiting various key enzymes involved in the

heme synthesis pathway) and by reducing the life span of circulating erythrocytes by increasing the fragility of cell membranes.[5]

Pregnant women exposed to lead are at an increased risk of adverse perinatal outcomes as well as nonpregnancy-related morbidity. Among adults in general, analyses of NHANES data (1988 to 1994) indicate that BLLs greater than 10 μg/dL are associated with an increased risk of death from all causes (relative risk [RR], 1.59 [95% confidence interval (CI), 1.28 to 1.98]), cardiovascular disease (RR, 1.55 [95% CI, 1.16 to 2.07]), and cancer (RR, 1.69 [95% CI, 1.14 to 2.52]).[6] Exposure in adults can additionally lead to increased blood pressure and the incidence of hypertension, reproductive problems, and decreased kidney function.[7] The International Agency for Research on Cancer lists lead as a probable carcinogen, and the U.S. Report on Carcinogens also lists lead and lead compounds as "reasonably anticipated to be a human carcinogen."[8,9] Lead exposure during pregnancy can result in spontaneous abortion,[3] reduced fetal growth, premature birth, and cognitive deficiencies in the child.[3] As with young children, lead exposure during the critical initial neurological development of a fetus may be particularly harmful.[10] Pregnant women and nursing mothers with high BLLs may experience elevations in both systolic and diastolic blood pressure.[11]

Public health efforts to reduce exposure to lead in the United States (e.g., removal of lead from household paints and gasoline) are considered major successes. Although it is difficult to measure changes in morbidity attributable to lead exposure, the prevalence of elevated BLLs in adults has declined significantly over the past few decades.

Based on NHANES data, the percentage of adults with BLLs of 10 μg/dL or greater declined from 3.3 percent in 1988 to 1994 to 0.7 percent in 1999 to 2002 ($p<0.001$).[12] In 1999 to 2002, the multivariable-adjusted odds ratio of having a BLL of 10 μg/dL or greater was 2.91 (95% CI, 1.74 to 4.84) and 3.26 (95% CI, 1.83 to 5.81) for non-Hispanic black and Mexican American adults, respectively, compared with non-Hispanic white adults.[13] Among women of childbearing age, an estimated 1 percent have BLLs greater than 5 μg/dL.[3] In one analysis of pregnant women, the age-adjusted prevalence of elevated BLLs was less than 0.5 percent.[14]

Etiology and Natural History

Lead is a heavy metal that occurs naturally in the environment. Unique properties of lead (e.g., high malleability, low melting point, and resistance to corrosion) resulted in its widespread use in various industries. Lead has become widely distributed and mobilized in the environment, resulting in increasing human exposure and uptake over time.[15]

Common sources of lead exposure include lead-based paint, contaminated soil (e.g., by exterior lead-based paint or gasoline), lead-contaminated water (e.g., by lead plumbing), and dust contaminated by chipping or chalking of lead-based paint and tracked-in soil.[15] In the United States, leaded gasoline began to be phased out in 1973 and was banned by 1996. From 1980 to 2014, exposure to lead fumes from leaded gasoline decreased by 98 percent.[16] Lead-based paints were banned for use in housing in 1978. All houses built before 1978 are likely to contain some lead-based paint that ultimately deteriorates and causes a problem.[15] Although lead was restricted in plumbing material in 1986, older homes and neighborhoods may still contain lead service

lines, lead connections, or other lead-based plumbing materials.[17] The release of lead from lead-based plumbing materials into drinking water is variable and influenced by factors such as water softness, temperature, and acidity.[18] Flint, Michigan provides an example of increased lead contamination of drinking water related to changes in water sources and treatment, including the use of disinfectants.[19]

Like young children, adults may be exposed to lead-based paints and other household exposures. Adults may also be at risk of occupational lead exposure, exposure via hobbies (e.g., lead-glazed pottery), and ingestion of some lead-containing complementary and alternative treatments (e.g., Ayurvedic herbal medicine products). One survey of reproductive-age women in New York with elevated BLLs (10 to 25 µg/dL) found that 46 percent of exposures were occupational, 24 percent were due to home renovations, and 30 percent were unknown.[20] Among women with occupational exposures to lead fumes or dust, the most common occupational exposures were precision production (e.g., work involving soldering or the production of lead-containing materials); craft and repair operations; and among operators, fabricators, and laborers. Specific recommendations exist for medical surveillance of pregnant women with occupational exposure to lead.[21]

Once exposed to lead, nutritional factors in both children and adults are known to affect lead absorption and toxicity. Iron- or calcium-deficient diets may lead to more efficient absorption of lead in children and adults.[22] Interactions between micronutrients and exposure to lead are also important in pregnancy. Studies suggest that maternal calcium consumption may affect bone resorption based on the toxicokinetics of lead during different stages of pregnancy.[23] During pregnancy, increased mobilization of lead may occur from bone stores that provide for fetal developmental needs.[24] Once absorbed, lead is then distributed to the blood, soft tissues, and bone. In blood, 99 percent of lead is bound to the erythrocyte, and the remaining 1 percent is free in the plasma to exchange with soft tissues (kidney, brain, liver, and bone marrow). More than 90 percent of lead in the body is stored in bone, and this might be mobilized in periods of high turnover such as pregnancy and lactation.[3]

During pregnancy, BLLs have been found to follow a U-shaped curve with a nadir between 12 and 20 weeks. The rate at which BLLs rise in late pregnancy varies by age (higher among older women) and is associated with calcium intake (lower in women taking calcium supplements).[24-26] After delivery, breastfeeding women experience a rise in lead levels that is attributed to increased lead absorption and increased lead mobilization from deeper storage (i.e., bone).[27]

Risk Factors

Risk factors for lead exposure include socioeconomic disadvantage; living in an area with lead industry; renovation or deterioration of older lead-painted houses; and previously living in a developing country where leaded gasoline is still used.[15,28] Socioeconomic factors associated with lead exposure include lower family income, older age of housing, and poorer nutritional status.

In a New York study of low-income pregnant women, foreign-born women were 8 times more likely to have elevated BLLs compared with women born in the United States.[29] The American

College of Obstetricians and Gynecologists (ACOG) and the CDC also list the following as risk factors for lead exposure in pregnant women: living near a point source of lead; working with lead or living with someone who does; using lead-glazed ceramic pottery; eating nonfood substances (e.g., pica); using complementary and alternative therapies; using imported cosmetics; engaging in high-risk hobbies; renovating old homes without lead hazards in place; consuming lead-contaminated drinking water; having a previous history of lead exposure; and living with someone diagnosed with an elevated BLL.[3,30]

Specific risk factors may vary in different communities. For example, exposures that occur through local water sources, lead pipes, and culturally-linked sources such as folk remedies, imported food and candy, and traditional pottery used for cooking[31,32] may influence lead exposure on the local level. The CDC recommends that state or local health departments provide information to clinicians on community-specific risk factors that can be used to determine the need for screening in pregnant women.[3] The CDC also recommends developing validated questionnaires at the community level since risk factors may vary significantly between communities.

Rationale for Screening/Screening Strategies

Current clinical guidelines and policies emphasize primary prevention of lead exposure. The rationale for screening pregnant women is to identify and reduce sources of lead exposure to reduce the risk of pregnancy complications and decrease the risk of lead exposure to the developing fetus and infant. Potential benefits for the pregnant women includes reduction of perinatal complications and prevention of general complications associated with adult lead exposure. As the prevalence of elevated BLLs has declined, there has been a shift from universal to targeted screening that incorporates primary prevention education.[33] Although several questionnaires have been developed to identify children at higher risk of lead exposure, none have been developed specifically for pregnant women. Venous blood sampling is the recommended screening strategy for pregnant women when lead exposure is suspected.[3,30]

Interventions/Treatment

The management of elevated BLLs in pregnant women varies depending on the confirmed BLL and other factors. Types of interventions include education and environmental strategies, nutritional interventions, and chelation therapy. Identifying the source of lead exposure is key to preventing ongoing or repeated exposure and remains the mainstay of treatment for lead exposure.

Educational and Environmental Interventions

Educational interventions address awareness of lead exposure pathways, hygiene, and household dust control measures to prevent ingestion of dust and soil. Environmental and household interventions include specialized cleaning, repairs, maintenance, soil abatement (e.g., removal and replacement), painting, and temporary containment of lead hazards. For pregnant women, additional education includes advice on strategies to decrease exposure to children who are

breastfeeding. The CDC suggests that breastfeeding be discouraged in women with BLLs of 40 µg/dL or greater; however, a 2012 policy statement from the American Academy of Pediatrics on breastfeeding does not include a recommendation to discourage breastfeeding for women with BLLs of 40 µg/dL or greater.[30,34] Current guidelines state that women with levels of 5 to 39 µg/dL may breastfeed, but infant BLLs should be measured, and breastfeeding should be discontinued if infant BLLs rise above 5 µg/dL.

Nutritional Interventions

The role of nutritional supplementation in reducing BLLs among pregnant women with elevated BLLs is unclear. Calcium, dietary iron, and other supplements are thought to decrease the intestinal absorption of lead. For lead, this theory is supported by epidemiologic studies that demonstrate an increased prevalence of iron deficiency among children with lead poisoning.[35,36] However, the association is inconsistent and evidence in iron-replete children is lacking. Nonetheless, calcium and vitamin C supplementation is often recommended for women with elevated BLLs.[30]

Chelation Therapy

In adults, chelation therapy may more rapidly decrease BLLs and relieve acute lead symptoms. Initiation of chelation is recommended for individuals with BLLs greater than 100 µg/dL and should also be considered for levels between 80 and 100 µg/dL in asymptomatic individuals and for symptomatic patients with BLLs between 50 and 80 µg/dL.[37] 2,3-dimercaptosuccinic acid (DMSA), succimer, and calcium disodium ethylenediaminetetraacetate (CaEDTA) are commonly used chelating agents. Because treatment with CaEDTA is associated with significant adverse effects, it must be administered in a hospital setting. The risks and benefits of chelation therapy have not been fully characterized among pregnant women. There are eight case reports of successful use of chelation therapy in pregnant women, all of whom had a BLL greater than 45 µg/dL.[38] The CDC recommends considering the use of chelation therapy when BLLs are greater than 45 µg/dL.[3] CaEDTA is considered pregnancy category B and DMSA is considered category C. Pregnant women undergoing chelation therapy should be managed by a clinician who is experienced with lead intoxication during pregnancy.

Current Clinical Practice/Recommendations of Other Groups

Current Clinical Practice

There are no available data regarding the prevalence of health care providers who screen pregnant women for elevated BLLs. The states of Minnesota[39] and New York[40] recommend routine risk factor assessment for lead exposure, as do ACOG and the CDC.[3,30] The CDC recommends targeted screening for elevated BLLs through venous blood sampling based on risk factors for lead exposure in individual communities.

The accuracy of screening questionnaires for predicting elevated BLLs in pregnant women is uncertain. No validated questionnaire exists for identifying pregnant women at high risk of lead exposure. The state of Minnesota[39] provides a 10-question risk assessment tool, and the state of

New York provides a five-question risk assessment tool.[3] In both screening programs, BLL testing is recommended if a woman answers yes to one or more questions. However, neither of these tools has been validated in pregnant populations. Venous blood sampling is the recommended screening method for maternal blood lead testing.[3,30]

Recommendations of Other Groups

Table 1 summarizes current screening recommendations from other groups. At the time of the previous USPSTF recommendation,[41] no other organizations had issued guidance about screening pregnant women for elevated BLLs. Since 2006, both the CDC and ACOG published recommendations stating that all pregnant women with risk factors for lead exposure should be screened for elevated BLLs using venous blood sampling and managed appropriately.[3,30]

Chapter 2. Methods

Key Questions and Analytic Framework

This systematic review followed a standard protocol consistent with USPSTF procedures.[42] The scope and Key Questions for this report were developed by Evidence-based Practice Center investigators in collaboration with the USPSTF and the Agency for Healthcare Research and Quality, and informed by evidence gaps identified from the prior review.[43] In addition, three Contextual Questions were requested by the USPSTF. Contextual Questions address topics important to the USPSTF recommendations, but are reviewed by summarizing evidence from key informative studies rather than by using systematic review methodology. Key Questions and Contextual Questions are listed below. Investigators created an analytic framework incorporating the Key Questions and outlining the patient populations, interventions, outcomes, and potential adverse effects (**Figure 1**). A research plan was externally reviewed and modified prior to finalization.

Key Questions

1a. Is there direct evidence that screening for elevated BLLs in asymptomatic pregnant women improves health outcomes (e.g., reduced cognitive problems in offspring, adverse perinatal outcomes, and adverse maternal outcomes)?
1b. Does the effectiveness of screening in asymptomatic pregnant women vary by gestational age?
2. What is the accuracy of questionnaires or clinical prediction tools that identify pregnant women who have elevated BLLs?
3. What are the harms of screening for elevated BLLs (with or without screening questionnaires) in asymptomatic pregnant women?
4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce BLLs and rates of gestational hypertension in asymptomatic pregnant women with elevated BLLs?
5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic pregnant women with elevated BLLs?
6. What are the harms of interventions in asymptomatic pregnant women with elevated BLLs?

Contextual Questions

1. What is the reliability of venous blood lead testing at various lead levels in pregnant women?
2. What is the association between reduced BLLs and improved health outcomes in asymptomatic pregnant women with elevated BLLs?
3. Are there valid risk prediction tools available that identify communities at highest risk for lead exposure that could be used in primary care practices to target screening efforts in pregnant women?

Key Question 1a focused on direct evidence of the effectiveness of screening for elevated BLLs for improving future health outcomes (e.g., reduced cognitive problems in offspring, reduced adverse perinatal outcomes, and reduced adverse maternal outcomes) compared with not screening. Key Question 1b evaluated the effectiveness of screening by gestational age. Because such direct evidence may be limited, the remainder of the analytic framework (Key Questions 2 through 6) evaluates the chain of indirect evidence needed to link screening with improved health outcomes. Links in the chain of indirect evidence include the accuracy of screening for identifying pregnant women with elevated BLLs, the effectiveness of interventions for treating identified elevated BLLs and reducing the incidence of complications, the association between improvements in intermediate outcomes and clinical health outcomes, and harms (including infant harms) associated with screening and treatments. Implicit in the indirect chain of evidence is that, to understand benefits and harms of screening, it is necessary but not sufficient to show that pregnant women with elevated BLLs can be identified. It is also necessary to show that there are effective treatments for women identified with elevated BLLs.

A separate report covers screening for elevated BLLs in children.

Search Strategies

We searched the Cochrane Central Register of Controlled Trials (through March 2017), Cochrane Database of Systematic Reviews (through April 2017), and Ovid MEDLINE (1946 through March 2017) for relevant studies. Search strategies are available in **Appendix A1**. Searches were supplemented by review of studies included in the prior USPSTF review and by review of reference lists of other relevant studies. Searches were updated through June 2018. Ongoing surveillance was conducted through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence. The last surveillance was conducted on December 5, 2018.

Study Selection

Two reviewers independently evaluated each study to determine eligibility for inclusion based on predetermined inclusion and exclusion criteria developed for each Key Question (**Appendix A2**).

Populations of asymptomatic pregnant women were included, regardless of risk for elevated BLLs. Studies of screening questionnaires were included for Key Question 2. Comparisons were screening versus no screening (Key Questions 1 and 3); a questionnaire versus a reference standard for elevated BLL (i.e., venous BLL) (Key Question 2); and treatment versus placebo, no treatment, or usual care (Key Questions 4 through 6). Key Question 4 evaluated effects of interventions for elevated BLLs on intermediate outcomes (i.e., BLLs). Clinical outcomes were gestational hypertension, cognitive outcomes in offspring, and perinatal and maternal outcomes. Other outcomes were statistical markers of diagnostic accuracy, harms of testing (e.g., anxiety, distress, pain, or discomfort related to testing), and morbidity attributed to treatment (e.g., renal toxicity, sensitivity reactions). Inclusion was restricted to English-language articles, and studies only published as abstracts were excluded. Studies of nonhuman subjects were also excluded,

and studies had to report original data. Studies conducted in countries with a "very high" Human Development Index[39] (i.e., considered applicable to U.S. populations and practice) were included; studies from countries with a "high" Human Development Index were included if no other studies were available. For Key Questions 4 through 6 (treatments for elevated BLLs), studies of asymptomatic pregnant women conducted in any country that evaluated interventions that focused on the individual or family (e.g., counseling, nutritional interventions, residential hazard control techniques, and chelation therapy) were included; studies of policies, laws, or community-based interventions focused on the primary prevention of lead exposure were excluded. Study designs were randomized, controlled trials (RCTs) of screening and treatments; controlled clinical trials on effects of therapies on health outcomes; controlled clinical trials and prospective cohort studies on harms of therapies; and studies on diagnostic accuracy of screening questionnaires or capillary sampling. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists included studies and **Appendix A5** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. For studies that did not report measures of diagnostic accuracy but provided the necessary data, we calculated RRs, likelihood ratios, positive and negative predictive values, and 95 percent CI or p-values. Two investigators independently applied criteria developed by the USPSTF[42] to rate the quality of each study as good, fair, or poor (**Appendix A6**) and resolved discrepancies by consensus.

Data Synthesis

Two independent reviewers assessed the 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 between studies, and directness of evidence (**Table 2**).[42] Due to the limited nature of the evidence, meta-analyses were not possible and we discuss the evidence qualitatively.

External Review

The draft report was reviewed by content experts (**Appendix A7**), USPSTF members, Agency for Healthcare Research and Quality Project Officers, and collaborative partners, and has been posted for public comment; it has been revised accordingly.

Response to Public Comment

A draft version of the evidence report was posted for public comment on the USPSTF Web site

from October 30, 2018 to December 3, 2018. No changes to the report were made in response to public comments.

Chapter 3. Results

The search and selection of articles are summarized in the literature flow diagram. Two reviewers independently evaluated 3,147 unique citations and 233 full-text articles based on predefined criteria. Two studies met inclusion criteria for this review (N=984). There were no studies of screening in pregnant women and no studies reported health outcomes of interventions to reduce BLLs in asymptomatic pregnant women. One study reported the diagnostic accuracy of a clinical questionnaire for pregnant women[45] and one study reported effects of a nutritional intervention during pregnancy.[26] **Appendix A3** shows the results of the literature search and selection process, **Appendix A4** lists the included studies, and **Appendix A5** lists the excluded full-text papers.

Key Question 1a. Is There Direct Evidence That Screening for Elevated BLLs in Asymptomatic Pregnant Women Improves Health Outcomes?
Key Question 1b. Does the Effectiveness of Screening in Asymptomatic Pregnant Women Vary by Gestational Age?

As in the prior USPSTF review, no studies directly evaluated clinical benefits and harms of screening pregnant women for elevated BLLs versus no screening, or how effectiveness of screening varies according to the gestational age at which screening is performed.

Key Question 2. What Is the Accuracy of Questionnaires or Clinical Prediction Tools That Identify Pregnant Women Who Have Elevated BLLs?

Summary

One fair-quality observational study[45] included in the prior USPSTF review evaluated the accuracy of a questionnaire for identifying pregnant women with elevated BLLs using four questions from the five-question 1991 CDC questionnaire designed for identifying children at risk (N=314) (**Appendixes B1 and C1**). Women with a positive response to at least one of the four questions were more likely to have elevated BLLs than those who answered negatively to all four questions (RR, 2.39 [95% CI, 1.17 to 4.89]; *P*=0.01). However, diagnostic accuracy was poor, with a sensitivity of 75.7 percent and specificity of 46.2 percent. The most predictive single item was a "home built before 1960."

Evidence

The prior USPSTF review described one fair-quality cross-sectional study (n=314) of pregnant women in Ohio on the accuracy of the CDC lead questionnaire for screening children for risk of

elevated BLLs that was carried forward to this update.[7] No additional studies on the accuracy of instruments for identifying pregnant women with elevated BLLs were identified.

The CDC questionnaire is a five-item survey developed in 1991 that aims to assess residential, household, and personal risk factors for lead exposure in children. Specific items include the age of current housing and the condition of the paint; presence of household members and children with a BLL of 15 µg/dL or greater; exposure through [parental] work or hobbies; and a home in close proximity to lead industry.

The included study of pregnant women used four of the five items in the CDC questionnaire and eliminated an item on point source lead exposure from industries not relevant to this community. This study also included three additional questions.[45] The questions were answered based on responses to a self-administered questionnaire of 19 items and a logistic model to identify the most predictive factors. The study enrolled low-income women attending public health clinics. The majority of participants were age 35 years or younger, and a third were adolescents. Ninety-four percent were Medicaid eligible, 66 percent were white, and 28 percent were black. Thirteen percent of the study population (39/314) had BLLs of 10 µ/dL or greater, with a mean BLL of 12.6 µg/dL.

Based on the threshold of at least one positive answer to one of four questions, 57 percent of the enrolled women qualified as at high risk for lead exposure and had a significantly increased risk for having an elevated BLL (defined as ≥10 µg/dL). The modified CDC questionnaire had a sensitivity of 75.7 percent and specificity of 46.2 percent. The positive likelihood ratio was 1.4 and the negative likelihood ratio was 0.52.

Using logistic regression, three specific questions were identified as predicting elevated BLLs more accurately: question 1 in the CDC set (home built before 1960 with peeling paint) and two questions added to the CDC questions (being a current smoker and consuming >10 servings of canned food per week). The sensitivity and specificity of these questions were 59.5 and 67.2 percent, respectively, for a house built before 1960; 56.8 and 63.0 percent, respectively, for being a current smoker; and 18.9 and 91.6 percent, respectively, for consuming more than 10 servings of canned food per week. Answering "yes" to any of these three questions resulted in a sensitivity of 75.7 percent and specificity of 41.2 percent. The positive likelihood ratio for this three-question set was 1.4 and the negative likelihood ratio was 0.26. The exact method for selecting these three questions was not clearly reported.

Limitations of this study include lack of clarity on how patients were selected, no comparison group, and answers to the evaluated questions (four CDC questions and an additional three questions) being derived from a separate 19-question set. It was not clear if the interpretation of the questionnaire results was done without knowledge of the BLLs. In addition, the derived three-item instrument was not tested in an independent cohort.

Key Question 3. What Are the Harms of Screening for Elevated BLLs (With or Without Screening Questionnaires) in Asymptomatic Pregnant Women?

As in the prior report, no studies directly compared the harms of screening pregnant women for elevated BLLs in a screened population versus an unscreened population.

Key Question 4. Do Counseling and Nutritional Interventions, Residential Lead Hazard Control Techniques, or Chelation Therapy Reduce BLLs and Rates of Gestational Hypertension in Asymptomatic Pregnant Women With Elevated BLLs?

Summary

One new fair-quality RCT of healthy pregnant women in Mexico (N=670) with mean baseline BLLs of approximately 4 µg/dL found that calcium supplementation was associated with reduced BLLs versus placebo (difference, 11%; p=0.004; levels in each group not reported). Effects were more pronounced in women with baseline BLLs of 5 µg/dL or greater (**Appendixes B2 and C2**).

Evidence

The prior USPSTF report did not include any studies on effects of interventions to lower BLLs in asymptomatic pregnant women.

One new fair-quality RCT (n=670) of healthy pregnant women at less than 14 weeks' gestation attending Mexican Social Security Institute prenatal clinics compared a nightly dose of 1,200 mg of calcium until delivery versus placebo.[26] Women were not required to have an elevated BLL at baseline (mean BLL, 3.8 vs. 4.1 µg/dL).

Calcium supplementation was associated with an 11-percent greater reduction in BLL than placebo (p=0.004; BLLs in each group not reported).[26] The difference was largest during the second trimester (14% difference; p<0.01; third trimester difference, 8%; p=0.11). Stratifying the analysis according to baseline BLL showed greater effects of calcium supplementation in patients with elevated BLL at baseline. In women with a BLL of 5 µg/dL or greater at baseline, calcium supplementation was associated with a 17-percent greater reduction in BLL versus placebo, compared with a 7-percent greater reduction in women with BLLs less than 5 µg/dL at baseline.

Limitations of this study include unclear methods of allocation (e.g., enrollment of any healthy pregnant woman, and not identifying an asymptomatic group with elevated BLLs at baseline), lack of blinding of patients or outcome assessors, and small population differences at baseline,

including dietary calcium intake.

Secondary analyses found a dose-response association between adherence with calcium supplementation and greater effects on blood lead concentration. Adherence of 50 percent or greater with calcium doses was associated with BLLs 15 percent lower than in the placebo group ($p<0.001$), taking more than 67 percent of calcium doses resulted in 19 percent lower levels ($p<0.001$), and taking more than 75 percent of calcium doses resulted in 24 percent lower levels ($p<0.001$). In women with an elevated BLL at baseline, the difference between calcium and placebo in BLL reduction among more adherent women was smaller (3%) and not statistically significant.

There were no studies of the effects of other interventions to reduce elevated BLLs in pregnant women.

Key Question 5. Do Counseling and Nutritional Interventions, Residential Lead Hazard Control Techniques, or Chelation Therapy Improve Health Outcomes in Asymptomatic Pregnant Women With Elevated BLLs?

As in the prior USPSTF report, no studies reported health outcomes following interventions to reduce BLLs in asymptomatic pregnant women.

Key Question 6. What Are the Harms of Interventions in Asymptomatic Pregnant Women With Elevated BLLs?

The prior USPSTF report found no studies on harms of interventions for lowering elevated BLLs in pregnant women. A subsequent RCT on effects of calcium supplementation on BLLs in pregnant women did not report harms (see Key Question 4).[26]

Contextual Questions

No studies were identified on the reliability of venous blood lead testing at various lead levels in pregnant women, the association between reduced BLLs and improved health outcomes in asymptomatic pregnant women with elevated blood lead concentrations, or accuracy of risk prediction tools in identifying communities at highest risk for lead exposure during pregnancy.

Chapter 4. Discussion

Summary of Review Findings

Evidence to determine the clinical benefits and harms of screening pregnant women for elevated BLLs versus not screening is extremely limited. No evidence directly evaluated the health benefits and harms of screening or the health outcomes or harms of interventions to treat elevated BLLs in pregnant women. Important gaps in the indirect chain of evidence include the lack of an accurate questionnaire to identify women at risk of elevated BLLs and the lack of interventions shown to be effective for reducing BLLs or improving clinical outcomes in women with elevated BLLs. **Table 2** summarizes the evidence reviewed for this update.

One observational study of a questionnaire designed to evaluate lead exposure in children modified for use in pregnant women found poor diagnostic accuracy, with noninformative likelihood ratios.[45] No studies of questionnaires specifically designed to assess lead exposure in pregnant women have been published. Accurate risk assessment instruments would facilitate improved targeted screening strategies.

Evidence on the effectiveness of nutritional interventions for pregnant women with elevated BLLs was limited to one fair-quality trial of calcium supplementation that showed a modest (~11%) reduction in BLLs versus placebo.[26] There were no studies of chelation therapy or residential interventions in pregnant women. There were no available studies to address the remaining Key Questions or the Contextual Questions. At present, no studies address when to screen during pregnancy or effects of interventions for lowering elevated BLLs in pregnancy on clinical outcomes.

Contextual Issues

Evidence on the intraindividual and interlaboratory reliability of BLL testing would be helpful for interpreting testing results, informing technical standards, and informing testing protocols and strategies. No risk prediction tools were identified that could be used in primary care practices to target screening of pregnant women living in communities at high risk for lead exposure.

Generalizability

The findings from the two studies included in this report are not generalizable. The study of the CDC questionnaire originally developed to assess risk in children had poor diagnostic accuracy in a pregnant population.[45] The single study of calcium supplementation to reduce BLLs was conducted in low- to moderate-income women in Mexico, with a high proportion of enrolled women regularly using lead-glazed ceramics for cooking meals (35%), and did not limit enrollment to women with asymptomatic elevated BLLs at baseline.[26] It is unclear whether this intervention would have similar effectiveness in a U.S. population given potential differences in

environments and nutrition. However, identifying culturally linked sources of lead exposure in U.S. pregnant populations could have an effect on risk.

Limitations

The major limitation of this review was the overall lack of evidence to address all Key Questions. Other limitations of this review include restriction to English-language articles, which could result in language bias. However, we did not identify non–English-language studies in our searches that otherwise met inclusion criteria. Despite searching for updated data, the available studies may represent outdated risk factors and treatments that are not as relevant in U.S. primary care settings. We included nonrandomized studies to evaluate the effectiveness of interventions for elevated BLLs. Such studies are more susceptible to confounding and bias, as reflected in the quality ratings we assigned. We did not attempt meta-analysis, given the lack of studies, and were unable to formally assess for publication bias due to the small number of studies.

Evidence for Priority Populations, Particularly Racial/Ethnic Minorities

Elevated BLLs primarily affect socioeconomically disadvantaged and minority populations. Different sources of lead exposure than have been previously considered are emerging in these populations, yet research in these groups remains limited.[31,32,46] Exposures related to community water sources, lead plumbing in schools, and factory emissions affecting neighborhood soil quality are just some of the emerging factors that are not widely incorporated into current screening questionnaires. Additional research is warranted to validate these potential associations in specific geographic locations and among at-risk populations, as the effect of these exposures on blood lead concentration in pregnant women is not well established. Culturally linked sources of lead poisoning such as imported candy, pottery, and cosmetics, specific to subpopulations living in the United States, may also provide information about risk in minority populations. For example, traditional folk remedies and imported digestive remedies that may contain high levels of lead are not monitored by the U.S. Food and Drug Administration, and are more common in Hispanic and Asian populations.[31,32] Nontraditional sources of lead exposure that come from items manufactured in other countries, such as leaded pots and pans, cosmetics, medicines, ceramics, and leaded crystal may also pose additional risk since little regulation exists to monitor, identify, and control these nonpaint exposures. Pregnant women who are exposed to these lesser recognized sources of lead exposure may also live in housing that has higher risk for lead exposure. The potential for multiple sources of risk associated with minority communities suggests the need for more focused strategies to address population-specific risks.

Future Research

Elevated BLLs are associated with serious health consequences. Additional research is urgently needed to better inform decisions regarding screening in pregnant women, including evaluations of newer testing methods and techniques. Development of questionnaires that incorporate current

risk factors for elevated BLLs with validation in contemporary populations of pregnant women in the United States is necessary. Ideally, randomized trials would recruit pregnant women from a range of racial/ethnic and socioeconomic strata, and evaluate the effects of screening on improving health outcomes as well as short- and long-term harms. These studies should address risk factors in pregnant women including occupational exposures, be tested in contemporary cohorts, and be validated in independent cohorts. An initial step would include conducting RCTs that evaluate effective interventions for lowering BLLs in pregnant women and that report intermediate and health outcomes, outcomes in newborns, and harms in both women and infants. Research on the intraindividual and interlaboratory reliability of BLL testing would be helpful for informing testing strategies.

Conclusions

Evidence on the benefits and harms of screening pregnant women for elevated BLLs is extremely limited, with no evidence on effects of screening or interventions for lowering elevated BLLs in pregnant women on health outcomes.

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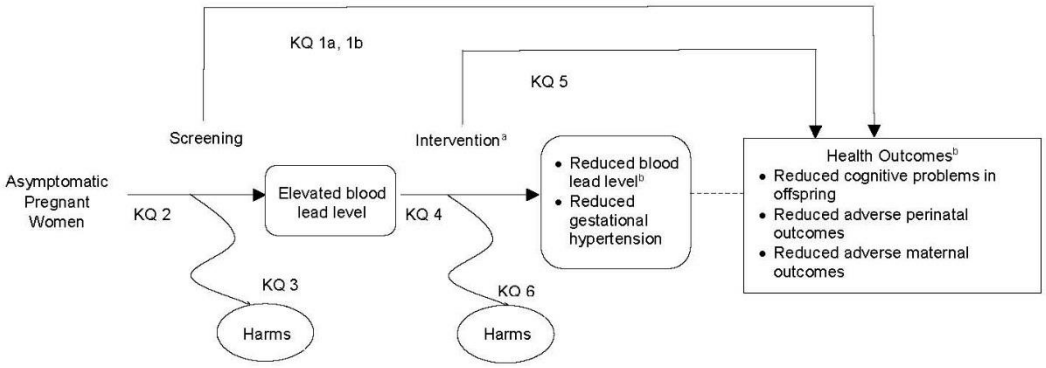
Figure 1. Analytic Framework and Key Questions



Abbreviation: KQ=key question.

[a] Interventions include counseling families to reduce lead exposure, nutritional interventions, residential hazard control techniques, and chelation therapy.
[b] Included outcomes measured in family members (e.g., siblings, pregnant women in the same household) subsequently identified as having elevated blood lead levels after the index family member was found to have an elevated blood lead level during screening.

Table 1. Current Recommendations From Other Organizations

Organization, Year	Screening Recommendation for Pregnant Women
American Academy of Family Physicians (AAFP), 2006	The AAFP recommends against routine screening for elevated blood lead levels in asymptomatic pregnant women.
Centers for Disease Control and Prevention (CDC), 2010	Universal screening is not recommended. Blood lead testing is recommended for pregnant and lactating women with one or more important risk factors for lead exposure and increased blood lead levels: • Recent immigration (from an area where ambient lead contamination is high) • Living near point source of lead (e.g., lead mines, smelters, battery recycling plants, home remodeling) • Pica (i.e., compulsive eating of nonfood items) • Occupational exposures (e.g., painters, women exposed to batteries or radiators, women living with someone who works in lead industry) • Environmental exposures (e.g., lead-contaminated soil, water, or food) • Use of lead-containing cosmetics • Cooking/storing in lead-glazed pottery • Use of herbal/alternative medicines (e.g., some Chinese herbs, Ayurvedic medicines)
American College of Obstetricians and Gynecologists (ACOG), 2012	Blood lead testing of all pregnant women in the United States is not recommended. Obstetric health care providers should consider the possibility of lead exposure in individual pregnant women by evaluating risk factors for exposure as part of a comprehensive health risk assessment and perform blood lead testing if a single risk factor is identified. Assessment of lead exposure should take place at the earliest contact with the pregnant patient. The ACOG guidelines refer to CDC recommendations regarding risk factors for exposure.

Abbreviations: AAFP=American Academy of Family Physicians; ACOG=American College of Obstetrics and Gynecologists; CDC=Centers for Disease Control and Prevention.

Table 2. Summary of Evidence

Key Question*	Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality†
1a, 1b	No studies	0	No studies	No studies	No studies	No studies	No studies
2	No studies	1 observational study	Questionnaire not designed specifically for pregnant women; used a higher BLL threshold than the CDC threshold of <5 µg/dL. No intention-to-treat analysis. Larger set of investigator-designed questions not reported.	Not applicable	One study conducted in a single setting in Ohio from 1990 to 1992.	One study used 4/5 questions from the CDC questionnaire for children and showed that women with a positive response to at least 1 of the 4 questions were more likely to have elevated BLLs than those who answered negatively to all 4 questions (RR, 2.39 [95% CI, 1.17 to 4.89]; p=0.01). The CDC questionnaire had a sensitivity of 75.7% and a sensitivity of 46.2%. The most predictive single item was "home built before 1960."	Fair
3	No studies	0	No studies	No studies	No studies	No studies	No studies
4	No studies	1 RCT	Enrolled any healthy pregnant woman; did not identify an asymptomatic group with elevated BLL at baseline. Limited subgroup analyses of women with elevated BLLs were available; some findings conflict with overall study results.	Not applicable	One study conducted in Mexico city; high proportion of participants regularly using lead-glazed ceramics for cooking meals (35%).	One RCT of healthy pregnant women (mean baseline BLL, ~4 µg/dL) in Mexico found that calcium supplementation was associated with reduced BLLs vs. placebo (difference, 11%; p=0.004; levels in each group not reported). In women with baseline BLL ≥5 µg/dL, calcium supplementation was associated with a 17% greater reduction in BLL vs. placebo, compared with a 7% greater reduction in those with lead levels <5 µg/dL at baseline.	Fair
5	No studies	0	No studies	No studies	No studies	No studies	No studies
6	No studies	0	No studies	No studies	No studies	No studies	No studies

* Key Question 1a. Is there direct evidence that screening for elevated BLLs in asymptomatic pregnant women improves health outcomes?
Key Question 1b. Does the effectiveness of screening in asymptomatic pregnant women vary by gestational age?
Key Question 2. What is the accuracy of questionnaires or clinical prediction tools that identify pregnant women who have elevated BLLs?
Key Question 3. What are the harms of screening for elevated BLLs in asymptomatic pregnant women?
Key Question 4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce BLLs and rates of gestational hypertension in asymptomatic pregnant women with elevated BLLs?
Key Question 5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic pregnant women with elevated BLLs?

Table 2. Summary of Evidence

Key Question 6. What are the harms of interventions in asymptomatic pregnant women with elevated BLLs?
† "Overall quality" is based on new evidence identified for this update.

Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control; RCT=randomized, controlled trial; RR=relative risk; U.S.=United States; USPSTF=U.S. Preventive Services Task Force.

Screening

Database: Ovid MEDLINE (R) 1946 to March Week 2, 2017

1 exp Lead/
2 exp Lead Poisoning/
3 1 or 2
4 exp mass screening/
5 exp "Surveys and Questionnaires"/
6 exp risk/
7 4 or 5 or 6
8 3 and 7
9 limit 8 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
10 exp pregnancy/
11 exp pregnancy complications/
12 exp fetus/
13 exp prenatal care/
14 exp Prenatal Exposure Delayed Effects/
15 exp Prenatal Injuries/
16 exp "Embryonic and Fetal Development"/
17 10 or 11 or 12 or 13 or 14 or 15 or 16
18 8 and 17
19 9 or 18
20 ((test* or assay* or sampl* or detect* or surveil* or screen* or questionnair* or survey* or (risk* adj3 (assess* or predict* or determin* or measur* or calculat*))) adj5 (lead or pb) adj7 (infan* or fetus or fetal* or prenat* or pregnan* or baby or babies or child* or toddler*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
21 19 or 20
22 exp diagnosis/
23 3 and 22
24 17 and 23
25 limit 24 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
26 24 or 25
27 ((test* or assay* or sampl* or detect* or surveil* or screen* or questionnair* or survey* or (risk* adj3 (assess* or predict* or determin* or measur* or calculat*))) adj5 (lead or pb) adj7 (infan* or fetus or fetal* or prenat* or pregnan* or baby or babies or child* or toddler*)).mp.
28 17 and 27
29 limit 27 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
30 28 or 29
31 26 or 30
32 21 or 31
33 limit 32 to humans
34 limit 33 to english language
35 limit 33 to abstracts
36 34 or 35

37 remove duplicates from 36
38 limit 37 to yr="2002 -Current"
39 limit 37 to yr="1902-2001"

Treatment

Database: Ovid MEDLINE (R) 1946 to March Week 2, 2017

1 exp Lead Poisoning/dh, dt, nu, su, th [Diet Therapy, Drug Therapy, Nursing, Surgery, Therapy]
2 exp Lead/ae, to [Adverse Effects, Toxicity]
3 ((treat* or therap* or interven* or counsel* or antidot* or remed* or cure or cured or curing or cures or chelat*) adj7 (lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*))).mp.
4 exp Lead Poisoning/ or exp Lead/
5 3 and 4
6 1 or 5
7 exp Therapeutics/
8 (th or dt or dh).fs.
9 exp counseling/
10 exp health education/
11 7 or 8 or 9 or 10
12 4 and 11
13 6 or 12
14 limit 13 to humans
15 limit 14 to english language
16 limit 14 to abstracts
17 15 or 16
18 remove duplicates from 17
19 limit 18 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
20 exp Pregnancy/
21 exp Pregnancy Complications/
22 exp fetus/
23 exp prenatal care/
24 exp Prenatal Exposure Delayed Effects/
25 exp Prenatal Injuries/
26 exp "Embryonic and Fetal Development"/
27 20 or 21 or 22 or 23 or 24 or 25 or 26
28 14 and 27
29 19 or 28
30 18 not 29

Screening and Treatment

Database: Cochrane Database of Systematic Reviews 2005 to April 19, 2017

1 ((treat* or therap* or interven* or antidot* or remed* or cure or cured or curing or cures or chelat*) adj7 (lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*))).mp.

2 ((screen* or ((routin* or annual* or yearly) adj5 (test* or diagnos* or assay* or exam*))) adj7 ((lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*)))).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 or 2

Database: EBM Reviews - Cochrane Central Register of Controlled Trials through March 2017

1 ((treat* or therap* or interven* or antidot* or remed* or cure or cured or curing or cures or chelat*) adj7 (lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*))).mp.
2 ((screen* or ((routin* or annual* or yearly) adj5 (test* or diagnos* or assay* or exam*))) adj7 ((lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*)
3 1 or 2

Appendix A2. Inclusion and Exclusion Criteria

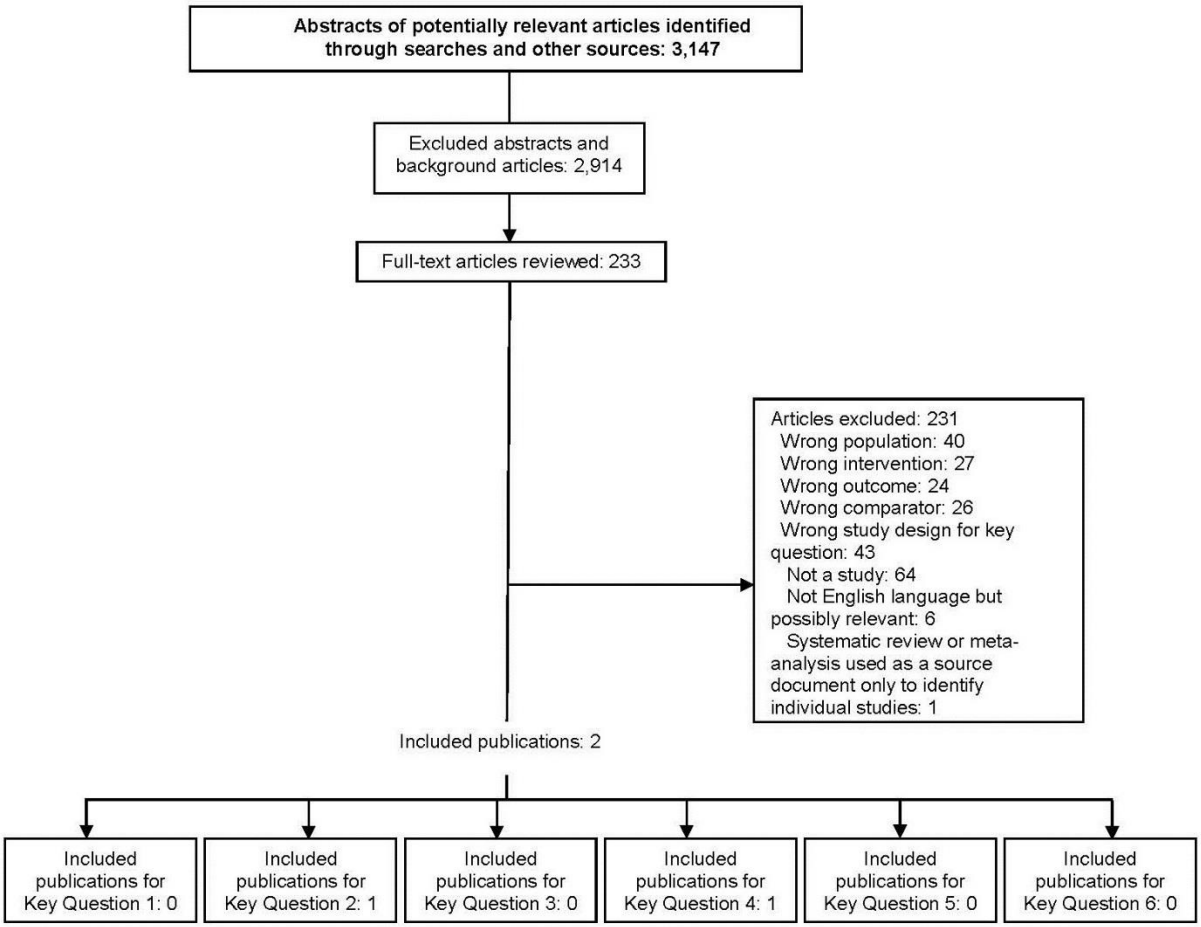
	Included	Excluded
Populations	**All KQs:** Asymptomatic pregnant women **KQ 2:** Asymptomatic pregnant women and asymptomatic nonpregnant adults	All other populations
Screening tests	**KQs 1, 3:** Measurement of venous blood lead level, with or without screening questionnaires or risk prediction tools **KQ 2:** Questionnaires or risk prediction tools that identify adults who are more or less likely to have elevated blood lead levels (defined by a minimum threshold of 5 µg/dL)	All other screening tests, including point-of-care blood lead level assays that are not approved by the U.S. Food and Drug Administration and are not available in the United States
Interventions	**KQs 4–6:** Studies assessing interventions aimed at reducing blood lead levels, including one or more of the following: counseling families to reduce lead exposure, nutritional interventions, residential hazard control techniques, and chelation therapy	Policies, laws, or community-based interventions focused on the primary prevention of lead exposure
Comparisons	**KQs 1, 3:** Screened vs. nonscreened groups **KQ 1b:** Women screened early vs. later in pregnancy **KQ 2:** Measurement of blood lead levels using venous sampling **KQs 4–6:** Treatment vs. placebo, inactive control, or no treatment	All other comparisons, including head-to-head comparisons of two different interventions
Outcomes	**KQs 1, 5:** Validated measures of cognitive and neurobehavioral outcomes in offspring, including assessment of IQ or development*; rates of adverse perinatal outcomes (e.g., premature birth, low birth weight); rates of adverse maternal outcomes (e.g., chronic kidney disease, cognitive decline, mortality) **KQ 2:** Sensitivity, specificity, discrimination, and calibration **KQ 3:** Anxiety or distress; false-positive results or blood lead levels <5 µg/dL, leading to repeat testing, unnecessary treatment, or both **KQ 4:** Reduction in blood lead level*; reduction in gestational hypertension **KQ 5:** Reduction in adverse perinatal outcomes and cognitive problems in offspring **KQ 6:** Anxiety or distress; inconvenience associated with intervention (e.g., need for temporary housing due to home lead abatement, work absenteeism associated with followup testing and treatment); morbidity attributed to chelation therapy (e.g., renal toxicity, sensitivity reactions); adverse effects of nutritional supplements (e.g., nausea)	All other outcomes, including measures of household lead dust
Study designs	**KQs 1, 4:** RCTs **KQ 2:** Observational studies assessing the accuracy of screening questionnaires for predicting elevated blood lead levels **KQ 3:** RCTs, CCTs, or prospective cohort studies **KQ 5:** RCTs and CCTs **KQ 6:** RCTs, CCTs, prospective cohort studies with a concurrent control group, and case-control studies	Systematic reviews†, case series, case reports, or comparison with historical controls
Quality	Studies rated good or fair quality	Studies rated poor quality
Clinical Setting	**All KQs:** Settings applicable to U.S. primary care settings where women receive prenatal care, including obstetrics/gynecology outpatient and family medicine clinics **KQs 4–6:** The above plus settings referable from primary care settings	All other settings, including community health case-finding (e.g., blood lead level monitoring after known environmental exposure)
Country Setting	**KQs 1–3:** Research conducted in the United States or in populations similar to U.S. populations with services and interventions applicable to U.S. practice (i.e., countries with a United Nations Human Development Index of "Very High" or "High" when no evidence exists from "Very High" countries) **KQs 4–6:** Any country	**KQs 1–3:** Research not relevant to the United States or conducted in countries with a Human Development Index other than "Very High"
Language	English language	Languages other than English

Appendix A2. Inclusion and Exclusion Criteria

* We included outcomes measured in family members (e.g. siblings, pregnant women in the same household) subsequently identified as having elevated blood lead levels after the index family member was found to have an elevated blood lead level during screening.
† Systematic reviews are excluded from the evidence review. However, we conducted a separate search to identify relevant systematic reviews published since the last review to ensure that our database searches captured all relevant studies.

Abbreviations: CCT=controlled clinical trial; IQ=intelligence quotient; KQ=Key Question; RCT=randomized, controlled trial; U.S.=United States.

Appendix A3. Literature Flow Diagram



Appendix A4. Included Studies

1. Ettinger AS, Lamadrid-Figueroa H, Tellez-Rojo MM, et al. Effect of calcium supplementation on blood lead levels in pregnancy: a randomized placebo-controlled trial. Environ Health Perspect. 2009;117(1):26-31. doi: 10.1289/ehp.11868. PMID: 19165383.

2. Stefanak MA, Bourguet CC, Benzies-Styka T. Use of the Centers for Disease Control and Prevention childhood lead poisoning risk questionnaire to predict blood lead elevations in pregnant women. Obstet Gynecol. 1996;87(2):209-12. doi: 10.1016/0029-7844(95)00397-5. PMID: 8559525.

Appendix A5. Excluded Studies

1. Abendroth K. [Excellent effect of sodium-citrate-EDTA-combination therapy in severe lead poisoning during pregnancy]. Dtsch Gesundheitsw. 1971;26(45):2130-1. PMID: 5004297. Excluded: Not English but possibly relevant.
2. Alfaro C, Vincelet C, Lombrail P, et al. [Evaluation of the screening strategy for lead poisoning in 1-to-3-year-old children monitored in maternal-child welfare centers in Paris]. Rev Epidemiol Sante Publique. 1993;41(6):473-9. PMID: 8296033. Excluded: Not English but possibly relevant.
3. Alpert JJ. Screening for lead poisoning. Pediatrics. 1970;45(4):721-2. PMID: 5438185. Excluded: Not a study.
4. Altmann P, Maruna RF, Maruna H, et al. [Lead detoxication effect of a combined calcium phosphate and ascorbic acid therapy in pregnant women with increased lead burden (author's transl)]. Wien Med Wochenschr. 1981;131(12):311-4. PMID: 7293190. Excluded: Not English but possibly relevant.
5. Anderson MK, Amrich M, Decker KL, et al. Using state lead poisoning surveillance system data to assess false positive results of capillary testing. Matern Child Health J. 2007;11(6):603-10. doi: 10.1007/s10995-007-0196-1. PMID: 17340181. Excluded: Wrong study design for Key Question.
6. Andrews KW, Savitz DA, Hertz-Picciotto I. Prenatal lead exposure in relation to gestational age and birth weight: a review of epidemiologic studies. Am J Ind Med. 1994;26(1):13-32. PMID: 8074121. Excluded: Not a study.
7. Anonymous. The Treatment of Lead-exposed Children (TLC) trial: design and recruitment for a study of the effect of oral chelation on growth and development in toddlers. Paediatr Perinat Epidemiol. 1998;12(3):313-33. PMID: 9690266. Excluded: Not a study.
8. Anonymous. Safety and efficacy of succimer in toddlers with blood lead levels of 20-44 microg/dL. Treatment of Lead-Exposed Children (TLC) Trial Group. Pediatr Res. 2000;48(5):593-9. doi: 10.1203/00006450-200011000-00007. PMID: 11044477. Excluded: Wrong population.
9. Arbuckle TE, Liang CL, Morisset AS, et al. Maternal and fetal exposure to cadmium, lead, manganese and mercury: The MIREC study. Chemosphere. 2016;163:270-82. doi: 10.1016/j.chemosphere.2016.08.023. PMID: 27540762. Excluded: Wrong study design for Key Question.
10. Aschengrau A, Beiser A, Bellinger D, et al. The impact of soil lead abatement on urban children's blood lead levels: phase II results from the Boston Lead-In-Soil Demonstration Project. Environ Res. 1994;67(2):125-48. doi: 10.1006/enrs.1994.1069. PMID: 7982389. Excluded: Wrong intervention.
11. Aschengrau A, Hardy S, Mackey P, et al. The impact of low technology lead hazard reduction activities among children with mildly elevated blood lead levels. Environ Res. 1998;79(1):41-50. doi: 10.1006/enrs.1998.3858. PMID: 9756679. Excluded: Wrong outcome.
12. Awasthi S, Awasthi R, Srivastav RC. Maternal blood lead level and outcomes of pregnancy in Lucknow, North India. Indian Pediatr. 2002;39(9):855-60. PMID: 12368533. Excluded: Wrong study design for Key Question.
13. Baghurst PA, Robertson EF, McMichael AJ, et al. The Port Pirie Cohort Study: lead effects on pregnancy outcome and early childhood development. Neurotoxicology. 1987;8(3):395-401. PMID: 2443882. Excluded: Wrong study design for Key Question.
14. Bajorek MM. Screening children for lead poisoning. West J Med. 1995;163(1):64. PMID: 7667984. Excluded: Not a study.

15. Baloh R, Sturm R, Green B, et al. Neuropsychological effects of chronic asymptomatic increased lead absorption. A controlled study. Arch Neurol. 1975;32(5):326-30. PMID: 1137507. Excluded: Wrong study design for Key Question.
16. Bartsocas CS, Grunt JA, Boylen GW, Jr., et al. Oral D-penicillamine and intramuscular BAL+EDTA in the treatment of lead accumulation. Acta Paediatr Scand. 1971;60(5):553-8. PMID: 4999890. Excluded: Wrong study design for Key Question.
17. Batagol R. Australian Drug Evaluation Committee: Medicines in pregnancy-An Australian categorisation of risk of drug use in pregnancy, 4th. Australian Government Publishing Service, Canberra, Australia; 1999. Excluded: Not a study.
18. Beck RB, Rosenbaum KN, Byers PH, et al. Ultrastructural findings in fetal penicillamine syndrome. Presentation and abstract, March of Dimes 14th Annual Birth Defects Conference, San Diego, CA; 1981. Excluded: Wrong outcome.
19. Bellinger D. Prenatal/early postnatal exposure to lead and risk of developmental impairment. Birth Defects Orig Artic Ser. 1989;25(6):73-97. PMID: 2481518. Excluded: Not a study.
20. Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics. 1992;90(6):855-61. PMID: 1437425. Excluded: Wrong study design for Key Question.
21. Benson PF, Chisolm JJ, Jr. A reliable qualitative urine coproporphyrin test for lead intoxication in young children. J Pediatr. 1960;56:759-67. PMID: 13799015. Excluded: Wrong intervention.
22. Besunder JB, Super DM, Anderson RL. Comparison of dimercaptosuccinic acid and calcium disodium ethylenediaminetetraacetic acid versus dimercaptopropanol and ethylenediaminetetraacetic acid in children with lead poisoning. J Pediatr. 1997;130(6):966-71. PMID: 9202621. Excluded: Wrong comparator.
23. Bhattacharya A, Shukla R, Auyang ED, et al. Effect of succimer chelation therapy on postural balance and gait outcomes in children with early exposure to environmental lead. Neurotoxicology. 2007;28(3):686-95. doi: 10.1016/j.neuro.2007.03.007. PMID: 17499360. Excluded: Wrong outcome.
24. Binns HJ, Kim D, Campbell C. Targeted screening for elevated blood lead levels: populations at high risk. Pediatrics. 2001;108(6):1364-6. PMID: 11731660. Excluded: Not a study.
25. Binns HJ, LeBailly SA, Fingar AR, et al. Evaluation of risk assessment questions used to target blood lead screening in Illinois. Pediatrics. 1999;103(1):100-6. PMID: 9917446. Excluded: Wrong comparator.
26. Binns HJ, LeBailly SA, Poncher J, et al. Is there lead in the suburbs? Risk assessment in Chicago suburban pediatric practices. Pediatric Practice Research Group. Pediatrics. 1994;93(2):164-71. PMID: 8121725. Excluded: Wrong comparator.
27. Blanksma LA, Sachs HK, Murray EF, et al. Failure of the urinary delta-aminolevulinic acid test to detect pediatric lead poisoning. Am J Clin Pathol. 1970;53(6):956-62. PMID: 5515391. Excluded: Wrong intervention.
28. Blumenthal S, Davidow B, Harris D, et al. A comparison between two diagnostic tests for lead poisoning. Am J Public Health. 1972;62(8):1060-4. PMID: 5046445. Excluded: Wrong intervention.
29. Boreland F, Lesjak M, Lyle D. Evaluation of home lead remediation in an Australian mining community. Sci Total Environ. 2009;408(2):202-8. doi: 10.1016/j.scitotenv.2009.10.013. PMID: 19853886. Excluded: Wrong population.
30. Borja-Aburto VH, Hertz-Picciotto I, Rojas Lopez M, et al. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol. 1999;150(6):590-7. PMID: 10489998. Excluded: Wrong study design for Key Question.

Appendix A5. Excluded Studies

31. Bossarte RM, Brown MJ, Jones RL. Blood lead misclassification due to defective LeadCare blood lead testing equipment. Clin Chem. 2007;53(5):994-5. doi: 10.1373/clinchem.2006.082404. PMID: 17468412. Excluded: Not a study.

32. Bouhouch RR, El-Fadeli S, Andersson M, et al. Effects of wheat-flour biscuits fortified with iron and EDTA, alone and in combination, on blood lead concentration, iron status, and cognition in children: a double-blind randomized controlled trial. Am J Clin Nutr. 2016;104(5):1318-26. doi: 10.3945/ajcn.115.129346. PMID: 27733396. Excluded: Wrong intervention.

33. Bradberry S, Vale A. Dimercaptosuccinic acid (succimer; DMSA) in inorganic lead poisoning. Clin Toxicol. 2009;47(7):617-31. doi: 10.1080/15563650903174828. PMID: 19663612. Excluded: Not a study.

34. Bradley JE, Baumgartner RJ. Subsequent mental development of children with lead encephalopathy, as related to type of treatment. J Pediatr. 1958;53(3):311-5. PMID: 13576382. Excluded: Wrong population.

35. Braun JM, Hornung R, Chen A, et al. Effect of Residential Lead-Hazard Interventions on Childhood Blood Lead Concentrations and Neurobehavioral Outcomes: A Randomized Clinical Trial. JAMA Pediatr. 2018;172(10):934-42. doi: 10.1001/jamapediatrics.2018.2382. PMID: 30178064. Excluded: Wrong intervention.

36. Briss PA, Rosenblum LS. Screening strategies for lead poisoning. JAMA. 1993;270(21):2556; author reply -7. PMID: 8230637. Excluded: Not a study.

37. Bronson MA, Renier CM. The location of residence as a basis for childhood lead poisoning screening programs. Am J Public Health. 1995;85(4):589-90. PMID: 7702132. Excluded: Not a study.

38. Browder A, Joselow M, Foster J. Screening for detection of childhood lead poisoning in Newark. J Med Soc N J. 1974;71(1):45-8. PMID: 4520978. Excluded: Not a study.

39. Browder A, Joselow M, Louria DB, et al. Evaluation of screening programs for childhood lead poisoning by analysis of hospital admissions. Am J Public Health. 1974;64(9):914-5. PMID: 4425003. Excluded: Not a study.

40. Brown MJ, McLaine P, Dixon S, et al. A randomized, community-based trial of home visiting to reduce blood lead levels in children. Pediatrics. 2006;117(1):147-53. doi: 10.1542/peds.2004-2880. PMID: 16396872. Excluded: Wrong population.

41. Brown MJ, Meehan PJ. Health effects of blood lead levels lower than 10 mg/dl in children. Am J Public Health. 2004;94(1):8-9; author reply PMID: 14713682. Excluded: Not a study.

42. Brown SJ. Treatment and prevention of childhood lead poisoning: new approach. Wis Med J. 1973;72(8):175-7. PMID: 4199056. Excluded: Not a study.

43. Burke BL, Jr. Lead poisoning treatment. J Pediatr. 2006;149(3):428; author reply -9. doi: 10.1016/j.jpeds.2006.02.030. PMID: 16939771. Excluded: Not a study.

44. Burns MS, Shah LH, Marquez ER, et al. Efforts to identify at-risk children for blood lead screening in pediatric clinics--Clark County, Nevada. Clin Pediatr 2012;51(11):1048-55. doi: 10.1177/0009922812458352. PMID: 22935218. Excluded: Wrong outcome.

45. Byers RK, Maloof C. Edathamil calcium-disodium (versenate) in treatment of lead poisoning in children. AMA Am J Dis Child. 1954;87(5):559-69. PMID: 13157613. Excluded: Wrong study design for Key Question.

46. Campbell C, Gracely E, Tran M, et al. Primary prevention of lead exposure--blood lead results at age two years. Int J Environ Res Public Health. 2012;9(4):1216-26. doi: 10.3390/ijerph9041216. PMID: 22690192. Excluded: Wrong outcome.

47. Campbell C, Tran M, Gracely E, et al. Primary prevention of lead exposure: the Philadelphia lead safe homes study. Public Health Rep. 2011;126 Suppl 1:76-88. PMID: 21563715. Excluded: Wrong population.

48. Campbell JR, Schaffer SJ. Predicting the outcome of the CaNa2EDTA challenge test in children with moderately elevated blood lead levels. Environ Health Perspect. 1999;107(6):437-40. PMID: 10339443. Excluded: Wrong intervention.

49. Carpenter JW. Pediatric lead level screening. Alaska Med. 1993;35(2):173. PMID: 8238773. Excluded: Wrong study design for Key Question.

50. Casey R, Wiley C, Rutstein R, et al. Prevalence of lead poisoning in an urban cohort of infants with high socioeconomic status. Clin Pediatr. 1994;33(8):480-4. PMID: 7955789. Excluded: Wrong population.

51. Casey R, Wiley C, Rutstein R, et al. Longitudinal assessment for lead poisoning. Clin Pediatr 1996;35(2):58-61. PMID: 8775476. Excluded: Wrong intervention.

52. Centers for Disease Control and Prevention. Blood lead levels among children in a managed-care organization--California, October 1992-March 1993. MMWR. 1995;44(34):627-9, 35. PMID: 7643848. Excluded: Wrong outcome.

53. Chen A, Rhoads GG, Cai B, et al. The effect of chelation on blood pressure in lead-exposed children: a randomized study. Environ Health Perspect. 2006;114(4):579-83. PMID: 16581549. Excluded: Wrong outcome.

54. Chen A, Schwarz D, Radcliffe J, et al. Maternal IQ, child IQ, behavior, and achievement in urban 5-7 year olds. Pediatr Res. 2006;59(3):471-7. doi: 10.1203/01.pdr.0000199910.16681.f0. PMID: 16492992. Excluded: Wrong study design for Key Question.

55. Chisolm JJ, Jr. Chronic lead intoxication in children. Dev Med Child Neurol. 1965;7(5):529-36. PMID: 4956085. Excluded: Not a study.

56. Chisolm JJ, Jr. The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. J Pediatr. 1968;73(1):1-38. PMID: 4969284. Excluded: Not a study.

57. Chisolm JJ. Screening techniques for undue lead exposure in children: biological and practical considerations. J Pediatr. 1971;79(5):719-25. PMID: 4941955. Excluded: Not a study.

58. Chisolm JJ, Jr. Treatment of lead poisoning. Mod Treat. 1971;8(3):593-611. PMID: 5001054. Excluded: Not a study.

59. Chisolm JJ, Jr. Screening for lead poisoning in children. Pediatrics. 1973;51(2):280-3. PMID: 4695862. Excluded: Not a study.

60. Chisolm JJ, Jr. Management of increased lead absorption and lead poisoning in children. N Engl J Med. 1973;289(19):1016-8. doi: 10.1056/NEJM197311082891906. PMID: 4742201. Excluded: Not a study.

61. Chisolm JJ, Jr. Chelation therapy in children with subclinical plumbism. Pediatrics. 1974;53(3):441-3. PMID: 4205583. Excluded: Not a study.

62. Chisolm JJ, Jr. BAL, EDTA, DMSA and DMPS in the treatment of lead poisoning in children. J Toxicol Clin Toxicol. 1992;30(4):493-504. PMID: 1331490. Excluded: Not a study.

63. Chisolm JJ, Jr., Harrison HE. The treatment of acute lead encephalopathy in children. Pediatrics. 1957;19(1):2-20. PMID: 13400575. Excluded: Wrong population.

64. Chisolm JJ, Jr., Kaplan E. Lead poisoning in childhood--comprehensive management and prevention. J Pediatr. 1968;73(6):942-50. PMID: 4972778. Excluded: Not a study.

65. Chisolm JJ, Jr., Mellits ED, Keil JE, et al. A simple protoporphyrin assay-microhematocrit procedure as a screening technique for increased lead absorption in young children. J Pediatr. 1974;84(4):490-6. PMID: 4834244. Excluded: Wrong intervention.

66. Chisolm JJ, Jr., Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. J Pharmacol Exp Ther. 1985;235(3):665-9. PMID: 4078728. Excluded: Wrong comparator.

67. Chomchai C, Padungtod C, Chomchai S. Predictors of elevated blood lead level in Thai children: a pilot study using risk assessment questionnaire. J Med Assoc Thai. 2005;88 Suppl 8:S53-9. PMID: 16856427. Excluded: Wrong outcome.

68. Clark S, Grote J, Wilson J, et al. Occurrence and determinants of increases in blood lead levels in children shortly after lead hazard control activities. Environ Res. 2004;96(2):196-205. doi: 10.1016/j.envres.2003.11.006. PMID: 15325880. Excluded: Wrong comparator.

69. Clinical and Laboratory Standards Institute. Measurement procedures for the determination of lead concentrations in blood and urine. Second ed; 2013. Excluded: Not a study.

70. Coffin R, Phillips JL, Staples WI, et al. Treatment of lead encephalopathy in children. J Pediatr. 1966;69(2):198-206. PMID: 4957770. Excluded: Wrong population.

71. Cooke RE, Glynn KL, Ullmann WW, et al. Comparative study of a micro-scale test for lead in blood, for use in mass screening programs. Clin Chem. 1974;20(5):582-5. PMID: 4826953. Excluded: Wrong intervention.

72. Council on Environmental Health. Prevention of childhood lead toxicity. Pediatrics. 2016;138(1)doi: 10.1542/peds.2016-1493. Excluded: Not a study.

73. Counter SA, Ortega F, Shannon MW, et al. Succimer (meso-2,3-dimercaptosuccinic acid (DMSA)) treatment of Andean children with environmental lead exposure. Int J Occup Environ Health. 2003;9(2):164-8. doi: 10.1179/oeh.2003.9.2.164. PMID: 12848245. Excluded: Wrong population.

74. Creighton S, Hafner JW, Aldag JC. Effectiveness of a pediatric verbal lead exposure screening protocol in emergency department patients. Pediatr Emerg Care. 2013;29(2):156-61. doi: 10.1097/PEC.0b013e3182808abe. PMID: 23364376. Excluded: Wrong outcome.

75. Dalton MA, Sargent JD, Stukel TA. Utility of a risk assessment questionnaire in identifying children with lead exposure. Arch Pediatr Adolesc Med. 1996;150(2):197-202. PMID: 8556126. Excluded: Wrong population.

76. Davis JR. Reliability of urinary delta-aminolevulinic acid as a mass screening technic for childhood exposure to lead. Am J Clin Pathol. 1970;53(6):967-9. PMID: 5509833. Excluded: Not a study.

77. De la Burde B, Choate MS, Jr. Does asymptomatic lead exposure in children have latent sequelae? J Pediatr. 1972;81(6):1088-91. PMID: 4643025. Excluded: Wrong study design for Key Question.

78. DeBaun MR, Sox HC, Jr. Setting the optimal erythrocyte protoporphyrin screening decision threshold for lead poisoning: a decision analytic approach. Pediatrics. 1991;88(1):121-31. PMID: 2057248. Excluded: Wrong intervention.

79. Delves HT. Blood collection for screening children for exposure to lead. Clin Chem. 1996;42(6 Pt 1):983-5. PMID: 8665698. Excluded: Not a study.

80. Dietrich KN, Ware JH, Salganik M, et al. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics. 2004;114(1):19-26. PMID: 15231903. Excluded: Wrong population.

81. Dillard RA. Detection, evaluation, and management of children exposed to lead. Texas Med. 1978;74(11):65-8. PMID: 725776. Excluded: Not a study.

82. Donahue LA, Brennan GG. Lyophilized urea in Traverts solution for the treatment of lead encephalopathy. J Med Soc N J. 1962;59:456-9. PMID: 13887157. Excluded: Wrong population.

83. Dyal B. Are lead risk questionnaires adequate predictors of blood lead levels in children? Public Health Nurs. 2012;29(1):3-10. doi: 10.1111/j.1525-1446.2011.00961.x. PMID: 22211746. Excluded: Wrong comparator.

84. Edwards KS, Forsyth BW. Lead screening at pediatric teaching programs. Am J Dis Child. 1989;143(12):1455-7. PMID: 2589277. Excluded: Wrong outcome.

Appendix A5. Excluded Studies

85. Esernio-Jenssen D, Bush V, Parsons PJ. Evaluation of VACUTAINER PLUS Low Lead tubes for blood lead and erythrocyte protoporphyrin testing. Clin Chem. 1999;45(1):148-50. PMID: 9895358. Excluded: Not a study.

86. Esteban E, Rubin CH, Jones RL, et al. Hair and blood as substrates for screening children for lead poisoning. Arch Environ Health. 1999;54(6):436-40. doi: 10.1080/00039899909603376. PMID: 10634234. Excluded: Wrong intervention.

87. Etchevers A, Glorennec P, Le Strat Y, et al. Screening for elevated blood lead levels in children: assessment of criteria and a proposal for new ones in France. Int J Environ Res Public Health. 2015;12(12):15366-78. doi: 10.3390/ijerph121214989. PMID: 26633457. Excluded: Wrong outcome.

88. Ettinger AS, Lamadrid-Figueroa H, Mercado-Garcia A, et al. Effect of calcium supplementation on bone resorption in pregnancy and the early postpartum: a randomized controlled trial in Mexican women. Nutr J. 2014;13(1):116. doi: 10.1186/1475-2891-13-116. PMID: 25511814. Excluded: Wrong outcome.

89. Farrar HC, McLeane LR, Wallace M, et al. A comparison of two dosing regimens of succimer in children with chronic lead poisoning. J Clin Pharmacol. 1999;39(2):180-3. PMID: 11563411. Excluded: Wrong comparator.

90. Fisher AA. Safety of ethylenediamine tetraacetate in the treatment of lead poisoning in persons sensitive to ethylenediamine hydrochloride. Cutis. 1991;48(2):105-6. PMID: 1935232. Excluded: Not a study.

91. France EK, Gitterman BA, Melinkovich P, et al. The accuracy of a lead questionnaire in predicting elevated pediatric blood lead levels. Arch Pediatr Adolesc Med. 1996;150(9):958-63. PMID: 8790128. Excluded: Wrong population.

92. Friedlander MA, Brooks CT, Sheehe PR. Blood pressure and creatinine clearance in lead-exposed children: the effect of treatment. Arch Environ Health. 1981;36(6):310-5. PMID: 7316569. Excluded: Wrong comparator.

93. Galke W, Clark S, Wilson J, et al. Evaluation of the HUD lead hazard control grant program: early overall findings. Environ Res. 2001;86(2):149-56. doi: 10.1006/enrs.2001.4259. PMID: 11437461. Excluded: Wrong comparator.

94. Gardella C. Lead exposure in pregnancy: a review of the literature and argument for routine prenatal screening. Obstet Gynecol Surv. 2001;56(4):231-8. PMID: 11285436. Excluded: Not a study.

95. Garza A. Screening strategies for lead poisoning. JAMA. 1993;270(21):2555; author reply 6-7. PMID: 8230634. Excluded: Not a study.

96. Gause D, Chase W, Foster J, et al. Reduction in lead levels among children in Newark. J Med Soc N J. 1977;74(11):958-60. PMID: 269968. Excluded: Wrong study design for Key Question.

97. Gellert GA, Wagner GA, Maxwell RM, et al. Lead poisoning: from screening to primary prevention. Pediatrics. 1994;93(2):343-4. PMID: 8121754. Excluded: Not a study.

98. Gemmel DJ. Use of the Centers for Disease Control and Prevention childhood lead poisoning risk questionnaire to predict blood lead elevations in pregnant women. Obstet Gynecol. 1996;88(1):159-60. doi: 10.1016/0029-7844(96)88088-4. PMID: 8684754. Excluded: Not a study.

99. Ginot L, Fontaine A, Cheymol J, et al. [Evaluating the effectiveness of child lead poisoning prevention programs]. Rev Epidemiol Sante Publique. 2003;51(4):427-38. PMID: 13679735. Excluded: Not English but possibly relevant.

100. Glotzer DE, Weitzman M, Aschengrau A, et al. Economic evaluation of environmental interventions for low-level childhood lead poisoning. Ambulatory Child Health. 1997;3(3):255-67. Excluded: Wrong outcome.

101. Goldman LR. Lead screening. Pediatrics. 1993;91(4):854-5. PMID: 8464688. Excluded: Not a study.

Appendix A5. Excluded Studies

102. Goodlad JK, Marcus DK, Fulton JJ. Lead and Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms: a meta-analysis. Clin Psychol Rev. 2013;33(3):417-25. doi: 10.1016/j.cpr.2013.01.009. PMID: 23419800. Excluded: Wrong intervention.

103. Graziano JH, Lolacono NJ, Meyer P. Dose-response study of oral 2,3-dimercaptosuccinic acid in children with elevated blood lead concentrations. J Pediatr. 1988;113(4):751-7. PMID: 2845043. Excluded: Wrong comparator.

104. Graziano JH, Lolacono NJ, Moulton T, et al. Controlled study of meso-2,3-dimercaptosuccinic acid for the management of childhood lead intoxication. J Pediatr. 1992;120(1):133-9. PMID: 1309865. Excluded: Wrong comparator.

105. Groleau V, Herold RA, Schall JI, et al. Blood lead concentration is not altered by high-dose vitamin D supplementation in children and young adults with HIV. J Pediatr Gastroenterol Nutr. 2013;56(3):316-9. doi: 10.1097/MPG.0b013e3182758c4a. PMID: 23059649. Excluded: Wrong population.

106. Gutgesell ME. Lead screening in the general pediatric clinic. Va Med Q. 1996;123(3):190-1. PMID: 8752964. Excluded: Wrong comparator.

107. Hankin L, Hanson KR, Kornfeld JM, et al. Simplified method for mass screening for lead poisoning based on delta-aminolevulinic acid in urine. Clin Pediatr. 1970;9(12):707-12. PMID: 5487477. Excluded: Wrong intervention.

108. Hanna TL, Dietzler DN, Smith CH, et al. Erythrocyte porphyrin analysis in the detection of lead poisoning in children: evaluation of four micromethods. Clin Chem. 1976;22(2):161-8. PMID: 1248115. Excluded: Wrong intervention.

109. Haust HL, Ali H, Haines DS, et al. Short-term administration of dimercaptopropanol (BAL) and calcium disodium edetate (EDTA) for diagnostic and therapeutic lead mobilization. Int J Biochem. 1980;12(5-6):897-904. PMID: 6778726. Excluded: Wrong population.

110. Heavey E. Lead poisoning: When an entire community is exposed. Nursing. 2016;46(9):28-33. doi: 10.1097/01.NURSE.0000490212.15944.5e. PMID: 27556165. Excluded: Not a study.

111. Hernandez-Avila M, Gonzalez-Cossio T, Hernandez-Avila JE, et al. Dietary calcium supplements to lower blood lead levels in lactating women: a randomized placebo-controlled trial. Epidemiology. 2003;14(2):206-12. doi: 10.1097/01.Ede.0000038520.66094.34. PMID: 12606887. Excluded: Wrong population.

112. Holmes SE, Drutz JE, Buffone GJ, et al. Blood lead levels in a continuity clinic population. J Toxicol Clin Toxicol. 1997;35(2):181-6. PMID: 9120888. Excluded: Wrong population.

113. Holtrop TG, Yee HY, Simpson PM, et al. A community outreach lead screening program using capillary blood collected on filter paper. Arch Pediatr Adolesc Med. 1998;152(5):455-8. PMID: 9605028. Excluded: Wrong population.

114. Hu H, Tellez-Rojo MM, Bellinger D, et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect. 2006;114(11):1730-5. PMID: 17107860. Excluded: Wrong study design for Key Question.

115. Iniguez JL, Leverger G, Dollfus C, et al. Lead mobilization test in children with lead poisoning: validation of a 5-hour edetate calcium disodium provocation test. Arch Pediatr Adolesc Med. 1995;149(3):338-40. PMID: 7858698. Excluded: Wrong study design for Key Question.

116. Jacobziner H, Raybin HW. Lead poisoning treated with bal. N Y State J Med. 1964;64:441. PMID: 14118322. Excluded: Not a study.

117. Janakiraman V, Ettinger A, Mercado-Garcia A, et al. Calcium supplements and bone resorption in pregnancy: a randomized crossover trial. Am J Prev Med. 2003;24(3):260-4. PMID: 12657345. Excluded: Wrong outcome.

Appendix A5. Excluded Studies

118. Jin Y, Yu F, Liao Y, et al. Therapeutic efficiency of succimer used with calcium and ascorbic acid in the treatment of mild lead-poisoning. Environ Toxicol Pharmacol. 2011;31(1):137-42. doi: 10.1016/j.etap.2010.09.015. PMID: 21787678. Excluded: Wrong comparator.

119. Jordan CM, Yust BL, Robison LL, et al. A randomized trial of education to prevent lead burden in children at high risk for lead exposure: efficacy as measured by blood lead monitoring. Environ Health Perspect. 2003;111(16):1947-51. PMID: 14644671. Excluded: Wrong intervention.

120. Kahn CA, Kelly PC, Walker WO, Jr. Lead screening in children with attention deficit hyperactivity disorder and developmental delay. Clin Pediatr. 1995;34(9):498-501. PMID: 7586924. Excluded: Wrong population.

121. Kalra V, Dua T, Kumar V, et al. Succimer in symptomatic lead poisoning. Indian Pediatr. 2002;39(6):580-5. PMID: 12084955. Excluded: Not a study.

122. Kaplowitz SA, Perlstadt H, D'Onofrio G, et al. The predictive value of self-report questions in a clinical decision rule for pediatric lead poisoning screening. Public Health Rep. 2012;127(4):375-82. PMID: 22753980. Excluded: Wrong study design for Key Question.

123. Kaplowitz SA, Perlstadt H, Perlstadt H, et al. Comparing lead poisoning risk assessment methods: census block group characteristics vs. zip codes as predictors. Public Health Rep. 2010;125(2):234-45. PMID: 20297750. Excluded: Wrong study design for Key Question.

124. Kassner J, Shannon M, Graef J. Role of forced diuresis on urinary lead excretion after the ethylenediaminetetraacetic acid mobilization test. J Pediatr. 1990;117(6):914-6. PMID: 2123241. Excluded: Wrong intervention.

125. Kaul B, Slavin G, Davidow B. Free erythrocyte protoporphyrin and zinc protoporphyrin measurements compared as primary screening methods for detection of lead poisoning. Clin Chem. 1983;29(8):1467-70. PMID: 6872205. Excluded: Wrong intervention.

126. Kawatu D, Weinberger HL, Blatt SD. Universal versus selective screening for lead in children. Pediatrics. 1995;95(1):157-9. PMID: 7770298. Excluded: Not a study.

127. Kazal LA, Jr. The failure of CDC screening questionnaire to efficiently detect elevated lead levels in a rural population of children. J Fam Pract. 1997;45(6):515-8. PMID: 9420588. Excluded: Wrong population.

128. Kegler MC, Malcoe LH. Results from a lay health advisor intervention to prevent lead poisoning among rural Native American children. Am J Public Health. 2004;94(10):1730-5. PMID: 15451742. Excluded: Wrong intervention.

129. Kegler MC, Malcoe LH, Fedirko V. Primary prevention of lead poisoning in rural Native American children: behavioral outcomes from a community-based intervention in a former mining region. Fam Community Health. 2010;33(1):32-43. doi: 10.1097/FCH.0b013e3181c4e252. PMID: 20010003. Excluded: Wrong intervention.

130. Kimbrough RD, LeVois M, Webb DR. Management of children with slightly elevated blood lead levels. Pediatrics. 1994;93(2):188-91. PMID: 8121729. Excluded: Wrong study design for Key Question.

131. Knighton AJ, Payne NR, Speedie S. Lead Testing in a Pediatric Population: Underscreening and Problematic Repeated Tests. J Public Health Manag Pract. 2016;22(4):331-7. doi: 10.1097/PHH.0000000000000344. PMID: 26418307. Excluded: Wrong outcome.

132. Kornfeld JM, Ullmann WW, Hankin L. Modifications and use of the dipstick test, based on urinary delta-aminolevulinic acid (ALA), for the detection of lead poisoning in children. Clin Toxicol. 1972;5(1):7-16. doi: 10.3109/15563657208990503. PMID: 5043281. Excluded: Wrong intervention.

133. Kotok D. Development of children with elevated blood lead levels: a controlled study. J Pediatr. 1972;80(1):57-61. PMID: 5016353. Excluded: Wrong study design for Key Question.

134. Lanphear BP. The paradox of lead poisoning prevention. Science. 1998;281(5383):1617-8. PMID: 9767027. Excluded: Not a study.

Appendix A5. Excluded Studies

135. Lanphear BP. Childhood lead poisoning prevention: too little, too late. JAMA. 2005;293(18):2274-6. doi: 10.1001/jama.293.18.2274. PMID: 15886384. Excluded: Not a study.

136. Liebelt EL, Shannon MW. Oral chelators for childhood lead poisoning. Pediatr Ann. 1994;23(11):616-9, 23-6. PMID: 7838614. Excluded: Not a study.

137. Lin-Fu JS. Screening for lead poisoning. Pediatrics. 1970;45(4):720-1. PMID: 5438184. Excluded: Not a study.

138. Lin-Fu JS. Diagnostic and screening procedures for lead poisoning. Pediatrics. 1971;48(3):488-9. PMID: 5094354. Excluded: Not a study.

139. Lioy PJ, Yiin LM, Adgate J, et al. The effectiveness of a home cleaning intervention strategy in reducing potential dust and lead exposures. J Expo Anal Environ Epidemiol. 1998;8(1):17-35. PMID: 9470102. Excluded: Wrong outcome.

140. Liu J, Gao D, Chen Y, et al. Lead exposure at each stage of pregnancy and neurobehavioral development of neonates. Neurotoxicology. 2014;44:1-7. doi: 10.1016/j.neuro.2014.03.003. PMID: 24704588. Excluded: Wrong study design for Key Question.

141. Liu X, Dietrich KN, Radcliffe J, et al. Do children with falling blood lead levels have improved cognition? Pediatrics. 2002;110(4):787-91. PMID: 12359796. Excluded: Wrong population.

142. Lockitch G. Perspectives on lead toxicity. Clin Biochem. 1993;26(5):371-81. PMID: 8299207. Excluded: Not a study.

143. Mabry IR. Screening for elevated blood lead levels in children and pregnant women. Am Fam Phys. 2008;78(10):1201-2. PMID: 19035069. Excluded: Not a study.

144. Madlock YS, Bradley E. Childhood lead poisoning prevention program Memphis and Shelby County Health Department. Tenn Med. 2002;95(10):418-20. PMID: 12369542. Excluded: Not a study.

145. Mankikar D, Campbell C, Greenberg R. Evaluation of a home-based environmental and educational intervention to improve health in vulnerable households: Southeastern Pennsylvania lead and healthy homes program. Int J Environ Res Public Health. 2016;13(9):09. doi: 10.3390/ijerph13090900. PMID: 27618087. Excluded: Wrong intervention.

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147. Marcus SM. Treatment of lead-exposed children. Pediatrics. 1996;98(1):161-2; author reply 3. PMID: 8668396. Excluded: Not a study.

148. Marcus SM, Joselow MM, Kemp F, et al. Warning: spurious elevations of blood lead in micro puncture techniques. J Pediatr. 1977;91(1):164. PMID: 874656. Excluded: Not a study.

149. Margulis HL. The control and prevention of pediatric lead poisoning in East Orange, New Jersey. J Environ Health. 1977;39(5):362-5. PMID: 10235755. Excluded: Not a study.

150. Markiewicz T. Recognizing, treating, and preventing lead poisoning. Am J Nurs. 1993;93(10):59-62, 4. PMID: 8213948. Excluded: Not a study.

151. Markowitz ME, Bijur PE, Ruff H, et al. Effects of calcium disodium versenate (CaNa2EDTA) chelation in moderate childhood lead poisoning. Pediatrics. 1993;92(2):265-71. PMID: 8337028. Excluded: Wrong study design for Key Question.

152. Markowitz ME, Sinnett M, Rosen JF. A randomized trial of calcium supplementation for childhood lead poisoning. Pediatrics. 2004;113(1 Pt 1):e34-9. PMID: 14702492. Excluded: Wrong population.

153. Mazur LJ, Moyer VA, Lally PA, et al. Evaluation of a lead screening program in Houston, Tex. Tex Med. 1996;92(1):54-7. PMID: 8599168. Excluded: Wrong outcome.

Appendix A5. Excluded Studies

154. McCabe EB, Challop RS. Simple rapid test for lead poisoning. J Pediatr. 1972;80(5):893-4. PMID: 5018404. Excluded: Not a study.

155. McCloskey LJ, Bordash FR, Ubben KJ, et al. Decreasing the cutoff for elevated blood lead (EBL) can decrease the screening sensitivity for EBL. Am J Clin Pathol. 2013;139(3):360-7. doi: 10.1309/AJCP5RKWF3IZTCTO. PMID: 23429373. Excluded: Wrong study design for Key Question.

156. McKay CA, Jr. Role of chelation in the treatment of lead poisoning: discussion of the Treatment of Lead-Exposed Children Trial (TLC). J Med Toxicol. 2013;9(4):339-43. doi: 10.1007/s13181-013-0341-8. PMID: 24178899. Excluded: Not a study.

157. Miranda ML, Dolinoy DC, Overstreet MA. Mapping for prevention: GIS models for directing childhood lead poisoning prevention programs. Environmental Health Perspectives. 2002;110(9):947-53. PMID: 12204831. Excluded: Not a study.

158. Mitchell DG, Aldous KM, Ryan FJ. Mass screening for lead poisoning: Capillary blood sampling and automated Delves-cup atomic-absorption analysis. N Y State J Med. 1974;74(9):1599-603. PMID: 4527069. Excluded: Wrong intervention.

159. Montoya-Cabrera MA, Maldonado-Torres L, Velazwuez-Gutierrez L, et al. [Treatment of saturnism with a low dose of calcium disodium EDTA]. Arch Invest Med (Mex). 1974;5(3):603-8. PMID: 4218477. Excluded: Not English but possibly relevant.

160. Moriarty RW. Screening to prevent lead poisoning. Pediatrics. 1974;54(5):626-8. PMID: 4453465. Excluded: Not a study.

161. Muniz MA, Dundas R, Mahoney MC. Evaluation of a childhood lead questionnaire in predicting elevated blood lead levels in a rural community. J Rural Health. 2003;19(1):15-9. PMID: 12585770. Excluded: Wrong population.

162. Ness R. Practice guidelines for childhood lead screening in primary care. J Pediatr Health Care. 2013;27(5):395-9. doi: 10.1016/j.pedhc.2012.12.013. PMID: 23465780. Excluded: Not a study.

163. Newton WP. Screening for lead poisoning in a suburban practice. J Fam Pract. 1995;41(1):95-6. PMID: 7798071. Excluded: Not a study.

164. Nicholson JS. A community-based intervention for low-income families to reduce children's blood lead levels between 3–9.9 μg/Dl. Children's Health Care. 2017:1-18. doi: 10.1080/02739615.2017.1370673. Excluded: Wrong population.

165. Nicholson JS, Cleeton M. Validation and assessment of pediatric lead screener questions for primary prevention of lead exposure. Clin Pediatr. 2016;55(2):129-36. doi: 10.1177/0009922815584944. PMID: 25986443. Excluded: Wrong comparator.

166. Nordin JD, Rolnick SJ, Griffin JM. Prevalence of excess lead absorption and associated risk factors in children enrolled in a midwestern health maintenance organization. Pediatrics. 1994;93(2):172-7. PMID: 8121726. Excluded: Wrong comparator.

167. Nussbaumer-Streit B, Yeoh B, Griebler U, et al. Household interventions for preventing domestic lead exposure in children. Cochrane Database Syst Rev. 2016 (10). Excluded: Wrong intervention.

168. O'Connor ME, Rich D. Children with moderately elevated lead levels: is chelation with DMSA helpful? Clin Pediatr (Phila). 1999;38(6):325-31. doi: 10.1177/000992289903800602. PMID: 10378089. Excluded: Wrong population.

169. O'Donohoe NV. Lead poisoning in childhood treated by the subcutaneous administration of a chelating agent. Arch Dis Child. 1956;31(158):321-3. PMID: 13363476. Excluded: Not a study.

170. Orava S, Brogan GX, Jr., Mofenson H, et al. Evaluation of two strategies for complying with state-mandated lead screening in the emergency department. Naussau-Suffolk Lead Committee, Naussau-Suffolk Lead Center. Acad Emerg Med. 1999;6(8):849-51. PMID: 10463559. Excluded: Wrong study design for Key Question.

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171. Ossiander EM. A systematic review of screening questionnaires for childhood lead poisoning. J Public Health Manag Pract. 2013;19(1):E21-9. doi: 10.1097/PHH.0b013e3182249523. PMID: 22668673. Excluded: Systematic review or meta-analysis used as a source document only to identify individual studies.

172. Parsons PJ, Raciti K, Esernio-Jenssen D. Evaluation and improvement of sample collection procedures for the determination of blood lead Center for Disease Control and Prevention. Atlanta: Centers for Disease Control and Prevention: 1993. Excluded: Wrong population.

173. Paulozzi LJ, Shapp J, Drawbaugh RE, et al. Prevalence of lead poisoning among two-year-old children in Vermont. Pediatrics. 1995;96(1 Pt 1):78-81. PMID: 7596728. Excluded: Wrong comparator.

174. Pawel MA, Frantz CN, Pisetsky IB. Screening for lead poisoning with the urinary ALA test. HSMHA Health Rep. 1971;86(11):1030-6. PMID: 5138281. Excluded: Wrong study design for Key Question.

175. Polivka BJ, Salsberry P, Casavant MJ, et al. Comparison of parental report of blood lead testing in children enrolled in Medicaid with Medicaid claims data and blood lead surveillance reports. J Community Health. 2006;31(1):43-55. PMID: 16482765. Excluded: Wrong intervention.

176. Prashant V, Prashant A, Devanand D, et al. Screening of school children for blood lead levels and attempts to reduce them by nonpharmacological means in a coastal city of India. Indian J Med Sci. 2008;62(5):185-92. PMID: 18579977. Excluded: Wrong population.

177. Pueschel SM, Kopito L, Schwachman H. Children with an increased lead burden. A screening and follow-up study. JAMA. 1972;222(4):462-6. PMID: 4677833. Excluded: Wrong study design for Key Question.

178. Rainey PM, Schonfeld DJ. Comparability of capillary and venous blood samples for lead screening. JAMA. 1994;272(19):1482. PMID: 7966831. Excluded: Not a study.

179. Ranmuthugala G, Karr M, Mira M, et al. Opportunistic sampling from early childhood centres: a substitute for random sampling to determine lead and iron status of pre-school children? Aust N Z J Public Health. 1998;22(4):512-4. PMID: 9659783. Excluded: Wrong comparator.

180. Rastogi S, Nandlike K, Fenster W. Elevated blood lead levels in pregnant women: identification of a high-risk population and interventions. J Perinat Med. 2007;35(6):492-6. doi: 10.1515/JPM.2007.131. PMID: 18052836. Excluded: Wrong study design for Key Question.

181. Raymond J, Wheeler W, Brown MJ, et al. Lead screening and prevalence of blood lead levels in children aged 1-2 years--Child Blood Lead Surveillance System, United States, 2002-2010 and National Health and Nutrition Examination Survey, United States, 1999-2010. MMWR Suppl. 2014;63(2):36-42. PMID: 25208256. Excluded: Wrong study design for Key Question.

182. Reuben A, Caspi A, Belsky D, et al. Association of childhood blood levels with cognitive function and socioeconomic status at age 38 years and with IQ change and socioeconomic mobility between childhood and adulthood. JAMA. 2017;317(12):1244-51. PMID: 28350927. Excluded: Wrong population.

183. Roberts JR, Hulsey TC, Curtis GB, et al. Using geographic information systems to assess risk for elevated blood lead levels in children. Public Health Rep. 2003;118(3):221-9. PMID: 12766217. Excluded: Wrong study design for Key Question.

184. Robin LF, Beller M, Middaugh JP. Statewide assessment of lead poisoning and exposure risk among children receiving Medicaid services in Alaska. Pediatrics. 1997;99(4):E9. PMID: 9099784. Excluded: Wrong population.

185. Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med. 2001;344(19):1421-6. doi: 10.1056/NEJM200105103441902. PMID: 11346806. Excluded: Wrong population.

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186. Rolnick SJ, Nordin J, Cherney LM. A comparison of costs of universal versus targeted lead screening for young children. Environ Res. 1999;80(1):84-91. doi: 10.1006/enrs.1998.3879. PMID: 9931230. Excluded: Wrong comparator.

187. Rooney BL, Hayes EB, Allen BK, et al. Development of a screening tool for prediction of children at risk for lead exposure in a midwestern clinical setting. Pediatrics. 1994;93(2):183-7. PMID: 8121728. Excluded: Wrong comparator.

188. Ruff HA, Bijur PE, Markowitz M, et al. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. JAMA. 1993;269(13):1641-6. PMID: 8455297. Excluded: Wrong outcome.

189. Sachs HK. Effect of a screening program on changing patterns of lead poisoning. Environ Health Perspect. 1974;7:41-5. PMID: 4831147. Excluded: Wrong study design for Key Question.

190. Sargent JD, Dalton M, Klein RZ. Diagnostic testing unwarranted for children with blood lead 10 to 14 microg/dL. Pediatrics. 1999;103(4):e51. PMID: 10103343. Excluded: Wrong study design for Key Question.

191. Sargent JD, Dalton MA. Rethinking the threshold for an abnormal capillary blood lead screening test. Arch Pediatr Adolesc Med. 1996;150(10):1084-8. PMID: 8859143. Excluded: Wrong population.

192. Sathyanarayana S, Beaudet N, Omri K, et al. Predicting children's blood lead levels from exposure to school drinking water in Seattle, Washington, USA. Ambul Pediatr. 2006;6(5):288-92. doi: 10.1016/j.ambp.2006.07.001. PMID: 17000419. Excluded: Wrong study design for Key Question.

193. Schaffer SJ, Kincaid MS, Endres N, et al. Lead poisoning risk determination in a rural setting. Pediatrics. 1996;97(1):84-90. PMID: 8545231. Excluded: Wrong population.

194. Schaffer SJ, Szilagyi PG, Weitzman M. Lead poisoning risk determination in an urban population through the use of a standardized questionnaire. Pediatrics. 1994;93(2):159-63. PMID: 8121724. Excluded: Wrong comparator.

195. Schell LM, Denham M, Stark AD, et al. Relationship between blood lead concentration and dietary intakes of infants from 3 to 12 months of age. Environ Res. 2004;96(3):264-73. doi: 10.1016/j.envres.2004.02.008. PMID: 15364593. Excluded: Wrong population.

196. Schlenker TL, Baxmann R, McAvoy P, et al. Primary prevention of childhood lead poisoning through community outreach. WMJ. 2001;100(8):48-54. PMID: 12685297. Excluded: Wrong intervention.

197. Schlenker TL, Fritz CJ, Mark D, et al. Screening for pediatric lead poisoning. Comparability of simultaneously drawn capillary and venous blood samples. JAMA. 1994;271(17):1346-8. PMID: 8158820. Excluded: Wrong population.

198. Schlenker TL, Fritz CJ, Murphy A, et al. Feasibility and effectiveness of screening for childhood lead poisoning in private medical practice. Arch Pediatr Adolesc Med. 1994;148(7):761-4. PMID: 8019635. Excluded: Wrong outcome.

199. Schneider J, Aurori B, Armenti L, et al. Impact of community screening on diagnosis, treatment, and medical findings of lead poisoning in children. Public Health Rep. 1981;96(2):143-9. PMID: 7208798. Excluded: Wrong outcome.

200. Schonfeld DJ, Cullen MR, Rainey PM, et al. Screening for lead poisoning in an urban pediatric clinic using samples obtained by fingerstick. Pediatrics. 1994;94(2 Pt 1):174-9. PMID: 8036069. Excluded: Wrong study design for Key Question.

201. Schonfeld DJ, Rainey PM, Cullen MR, et al. Screening for lead poisoning by fingerstick in suburban pediatric practices. Arch Pediatr Adolesc Med. 1995;149(4):447-50. PMID: 7704175. Excluded: Wrong study design for Key Question.

202. Shannon M, Graef J, Lovejoy FH, Jr. Efficacy and toxicity of D-penicillamine in low-level lead poisoning. J Pediatr. 1988;112(5):799-804. PMID: 3361395. Excluded: Wrong population.

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203. Shannon MW, Townsend MK. Adverse effects of reduced-dose d-penicillamine in children with mild-to-moderate lead poisoning. Ann Pharmacother. 2000;34(1):15-8. PMID: 10669180. Excluded: Wrong comparator.

204. Shao L, Zhang L, Zhen Z. Interrupted time series analysis of children's blood lead levels: A case study of lead hazard control program in Syracuse, New York. PLoS ONE. 2017;12(2):e0171778. doi: 10.1371/journal.pone.0171778. PMID: 28182688. Excluded: Wrong study design for Key Question.

205. Sinclair DF, Dohnt BR. Sampling and analysis techniques used in a blood lead survey of 1241 children in Port Pirie, South Australia. Clin Chem. 1984;30(10):1616-9. PMID: 6478591. Excluded: Wrong intervention.

206. Smith HD. Lead poisoning in children and its therapy with EDTA. Ind Med Surg. 1959;28(3):148-51; discussion 51-5. PMID: 13630577. Excluded: Not a study.

207. Smith HD, King LR, Margolin EG. Treatment of lead encephalopathy. The combined use of edetate and hemodialysis. Am J Dis Child. 1965;109:322-4. PMID: 14261012. Excluded: Wrong population.

208. Snyder DC, Mohle-Boetani JC, Palla B, et al. Development of a population-specific risk assessment to predict elevated blood lead levels in Santa Clara County, California. Pediatrics. 1995;96(4 Pt 1):643-8. PMID: 7567324. Excluded: Wrong population.

209. Specter MJ, Guinee VF, Davidow B. The unsuitability of random urinary delta aminolevulinic acid samples as a screening test for lead poisoning. J Pediatr. 1971;79(5):799-804. PMID: 5116703. Excluded: Wrong outcome.

210. Stark AD, Quah RF, Meigs JW, et al. Relationship of sociodemographic factors to blood lead concentrations in New Haven children. J Epidemiol Community Health. 1982;36(2):133-9. PMID: 7119656. Excluded: Wrong study design for Key Question.

211. Striph KB. Prevalence of lead poisoning in a suburban practice. J Fam Pract. 1995;41(1):65-71. PMID: 7798067. Excluded: Wrong comparator.

212. Swindell SL, Charney E, Brown MJ, et al. Home abatement and blood lead changes in children with class III lead poisoning. Clin Pediatr (Phila). 1994;33(9):536-41. doi: 10.1177/000992289403300905. PMID: 8001322. Excluded: Wrong comparator.

213. Tejeda DM, Wyatt DD, Rostek BR, et al. Do questions about lead exposure predict elevated lead levels? Pediatrics. 1994;93(2):192-4. PMID: 8121730. Excluded: Wrong population.

214. Thurtle N, Greig J, Cooney L, et al. Description of 3,180 courses of chelation with dimercaptosuccinic acid in children < 5 y with severe lead poisoning in Zamfara, Northern Nigeria: a retrospective analysis of programme data. PLoS Medicine. 2014;11(10):e1001739. doi: 10.1371/journal.pmed.1001739. PMID: 25291378. Excluded: Wrong population.

215. Tressou J, Crepet A, Bertail P, et al. Probabilistic exposure assessment to food chemicals based on extreme value theory. Application to heavy metals from fish and sea products. Food Chem Toxicol. 2004;42(8):1349-58. doi: 10.1016/j.fct.2004.03.016. PMID: 15207386. Excluded: Wrong study design for Key Question.

216. Triantafyllidou S, Gallagher D, Edwards M. Assessing risk with increasingly stringent public health goals: the case of water lead and blood lead in children. J Water Health. 2014;12(1):57-68. doi: 10.2166/wh.2013.067. PMID: 24642433. Excluded: Wrong study design for Key Question.

217. Triantafyllidou S, Le T, Gallagher D, et al. Reduced risk estimations after remediation of lead (Pb) in drinking water at two US school districts. Sci Total Environ. 2014;466-467:1011-21. doi: 10.1016/j.scitotenv.2013.07.111. PMID: 23988746. Excluded: Wrong outcome.

218. Verebey K. Filter paper-collected blood lead testing in children. Clin Chem. 2000;46(7):1024-8. PMID: 10894859. Excluded: Not a study.

219. Verebey K, Rosen JF, Schonfeld DJ, et al. Blood collection and analytical considerations in blood lead screening in children. Clin Chem. 1995;41(3):469-70. PMID: 7882527. Excluded: Not a study.

220. Veyhe AS, Hofoss D, Hansen S, et al. The Northern Norway Mother-and-Child Contaminant Cohort (MISA) Study: PCA analyses of environmental contaminants in maternal sera and dietary intake in early pregnancy. Int J Hyg Environ Health. 2015;218(2):254-64. doi: 10.1016/j.ijheh.2014.12.001. PMID: 25556042. Excluded: Wrong study design for Key Question.

221. Vitale LF, Rosalinas-Bailon A, Folland D, et al. Oral penicillamine therapy for chronic lead poisoning in children. J Pediatr. 1973;83(6):1041-5. PMID: 4757518. Excluded: Wrong comparator.

222. Wang ST, Pizzolato S, Peter F. Microsampling technique and determination of blood lead by Zeeman atomic absorption spectrophotometry. Sci Total Environ. 1988;71(1):37-43. PMID: 3358115. Excluded: Wrong outcome.

223. Wasserman LR. The effects of a family-based educational intervention on the prevention of lead poisoning in children (EdD). 2002. Excluded: Wrong study design for Key Question.

224. Watt GC, Britton A, Gilmour WH, et al. Is lead in tap water still a public health problem? An observational study in Glasgow. BMJ. 1996;313(7063):979-81. PMID: 8892418. Excluded: Wrong study design for Key Question.

225. Wei Z, Markowitz M, clement I. Therapeutic effectiveness of calcium supplementation on moderate lead poisoning in children: a double-blind randomized clinical trial. Zhonghua Er Ke Za Zhi. 1998;36(3):146-8. Excluded: Not English but possibly relevant.

226. Willis FR, Rossi E, Bulsara M, et al. The Fremantle lead study. J Paediatr Child Health. 1995;31(4):326-31. PMID: 7576892. Excluded: Wrong study design for Key Question.

227. Wolf AW, Jimenez E, Lozoff B. Effects of iron therapy on infant blood lead levels. J Pediatr. 2003;143(6):789-95. doi: 10.1067/S0022-3476(03)00540-7. PMID: 14657829. Excluded: Wrong population.

228. Yiin LM, Lioy PJ, Rhoads GG. Impact of home carpets on childhood lead intervention study. Environ Res. 2003;92(2):161-5. PMID: 12854696. Excluded: Wrong comparator.

229. Zabel EW, Falken MC, Sonnabend M, et al. Prevalence of elevated blood lead levels and evaluation of a lead-risk-screening questionnaire in rural Minnesota. J Environ Health. 2005;68(2):9-15, 36. PMID: 16220717. Excluded: Wrong comparator.

230. Zheng J, Huynh T, Gasparon M, et al. Human health risk assessment of lead from mining activities at semi-arid locations in the context of total lead exposure. Environ Sci Pollut Res Int. 2013;20(12):8404-16. doi: 10.1007/s11356-013-2145-4. PMID: 24122159. Excluded: Wrong study design for Key Question.

231. Zierold KM, Havlena J, Anderson H. Exposure to lead and length of time needed to make homes lead-safe for young children. Am J Public Health. 2007;97(2):267-70. doi: 10.2105/AJPH.2005.067603. PMID: 17194869. Excluded: Wrong outcome.

Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of ratings based on 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

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 above criteria:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; accurate diagnostic procedures and measurements applied equally to cases and controls; and appropriate attention to confounding variables
Fair: Recent, relevant, and without major apparent selection or diagnostic workup bias, but response rate less than
80 percent or attention to some but not all important confounding variables
Poor: Major selection or diagnostic workup bias, response rate less than 50 percent, or inattention to confounding variables

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts

- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- 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 (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are 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 followup; 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 used for RCTs.
Poor: Studies are 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 equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Diagnostic Accuracy Studies

Criteria:
- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of ratings based on above criteria:
Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients

Poor: Has a fatal flaw, such as: Uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients

*Reference: U.S. Preventive Services Task Force Procedure Manual. July 2017. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix A7. Expert Reviewers of the Draft Report

- Jennifer A. Lowry, MD, Chief, Section of Toxicology and Environmental Health, Children's Mercy
- Suril Mehta, MPH, Health Scientist, Office of the Report on Carcinogens, U.S. National Toxicology Program, National Institute of Environmental Health Sciences
- Matthew Strickland, PhD, MPH, Associate Professor of Epidemiology, School of University Health Sciences, University of Nevada, Reno
- Federal Partners from the United States Environmental Protection Agency
  - Ruth A. Etzel, MD, PhD, Director, Office of Children's Health Protection, United States Environmental Protection Agency
- Additional Federal Partners from the Centers for Disease Control and Prevention
  - Brandy Peaker, MD, MPH, CDC Liason, Centers for Disease Control and Prevention

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings.

Appendix B1. Data Abstraction of Pregnancy Diagnostic Accuracy Study

Study, year	Screening test	Definition of a positive screening exam	Reference standard	Type of study	Country Setting	Population characteristics	Sample size Proportion with condition	Proportion unexaminable by screening test
Stefanak, 1996[45]	CDC Lead Poisoning Risk Questionnaire	A positive response to any of the 4 relevant questions from the CDC Lead Poisoning Risk Questionnaire	Venous blood lead testing	Prospective cohort	Prenatal clinics United States	Mean age: NR Race: 66% white, 28% black Mean blood lead: 12.6 µg/dL	n=314 Prevalence of elevated blood lead: 13%	4.8% (15/314)
	Three questions regarding housing, smoking, and consumption of canned foods	A positive response to any of the 3 relevant questions	See above	See above	See above	See above	See above	See above

Appendix B1. Data Abstraction of Pregnancy Diagnostic Accuracy Study

Study, year	Analysis of screening failures	Proportion who underwent reference standard and included in analysis	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Quality rating	Comments
Stefanak, 1996[45]	NR	299/315 (95.2%)	75.7% (NR)	46.2% (NR)	11 (NR) [Calculated]	0.26 (NR)	16.6% (NR) [Calculated]	93.1% (NR)	Poor	Also reports accuracy results for a different set of questions (i.e., not the CDC questions)
	See above	See above	89.2% (NR)	96.4% (NR)	25 (NR) [Calculated]	0.11 (NR) [Calculated]	41.2% (NR)	17.7% (NR)	Poor	

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; NR=not reported.

Appendix B2. Data Abstraction of Pregnancy Trials

Author, year	Study design	Setting Country	Study duration Mean followup	Interventions (N)	Inclusion criteria	Patient characteristics
Ettinger, 2009[26]	RCT	Prenatal clinics Mexico	8 months	A. Calcium 1,200 mg at bedtime (n=334) B. Placebo (n=336)	Pregnant women <14 weeks' gestation, without a high-risk pregnancy	A vs. B Mean age: 26.9 vs. 25.9 years (p<0.05) Race: NR Number of pregnancies: 2.0 vs. 2.1 Blood lead: 3.8 vs. 4.1 µg/dL

Appendix B2. Data Abstraction of Pregnancy Trials

Author, year	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup	Adjusted variables for statistical analysis (for observational studies)	Intermediate outcomes	Clinical health outcomes	Adverse events	Quality rating	Funding source
Ettinger, 2009[26]	Enrolled: 670 Analyzed: 557 Withdrawals: Unclear Loss to followup: 14% (46/334) vs. 18% (59/336); RR, 0.78 (95% CI, 0.55 to 1.12)	N/A	A vs. B. Blood lead level: 11% mean reduction in treatment group vs. placebo (p=0.04)	NR	NR	Fair	U.S. NIEHS

Abbreviations: CI=confidence interval; NIEHS=National Institute of Environmental Health Sciences; N/A=not applicable; NR=not reported; RR=relative risk; U.S.=United States.

Appendix C1. Quality Assessment of Pregnancy Diagnostic Accuracy Study

Author, year	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index text?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did patients receive the same reference standard?	Were all patients included in the analysis?	Quality rating
Stefanak, 1996[45]	Unclear	Yes	Yes	Unclear	Yes	Yes, but not the current	Unclear	Yes	Yes	Yes	No (299/314)	Fair

Appendix C2. Quality Assessment of Pregnancy Trial

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and with-drawals reported?	Loss to followup differential/ high?	Analyze people in the groups in which they were randomized?	Quality rating
Ettinger, 2009[26]	Unclear	Unclear	Yes; except age	Yes	Unclear	Unclear; but described as double blind	Yes	Yes	No	Yes	Fair