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

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Suggested Citation

Structured Abstract

**Background:** In 2006, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against routine screening for elevated blood lead levels in asymptomatic children ages 1 to 5 years who are at increased risk for lead poisoning (I recommendation), and recommended against routine screening in those at average risk (D recommendation).

**Purpose:** To synthesize evidence on the effects of screening, testing, and treatment for elevated blood lead levels in children age 5 years and younger in the primary care setting, to update a prior USPSTF review on screening for elevated blood lead levels in childhood.

**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 children age 5 years and younger.

**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 (Results):** A total of 22 studies were included in this review (N=10,449). No studies directly evaluated clinical benefits or harms of screening versus not screening children for elevated blood lead levels. More than one positive answer on the five-item 1991 Centers for Disease Control and Prevention screening questionnaire was associated with a pooled sensitivity of 48 percent (95% confidence interval [CI], 31.4% to 65.6%) and specificity of 58 percent (95% CI, 39.9% to 74.0%) for identifying children with a venous blood level greater than 10 µg/dL (5 studies; N=2,265). Adapted versions of the questionnaire did not demonstrate improved accuracy. Capillary blood lead testing demonstrated sensitivity of 87 to 91 percent and specificity greater than 90 percent, compared with venous measurement (4 studies; N=1,431). Counseling and nutritional interventions or residential lead hazard control techniques did not reduce blood lead concentrations in asymptomatic children, but studies were few and had methodological limitations (7 studies; N=1,419). A trial of dimercaptosuccinic acid chelation therapy found reduced blood lead levels in children at 1 week to 1 year but not at 4.5 to 6 years (N=780), while another trial found no effect at 1 and 6 months (N=39). Seven-year followup assessments showed no effect on neuropsychological development; a small deficit in linear growth (height difference at 7 years in treated patients, 1.17 cm [95% CI, 0.41 to 1.93 cm]) and poorer cognitive outcomes reported as the Attention and Executive Functions subscore of the Developmental Neuropsychological Assessment (unadjusted difference, -1.8 [95% CI, -4.5 to 1.0]; adjusted $P=0.045$) in children treated with dimercaptosuccinic acid chelation.
**Limitations:** Limited to English-language articles; quality and applicability of studies were limited due to study design, poor reporting of statistical outcomes, and loss to followup. Studies were lacking on the effectiveness of screening or treatments in reducing elevated blood lead levels or improving health outcomes in children. There was no direct evidence on the harms of screening children for elevated blood lead levels.

**Conclusions:** Evidence on the benefits and harms of screening children for elevated blood lead levels is lacking. Screening questionnaires are not accurate for identifying children with elevated blood lead levels. Capillary blood testing is slightly less accurate than venous blood testing for identification of elevated blood lead levels. Treatment studies of chelating agents, often combined with environmental or household interventions, were not associated with sustained effects on blood lead levels but were associated with harms.
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Chapter 1. Introduction and Background

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

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 in children. This update focuses on studies published since the prior USPSTF systematic review\(^1\) of this topic as well as studies included in the prior review.

In 2006, the USPSTF found insufficient evidence for screening asymptomatic children ages 1 to 5 years at increased risk for elevated blood lead levels (BLLs) (I recommendation). The USPSTF recommended against routine screening for elevated BLLs in asymptomatic children ages 1 to 5 years who are at average risk (D recommendation) based on evidence that did not support any benefits conferred with detection or early intervention among children with asymptomatic or mild/moderate lead levels. In addition, good-quality evidence from the 2006 review showed that interventions did not result in sustained decreases in BLLs, and chelation treatment specifically was associated with a slight diminution in cognitive performance.

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 children.\(^2\) Previously, children with a BLL of 10 µg/dL or greater were identified as having a blood lead “level of concern,” and the CDC recommended that identification of children with a BLL of 10 µg/dL or greater should prompt public health action and followup testing by state or local health departments.\(^3\) However, in 2012, the CDC’s Advisory Committee for Childhood Lead Poisoning Prevention (ACCLPP) lowered the level, because no safe level of lead exposure has been established, and it determined that a threshold of 10 µg/dL or greater likely misses children at risk of adverse health effects.\(^4\) The ACCLPP recommended using a reference range value based on the estimated 97.5 percentile of the BLL distribution among children ages 1 to 5 years calculated from two 2-year cycles of National Health and Nutritional Examination Survey (NHANES) data.\(^4\) In 2010, the upper value of the reference range was 5 µg/dL.\(^2\) The ACCLPP also recommended that clinicians monitor children with BLLs between 5 and 10 µg/dL based on evidence that higher BLLs are associated with IQ deficits, attention-related behaviors, and poor academic achievement.\(^4\) Current reference ranges are based on population levels from NHANES BLL distribution; these do not define safe lead levels but are the level at which further clinical monitoring and treatment is recommended. The reference range may continue to change with population prevalence.
Prevalence and Burden of Disease/Illness

Lead causes a number of adverse health effects primarily affecting the central nervous, hematopoietic, hepatic, and renal systems. 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 or ingestion of lead-containing products in children. Clinical symptoms of acute lead exposure include muscle pain, fatigue, abdominal pain, headache, vomiting, seizures, and coma.

Many health effects associated with chronic exposure to elevated BLLs are irreversible. Compared with other organ systems, the nervous system is the most sensitive and chief target for lead-induced toxicity. The severity of lead toxicity is correlated with higher BLLs and may include delirium, lack of coordination, convulsions, paralysis, coma, ataxia, and death. 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.

Adverse effects in children include behavioral and learning problems, lower IQ and hyperactivity, impaired growth, hearing problems, and anemia. Young children absorb lead at a higher rate (40% to 50% of ingested lead) compared to adults (3% to 10%) and are especially vulnerable to the neurological effects of lead. The developing nervous system is thought to absorb a higher fraction of blood lead compared with adults. New findings also suggest lead exposure in children can result in a range of cardiovascular, immunological, and endocrine adverse health effects. Few studies of the long-term consequences of childhood lead poisoning exist. However, in a 50-year followup of 35 adult survivors of childhood lead poisoning, all of whom had been symptomatic, cognitive dysfunction, hypertension, and offspring with learning disabilities were more prevalent than in matched adult controls.

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 percentages of children and adults with elevated BLLs have declined significantly over the past few decades.

Data from the 1976 to 1980 cycle of NHANES estimated that 88 percent of children ages 1 to 5 years had BLLs of 10 µg/dL or greater. This percentage fell sharply in the following decades to 4.4 percent from 1991 to 1994, then 1.6 percent during the 1999 to 2002 cycle, and was estimated to be 0.8 percent in the most recent 2007 to 2010 survey cycle. NHANES data from 2007 to 2010 estimated that 3.1 percent of children ages 1 to 2 years had BLLs of 5 µg/dL or greater. Estimates varied by race/ethnicity, socioeconomic status, and age of housing. Among children ages 1 to 2 years, 7.7 percent of non-Hispanic black children had BLLs of 5 µg/dL or greater, compared with 3.2 percent of non-Hispanic white children and 1.6 percent of Mexican American children; 3.1 percent of males and 3.2 percent of females had BLLs of 5 µg/dL or greater in the same survey. Differences were also observed based on socioeconomic status; 6.0 percent of children living in a household with a poverty-to-income ratio of less than 1.3 had BLLs of 5 µg/dL or greater, compared with 0.5 percent of children living in a household with a
poverty-to-income ratio of 1.3 or greater (ratio <1.00 indicates an income below the official definition of poverty). During the NHANES 1999 to 2002 cycle, children living in pre-1950 housing were 10 times more likely to have BLLs of 5 µg/dL or greater than children living in homes built after 1978. By the 2007 to 2010 cycle, children living in pre-1950 housing were 4 times more likely to have BLLs of 5 µg/dL or greater than children living in homes built after 1978.13

**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.14

Common sources of lead exposure include the following: lead-based paint, contaminated soil (e.g., by exterior lead-based paint, historical lead emitting industrial sites, or gasoline), lead-contaminated water (e.g., by lead plumbing), and dust contamination by chipping or chalking of lead-based paint and tracked-in soil.14 In the United States, leaded gasoline began to be phased out in 1973 and was banned by 1996. From 1980 to 2010, exposure to lead fumes from leaded gasoline decreased by 89 percent.15 Lead-based paints were banned for use in housing in 1978. All houses built before 1978 are likely to contain some lead-based paint and the deterioration of this paint is an important source of lead in older homes.14 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.16 The release of lead from lead-based plumbing materials into drinking water is variable and influenced by factors such as water softness, temperature, acidity, and corrosion control techniques.17 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.18

Children are exposed to lead in a variety of ways. Since the removal of lead from gasoline, lead-based paint has become the major source of lead exposure for children in the United States.19 Other important pediatric sources of lead exposure include elevated maternal blood lead concentration during pregnancy and breastfeeding; exposure to lead-contaminated soil, food, or water; and lead in toys.2 Young children frequently place objects in their mouths resulting in ingestion of lead-contaminated dust and soil. Children and infants may be exposed to lead via drinking water or reconstituted formula,20 placental transfer of lead during pregnancy to the fetus, or maternal transfer of lead to infants through breast milk.21 Children can be exposed to lead via take-home exposures by adults who work with lead.19 Parental take-home exposures from work or hobbies can be easily transferred to children through lead dust found on hair, clothes, or tools. Compared with adults, children have a higher rate of physiological uptake of lead.

Once exposed, nutritional factors are known to affect lead absorption and toxicity. Iron-deficient or calcium-deficient diets may lead to more efficient lead absorption.22 Following absorption, lead is distributed to the blood, soft tissues, and bone. In blood, 99 percent of lead is bound to erythrocytes 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.23

**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 developing countries where leaded gasoline is still used.14 Among children, socioeconomic factors such as lower family income, older age of housing, and poorer nutritional status predict exposure to lead.4,13

**Rationale for Screening/Screening Strategies**

Current clinical guidelines and policies emphasize primary prevention of lead exposure. The rationale for screening in primary care settings is to identify children for whom primary prevention was unsuccessful, so that interventions can be initiated to reduce lead levels and minimize or prevent the neurodevelopmental adverse effects of lead poisoning.

As the prevalence of elevated BLLs has declined, clinical practice has shifted from universal to targeted screening that incorporates education about primary prevention.24 Several questionnaires have been developed to identify children at higher risk of elevated BLLs. The mostly widely used is the CDC questionnaire, developed in 1991, which consists of five questions about living in or visiting a house built before 1960 with chipping paint or undergoing renovation; having a sibling or close contact being followed or treated for lead poisoning (BLL ≥15 µg/dL); living with an adult who is exposed to lead through work or hobbies; and living near lead-based industry. The CDC has recommended the use of the questionnaire, with a positive or “don’t know” answer to any of the five questions indicating the need for a blood lead test.25 However, given more recent recognition of the limitations of this questionnaire, the CDC recommends that public and clinical health professionals collaborate to develop screening plans that are responsive to local conditions by using local data.25

Screening options to detect an elevated BLL include 1) directly measuring the BLL through venous or capillary blood sampling or 2) measuring the effect of lead exposure on hemoglobin synthesis using either a free erythrocyte or zinc protoporphyrin (EP) assay (via venous blood sampling).24 Measuring BLLs using capillary blood sampling is simpler than venous sampling and is the recommended initial method for lead screening.26 However, if performed incorrectly, capillary samples may be contaminated with exogenous lead and can yield false-positive results.27 Potential sources of contamination include inadequate use of gloves by phlebotomists, use of alcohol wipes contaminated with lead-based ink, inadequate cleansing of the child’s finger, and failure to wipe off the first drop of blood.24 Patients who have elevated BLLs on capillary samples must have confirmatory venous blood testing.28 EP levels usually are not elevated until BLLs are greater than 30 µg/dL. Therefore, EP levels are not an accurate assessment of lower levels of lead toxicity and are not recommended for screening.24 In addition, EP levels are elevated in other conditions, including iron deficiency and inherited porphyrias.24
Interventions/Treatment

The management of elevated BLLs in children varies depending on the confirmed BLL and other factors. Identifying the source of lead exposure is a key to preventing ongoing or repeated exposure and remains the mainstay of treatment for lead exposure.

Educational and Environmental Interventions

Educational interventions address parental awareness of lead exposure pathways, hygiene, and household dust control measures to prevent ingestion of dust and soil. Environmental (household) interventions include specialized cleaning, repairs, maintenance, soil abatement (e.g., removal and replacement), painting, and temporary containment of lead hazards.

Nutritional Interventions

The role of nutritional supplementation in reducing blood lead concentration among children with elevated BLLs is unclear. Calcium, dietary iron, and other supplements are thought to decrease the intestinal absorption of lead. This is supported by epidemiologic studies that have demonstrated an increased prevalence of iron deficiency among children with lead poisoning.29,30 However, the association is inconsistent, and evidence of an association between iron intake and lead levels in iron-replete children is lacking.

Chelation Therapy

In children, chelation therapy is recommended for severe lead toxicity (defined by a venous BLL of ≥70 µg/dL or having symptoms of encephalopathy) and moderate toxicity (symptomatic or BLL between 45 and 69 µg/dL) and is generally reserved for symptomatic individuals. Chelating agents work as binding agents that remove metals (i.e., lead) from the blood and soft tissues, including the brain, to reverse acute encephalopathy and alleviate vomiting, abdominal pain, anemia, and renal insufficiency caused by lead toxicity. Dimercaprol (dimercaptosuccinic acid [DMSA] or succimer) is a commonly used agent for the oral chelation of lead in children with levels at or above 45 µg/dL,31 and d-penicillamine is rarely used in patients who do not tolerate DMSA. In regions where cost is an issue, d-penicillamine may be used, but it is not recommended as a first-line agent. However, multiple potential harms of chelation therapy have been described, including side effects such as rash, neutropenia, elevation of serum liver transaminases, and gastrointestinal upset, in addition to acute side effects such as injection site pain, nausea, vomiting, headache, paresthesias, and tremor.32 Serious adverse reactions may include hypertension, tachycardia, infection site abscess, and fever.28

Current Clinical Practice/Recommendations of Other Groups

Current Clinical Practice

Data are lacking on the current proportion of primary providers who screen asymptomatic children for elevated BLLs. A 1996 survey (N=734) of pediatricians, members of the American Academy of Pediatrics (AAP), found that 53 percent reported screening all patients ages 9 to 36
months, 39 percent reported screening some patients, and 8 percent reported screening none of their patients. Among physicians who reported screening for elevated BLLs, 96 percent used a BLL assay and 3 percent used a porphyrin assay. Of those who used a BLL assay, 39 percent collected blood for screening using a finger stick method and 52 percent collected blood using venipuncture (9% did not report the method used). The primary risk factors that selective screeners identified were history of pica (94%), living in an older home with recent renovations (92%), living in an older home with peeling paint (93%), and having a sibling who had an elevated BLL (88%).

When a child with an elevated BLL is identified, confirmatory and repeat testing is recommended, followed by management based on lead levels and symptoms. Important management strategies for asymptomatic children with BLLs of 45 µg/dL or less include removing the source of lead exposure, testing close contacts and other children in the household at risk, and lead abatement and education. For children who are symptomatic or with higher blood lead concentration (≥45 µg/dL), in addition to the management strategies mentioned above, emergent consultation with an expert is recommended for consideration of hospitalization, stabilization, and chelation therapy based on the degree of symptoms. Specific guidelines exist for followup depending on the degree of elevation of BLL.

Recommendations of Other Groups

Table 1 summarizes current screening recommendations from other organizations. Contrary to the 2006 USPSTF recommendation, existing recommendations from the AAP, CDC, and American College of Preventive Medicine all state that children at high risk for lead exposure should receive screening. The American College of Preventive Medicine defines high-risk groups as those receiving Medicaid or WIC, living in a community with 12 percent or greater prevalence of BLLs at 10 µg/dL or greater, living in a community with 27 percent or greater of homes built before 1950, or meeting one or more high-risk criteria of a lead screening questionnaire. Questionnaires tailored to specific communities may include questions about the use of home remedies and cosmetics, country of origin, and behavioral risk factors. Bright Futures recommends screening in accordance with state law, and universal screening at ages 12 and 24 months in states with no screening program in place. In 2016, AAP recommended screening according to federal, state, and local requirements, with targeted screening of populations including immigrant, refugee, and internationally adopted children when they arrive in the United States; children ages 12 to 24 months living in communities with 25 percent or greater of housing built before 1960 or a 5 percent or greater prevalence of BLLs of 5 µg/dL or greater; and children with identified lead hazards or a home built before 1960 that is in poor repair or renovated in the past 6 months.
Chapter 2. Methods

Key Questions and Analytic Framework

This systematic review followed a standard protocol in accordance with USPSTF procedures. 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. 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, as well as the direct and indirect pathways from screening to health outcomes (Figure 1). A research plan was externally reviewed and modified prior to finalization.

Key Questions

1. Is there direct evidence that screening for elevated BLLs in asymptomatic children age 5 years and younger improves health outcomes (i.e., reduced cognitive or behavioral problems or learning disorders)?
2a. What is the accuracy of questionnaires or clinical prediction tools that identify children who have elevated BLLs?
2b. What is the accuracy of capillary blood lead testing in children?
3. What are the harms of screening for elevated BLLs (with or without screening questionnaires) in children?
4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce BLLs in asymptomatic children with elevated BLLs?
5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic children with elevated BLLs?
6. What are the harms of interventions in asymptomatic children with elevated BLLs?

Contextual Questions

1. What is the reliability of capillary and venous BLL testing at various lead levels in children?
2. What is the association between reduced BLLs and improved health outcomes in asymptomatic children 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 children?

Key Question 1 focused on direct evidence of the effectiveness of screening asymptomatic children age 5 years and younger for elevated BLLs for improving future health outcomes (e.g., reduced cognitive problems, reduced behavioral problems, and reduced learning disorders).
compared with not screening. Screening refers to diagnostic testing of BLLs to identify children with unrecognized elevation of lead levels. 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 improvement in important health outcomes. Links in the chain of indirect evidence include the accuracy of screening for identifying children with elevated BLLs, the effectiveness of interventions for treating children identified with elevated BLLs and reducing the incidence of complications, the association between improvements in intermediate outcomes and clinical health outcomes, and 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 children with elevated BLLs can be identified. It is also necessary to show that there are effective treatments for children identified with elevated BLLs.

A separate report addresses screening for elevated BLLs in pregnant women.

### Search Strategies

Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through March 2017), Ovid MEDLINE (1946 through March 2017), all studies from prior reviews, and reference lists of included studies were searched for relevant studies. Search strategies are available in Appendix A1. An additional Ovid MEDLINE search (through October 2017) was conducted for the Contextual Questions after the initial search did not identify any studies meeting inclusion criteria. 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 and therefore the related USPSTF recommendation. The last surveillance was conducted on December 5, 2018.

### Study Selection

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

Populations of asymptomatic children age 5 years and younger were included, regardless of risk for elevated BLLs, but we accepted studies that included children older than age 5 years when the majority of the study population was age 5 years and younger. Studies of high- or low-risk populations were included for all Key Questions. Testing approaches included screening questionnaires and venous or capillary blood lead testing. Comparisons were screening versus no screening (Key Question 1); a questionnaire versus a reference standard (i.e., venous lead level) (Key Question 2a); capillary versus venous BLL testing (Key Question 2b); and treatment versus no treatment, placebo, or inactive control (Key Questions 3 through 5). Intermediate outcomes (e.g., BLLs) were included, as well as clinical outcomes using validated measures of cognitive or neurobehavioral outcomes in children. Other outcomes were measures of diagnostic accuracy (Key Question 2) and harms of testing (e.g., anxiety, distress, pain, or discomfort related to
testing) and treatment. 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. Included studies for Key Questions 4 through 6 (treatment of elevated BLLs) were studies of asymptomatic children conducted in any country that evaluated interventions that focused on the individual or family (i.e., counseling, nutritional interventions, residential hazard control techniques, and chelation therapy). Studies on effects of policies, laws, or community-based interventions focused on the primary prevention of lead exposure were excluded. For harms, 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 were included. 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 relative risks (RRs), likelihood ratios, positive and negative predictive values, and 95 percent CIs or p-values. Two investigators independently applied criteria developed by the USPSTF \(^38\) 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). \(^38\) For diagnostic accuracy of clinical questionnaires, comparable studies were pooled using a random-effects model with the ‘metandi’ command in Stata version 14.2 and created hierarchical summary receiver operating characteristic (ROC) plots using the ‘metandiplot’ function. \(^40,41\) The “metandi” command is a meta-analysis function for diagnostic test accuracy studies in which both the index test under study and the reference test (gold standard) are dichotomous. It assumes a bivariate normal distribution for random effects as a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives within each study, and a bivariate normal model for the logit transforms of sensitivity and specificity between studies. Forest plots (without a summary measure) and summary ROC plots were also created using Review Manager version 5.3. \(^42\)
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

The draft report was posted for public comment on the USPSTF Web site from October 30, 2018 to December 3, 2018. Comments encompassed requests to include results from studies of primary prevention and challenges in assessing clinical effects of lead exposure, which can take several years to manifest. However, primary prevention of lead exposure is out of scope for this review, which focused on screening and interventions to identify and reduce already elevated BLLs. As noted in the Results, studies on the long-term effects of screening or treatment of elevated BLLs are lacking.
Chapter 3. Results

The search and selection of articles are summarized in the literature flow diagram. Two reviewers independently identified 3,147 unique citations and 233 full-text articles based on predefined criteria (Appendix A2). A total of 21 studies met inclusion criteria for this review (N=10,449). 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 1. Is There Direct Evidence That Screening for Elevated BLLs in Asymptomatic Children Age 5 Years and Younger Improves Health Outcomes?

As in the prior USPSTF review, no studies directly compared the effectiveness of screening versus no screening for elevated BLLs in children age 5 years and younger on health outcomes.

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

Summary

Nine fair-quality studies (six included in the prior USPSTF report) reported the diagnostic accuracy of questionnaires or clinical prediction tools for identifying asymptomatic children with elevated BLLs, defined as a BLL greater than 10 µg/dL. All studies used a BLL greater than 10 µg/dL as the reference standard. Five fair-quality studies that used the threshold of one or more positive answers on the five-item 1991 CDC screening questionnaire reported a pooled sensitivity of 48 percent (95% CI, 31.4% to 65.6%) and specificity of 58 percent (95% CI, 39.9% to 74.0%) for identifying children with a venous BLL of 10 µg/dL or greater.

Four fair-quality studies that used versions of the CDC questionnaire modified for specific populations or settings did not demonstrate improved accuracy (sensitivity range, 25% to 68%; specificity range, 49% to 58%).

Evidence

The prior USPSTF review found fair evidence that a validated questionnaire can correctly identify 64 to 87 percent of children at high risk in urban and suburban populations with BLLs of 10 µg/dL or greater. However, eight of the studies in the prior review did not meet criteria for this update and were excluded due to having the wrong comparison or reference standard. The prior report also found fair evidence that a validated questionnaire had not been adequately evaluated as a screening tool to detect higher BLLs (e.g., ≥20 to 25 µg/dL) or lead exposure in
specific populations (e.g., migrant workers, rural communities). Five studies from the prior review on accuracy of screening instruments met inclusion criteria for this update.$^{45,47,48,50,51}$ Four additional studies were identified for this update.$^{43,44,46,49}$

Nine studies reported on the diagnostic accuracy of questionnaires or clinical prediction tools for identification of children with elevated BLLs (Appendices B1 and C1).$^{43-51}$ Five studies evaluated the accuracy of the 1991 CDC questionnaire and four evaluated versions of the CDC questionnaires modified for specific populations and settings.$^{43-51}$ The CDC questionnaire is a five-question 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 the child’s housing and the condition of the paint; siblings or playmates with BLLs of 15 µg/dL or greater; parental exposure through work or hobbies; and a home in close proximity to lead industry. Sample sizes ranged from 167 to 2,978 (total N=6,873). Mean age was not reported in six studies, was reported as 9 months in one study,$^{43}$ and reported as 28 and 31 months in two other studies.$^{47,49}$ Females comprised 46 to 51 percent of participants in five studies and sex was not reported in the other five. Seven studies were conducted in urban or suburban communities and three studies were conducted in rural communities. Two of the studies identified their population as high risk,$^{44,46}$ and others did not characterize study populations by risk level; however, many of the populations surveyed were from public programs such as Medicaid or public health clinics. In all studies, children were reported as asymptomatic. The prevalence of children with a BLL of 10 µg/dL or greater ranged from 2.2 percent$^{47}$ to 29 percent.$^{43}$ In study populations characterized as higher risk, the prevalence of an elevated BLL of 10 µg/dL or greater ranged from 7.7 to 22 percent.$^{44,46}$ Nine studies were rated as fair quality. One poor-quality, retrospective study was excluded from this analysis.$^{60}$ Methodologic shortcomings included unclear enrollment methods and exclusion of some patients from analysis (Table 3). The poor-quality study performed retrospective surveys of exposures after BLL was known.

Five fair-quality, cross-sectional studies (total N=2,265) conducted in mostly urban$^{43-46}$ and one rural U.S. community (n=368)$^{47}$ evaluated the diagnostic accuracy of the 1991 CDC questionnaire$^3$ for identification of children with venous BLLs of 10 µg/dL or greater. The studies used a threshold of one or more positive answers from the five-question survey to indicate a positive screen. Across studies, sensitivity ranged from 32 to 83 percent and specificity ranged from 32 to 80 percent, with a pooled sensitivity of 48 percent (95% CI, 31.4% to 65.6%) and pooled specificity of 58 percent (95% CI, 39.9% to 74.0%) (Figure 2).$^{43-47}$ The positive likelihood ratio was 1.15 and the negative likelihood ratio was 0.89, indicating that either a positive or negative screen had little effect on informing the likelihood of elevated BLLs.

Four diagnostic accuracy studies$^{48-51}$ evaluated a modified 1991 CDC questionnaire by changing some of the language in the CDC questions$^3$ or expanding the CDC questionnaire by adding additional questions to address local risk factors to adapt the questionnaire for use in specific study populations. One study conducted in a low-income, inner city population (n=2,978) found that the adapted questionnaire had low accuracy for identifying children with elevated BLLs (sensitivity, 57%; specificity, 51%).$^{48}$ Another study (n=705) conducted in a rural setting$^{51}$ used two items from the CDC questionnaire and two additional items for rural community risk factors and found limited benefit in detecting rural children at higher risk. Compared with the CDC questionnaire, there was a 12-percent increase in sensitivity for identifying children with BLLs
of 10 µg/dL or greater (75% vs. 88%) and a 5-percent increase in negative predictive values (93% vs. 98%) using the modified questionnaire. A smaller study (n=171) conducted in rural New York\textsuperscript{50} that added six items to the CDC questionnaire found no difference compared with the standard CDC questionnaire for predicting elevated BLLs (sensitivity, 50% vs. 50%). Another study conducted in an urban population (n=754)\textsuperscript{49} with a 3.1 percent prevalence of a BLL of 10 µg/dL or greater found that adding two items to the CDC questionnaire did not increase accuracy for detection of children with elevated BLLs.

**Key Question 2b. What Is the Accuracy of Capillary Blood Lead Testing in Children?**

**Summary**

Four fair-quality studies conducted in the urban United States\textsuperscript{27,61-63} found that capillary blood lead testing was associated with sensitivity of 87 to 91 percent and specificity greater than 90 percent (92% to 99%) for identification of elevated BLL compared with venous sampling; two of the studies were included in the prior USPSTF review.

**Evidence**

The prior USPSTF report included two studies that compared the accuracy of capillary versus venous blood lead testing.\textsuperscript{27,63} We identified four fair-quality cohort studies assessing the diagnostic accuracy of capillary testing compared with venous sampling for elevated BLLs,\textsuperscript{27,61-63} including the two studies in the prior report (Appendices B2 and C1).\textsuperscript{27,63} All four studies were conducted in the urban United States and were published between 1994 and 1998. Sample sizes ranged from 124 to 513 participants (total N=1,431). The mean age was 3 years in one study\textsuperscript{63} and was not reported in the other studies. Females comprised 41 to 47 percent of the sample in three studies; the fourth study did not report sex. Two studies predominately enrolled black children,\textsuperscript{61,63} and one study evaluated a more diverse study population (38% white, 28% black, 21% Hispanic, and 6% Asian\textsuperscript{27}); the fourth study did not report race/ethnicity.\textsuperscript{62} Among the three studies that reported baseline BLLs, the proportion of children with a BLL of 10 µg/dL or greater ranged from 21 to 31 percent.\textsuperscript{27,61,62} Methodologic shortcomings of the studies included unclear methods of patient enrollment and exclusion of some patients from analysis.

At a BLL cutoff of 10 µg/dL or greater in capillary sampling, three studies reported sensitivities ranging from 87 to 94 percent, and specificities ranging from 92 to 99 percent (N=1,136).\textsuperscript{27,61,62} For a BLL cutoff of 15 µg/dL or greater, three studies reported sensitivities ranging from 36 to 83 percent and specificities from 95 to 98 percent.\textsuperscript{27,61,62} For a BLL cutoff of 20 µg/dL or greater, three studies reported sensitivities ranging from 78 to 96 percent and specificities from 91 to 100 percent (N=918).\textsuperscript{27,61,63}

One study evaluated different preparation methods for capillary blood sampling (N=295)\textsuperscript{63} (alcohol wipe; alcohol wipe and silicone barrier; soap and water followed by alcohol wipe; or soap and water, alcohol wipe, and 1% nitric acid solution). Using a capillary sampling threshold
of greater than 20 µg/dL, the most commonly employed sampling method (i.e., soap and water plus alcohol) had the highest specificity (100%) and similar sensitivity (88%) compared with the other methods (sensitivity, 86% to 96%; specificity, 91% to 96%).

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

As in the prior USPSTF report, no studies evaluated the harms of screening versus not screening for elevated BLLs in children.

**Key Question 4. Do Counseling and Nutritional Interventions, Residential Lead Hazard Control Techniques, or Chelation Therapy Reduce BLLs in Asymptomatic Children With Elevated BLLs?**

**Summary**

One large, good-quality RCT included in the prior USPSTF review found that chelation therapy with DMSA in children with a mean blood lead concentration of 20 to 45 µg/dL was associated with decreased blood lead concentrations versus placebo at 1 week, 6 months, and 1 year, but there were no effects at longer-term followup at 4.5 to 6 years.64-67 One fair-quality RCT included in the prior USPSTF review found no differences between chelation therapy versus placebo in blood lead concentration at 1 or 6 months.68

There was insufficient evidence from two poor-quality studies to determine effects of nutritional supplementation on BLLs. Three fair-quality RCTs from the United States and Australia (all included in the prior USPSTF review) found no clear effects of home lead remediation in lowering blood lead concentrations.

**Evidence**

The prior USPSTF review found that chelating agents may result in short-term reductions in blood lead concentrations in children but that reductions may not be sustained over longer periods in the absence of repeated or continuing chelation therapy or environmental interventions. Effects of cleaning, abatement, and education on blood lead concentrations were mixed, based on a descriptive summary of 11 studies. The prior USPSTF review also found conflicting evidence on the effects of nutritional interventional on elevated BLLs, based on a descriptive summary of 16 studies.

Seven RCTs64-73 (reported in 10 publications) evaluated the effects of interventions to reduce blood lead concentrations in asymptomatic children with elevated BLLs (Appendixes B3 and
C2); four of the studies were included in the prior USPSTF review.\textsuperscript{64-67,71,68} Two studies evaluated chelation therapy,\textsuperscript{64-68} two studies evaluated counseling and nutritional interventions,\textsuperscript{71,72} and three studies evaluated residential lead hazard control techniques.\textsuperscript{69,70,73} Sample sizes ranged from 39 to 780 (total N=1,419). Five studies were conducted in the United States and one study each in Australia and Costa Rica. The mean age of study participants was 1.6 to 3.6 years and sex distribution was balanced in studies that provided this information (44\% to 58\% female). One study was rated good quality, four fair quality, and two poor quality. The poor-quality studies lacked descriptions of randomization methodology, allocation concealment, and masking, and one study had poor followup; the poor-quality studies were included because no fair- or good-quality studies were available.

**Chelation**

One fair\textsuperscript{68} and one good-quality\textsuperscript{64-67} trial found inconsistent effects of DMSA chelation therapy on blood lead concentrations in asymptomatic children with BLLs of 20 to 45 \(\mu\)g/dL at baseline.\textsuperscript{64-68} Although the good-quality trial found that chelation therapy was associated with lower blood lead concentrations versus placebo at 1 week, 6 months, and 1 year, it found no differences at 4 to 5.6 years. The fair-quality trial found no effect of chelation therapy on BLLs at 1 or 6 months. Both trials were included in the prior report.

The Treatment of Lead-Exposed Children (TLC) study, a good-quality RCT (n=780), evaluated 12- to 33-month-old children with blood lead concentration between 20 and 44 \(\mu\)g/dL.\textsuperscript{64-67} All children received vitamin and mineral supplements and had home inspections with lead abatement. Children were randomized to treatment with DMSA (1,050 mg/m\(^2\) per day for 7 days, then 700 mg/m\(^2\) for 19 days) or placebo. Children could be treated with DMSA up to three times, with a goal blood lead concentration of less than 15 \(\mu\)g/dL. DMSA was associated with a mean difference in blood lead concentration at 1 week that was 11 \(\mu\)g/dL lower than placebo. However, blood lead concentrations increased once treatment was completed, and at 52 weeks the mean difference had decreased to 2.7 \(\mu\)g/dL in favor of DMSA (95\% CI, 1.9 to 3.5 \(\mu\)g/dL).\textsuperscript{67} In a followup study of 7-year-old participants (approximately 4.5 to 6 years after treatment), mean blood lead concentrations were identical in both groups (8.0 \(\mu\)g/dL).\textsuperscript{65}

A small, fair-quality study (n=39)\textsuperscript{68} randomized children ages 2.5 to 5 years with blood lead concentrations between 30 and 45 \(\mu\)g/dL to one course of DMSA or control. DMSA was dosed according to weight (\(\leq\)15 kg, 100 mg dose; >15 kg, 200 mg dose), and each dose was administered three times a day for 5 days followed by twice a day for 14 days. There were no significant differences in mean blood lead concentrations at 1 month (27.4 \(\mu\)g/dL [standard deviation (SD), 7.5] vs. 33.2 \(\mu\)g/dL [SD, 10.3]; \(p=0.16\)) or at 6 months (28.8 \(\mu\)g/dL [SD, 6.4] vs. 25.1 \(\mu\)g/dL [SD, 6.8]; \(p=0.06\)).

**Nutritional Interventions**

Two poor-quality studies provided insufficient evidence to determine the effects of nutritional interventions on blood lead concentrations.\textsuperscript{71,72} One double-blind, placebo-controlled trial conducted in New York City (n=88) that was included in the prior review evaluated the effects of calcium supplementation on blood lead concentrations but had high attrition (34\%) and
inadequate descriptions of randomization, allocation concealment, and masking techniques.\textsuperscript{71} The other study evaluated effects of iron supplementation in Costa Rican children\textsuperscript{72} with elevated blood lead concentrations (mean, 10.98 µg/dL) at baseline. Results were difficult to interpret because iron supplementation was given to children who were iron depleted and placebo was given to children who were iron replete, with no matching on blood lead concentrations. Children were randomized to either intramuscular iron or oral iron. Iron was associated with a decrease in blood lead concentration in iron-deplete children and placebo was associated with slightly increased BLLs in iron-replete children, but it is unclear how baseline iron levels may have affected blood lead concentrations independent of iron supplementation. Another limitation of the trial is that results were reported for the subgroup of patients in the iron-deplete group who received oral iron, but not for those who received intramuscular iron.

**Residential Lead Hazard Control Techniques**

Three fair-quality RCTs found no clear effects of home lead abatement in lowering blood lead concentrations in asymptomatic children with elevated BLLs at baseline.\textsuperscript{69,70,73} None of the studies were included in the prior review and home lead abatement interventions differed in each trial.

One trial (n=175) randomized children younger than age 28 months in Rhode Island with blood lead concentrations of 15 to 19 µg/dL\textsuperscript{70} to a home intervention (five home visits that included testing samples, tailored education, and assessment of nutrition and parent-child interaction plus lead remediation strategies) or control intervention (one to two standard educational visits from an outreach worker). Blood lead concentrations in both groups decreased, but there was no significant difference between the intervention and control groups at 3, 6, or 12 months after baseline.

Another fair-quality trial (n=90)\textsuperscript{69} conducted in Australia randomized pairs of 12- to 60-month-old children with mean blood lead concentrations between 15 and 30 µg/dL matched by age and BLL to home remediation and lead abatement versus delayed intervention for 1 year. Despite reductions in home lead concentrations after intervention, the effects of remediation on mean BLL were small (17.5 vs. 17.9 µg/dL; mean change, 1% [95% CI, -11% to 11%]), with no significant difference between groups.

A fair-quality trial (n=84)\textsuperscript{73} conducted in Florida enrolled asymptomatic children from the WIC and Head Start programs and the local health department with blood lead concentrations of 3 to 10 µg/dL (mean, 5.29 µg/dL [range, 3.0 to 9.3 µg/dL]). Participants were randomized to receive an educational brochure, a home cleaning kit, a formal home inspection and remediation, or passive control. The educational brochure included information about diet, cleaning, and habits to reduce lead exposure. The home cleaning kit included a HEPA (high-efficiency particulate air) vacuum, trisodium phosphate detergent, gloves, rags, and buckets. The formal inspection/remediation group received a home risk assessment by a professional company that included dust wipe samples that were evaluated with on-site X-ray fluorescence spectrometry and laboratory testing. The inspection was followed by a second home visit and a written report with a range of optional steps on how to decrease lead exposure. The passive control group received no intervention or information. All groups experienced a decrease in blood lead
concentration of 2.26 to 2.99 µg/dL over 6 to 12 months, with no significant difference between groups.

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

**Summary**

One good-quality randomized study included in the prior USPSTF review found no differences between chelation therapy versus placebo on neuropsychological outcomes despite a decrease in blood lead concentrations following chelation therapy.65-67

There was no evidence on effects of counseling and nutritional interventions or residential lead hazard control techniques on health outcomes in asymptomatic children with elevated blood lead concentrations at baseline.

**Evidence**

The prior USPSTF review found no clear evidence to support a clinical benefit from chelation therapy in children with elevated blood lead concentrations at baseline, based on one trial,65-67 and found no studies on effects of environmental or nutritional interventions on health outcomes.

The TLC65-67 trial (N=780) of DMSA chelation therapy versus placebo (see Key Question 4 for study details), included in the prior USPSTF review, was the only study to evaluate the effect of interventions for lowering elevated blood lead concentrations on health outcomes in children by measuring neuropsychological outcomes. At 36 months, there were no significant differences between chelation therapy and placebo in the Wechsler Preschool and Primary Scale of Intelligence-Revised, the Developmental Neuropsychological Assessment, or the Conners’ Parent Rating Scale-Revised. In a followup study65 of the same children at age 7 years (4.5 to 6 years after treatment), chelation therapy was associated with lower (worse) scores on the adjusted Attention and Executive Functions subscore of the Developmental Neuropsychological Assessment (unadjusted difference, -1.8 [95% CI, -4.5 to 1.0]; adjusted p=0.045). There were no statistically significant effects on any other cognitive, neuropsychiatric, or behavioral outcome.

We identified no new study on effects of chelation therapy, environmental interventions, or nutritional interventions on health outcomes. Evidence on the effects of interventions for lowering blood lead concentrations on health outcomes remains very limited.
Key Question 6. What Are the Harms of Interventions in Asymptomatic Children With Elevated BLLs?

Summary

One good-quality RCT\textsuperscript{64,67} and one poor-quality observational study\textsuperscript{74} reported adverse effects of chelation therapy. The good-quality RCT found that children treated with DMSA had a small but statistically significant decrease in height growth over 34 months and slightly poorer scores on attention and executive function tests at age 7 years (Appendixes B3 and C2).\textsuperscript{65}

The poor-quality study reported adverse events associated with the less commonly used chelator d-penicillamine, including leukopenia, thrombocytopenia, urticarial and maculopapular rashes, urinary incontinence, abdominal pain, and diarrhea.\textsuperscript{74}

No study evaluated harms of counseling, nutritional interventions, or residential lead hazard control techniques.

Evidence

The prior USPSTF report found adverse effects of environmental interventions including transient elevation in blood lead concentrations, inconvenience associated with abatement work or relocation, and cost-benefit considerations, but the number of studies on which these narrative findings was based was unclear. It also identified adverse effects after DMSA chelation therapy that included mild gastrointestinal (vomiting and diarrhea) and systemic symptoms, rashes, transient hyperphosphatasemia, neutropenia, eosinophilia, and elevations in serum aminotransferases. Most evidence from the prior report did not meet our inclusion criteria due to study design, lack of comparison group, wrong outcomes, or lack of a reference standard. The prior USPSTF review included data on harms from one good-quality RCT, which was also included in this update.

The TLC trial compared DMSA chelation therapy with placebo in children ages 12 to 33 months with blood lead concentrations between 20 and 44 µg/dL (N=780).\textsuperscript{67} DMSA was associated with a small but statistically significant decrease in height growth over 34 months (difference of 0.35 cm [95% CI, 0.05 to 0.72 cm]) and slightly poorer scores on attention and executive function tests (unadjusted difference of -1.8; adjusted effect P=0.045) at age 7 years. There were no significant differences in laboratory values, including neutrophil count, platelet count, aminotransferase concentrations, and alkaline phosphatase concentration.\textsuperscript{64,67} Children treated with DMSA were more likely to have evidence of minor traumatic injuries on physical examination (14.9% vs. 9.9%).\textsuperscript{64} However, a mechanism for this association is not known or theorized.

A poor-quality retrospective cohort study (n=75) evaluated d-penicillamine in children with blood lead concentration of 25 to 40 µg/dL.\textsuperscript{74} Twenty-nine adverse events were reported in 37 percent of study participants, including leukopenia (11%; white blood cell count <4,000/mm\textsuperscript{3}), rash (9%), low platelet count (9%; <300/mm\textsuperscript{3}), enuresis (4%), abdominal pain (3%), and
hematuria (1%) (Appendix C3). No study identified harms of counseling, nutritional interventions, or residential lead hazard control techniques.

**Contextual Question 1. What Is the Reliability of Capillary and Venous BLL Testing at Various Lead Levels in Children?**

Understanding whether current methods for testing for elevated BLLs is reliable would be helpful for confirming that a standard, predictable measure of blood lead exists and for informing testing strategies. We sought evidence to determine whether children are consistently classified as having elevated BLL at standard thresholds and whether tests perform reliably between laboratories and between patients across the minimum or standard threshold of BLLs. However, we found no studies on these aspects of reliability of BLL testing in children.

**Contextual Question 2. What Is the Association Between Reduced BLLs and Improved Health Outcomes in Asymptomatic Children With Elevated BLLs?**

One good-quality randomized study (in four publications) addressed the association between reduced BLLs and improved health outcomes in children with elevated BLLs. The previously described TLC study of chelation therapy with DMSA65-67 (n=780) found an inverse relationship between cognitive test scores and changes in blood level concentration, with a decrease in cognitive test scores of 3.2 to 3.3 points for every 10-µg/dL increase in BLL. However, there was no correlation between short-term decreases in blood lead concentration and long-term cognitive test scores in the DMSA group compared with placebo.66

**Contextual Question 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 Children?**

We identified no studies on the accuracy of community-level risk prediction tools for use in primary care screening to identify children at highest risk for lead exposure. Risk assessment tools for individuals are addressed in Key Question 1.
Chapter 4. Discussion

Summary of Review Findings

Consistent with the prior USPSTF review,1 no study directly evaluated benefits or harms of screening children for elevated BLLs compared with no screening. As in the prior USPSTF review, we found four additional studies of instruments to identify children at higher risk of elevated BLLs to guide targeted screening, all of which had poor diagnostic accuracy. This update also confirms there are no clear effects of interventions for lowering elevated BLLs in affected children or for improving neurodevelopmental outcomes. Evidence reviewed for this update is summarized in Table 2.

Given the decreased prevalence of elevated BLLs in the U.S. pediatric population (from 88% between 1976 and 1980 to 0.8% from 2007 to 2010), targeted screening strategies have been suggested.4 The most commonly used risk assessment instrument is the CDC questionnaire. However, studies found poor diagnostic accuracy of the 1991 CDC questionnaire for identifying children with elevated BLLs, with noninformative likelihood ratios.3 In addition, the CDC questionnaire was created in 1991 and no study on its accuracy has been published since 1997, potentially limiting the applicability of currently available evidence to contemporary clinical practice. Accordingly, screening recommendations from the CDC, AAP, and other organizations note the limitations of this questionnaire. The CDC recommends that public and clinical health professionals collaborate to develop screening plans that are responsive to local conditions by using local data, with universal screening in the absence of such plans.25,75 Accurate risk assessment instruments would facilitate improved targeted screening strategies, and some states have adapted the CDC questionnaire with items addressing local risk factors. However, studies on modified versions of the CDC questionnaire for specific settings and populations also showed poor accuracy for identifying children at risk for elevated BLLs.48-51 In lieu of accurate screening instruments for identifying children to screen, alternative strategies such as universal screening or screening targeted at communities with high prevalence of elevated BLLs could be effective.44

A recent systematic review76 of screening questionnaires for elevated BLLs reported sensitivities ranging from 0.25 to 0.87 and specificities ranging from 0.31 to 0.80, but it included other questionnaires, did not report results for the CDC questionnaire separately, included studies that evaluated different cutoffs for a positive questionnaire, or did not use venous samples as the reference standard. Our findings regarding the poor accuracy of the CDC questionnaire are generally consistent with this review.

Four studies evaluated the diagnostic accuracy of capillary blood lead testing compared with venous measurement.27,61-63 Capillary sampling is slightly less sensitive than venous sampling, with comparable specificity, provided that contamination is avoided using standard techniques. Factors that may inform the decision to perform capillary versus venous sampling for screening include the tradeoffs between slightly worse accuracy and greater convenience or patient preferences. Both methods require confirmation of elevated BLLs. The prior review provided descriptive information of some diagnostic tests but did not evaluate the diagnostic accuracy of...
There is limited evidence on the effectiveness of interventions for elevated BLLs on neurodevelopmental outcomes and BLLs. One trial showed short-term (through 1 year) effects of DMSA chelation therapy on lowering BLLs versus placebo in children with moderately elevated BLLs (20 to 44 µg/dL) at baseline, but no clear effects on longer-term BLLs or neurodevelopmental outcomes, and some data indicating potential harms (hematological and other laboratory parameters and growth).\textsuperscript{64-67} A small, fair-quality trial found no effects of DMSA chelation therapy on BLLs.\textsuperscript{68} No trial evaluated effects of chelation therapy in children with BLLs less than 20 µg/dL, but chelation therapy in children with blood lead concentrations in this range is not recommended in the absence of severe symptoms. Evidence on residential interventions was limited and showed no clear effects on blood lead concentrations, while evidence on nutritional interventions (calcium or iron supplementation) was of poor quality and insufficient to determine effects on clinical outcomes. The prior review found limited and contradictory effects of nutritional interventions, no studies on outcomes related to residential lead hazard control, and short term reductions in BLL from chelation therapy, with no sustained effect over longer periods.

**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. Newer recommendations suggest the use of a population-based reference value as the “level of concern” to identify children and environments associated with lead hazards.\textsuperscript{77} Lowering the reference value may affect the accuracy and precision of blood collection and analysis, suggesting that further evidence on test reliability would be advantageous. The World Health Organization has noted the potential benefits of portable point-of-care testing and recommends a highly accurate method with a low limit of detection for the general population in which relatively low levels of exposure exist.\textsuperscript{78} The association between reduced BLLs and improved health outcomes was addressed in one treatment trial, which found that short-term decreases in blood lead concentrations induced by treatment with DMSA did not correlate with long-term cognitive test scores.\textsuperscript{66}

**Limitations**

This review has several limitations. First, there was an overall lack of evidence to address all Key Questions. Second, despite searching for updated data, the available studies evaluating the effectiveness of risk-based questionnaires were published between 1994 and 2003 and may not assess contemporary risk factors. Current clinical practice uses a reference BLL of greater than 5 µg/dL, based on updated CDC guidance, but several of the studies included in this review used the older reference value of 10 µg/dL. Despite changing reference values, included studies of diagnostic accuracy may also not reflect the amount of potential error in measures of continuous BLLs, as these are prone to miscategorization due to the dichotomization of results, regardless of which threshold is used. Third, nonrandomized studies were included to evaluate the
effectiveness of interventions for elevated BLLs, but these are more susceptible to confounding and bias than well conducted RCTs, leading to downgrading of study quality. Fourth, direct correlation of environmental lead exposures with longer-term health outcomes is difficult to study and characterize, since these exposures often have subtle clinical effects. Fifth, the review focused on screening and treatment of individuals in primary care settings, excluding community and public health approaches that could inform screening practices at the population level. The review restricted inclusion 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. Finally, we did not attempt meta-analysis for outcomes other than diagnostic accuracy, given the small number of studies and clinical and methodological diversity within the studies, and we 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 predominantly affect socioeconomically disadvantaged and minority children. Different sources of lead exposure than previously considered are emerging in these populations, yet research on screening and prevention in these populations remains limited.\textsuperscript{79-81} Exposures related to community water sources, lead pipes in schools, and factory emissions affecting neighborhood soil quality are some of the emerging factors that are not well incorporated into current screening questionnaires. Additional research is warranted to validate these potential associations in specific geographic locations and among at-risk populations. 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.\textsuperscript{80,81} Nontraditional sources of lead exposure that come from items manufactured in other countries, such as leaded pots and pans, cosmetics, medicines, ceramics, candy, and leaded crystal may also pose additional risk since little regulation exists to monitor, identify, and control these nonpaint exposures. Children who are exposed to less commonly recognized sources of lead exposure also often live in areas with a higher risk for housing-related source exposures.\textsuperscript{79} The dual risk associated with minority communities calls for a more focused strategy to deal with population-specific risks.

Future Research

Elevated BLLs are associated with serious health consequences. Additional research is needed to better inform decisions regarding screening for elevated BLLs in children. Effective screening could identify lead-contaminated residential environments and abate them, not only to improve the health of the child but also for siblings and others in the household. While remediation of lead exposures in a specific residence may be too late for a child who already is exposed, interventions could prevent exposures in subsequent generations of children who may reside in that residence. Development of questionnaires that incorporate current risk factors for elevated
BLLs with validation in contemporary populations of children in the United States is necessary. Research is needed to evaluate the effectiveness of treatments for elevated BLLs such as counseling, nutritional interventions (such as calcium), and residential lead hazard control techniques in trials with adequate sample sizes to inform treatment strategies. While there is limited evidence for a clinical benefit of nutritional supplementation in reducing BLLs in children, epidemiological evidence is supported by studies of the toxicokinetics of lead in childhood and could be further validated by well-designed research studies. Ideally, randomized trials would recruit children from a range of racial/ethnic and socioeconomic strata, and evaluate the effects of screening on improving health outcomes as well as harms in the short and long term. However, randomized trials may not be feasible or appropriate for lead screening or some interventions of environmental health exposures due to ethical issues. Research on newer methods for testing for elevated BLLs, such as point-of-care testing, and 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 children for lead poisoning is lacking. Screening questionnaires are not accurate for identifying children with elevated BLLs. Capillary blood testing is slightly less accurate than venous blood testing for identification of elevated BLLs. Treatment studies of chelating agents, often combined with environmental or household interventions, were not associated with sustained effects on BLLs but were associated with harms.
References


Abbreviation: KQ=key question.

a Interventions include counseling families to reduce lead exposure, nutritional interventions, residential hazard control techniques, and chelation therapy.

b 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.
Figure 2. Sensitivity and Specificity of CDC Screening Questionnaire (>1 Positive Answers and >10 µg/dL Venous BLL)

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<tbody>
<tr>
<td>Casey, 1994, n = 167</td>
<td>0.40 (0.26 to 0.55)</td>
<td>0.60 (0.50 to 0.69)</td>
</tr>
<tr>
<td>Dalton, 1990, n = 516</td>
<td>0.70 (0.60 to 0.79)</td>
<td>0.32 (0.27 to 0.37)</td>
</tr>
<tr>
<td>Kazal, 1997, n = 308</td>
<td>0.43 (0.10 to 0.82)</td>
<td>0.74 (0.69 to 0.79)</td>
</tr>
<tr>
<td>Robin, 1997, n = 967</td>
<td>0.83 (0.36 to 1.00)</td>
<td>0.39 (0.35 to 0.42)</td>
</tr>
<tr>
<td>Snyder, 1995, n = 247</td>
<td>0.32 (0.13 to 0.57)</td>
<td>0.80 (0.74 to 0.85)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.48 (0.31 to 0.66)</td>
<td>0.58 (0.39 to 0.74)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BLL = blood lead level; CDC = Centers for Disease Control and Prevention.
Table 1. Current Recommendations From Other Organizations

<table>
<thead>
<tr>
<th>Organization, Year</th>
<th>Screening Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Family Physicians (AAFP) 2006&lt;sup&gt;36&lt;/sup&gt;</td>
<td>The AAFP adopted the 2006 USPSTF recommendations for children. Recommendations state that evidence is insufficient to recommend for or against routine screening for elevated BLLs in asymptomatic children ages 1 to 5 years who are at increased risk. The AAFP recommends against routine screening for elevated BLLs in asymptomatic children ages 1 to 5 years who are at average risk.</td>
</tr>
<tr>
<td>American Academy of Pediatrics (AAP) 2016&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Providers should test asymptomatic children for elevated blood lead concentrations according to federal, local, and state requirements. Immigrant, refugee, and internationally adopted children also should be tested for blood lead concentrations when they arrive in the United States due to increased risk. Recommends targeted screening of children ages 12 to 24 months living in communities with ≥25% of housing built before 1960 or a prevalence of BLLs ≥5 μg/dL of ≥5%; children who live in or visit a home or child care facility with an identified lead hazard; and children living in a home built before 1960 in poor repair or renovated in the past 6 months.</td>
</tr>
<tr>
<td>American Academy of Pediatrics (AAP)/Bright Futures&lt;sup&gt;35&lt;/sup&gt; 2012</td>
<td>Screening for lead poisoning should be done in accordance with state law as applicable. For children who live in states that do not have a state screening program in place, the AAP recommends universal screening for children at ages 12 and 24 months.</td>
</tr>
<tr>
<td>American College of Preventive Medicine (ACPM) 2001&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Screening for elevated BLLs via venous or capillary blood lead testing should be conducted for children at age 1 year, only if they are identified as being at high risk for elevated BLLs. Criteria for being at high risk include receipt of Medicaid or WIC, living in a community with ≥12% prevalence of BLLs at ≥10 μg/dL, living in a community with ≥27% of homes built before 1950, or meeting one or more high-risk criteria of a lead screening questionnaire. This questionnaire should include both questions suggested by the CDC in its 1997 guidelines and questions developed for and tailored to specific communities. These questions may pertain to use of home remedies and cosmetics, country of origin, and behavioral risk factors. Risk assessment for lead exposure should be performed beginning during prenatal visits and continuing until age 6 years.</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention (CDC) 2010&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Guidelines emphasize primary prevention of lead poisoning and recommend that clinicians educate families about prevention of lead exposure and provide environmental assessments to identify sources of lead exposure before testing children for lead poisoning.</td>
</tr>
<tr>
<td>Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) 2012&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Blood lead screening remains necessary to identify children for whom primary prevention is unsuccessful. Screening for lead poisoning should be done in accordance with state law as applicable. For children who live in states that do not have a state screening program in place, the ACCLPP recommends universal screening for children at ages 12 and 24 months.</td>
</tr>
</tbody>
</table>

**Abbreviations:** AAFP=American Academy of Family Physicians; AAP=American Academy of Pediatrics; ACCLPP=Advisory Committee on Childhood Lead Poisoning Prevention; ACPM=American College of Preventive Medicine; BLL=blood lead level; CDC=Centers for Disease Control and Prevention; USPSTF=U.S. Preventive Services Task Force.
Table 2. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question*</th>
<th>Main Findings From Prior USPSTF Reviews</th>
<th>Number and Type of Studies Identified for Update</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of Findings</th>
<th>Strength of Evidence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No studies</td>
<td>0</td>
<td>No studies</td>
<td>No studies</td>
<td>Not applicable</td>
<td>No studies</td>
<td>Insufficient</td>
</tr>
<tr>
<td>2a</td>
<td>Not previously reviewed‡</td>
<td>10 cross-sectional studies</td>
<td>All studies conducted from 1994 to 2003; studies used the 1991 CDC questionnaire or a modified version of this survey.</td>
<td>Consistent</td>
<td>Moderate</td>
<td>Five studies that used the threshold of ≥1 positive answers on the 5-item 1991 CDC screening questionnaire reported a pooled sensitivity of 48% (95% CI, 31.4% to 65.6%) and specificity of 58% (95% CI, 39.9% to 74.0%) for identifying children with a venous BLL ≥10 µg/dL. Four studies that used versions of the CDC questionnaire modified for specific populations or settings did not demonstrate improved accuracy (sensitivity range, 25% to 68%; specificity range, 49% to 58%).</td>
<td>Moderate</td>
</tr>
<tr>
<td>2b</td>
<td>Not previously reviewed‡</td>
<td>4 observational studies</td>
<td>None</td>
<td>Consistent</td>
<td>Moderate</td>
<td>Four studies conducted in urban areas of the U.S. found capillary BLL testing associated with sensitivity of 87% to 91% and specificity &gt;90% (92% to 99%) for identification of elevated BLL compared with venous sampling.</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>No studies</td>
<td>0</td>
<td>No studies</td>
<td>No studies</td>
<td>Not applicable</td>
<td>No studies</td>
<td>Insufficient</td>
</tr>
<tr>
<td>4</td>
<td>Not previously reviewed‡</td>
<td>7 RCTs or observational studies (in 10 publications)</td>
<td>Poor-quality studies of nutritional interventions do not provide adequate data to assess treatment effects.</td>
<td>Consistent</td>
<td>Low to moderate</td>
<td>One large RCT found that chelation therapy with DMSA in children with a mean BLL of 20 to 45 µg/dL was associated with decreased BLL vs. placebo at 1 week, 6 months, and 1 year, but there were no effects at longer-term followup at 4.5 to 6 years. One RCT found no differences between chelation and placebo in BLL at 1 or 6 months. There was insufficient evidence from 2 studies to determine effects of nutritional supplementation. Three studies of residential lead hazard control techniques found no difference in BLL between intervention or control groups.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
### Table 2. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Main Findings From Prior USPSTF Reviews</th>
<th>Number and Type of Studies Identified for Update</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of Findings</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>No clear evidence to support a clinical benefit from chelation therapy in children with elevated BLL at baseline, based on 1 trial; no studies on effects of environmental or nutritional interventions on health outcomes.</td>
<td>1 RCT (in 3 publications)</td>
<td>Based on 1 RCT of 780 U.S. children, the adjusted treatment effect on one cognitive testing subscore showed a statistically significant but small improvement in the placebo group (p=0.045). No other significant outcomes for all other effects of treatment on cognitive, neuropsychiatric, and behavioral testing scores.</td>
<td>Consistent</td>
<td>Moderate</td>
<td>One randomized study found no differences between chelation therapy and placebo in neuropsychological outcomes, despite a decrease in BLL following chelation. There was no evidence on effects of counseling and nutritional interventions or residential lead hazard control techniques on health outcomes in asymptomatic children with elevated BLL at baseline.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
### Table 2. Summary of Evidence

<table>
<thead>
<tr>
<th>Key Question*</th>
<th>Main Findings From Prior USPSTF Reviews</th>
<th>Number and Type of Studies Identified for Update</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Applicability</th>
<th>Summary of Findings</th>
<th>Strength of Evidence†</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Adverse effects of environmental interventions included transient BLL, inconvenience associated with abatement work or relocation, and cost-benefit considerations. Adverse effects after chelation treatment included mild GI and systemic symptoms, rashes, transient hyperphosphatemia, neutropenia, eosinophilia, and elevations in serum aminotransferases.</td>
<td>1 RCT (in 3 publications) and 1 observational study</td>
<td>One poor-quality study reported intermediate outcomes associated with adverse effects of treatment.</td>
<td>Consistent</td>
<td>Moderate to high for harms</td>
<td>One good-quality and 1 poor-quality study reported adverse effects of chelation therapy. The good-quality study found that children treated with DMSA had a small but statistically significant decrease in height growth over 34 months and slightly poorer scores on attention and executive function tests at age 7 years. One poor-quality study reported adverse events associated with the less commonly used chelator d-penicillamine, including leukopenia, thrombocytopenia, urticarial and maculopapular rashes, urinary incontinence, abdominal pain, and diarrhea. No study identified harms of counseling, nutritional interventions, or residential lead hazard control techniques.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*Key Question 1. Is there direct evidence that screening for elevated BLLs in asymptomatic children age 5 years and younger improves health outcomes (i.e., reduced cognitive or behavioral problems or learning disorders)?

Key Question 2a. What is the accuracy of questionnaires or clinical prediction tools that identify children who have elevated BLLs?

Key Question 2b. What is the accuracy of capillary blood lead testing in children?

Key Question 3. What are the harms of screening for elevated BLLs (with or without screening questionnaires) in children?

Key Question 4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce BLLs in asymptomatic children with elevated BLLs?

Key Question 5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic children with elevated BLLs?

Key Question 6. What are the harms of interventions in asymptomatic children with elevated BLLs?

†“EPC Assessment of Strength of Evidence” is based on new evidence identified for this update and relevant evidence from the prior report.

‡Key Questions in this review differ from the previous review and Key Question numbers in this review do not correspond to Key Question numbers in the prior review. For some questions, the number of studies included in the prior review was not precisely reported.

**Abbreviations:** BLL=blood lead level; CDC=Centers for Disease Control and Prevention; CI=confidence interval; DMSA=dimercaptosuccinic acid; GI=gastrointestinal; RCT=randomized, controlled trial; U.S.=United States; USPSTF=U.S. Preventive Services Task Force.
<table>
<thead>
<tr>
<th>Study, Year Setting Quality</th>
<th>Screening Test Definition of a Positive Screening Exam</th>
<th>Sample Size Proportion With Condition Population Characteristics</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey, 199443 United States Urban general pediatric department Fair</td>
<td>CDC Risk Assessment Questionnaire ≥1 positive answers</td>
<td>n=167 Elevated BLL: Overall ≥10 µg/dL: 29% (48/165) 10 to 14 µg/dL: 22% (36/165) 15 to 19 µg/dL: 4% (7/165) 20 to 44 µg/dL: 2.5% (4/165) 46 µg/dL: 0.5% (1/165) Low-risk vs. high-risk Mean age, months: 10 vs. 9 Female: 50% vs. 50% Ethnicity: 29% vs. 33% African American 62% vs. 62% White</td>
<td>Overall: 40% (19/48 [95% CI, 25.77 to 54.73]) By screening question: Peeling paint: 15% Renovation: 31% Sibling with Pb: 6% Adult's job with Pb: 2% Live near Pb industry: 6%</td>
<td>Overall: 60% (70/117 [95% CI, 50.36 to 68.78%]) By screening question: Peeling paint: 76% Renovation: 75% Sibling with Pb: 99% Adult's job with Pb: 97% Live near Pb industry: 98%</td>
</tr>
<tr>
<td>Dalton, 199644 United States Medical center Fair</td>
<td>CDC Risk Assessment Questionnaire Additional behavioral risk factor questions ≥1 positive or equivocal answers</td>
<td>n=516 Elevated BLL: Overall ≥10 µg/dL: 22% (101/463) ≥15 µg/dL: 6% (28/463) Mean age, months: NR (range, 6 to 72) Female: NR Ethnicity: NR</td>
<td>CDC Risk Factors Overall: 70.3% (95% CI, 60.39 to 78.98) Behavioral Risk Factors Playing near outside of house: 74.2% (95% CI, 64.60 to 82.44)</td>
<td>CDC Risk Factors Overall: 31.8% (95% CI, 27.00 to 36.84) Behavioral Risk Factors Playing near outside of house: 54.1% (95% CI, 28.05 to 37.98)</td>
</tr>
<tr>
<td>France, 199646 United States Multisite primary care network Fair</td>
<td>CDC Risk Assessment Questionnaire Additional risk factor questions ≥1 positive or equivocal answers</td>
<td>n=2,978 Mean BLL: 4.19 µg/dL Elevated BLL ≥10 µg/dL: 2.9% (85/2,978) Mean age: NR (range, 5 months to 6.5 years) Female: NR Ethnicity: NR</td>
<td>CDC + additional questions: 59.7% (95% CI, 48 to 72) CDC alone: 57% (95% CI, 45 to 69)</td>
<td>CDC + additional questions: 36% (95% CI, 34 to 38) CDC alone: 51% (95% CI, 49 to 53)</td>
</tr>
</tbody>
</table>
### Table 3. Characteristics and Results for Studies of Screening Questionnaires

<table>
<thead>
<tr>
<th>Study, Year Setting Quality</th>
<th>Screening Test Definition of a Positive Screening Exam</th>
<th>Sample Size Population Characteristics</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes, 1997&lt;sup&gt;49&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>n=754</td>
<td>Elevated BLL ≥10 µg/dL: 3.1% (25/801)</td>
<td>68% (95% CI, 46.50 to 85.05)</td>
</tr>
<tr>
<td>United States Continuity clinic at a children's hospital Fair</td>
<td>Additional risk factor questions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kazal, 1997&lt;sup&gt;47&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>n=368</td>
<td>Elevated BLL ≥10 µg/dL: 2.2% (8/368)  Mean age, months: 30.5 Female: 49% Ethnicity: 98% Navajo</td>
<td>CDC questions: 42.9% (95% CI, 9.90 to 81.59)</td>
</tr>
<tr>
<td>United States Rural clinic on a Navajo Reservation Fair</td>
<td>Additional risk factor questions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muniz, 2003&lt;sup&gt;50&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>n=171</td>
<td>Elevated BLL ≥10 µg/dL: 2.3% (4/171)  Mean age: NR (range, 9 to 24 months) Female: NR Ethnicity: NR</td>
<td>CDC questions: 25% (95% CI, NR)</td>
</tr>
<tr>
<td>United States Rural clinic Fair</td>
<td>Additional risk factor questions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robin, 1997&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Modified Health Care Financing Administration questionnaire</td>
<td>n=967</td>
<td>Elevated BLL ≥10 µg/dL: 0.6% (6/967)  Mean age: NR (range, 2 to 6 years) Female: 51.3% Ethnicity: Alaska native: 60% White: 28% Black: 5%</td>
<td>83.3% (95% CI, 35.88 to 99.58)</td>
</tr>
<tr>
<td>United States Urban and rural Medicaid recipients Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schaffer, 1996&lt;sup&gt;51&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>n=705</td>
<td>Elevated BLL ≥10 µg/dL: 8.4% (59/705)  Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR</td>
<td>CDC + additional questions: 75% (95% CI, NR)</td>
</tr>
<tr>
<td>United States Rural clinic Fair</td>
<td>Additional risk factor questions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Screening for Elevated Lead in Children**

37 Pacific Northwest EPC
Table 3. Characteristics and Results for Studies of Screening Questionnaires

<table>
<thead>
<tr>
<th>Study, Year Setting Quality</th>
<th>Screening Test Definition of a Positive Screening Exam</th>
<th>Sample Size Proportion With Condition Population Characteristics</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snyder, 199546 United States Public clinics Fair</td>
<td>CDC Risk Assessment Questionnaire Additional risk factor questions</td>
<td>n=247 Elevated BLL ≥10 µg/dL: 7.7% (19/247) Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR</td>
<td>CDC questions: 31.6% (95% CI, 12.58 to 56.55) Additional questions: 89.5% (95% CI, 66.86 to 98.70)</td>
<td>CDC questions: 79.8 (95% CI, 74.02 to 84.83) Additional questions: 37.3% (95% CI, 30.99 to 43.91)</td>
</tr>
</tbody>
</table>

Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control and Prevention; CI=confidence interval; NR=not reported; Pb=lead.
Appendix A1. Search Strategies

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.
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
Appendix A1. Search Strategies

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 intotoxic* 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 intotoxic* or ((high* or elevat*) adj3 level*)).mp.
Appendix A1. Search Strategies

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

<table>
<thead>
<tr>
<th>Populations</th>
<th>Include</th>
<th>Exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>All KQs: Asymptomatic children age ≤5 years</td>
<td>All other populations*</td>
<td></td>
</tr>
</tbody>
</table>

### Screening tests

- **KQs 1, 3:** Measurement of blood lead level (using any method) with or without screening questionnaires or risk prediction tools
- **KQ 2a:** Questionnaires or risk prediction tools that identify children who are more or less likely to have elevated blood lead levels (defined by a minimum threshold of 5 µg/dL)
- **KQ 2b:** Measurement of BLLs using capillary blood sampling

### 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

### Comparisons

- **KQs 1, 3:** Screened vs. nonscreened groups
- **KQ 2a:** Measurement of blood lead levels using venous blood sampling
- **KQ 2b:** Studies on accuracy of capillary sampling to detect elevated blood lead levels must include a comparison with venous sampling
- **KQs 4–6:** Treatment vs. placebo, inactive control, or no treatment

### Outcomes

- **KQs 1, 5:** Validated measures of cognitive and neurobehavioral outcomes in children, including assessment of IQ or development†
- **KQ 2a:** Sensitivity, specificity, discrimination, and calibration
- **KQ 2b:** Sensitivity, specificity, discrimination, calibration and measures of diagnostic accuracy
- **KQ 3:** Anxiety, distress, pain, or discomfort related to venous or capillary blood sampling; false-positive results or blood lead levels <5 µg/dL, leading to repeat testing, unnecessary treatment, or both
- **KQ 4:** Blood lead levels†
- **KQ 6:** Anxiety or distress; inconvenience associated with intervention (e.g., school absenteeism associated with followup testing); morbidity attributed to chelation therapy (e.g., renal toxicity, sensitivity reactions)

### Study designs

- **KQs 1, 4:** RCTs
- **KQ 2a:** Observational studies assessing the accuracy of screening questionnaires for predicting elevated blood lead levels
- **KQ 2b:** Observational studies assessing the accuracy of capillary sampling to measure blood lead levels
- **KQ 3:** RCTs, CCTs, and cohort studies
- **KQ 5:** RCTs and CCTs
- **KQ 6:** RCTs, CCTs, prospective cohort studies with a concurrent control group, and case-control studies

### Quality

- Studies rated good or fair quality
- Studies rated poor quality

### Clinical Setting

- Settings applicable to U.S. primary care settings, including pediatric outpatient clinics, community health clinics, and school-based clinics
- **KQs 4–6:** The above plus settings referable from primary care settings

### 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 other evidence is available)
- **KQs 4–6:** Any country

### Language

- English language
- Languages other than English

### Abbreviations:

- CCT = controlled clinical trial
- IQ = intelligence quotient
- KQs = Key Questions
- RCT = randomized, controlled trial
- U.S. = United States
Appendix A2. Inclusion and Exclusion Criteria

* Studies enrolling older children were eligible if at least 50% of the sample was age ≤5 years, or if studies report outcomes separately for children age ≤5 years.

† 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 were 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 have captured all relevant studies. We describe relevant systematic reviews in the Discussion section of the report.
Appendix A3. Literature Flow Diagram

Abstracts of potentially relevant articles identified through searches and other sources: 3,147

- Excluded abstracts and background articles: 2,914
- Full-text articles reviewed: 233

Articles excluded: 209
- Wrong population: 17
- Wrong intervention: 27
- Wrong outcome: 24
- Wrong comparator: 26
- Wrong study design for key question: 43
- Not a study: 64
- Not English language but possibly relevant: 6
- Systematic Review or meta-analysis used as a source document only to identify individual studies: 1
- Poor-quality: 1

Included publications: 24*

- Included publications for Key Question 1: 0
- Included publications for Key Question 2a: 4
- Included publications for Key Question 2b: 6
- Included publications for Key Question 3: 0
- Included publications for Key Question 4: 10
- Included publications for Key Question 5: 3
- Included publications for Key Question 6: 3

* Other sources include prior reports, targeted searches for contextual questions, reference lists of relevant articles, and systematic reviews. Publications may be included for more than one Key Question.


Appendix A4. List of Included Studies


### Appendix A5. List of Excluded Studies


## Appendix A5. List of Excluded Studies

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Title</th>
<th>Exclusion Reason</th>
</tr>
</thead>
</table>
Appendix A5. List of Excluded Studies


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Appendix A6. USPSTF Quality Rating Criteria

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
Appendix A6. USPSTF Quality Rating Criteria

- 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


- 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 Liaison, 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 Screening Questionnaire Studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Screening test</th>
<th>Definition of a positive screening exam</th>
<th>Reference standard</th>
<th>Type of study</th>
<th>Country Setting</th>
<th>Population characteristics</th>
<th>Sample size</th>
<th>Proportion with condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey, 1994</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>≥1 positive answers</td>
<td>Venous</td>
<td>Cross-sectional</td>
<td>United States Urban general pediatric department</td>
<td>Low-risk vs. high-risk Mean age, months: 10 vs. 9 Female: 50% vs. 50% Ethnicity: 29% vs. 33% African American 62% vs. 62% white</td>
<td>167</td>
<td>Elevated BLL, overall ≥10 µg/dL: 29% (48/165) 10 to 14 µg/dL: 22% (36/165) 15 to 19 µg/dL: 4% (7/165) 20 to 44 µg/dL: 2.5% (4/165) 46 µg/dL: 0.5% (1/165)</td>
</tr>
<tr>
<td>Dalton, 1996</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>≥1 positive or equivocal answers</td>
<td>Venous</td>
<td>Cross-sectional</td>
<td>United States Medical center</td>
<td>Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR</td>
<td>516</td>
<td>Elevated BLL, overall ≥10 µg/dL: 22% (101/463) ≥15 µg/dL: 6% (28/463)</td>
</tr>
<tr>
<td>France, 1996</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>≥1 positive or equivocal answers</td>
<td>Venous</td>
<td>Cross-sectional</td>
<td>United States Multisite primary care network</td>
<td>Mean age: NR (range, 5 months to 6.5 years) Female: NR Ethnicity: NR</td>
<td>2,978</td>
<td>Mean BLL: 4.19 µg/dL Elevated BLL ≥10 µg/dL: 2.9% (85/2978)</td>
</tr>
<tr>
<td>Holmes, 1997</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>Unclear</td>
<td>Venous</td>
<td>Cross-sectional</td>
<td>United States Continuity clinic at a children's hospital</td>
<td>Mean age, months: 28.44 (range, 9 to 72) Female: 46% Ethnicity: 39% Hispanic, 39% black, 18% white</td>
<td>754</td>
<td>Elevated BLL ≥10 µg/dL: 3.1% (25/801)</td>
</tr>
</tbody>
</table>
## Appendix B1. Data Abstraction of Screening Questionnaire Studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Proportion unexaminable by screening test</th>
<th>Analysis of screening failures</th>
<th>Proportion who underwent reference standard and included in analysis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey, 1994</td>
<td>n=2</td>
<td>NR</td>
<td>98% (165/167)</td>
<td>Overall: 40% (19/48) (25.77 to 54.73)</td>
<td>Overall: 60% (70/117) (50.36 to 68.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>By screening question: Peeling paint: 15% Renovation: 31% Sibling with Pb: 6% Adult's job with Pb: 2% Live near Pb industry: 6%</td>
<td>By screening question: Peeling paint: 76% Renovation: 75% Sibling with Pb: 99% Adult's job with Pb: 97% Live near Pb industry: 98%</td>
</tr>
<tr>
<td>Dalton, 1996</td>
<td>n=0</td>
<td>NR</td>
<td>89.7% (463/516)</td>
<td>Overall: 70.3% (60.39 to 78.98) Behavioral Risk Factors Playing near outside of house: 74.2% (64.60 to 82.44)</td>
<td>Overall: 31.8% (27.00 to 36.84) Behavioral Risk Factors Playing near outside of house: 54.1% (28.05 to 37.98)</td>
</tr>
<tr>
<td>France, 1996</td>
<td>n=562 (19%)</td>
<td>Prevalence of elevated BLL did not differ for those who did not complete screening questionnaire: 3.2% (p=0.51)</td>
<td>81% (2,416/2,978)</td>
<td>CDC + additional questions: 59.7% (48 to 72)</td>
<td>CDC + additional questions: 36% (34 to 38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CDC alone: 57% (45 to 69)</td>
<td>CDC alone: 51% (49 to 53)</td>
</tr>
<tr>
<td>Holmes, 1997</td>
<td>n=47 (5.9%)</td>
<td>NR</td>
<td>94% (754/801)</td>
<td>68% (46.50 to 85.05)</td>
<td>58% (53.93 to 61.23)</td>
</tr>
</tbody>
</table>
## Appendix B1. Data Abstraction of Screening Questionnaire Studies

### Screening for Elevated Lead in Children

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
<th>Negative predictive value (95% CI)</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey, 1994(^{43})</td>
<td>Overall: 1.0 (0.65 to 1.49) Peeling paint: 0.625 Renovation: 1.24 Sibling with Pb: 6.0 Adult's job: 0.67 Live near Pb: 3</td>
<td>Overall: 1.0 (0.77 to 1.33) Peeling paint: 1.12 Renovation: 0.92 Sibling with Pb: 0.95 Adult's job: 1.01 Live near Pb: 0.96</td>
<td>Overall: 29% (19/66) (21.09 to 37.94) Peeling paint: 20% Renovation: 34% Sibling with Pb: 75% Adult's job: 25% Live near Pb: 60%</td>
<td>Overall: 71% (76/99) (64.75 to 76.03) Peeling paint: 68% Renovation: 73% Sibling with Pb: 72% Adult's job: 71% Live near Pb: 72%</td>
<td>Fair</td>
</tr>
<tr>
<td>Dalton, 1996(^{44})</td>
<td>CDC risk factors: 1.03 (0.89 to 1.19) Playing near outside of house: 1.62 (0.97 to 1.27)</td>
<td>CDC risk factors: 0.93 (0.67 to 1.31) Playing near outside of house: 0.78 (0.54 to 1.13)</td>
<td>CDC risk factors: 22.33% (19.91 to 24.94) Playing near outside of house: 23.58% (21.23 to 26.12)</td>
<td>CDC risk factors: 79.31% (73.26 to 84.29) Playing near outside of house: 82.07% (76.11 to 86.80)</td>
<td>Fair</td>
</tr>
<tr>
<td>France, 1996(^{48})</td>
<td>CDC + additional questions: 0.93 (NR) CDC alone: 1.16 (NR)</td>
<td>CDC + additional questions: 1.12 (NR) CDC alone: 0.84 (NR)</td>
<td>CDC + additional questions: 2.6 (NR) CDC alone: NR</td>
<td>CDC + additional questions: NR CDC alone: NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Holmes, 1997(^{49})</td>
<td>1.60 (1.21 to 2.13)</td>
<td>0.56 (0.31 to 0.99)</td>
<td>5.21% (3.98 to 6.80)</td>
<td>98.13% (96.73 to 98.94)</td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Appendix B1. Data Abstraction of Screening Questionnaire Studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Screening test</th>
<th>Definition of a positive screening exam</th>
<th>Reference standard</th>
<th>Type of study</th>
<th>Country Setting</th>
<th>Population characteristics</th>
<th>Sample size</th>
<th>Proportion with condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazal, 1997&lt;sup&gt;47&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>Unclear</td>
<td>Venous</td>
<td>Cross-sectional</td>
<td>United States Rural clinic, Navajo Reservation</td>
<td>Mean age, months: 30.5 Female: 49% Ethnicity: 98% Navajo</td>
<td>n=368</td>
<td>Elevated BLL ≥10µg/dL: 2.2% (8/368)</td>
</tr>
<tr>
<td>Muniz, 2003&lt;sup&gt;50&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>≥1 positive or equivocal answers</td>
<td>Venous</td>
<td>Retrospective cohort</td>
<td>United States Rural clinic</td>
<td>Mean age: NR (range, 9 to 24 months) Female: NR Ethnicity: NR</td>
<td>n=171</td>
<td>Elevated BLL ≥10 µg/dL: 2.3% (4/171)</td>
</tr>
<tr>
<td>Robin, 1997&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Modified Health Care Financing Administration questionnaire</td>
<td>≥1 positive answers</td>
<td>Venous</td>
<td>Cross-sectional</td>
<td>United States Urban and rural Medicaid recipients</td>
<td>Mean age: NR (range, 2 to 6 years) Female: 51.3% Ethnicity: Alaska native: 60% White: 28% Black: 5%</td>
<td>n=967</td>
<td>Elevated BLL ≥10 µg/dL: 0.6% (6/967)</td>
</tr>
<tr>
<td>Schaffer, 1996&lt;sup&gt;51&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>≥1 positive or equivocal answers to the CDC questions</td>
<td>Venous (approximately 6% were capillary)</td>
<td>Cross-sectional</td>
<td>United States Rural clinic</td>
<td>Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR</td>
<td>n=705</td>
<td>Elevated BLL ≥10 µg/dL: 8.4% (59/705)</td>
</tr>
<tr>
<td>Snyder, 1995&lt;sup&gt;56&lt;/sup&gt;</td>
<td>CDC Risk Assessment Questionnaire</td>
<td>≥1 positive answers</td>
<td>Venous</td>
<td>Cross-sectional</td>
<td>United States Public clinics</td>
<td>Mean age: NR (range, 6 to 72 months) Female: NR Ethnicity: NR</td>
<td>n=247</td>
<td>Elevated BLL ≥10 µg/dL: 7.7% (19/247)</td>
</tr>
</tbody>
</table>
### Appendix B1. Data Abstraction of Screening Questionnaire Studies

<table>
<thead>
<tr>
<th>Study, year</th>
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<th>Proportion who underwent reference standard and included in analysis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazal, 1997&lt;sup&gt;47&lt;/sup&gt;</td>
<td>n=45 (12.2%)</td>
<td>NR</td>
<td>100%</td>
<td>CDC questions: 42.9% (9.90 to 81.59) CDC + additional questions: 42.9% (NR)</td>
<td>CDC questions: 68.52% (68.52 to 78.50) CDC + additional questions: 66.1% (NR)</td>
</tr>
<tr>
<td>Muniz, 2003&lt;sup&gt;30&lt;/sup&gt;</td>
<td>n=0</td>
<td>NR</td>
<td>100%</td>
<td>CDC questions: 25% (NR) CDC + additional questions: 50.0% (6.76 to 93.24)</td>
<td>CDC questions: 49% (NR) CDC + additional questions: 49.70 (41.88 to 57.53)</td>
</tr>
<tr>
<td>Robin, 1997&lt;sup&gt;45&lt;/sup&gt;</td>
<td>n=0</td>
<td>NR</td>
<td>100%</td>
<td>83.3% (35.88 to 99.58)</td>
<td>38.6% (35.50 to 41.77)</td>
</tr>
<tr>
<td>Schaffer, 1996&lt;sup&gt;51&lt;/sup&gt;</td>
<td>n=1 (0.1%)</td>
<td>NR</td>
<td>99.2% (705/711)</td>
<td>CDC + additional questions: 75% (NR) Condensed questionnaire from 4 items most likely to correctly identify patients: 88% (NR)</td>
<td>CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR</td>
</tr>
<tr>
<td>Snyder, 1995&lt;sup&gt;46&lt;/sup&gt;</td>
<td>n=0</td>
<td>NR</td>
<td>100%</td>
<td>CDC questions: 31.6% (12.58 to 56.55) Additional questions: 89.5% (66.86 to 98.70) CDC + additional questions: 89.5% (66.6 to 98.70)</td>
<td>CDC questions: 79.8 (74.02 to 84.83) Additional questions: 37.3% (30.99 to 43.91) CDC + additional questions: 31.6% (25.6 to 38.0)</td>
</tr>
</tbody>
</table>
### Appendix B1. Data Abstraction of Screening Questionnaire Studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
<th>Negative predictive value (95% CI)</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kazal, 1997&lt;sup&gt;47&lt;/sup&gt;</td>
<td>1.63 (0.68 to 3.91) CDC + additional questions: 1.27 (NR)</td>
<td>0.77 (0.41 to 1.48) CDC + additional questions: 0.79 (NR)</td>
<td>3.49% (1.48 to 7.98) CDC + additional questions: 2.7 (NR)</td>
<td>98.31% (96.83 to 99.11) CDC + additional questions: 98.1 (NR)</td>
<td>Fair</td>
</tr>
<tr>
<td>Muniz, 2003&lt;sup&gt;50&lt;/sup&gt;</td>
<td>CDC + additional questions: 0.99 (0.37 to 2.68)</td>
<td>CDC + additional questions: 1.01 (0.37 to 2.71)</td>
<td>CDC + additional questions: 2.33% (0.88 to 6.03)</td>
<td>CDC + additional questions: 97.65% (93.90 to 99.11)</td>
<td>Fair</td>
</tr>
<tr>
<td>Robin, 1997&lt;sup&gt;45&lt;/sup&gt;</td>
<td>1.36 (0.95 to 1.95)</td>
<td>0.43 (0.07 to 2.59)</td>
<td>0.84% (0.59 to 1.21)</td>
<td>99.73% (98.40 to 99.95)</td>
<td>Fair</td>
</tr>
<tr>
<td>Schaffer, 1996&lt;sup&gt;51&lt;/sup&gt;</td>
<td>CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR</td>
<td>CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR</td>
<td>CDC + additional questions: NR Condensed questionnaire from 4 items most likely to correctly identify patients: NR</td>
<td>CDC + additional questions: 98% Condensed questionnaire from 4 items most likely to correctly identify patients: 98% (NR)</td>
<td>Fair</td>
</tr>
<tr>
<td>Snyder, 1995&lt;sup&gt;46&lt;/sup&gt;</td>
<td>CDC questions: 1.57 (0.77 to 3.19) Additional questions: 1.43 (1.19 to 1.71) CDC + additional questions: 1.31 (1.09 to 1.56)</td>
<td>CDC questions: 0.86 (0.63 to 1.17) Additional questions: 0.28 (0.08 to 1.06) CDC + additional questions: 0.33 (0.09 to 1.25)</td>
<td>CDC questions: 11.54% (6.02 to 20.98) Additional questions: 10.6% (9.00 to 12.5) CDC + additional questions: 9.83% (8.36 to 11.52)</td>
<td>CDC questions: 93.33% (91.11 to 95.03) Additional questions: 97.7% (91.89 to 99.38) CDC + additional questions: 97.3% (90.54 to 99.27)</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Abbreviations:** BLL = blood lead level; CDC = Centers for Disease Control and Prevention; CI = confidence interval; LR = likelihood ratio; NR = not reported; Pb = lead.
## Appendix B2. Data Abstraction of Capillary Screening Studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Screening test</th>
<th>Definition of a positive screening exam</th>
<th>Reference standard</th>
<th>Type of study</th>
<th>Country Setting</th>
<th>Population Characteristics</th>
<th>Sample size</th>
<th>Proportion with condition</th>
<th>Proportion unexaminable by screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holtrop, 1998&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Capillary</td>
<td>≥10 µg/dL ≥15 µg/dL ≥20 µg/dL</td>
<td>Venous</td>
<td>Prospective cohort</td>
<td>United States Urban clinic</td>
<td>Mean age: NR Female sex: 41% Ethnicity: 97% black</td>
<td>n=124 Elevated BLL ≥10 µg/dL: 26% (31/120)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Parsons, 1997&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Capillary</td>
<td>≥10 µg/dL ≥15 µg/dL ≥20 µg/dL ≥25 µg/dL</td>
<td>Venous</td>
<td>Prospective cohort</td>
<td>United States County health clinics and university hospital</td>
<td>Mean age: NR (range, 0 to 12 years) Female sex: 43% Ethnicity: 38% white, 28% black, 21% Hispanic, 6% Asian</td>
<td>n=499 Elevated BLL ≥10 µg/dL: 30.5% Elevated BLL ≥15 µg/dL: 16.7% Elevated BLL ≥20 µg/dL: 9.9% Elevated BLL ≥25 µg/dL: 6.6%</td>
<td>5% (29/533)</td>
<td></td>
</tr>
<tr>
<td>Sargent, 1996&lt;sup&gt;62&lt;/sup&gt; See also: Sargent, 1996&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Capillary</td>
<td>≥8 µg/dL ≥10 µg/dL ≥12 µg/dL ≥15 µg/dL</td>
<td>Venous</td>
<td>Prospective cohort</td>
<td>United States Urban clinic</td>
<td>NR</td>
<td>n=513 Elevated BLL ≥10 µg/dL: 20.5% Elevated BLL ≥20 µg/dL: 2.3%</td>
<td>2.7% (16/586)</td>
<td></td>
</tr>
<tr>
<td>Schlenker, 1994&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Capillary Method 1: alcohol wipe Method 2: alcohol + silicone Method 3: soap and water + alcohol Method 4: soap and water, alcohol, and 1% nitric acid solution</td>
<td>≥20 µg/dL</td>
<td>Venous</td>
<td>Prospective cohort</td>
<td>United States Urban health department and clinics</td>
<td>Mean age: 3 years Female sex: 47% Ethnicity: 88% black</td>
<td>n=295 Elevated BLL: NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix B2. Data Abstraction of Capillary Screening Studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Proportion who underwent reference standard and included in analysis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
<th>Negative predictive value (95% CI)</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Holtrop, 1998</strong>&lt;sup&gt;61&lt;/sup&gt;</td>
<td>97% (120/124)</td>
<td>10 µg/dL: 94% (NR)</td>
<td>15 µg/dL: 75% (NR)</td>
<td>≥10 µg/dL: 94% (NR)</td>
<td>≥15 µg/dL: 37.5% (NR)</td>
<td>≥20 µg/dL: Not estimable</td>
<td>≥10 µg/dL: 0.06 (NR)</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Parsons, 1997</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>93.6% (499/533)</td>
<td>10 µg/dL: 87.5% (81.8 to 91.9)</td>
<td>15 µg/dL: 83.0% (74.8 to 89.5)</td>
<td>≥10 µg/dL: 93.2% (90.0 to 95.6)</td>
<td>≥15 µg/dL: 95.3% (92.8 to 97.2)</td>
<td>≥20 µg/dL: 97.3% (95.3 to 98.6)</td>
<td>≥25 µg/dL: 98.5% (96.9 to 99.4)</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Sargent, 1996</strong>&lt;sup&gt;62&lt;/sup&gt;</td>
<td>88% (513/586)</td>
<td>≥8 µg/dL: 100% (NR)</td>
<td>≥10 µg/dL: 91% (NR)</td>
<td>≥8 µg/dL: NR</td>
<td>≥10 µg/dL: 92.2% (NR)</td>
<td>≥12 µg/dL: NR</td>
<td>≥15 µg/dL: NR</td>
<td>Fair</td>
</tr>
<tr>
<td><strong>Schlenker, 1994</strong>&lt;sup&gt;63&lt;/sup&gt;</td>
<td>100%</td>
<td>Method 1: 95% (NR)</td>
<td>Method 2: 96% (NR)</td>
<td>Method 3: 94% (NR)</td>
<td>Method 2: 96% (NR)</td>
<td>Method 3: 100% (NR)</td>
<td>Method 4: 91% (NR)</td>
<td>Poor</td>
</tr>
</tbody>
</table>

**Abbreviations:** BLL=blood lead level; CI=confidence interval; NR=not reported.
### Appendix B3. Data Abstraction of Childhood Treatment Trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Setting Country</th>
<th>Study duration Mean followup</th>
<th>Interventions (N)</th>
<th>Inclusion criteria</th>
<th>Patient characteristics</th>
<th>Loss to followup</th>
<th>Adjusted variables for statistical analysis (for observational studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boreland, 2009&lt;sup&gt;65&lt;/sup&gt;</td>
<td>RCT</td>
<td>Lead-mining neighborhood Australia</td>
<td>Duration: mean 13 months</td>
<td>A. Immediate lead home remediation (n=45) B. Delayed lead home remediation (n=45)</td>
<td>Children ages 12 to 60 months with BLL 15 to 29 µg/dL</td>
<td>Age: 3.5 years Race: NR Sex: 58% female BLL: 15 to 19 µg/dL: 28% BLL: 20 to 24 µg/dL: 23% BLL: 25 to 29 µg/dL: 37% BLL: &gt;30 µg/dL: 12%</td>
<td>Loss to followup: 2% (1/45) vs. 2% (1/45)</td>
<td>Sex, location, lead loading, lead paint, dust proofing, soil lead, yard dust potential, general environment, and age at remediation</td>
</tr>
<tr>
<td>Brown, 2006&lt;sup&gt;70&lt;/sup&gt;</td>
<td>RCT</td>
<td>Rhode Island Department of Health United States</td>
<td>Duration: 1 year</td>
<td>A. 5 home visits from a nurse (n=92) B. Usual care, including educational outreach about lead poisoning (n=83)</td>
<td>Children age &lt;28 months with BLL 15 to 19 µg/dL</td>
<td>A vs. B Age: 19.1 vs. 18.8 months Race: 47% white, 40% Hispanic, 8% black vs. 39% white, 49% Hispanic, 10% black Sex: NR BLL: 16.5 vs. 16.6 µg/dL</td>
<td>Loss to followup: 13% (22/175)</td>
<td>NR</td>
</tr>
<tr>
<td>Nicholson, 2017&lt;sup&gt;73&lt;/sup&gt;</td>
<td>RCT</td>
<td>Urban children’s hospital United States</td>
<td>Duration: 6 months</td>
<td>A. Professional lead inspection and cleaning kit B. Professional lead inspection C. Cleaning kit D. EPA lead exposure pamphlets</td>
<td>Low income families with children age &lt;6 years and BLL 3 to 9.9 µg/dL</td>
<td>Age: 3.94 years Race: NR Sex: NR BLL, µg/dL (A vs. B vs. C vs. D): 5.18 vs. 5.75 vs. 5.25 vs. 5.02</td>
<td>Loss to followup: 8.3%</td>
<td>NR</td>
</tr>
<tr>
<td>O’Connor, 1999&lt;sup&gt;66&lt;/sup&gt;</td>
<td>RCT</td>
<td>Urban children’s hospital United States</td>
<td>Duration: 6 months</td>
<td>E. DMSA chelation 100 to 200 mg 3 times daily (dose weight-dependent) (n=19) F. Placebo (n=20)</td>
<td>Children ages 2.5 to 5 years with BLL 30 to 45 µg/dL</td>
<td>A vs. B Age: 39.8 vs. 40.8 months Race: NR Sex: 68% vs. 35% female Mean BLL: 34.9 vs. 33.0 µg/dL</td>
<td>Loss to followup: 5% (2/39)</td>
<td>NR</td>
</tr>
<tr>
<td>Treatment of Lead-Exposed Children (TLC) Trial Group, 2000&lt;sup&gt;64&lt;/sup&gt; See also: Rogan, 2001&lt;sup&gt;67&lt;/sup&gt;; Liu, 2002&lt;sup&gt;66&lt;/sup&gt;; Dietrich, 2004&lt;sup&gt;65&lt;/sup&gt;</td>
<td>RCT</td>
<td>Multiple urban clinics United States</td>
<td>Duration: 3 years</td>
<td>A. Succimer, dose dependent on body surface area (n=396) B. Placebo (n=384)</td>
<td>Children ages 12 to 33 months with BLL 20 to 44 µg/dL</td>
<td>A vs. B Age: 24 vs. 24 months Race: 78% black, 12% white, 6% Hispanic, 4% other vs. 76% black, 11% white, 7% Hispanic, 6% other Sex: 45% vs. 43% female BLL: 26 vs. 26 µg/dL</td>
<td>Loss to followup: 17% (69/396) vs. 15% (59/384)</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Appendix B3. Data Abstraction of Childhood Treatment Trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intermediate outcomes</th>
<th>Clinical health outcomes</th>
<th>Adverse events</th>
<th>Quality rating</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boreland, 2009&lt;sup&gt;68&lt;/sup&gt;</td>
<td>BLL: 17.5 vs. 17.9 µg/dL; mean change, 1% (95% CI, -11 to 11)</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Brown, 2006&lt;sup&gt;70&lt;/sup&gt;</td>
<td>BLL did not differ between groups at 3, 6, or 12 months (data only reported in a figure) Last available BLL test &gt;10 µg/dL: 51% vs. 51%; p=NS Any BLL test &gt;20 µg/dL: 8% vs. 11%; p=NS</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Nicholson, 2017&lt;sup&gt;73&lt;/sup&gt;</td>
<td>Change in BLL at 6 months: -2.54 vs. -2.99 vs. -2.46 vs. -2.26, no significant differences</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>O'Connor, 1999&lt;sup&gt;68&lt;/sup&gt;</td>
<td>1 month</td>
<td></td>
<td></td>
<td></td>
<td>Fair</td>
</tr>
<tr>
<td>Treatment of Lead-Exposed Children (TLC) Trial Group, 2000&lt;sup&gt;64&lt;/sup&gt;</td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
<td>Good</td>
</tr>
</tbody>
</table>

**Abbreviations:** BASC=Behavior Assessment System for Children; BLL=blood lead level; CI=confidence interval; CPRS=Conners’ Parent Rating Scale; CPT=Conners’ Continuous Performance Test; CVLT-C=California Verbal Learning Test-Children’s Version; NEPSY=a developmental neuropsychological assessment neuropsychological test; NESS=Neurological Examination for Soft Signs; NR=not reported; NS=not significant; RCT=randomized, controlled trial; WISC-III=Wechsler Intelligence Scale for Children-3rd edition; WLPB-R=Woodcock Language Proficiency Battery-Revised; WPPSI-R= Wechsler Preschool and Primary Scale of Intelligence-Revised.
### Appendix C1. Quality Assessment of Childhood Diagnostic Accuracy Studies

| Author, year | Was a consecutive or random sample of patients enrolled? | Was a case-control design avoided? | Did the study avoid inappropriate exclusions? | Was 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 test? | Was there an appropriate interval between index test 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 |
|--------------|----------------------------------------------------------|------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------------------|-----------------------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|-----------------|
| Casey, 1994 | Yes                                                      | Yes                                | Yes                                         | Unclear                                                                                         | Yes                              | Yes                                         | Yes                                                              | No                              | No                              | Yes                             | Yes             | Fair |
| Dalto, 1996  | No                                                       | Yes                                | Yes                                         | Unclear                                                                                         | Yes                              | Yes                                         | Yes                                                              | Unclear                        | No                              | Yes                             | No              | Fair |
| France, 1996| Unclear                                                  | Yes                                | Yes                                         | Yes                                                                                             | Yes                              | Yes                                         | Yes                                                              | Yes                             | Yes                             | Yes                             | Yes              | Fair |
| Holmes, 1997 | Yes                                                      | Yes                                | Yes                                         | Yes                                                                                             | Yes                              | Yes                                         | Yes                                                              | Yes                             | Yes                             | Yes                             | No              | Fair |
| Holtrop, 1998| Unclear                                                  | Yes                                | Yes                                         | Yes                                                                                             | Yes                              | Yes                                         | Yes                                                              | Yes                             | No                              | Yes                             | No              | Fair |
| Kazal, 1997  | Yes                                                      | Yes                                | Yes                                         | Unclear                                                                                         | Yes                              | Yes                                         | Yes                                                              | Yes                             | No                              | Yes                             | No              | Fair |
| Muniz, 2003  | Yes                                                      | Yes                                | Yes                                         | Unclear                                                                                         | Yes                              | Yes                                         | Yes                                                              | Yes                             | No                              | Yes                             | Yes              | Fair |
| Parsons, 1997| No                                                       | Yes                                | Yes                                         | Yes                                                                                             | Yes                              | Yes                                         | Yes                                                              | Yes                             | Yes                             | Yes                             | No              | Fair |
| Robin, Tejeda | Yes                                                      | Yes                                | Yes                                         | Unclear                                                                                         | Yes                              | Yes                                         | Yes                                                              | Yes                             | Yes                             | Yes                             | Yes              | Fair |
| Sargent, 1996| Unclear                                                  | Yes                                | Yes                                         | Yes                                                                                             | Yes                              | Yes                                         | Yes                                                              | Yes                             | Yes                             | Yes                             | Yes              | Fair |
| Schaffer, 1996| Yes                                                      | Yes                                | Yes                                         | Unclear                                                                                         | Yes                              | Yes                                         | Yes                                                              | Yes                             | No                              | No                              | No              | Fair |
| Schlenker, 1994| Yes                                                      | Yes                                | Yes                                         | Yes                                                                                             | Yes                              | Yes                                         | Yes                                                              | Yes                             | Yes                             | Yes                             | Unclear         | Fair |
| Snyder, 1994 | Yes                                                      | Yes                                | Yes                                         | Unclear                                                                                         | Yes                              | Yes                                         | Unclear                                                          | Yes                             | Yes                             | Unclear            | Yes             | Poor |
## Appendix C2. Quality Assessment of Childhood Trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
<th>Attrition and withdrawals reported?</th>
<th>Loss to followup differential/ high?</th>
<th>Analyze people in the groups in which they were randomized?</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boreland, 2009&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes; matched</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Brown, 2006&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No; not for the intervention group</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Markowitz, 2004&lt;sup&gt;71&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No/Yes (34% overall)</td>
<td>Yes</td>
<td>Poor</td>
</tr>
<tr>
<td>Nicholson, 2017&lt;sup&gt;73&lt;/sup&gt;</td>
<td>No (shuffled envelopes)</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>O'Connor, 1999&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No; not sex</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Treatment of Lead-Exposed Children (TLC) Trial Group, 2000&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td>Good</td>
</tr>
<tr>
<td>Wolf, 2003&lt;sup&gt;72&lt;/sup&gt;</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear; only BLL reported</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No/No</td>
<td>Yes</td>
<td>Poor</td>
</tr>
</tbody>
</table>

**Abbreviation:** BLL=blood lead level.
## Appendix C3. Quality Assessment of Childhood Cohort Studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>Were the groups comparable at baseline on key prognostic factors?</th>
<th>Did the study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>Were outcome assessors and/or data analysts blinded to the exposure being studied?</th>
<th>Did the article maintain comparable groups (report attrition, contamination, adherence, and cross-over)?</th>
<th>Did the study perform appropriate statistical analyses on potential confounders?</th>
<th>Is there important differential or overall high loss to followup?</th>
<th>Were outcomes prespecified and defined, and ascertained using accurate methods?</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shannon, 1988&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Yes; all</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No/No</td>
<td>Yes</td>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>