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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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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

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Prepared by:
Pacific Northwest Evidence-Based Practice Center
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Amy Cantor, MD, MPH
Rob Hendrickson, MD
Ian Blazina, MPH
Jessica Griffin, MS
Sara Grusing, BA
Marian McDonagh, PharmD

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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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Structured Abstract

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

Objective: To update a prior systematic review on screening for elevated blood lead levels in childhood for the U.S. Preventive Services Task Force.

Data Sources: Cochrane Central Register of Controlled Trials (to June 2018) and Cochrane Database of Systematic Reviews (to June 2018), MEDLINE (1946 to June 2018), and reference lists.

Study Selection: English-language trials and observational studies of screening effectiveness, test accuracy, benefits and harms of screening and interventions in asymptomatic children 5 and under.

Data Analysis: 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.

Results: No studies directly evaluated clinical benefits or harms of screening versus not screening children for elevated blood lead levels. Ten studies evaluated the diagnostic accuracy of questionnaires or clinical prediction tools to identify children with elevated blood lead levels. Five studies that used the threshold of ≥1 positive answers to the five-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 venous blood level >10 µg/dL. Four studies evaluating versions of the CDC questionnaire adapted for specific populations or settings did not demonstrate improved accuracy (sensitivity range 25% to 68%, specificity range 49% to 58%). Four studies of capillary blood lead testing demonstrated sensitivity of 87% to 91% and specificity >90% (range 92% to 99%) compared with venous measurement. Seven studies of varying quality found that, in asymptomatic children, counseling and nutritional interventions or residential lead hazard control techniques do not significantly reduce blood lead concentrations. One good-quality randomized trial found DMSA chelation therapy associated with lower blood lead levels at 1 week but not at longer-term followup, and one fair-quality trial found no effects of DMSA chelation therapy on blood lead levels at 1- and 6-month followup. One good-quality randomized trial did not find a significant difference in neuropsychological development following DMSA chelation therapy and found slightly less growth and poorer cognitive outcomes, based on 7-year followup assessments. In a poor-quality trial, adverse events associated with D-penicillamine chelation included leukopenia, thrombocytopenia, rashes, urinary incontinence, abdominal pain, and diarrhea.

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 follow up. Studies

were lacking on the effectiveness of screening and clinical outcomes related to screening in reducing elevated blood lead or improving health outcomes in children. There was no evidence on the harms of screening children for elevated blood lead.

Conclusions: Evidence on the benefits and harms of screening children for lead poisoning is lacking. Studies of the 1991 CDC questionnaire and alternative screening questionnaires indicate poor accuracy for identifying children with elevated lead levels. Capillary blood testing is slightly less accurate than venous blood levels for identification of elevated blood levels. Treatment studies of chelating agents, often combined with environmental or household interventions, demonstrate short-term reductions in blood lead levels in children that are not sustained over longer periods and are associated with short- and longer-term harms.

Table of Contents

Figures

Tables

Appendixes

Chapter 1. Introduction

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 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 concluded that the evidence was insufficient to recommend for or against routine screening for elevated blood lead levels in asymptomatic children aged 1 to 5 who are at increased risk (I recommendation). The Task Force recommended against routine screening for elevated blood lead levels in asymptomatic children aged 1 to 5 who are at average risk (D recommendation).

Condition Background

Condition Definition

For this report elevated blood lead level (BLL), or blood lead concentration, was defined according to the Centers for Disease Control and Prevention's (CDC's) reference level of 5 micrograms per deciliter (μg/dL).[2] Although no safe level of lead exposure has been established, this is the level at which further clinical monitoring or treatment is recommended for children.[2] Previously, children with a BLL ≥10 μg/dL were identified as having a blood lead "level of concern" and the CDC recommended that identification of children with BLLs ≥10 μg/dL 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 ≥10 μg/dL 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] As population prevalence changes, this reference range may change. The ACCLPP also recommended that clinicians monitor children with BLLs between 5 to 10 μg/dL on the basis of evidence that higher BLLs are associated with IQ deficits, attention-related behaviors, and poor academic achievement.[4]

Prevalence and Burden of Disease/Illness

Lead is known to cause a number of adverse health effects primarily affecting the central nervous, hematopoietic, hepatic, and renal systems.[5] 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.[5] Clinical symptoms of acute lead exposure include muscle pain, fatigue, abdominal pain, headache, vomiting, seizures, and coma.[5]

Many health effects associated with elevated BLLs are irreversible. Compared with other organ systems, the nervous system appears to be the most sensitive and chief target for lead-induced toxicity.[5] More severe manifestations occur at very high exposures and 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.[6]

Adverse effects in children include behavioral and learning problems, lower IQ and hyperactivity, impaired growth, hearing problems, and anemia.[7] Young children absorb lead at a higher rate (40 to 50 percent of ingested lead) compared to adults (3 to 10 percent) and are especially vulnerable to the neurological effects of lead.[8] The developing nervous system is thought to absorb a higher fraction of blood lead compared with adults.[9] New findings also suggest lead exposure in children can result in a range of cardiovascular, immunological, and endocrine adverse health effects.[4] 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,[10] hypertension,[11] and offspring with learning disabilities [12] 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 ≥10 μg/dL. 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.[2] NHANES data from 2007 to 2010 estimated that 3.1 percent of children ages 1 to 2 years had BLLs ≥5 μg/dL.[4] Estimates varied by race/ethnicity, socioeconomic status, and age of housing. Among children ages 1 to 2 years, 7.7 percent of non-Hispanic blacks had BLLs ≥5 μg/dL 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 ≥5 μg/dL in the same survey.[13] Differences were also observed based on socioeconomic status. 6.0 percent of children living in a household with a poverty-to-income ratio of <1.3 had BLLs ≥5 μg/dL compared with 0.5 percent of children living in a household with a poverty-to-income ratio of ≥1.3. Ratios below 1.00 indicate that the income for the respective family or unrelated individual is 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 ≥5 μg/dL compared with children living in homes built after 1978. By the 2007-to-2010 cycle, children living in pre-1950 housing were four times more likely to have BLLs ≥5 μg/dL compared with 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) have 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 in which lead contamination of drinking water was increased and impacted by 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] 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. 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.[3]

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, bone marrow). Over 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 lead levels. 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 recommends 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]

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 lead levels on capillary samples must have confirmatory venous blood testing.[28] EP levels usually are not elevated until lead levels 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 BLL is unclear. Calcium, dietary iron, and other supplements are thought to decrease the intestinal absorption of lead. This is supported by epidemiologic studies, such as studies that demonstrate an increased prevalence of iron deficiency among children with lead poisoning.[29,30] However, the association is inconsistent, and evidence on an association between iron intake and lead levels in iron-replete children is lacking.

Chelation Therapy

In children, chelation 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, in order to reverse acute encephalopathy and alleviate vomiting, abdominal pain, anemia, and renal insufficiency caused by lead toxicity. Dimercaprol (succimer; DMSA) is a commonly used agent for the oral chelation of lead in children with levels at or above 45µg/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 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 percent did not report the method used). The primary risk factors that selective screeners identify were history of pica (94 percent), living in an older home with recent renovations (92 percent), living in an older home with peeling paint (93 percent), and having a sibling who had an elevated BLL (88 percent).[33]

When a child with an elevated lead level is identified, confirmatory and repeat testing is recommended, followed by management based on lead levels and symptoms. Important management strategies for asymptomatic children with BLL ≤45 µg/dL 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 for asymptomatic children and children with BLL ≤45, emergent consultation with an expert is recommended for consideration of hospitalization, stabilization, and chelation therapy based upon the degree of symptoms. Specific guidelines exist for followup depending on the degree of elevation of BLL.[25]

Recommendations of Other Groups

Table 1 summarizes current screening recommendations from other groups. Contrary to the 2006 Task Force recommendation, existing recommendations from the AAP, CDC, and American College of Preventive Medicine (ACPM) all state that children at high risk for lead exposure should receive screening.[4,23,34-36] The ACPM defines high-risk groups as receiving 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. Questionnaires tailored to specific communities may include questions about the use of home remedies and cosmetics, country of origin, and behavioral risk factors.[34] 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.[35] In 2016 the AAP updated recommendations for screening asymptomatic children for elevated blood lead concentrations and recommended screening occur according to Federal, state, and local requirements, with targeted screening of populations including immigrant, refugee, and internationally adopted children when they arrive in the U.S; children ages 12 to 24 months living in communities with ≥25% of housing built before 1960 or a prevalence of children's blood lead concentrations ≥5 µg/dL of ≥5%; children with identified lead hazards or a home built before 1960 that is in poor repair or renovated in the past 6 months.[37]

Chapter 2. Methods

Key Questions and Analytic Framework

This systematic review followed a standard protocol in accordance with USPSTF procedures.[38] The scope and Key Questions for this report were developed by EPC investigators in collaboration with the USPSTF and AHRQ, and informed by evidence gaps identified from the prior review.[1] 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 blood lead levels 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 blood lead levels?

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

3. What are the harms of screening for elevated blood lead levels (with or without screening questionnaires) in children?
4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce blood lead levels in asymptomatic children with elevated blood lead levels?
5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic children with elevated blood lead levels?
6. What are the harms of interventions in asymptomatic children with elevated blood lead levels?

Contextual Questions

1. What is the reliability of capillary and venous blood lead level testing at various lead levels in children?
2. What is the association between reduced blood lead levels and improved health outcomes in asymptomatic children with elevated blood lead levels?
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 5 years and younger for elevated BLLs for improving future health outcomes (i.e., reduced cognitive problems, reduced behavioral problems and reduced learning disorders) compared with not screening. Screening refers to diagnostic testing of blood lead levels in order 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 blood lead levels, the effectiveness of interventions for treating children identified with elevated blood lead levels 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 those identified with elevated BLL.

A separate report addresses screening for elevated lead levels in pregnant women.

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through March 2017), and Ovid MEDLINE (1946 through March 2017) for relevant studies. Search strategies are available in **Appendix A1**. We also reviewed the reference lists of relevant review articles and studies meeting inclusion criteria. We conducted an additional Ovid MEDLINE search (through October 2017) for the contextual questions after the initial search did not identify any studies meeting inclusion criteria. We updated all searches through June 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**).

The target population was asymptomatic children aged 5 years and younger, but we accepted studies that included children older than 5 years of age when the majority of the study population was 5 years or younger. Included studies specified whether the target population was asymptomatic. Included testing approaches were studies of screening questionnaires and venous or capillary lead level testing. The comparison for KQ1 was screening vs. no screening; for KQ2 a questionnaire against reference standard for elevated blood lead level (i.e., venous lead level); and capillary versus venous blood lead level testing for KQ2b. We included intermediate outcomes (i.e., blood lead levels) and for clinical outcomes used validated measures of cognitive or neurobehavioral outcomes in children. Other outcomes were statistical markers of diagnostic accuracy, harms of testing (e.g., anxiety, distress, pain, or discomfort related to testing), and morbidity attributed to treatment. All Key Questions include studies of high- and low-risk

populations. We restricted inclusion to English-language articles and excluded studies only published as abstracts. Studies of nonhuman subjects were also excluded, and studies had to report original data. For Key Questions 1 through 3, we included studies conducted in the United States (U.S.). We also included studies conducted in countries with a "very high" Human Development Index[39] (considered applicable to U.S. populations and practice) and included studies from countries with a "high" Human Development Index if no other studies were available. For Key Questions 4 through 6 (treatments for elevated BLLs), we included 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) but excluded studies of policies, laws, or community-based interventions focused on the primary prevention of lead exposure. We included randomized controlled trials of screening and treatments, and also included controlled clinical trials on effects of therapies on health outcomes, controlled clinical trials and prospective cohort studies on harms of therapies, and studies on diagnostic accuracy of screening questionnaires or capillary sampling. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists 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 (RR), likelihood ratios, positive and negative predictive values, and 95 percent confidence intervals (CI) 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 A5**) 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," "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, we pooled comparable studies using the "metandi" command in Stata version 14.2 and created hierarchical summary 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 is 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 5.3.[42]

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, AHRQ Project Officers, and collaborative partners and will be posted for public comment and revised based on reviewer comments.

Chapter 3. Results

Key Question 1. Is There Direct Evidence That Screening for Elevated Blood Lead Levels in Asymptomatic Children Age 5 Years and Younger Improves Health Outcomes?

As in the prior USPSTF review, no study directly compared the effectiveness of screening versus no screening for elevated blood lead levels in children under 5 years of age on health outcomes.

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

Summary

Five fair-quality studies that used the threshold of ≥1 positive answers on the five-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 blood lead level ≥10 µg/dL.

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[1] found fair evidence that a validated questionnaire can correctly identify 64–87% of children at high risk in urban and suburban populations with blood lead levels ≥10 micro-g/dL. 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.[43-50] The prior report also found fair evidence that a validated questionnaire had not been adequately evaluated as a screening tool to detect higher blood lead levels (e.g., ≥20–25 micro-g/dL) or lead exposure in specific populations (e.g., migrant workers, rural communities). Six studies from the prior review on accuracy of screening instruments met inclusion criteria for this key question.[51-56]

Ten studies reported diagnostic accuracy of questionnaires or clinical prediction tools for identification of children with elevated blood lead levels (**Appendixes B1, C1**).[51-60] Five studies evaluated the accuracy of the 1991 CDC questionnaire and four evaluated versions of the CDC questionnaires modified for specific populations and settings.[51-55,57-60] 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 BLL ≥15 µg/dL, 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,[57] and 28 and 31 months in two other studies.[52,58] Females comprised 46% to 51% of participants in five studies while gender 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,[59,60] 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. All of the studies reported baseline lead levels. The prevalence of children with BLL ≥10 µg/dL was as low as 0.6% in one study [57] with 29% as the highest prevalence reported for baseline lead levels.[57] In studies defining the population as higher risk, the prevalence of elevated BLL ≥10 µg/dL ranged from 7.7% to 22%.[59,60] Nine studies were rated as fair quality, and one poor-quality study was not included in the analysis.[56] Methodologic shortcomings included unclear enrollment methods, exclusion of some patients from analysis, and, in the case of the poor-quality study, retrospective surveys of exposures after BLL was known (**Table 3**).

Five fair-quality, cross-sectional studies (total N=2,265) conducted in mostly urban[54,57,59,60] and one rural U.S. community (n=368)[52] evaluated the diagnostic accuracy of the 1991 CDC questionnaire[3] for identification of children with venous blood lead levels of ≥10 µg/dL. The studies used a threshold of ≥1 one positive answer from the 5-question survey to indicate a positive screen. Across studies, sensitivity ranged from 32% to 83% and specificity ranged from 32% to 80%, with a pooled sensitivity of 48% (95% CI 31.4 to 65.6%) and pooled specificity of 58% (95% CI 39.9 to 74.0%) (**Figure 2**).[52,54,57,59,60] Positive likelihood ratio was 1.15 and negative likelihood ratio was 0.89, indicating that either a positive or negative screen has little impact on informing the likelihood of elevated lead levels.

Four diagnostic accuracy studies[51,53,55,58] 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 in order 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 poor accuracy for identifying children with elevated BLLs (sensitivity 57%, specificity 51%).[51] Another study (n=705) conducted in a rural setting[55] used two items from the CDC questionnaire and two additional items for rural community risk factor 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 children having lead levels 10 µg/dL or higher (75% versus 88%) and a 5-percent increase in negative predictive values (0.93 versus 0.98) using the modified questionnaire. A smaller study (n=171) conducted in rural New York [53] that added six items to the CDC questionnaire found no difference compared with the standard CDC questionnaire for predicting elevated lead levels (sensitivity 50% versus 50%). An additional study conducted in an urban population (n=754)[58] with a 3.1% prevalence of BLL ≥10 µg/dL 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 urban areas of the U.S.[27,61-63] found capillary blood lead testing associated with sensitivity of 87% to 91% and specificity >90% (92% to 99%) for identification of elevated BLL compared with venous sampling.

Evidence

The prior USPSTF report included two studies that compared accuracy of capillary against venous blood lead testing.[27,63] We identified four fair-quality cohort studies assessing the diagnostic accuracy of capillary testing compared with venous sampling for elevated blood lead,[27,61-63] including the two studies in the prior report (**Appendixes B2, C1**).[27,63] All four studies were conducted in urban areas of the United States and were published between 1994 and 1998. Sample sizes ranged from 124 to 513 participants (total N=1,431). Mean age was 3 years in one study[63] and was not reported in the other studies. Females comprised slightly less than half of the sample in three studies, while the fourth study did not report sex. Two studies predominately enrolled black children,[61,63] while one study evaluated a more diverse study population (38% White, 28% Black, 21% Hispanic, and 6% Asian [27]); the fourth study did not report race or ethnicity.[62] Among the three studies that reported baseline lead levels, the proportion of children with blood lead ≥10 µg/dL ranged from 21% to 31%.[27,61,62] Methodologic shortcomings of the trials included unclear methods of patient enrollment and exclusion of some patients from analysis.

Three of the four studies reported diagnostic accuracy for the BLL cutoff of ≥10 µg/dL in capillary sampling and reported sensitivities ranging from 87% to 91% and specificities ranging from 92% to 99%.[27,61,62] For BLL cutoff of ≥15 µg/dL, three studies reported sensitivities ranging from 36% to 83% and specificities from 95% to 98%.[27,61,62] For a BLL cutoff of ≥20 µg/dL, three studies reported sensitivities ranging from 78% to 96% and specificities from 91% to 100%.[27,61,63]

One study evaluated different preparation methods for capillary blood sampling[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 >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 (sensitivities 86% to 96% and specificities 91% to 96%).

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

As in the prior USPTF report, no studies evaluated the harms of screening versus not screening children for elevated blood lead levels.

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

Summary

One large, good-quality RCT found chelation therapy with 2,3-dimercaprosuccinic acid (succimer; DMSA) in children with mean blood lead concentration 20 to 45 mcg/dL 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 4.5–6 years. One fair-quality RCT found no differences between chelation versus placebo in blood lead concentration at 1 or 6 months.

There was insufficient evidence from two poor-quality studies to determine effects of nutritional supplementation. Three fair-quality RCTs from the U.S. and Australia found no clear effects of home lead abatement 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. There were mixed results on the effect of cleaning, abatement, and education on blood lead concentrations based on descriptive outcomes of eleven studies and conflicting and contradictory narrative evidence for nutritional interventions on children's blood lead concentrations, based on 16 studies.

We identified seven RCTs[64-73] (reported in 10 publications) on effects of therapies on reducing blood lead concentrations in asymptomatic children with elevated blood lead concentrations (**Appendixes B3, C2**). Five of these studies were included in the prior review. Two studies evaluated chelation therapy, two studies evaluated counseling and nutritional interventions, and three studies evaluated residential lead hazard control techniques. Sample sizes ranged from 39 to 780 (total N=1,419). Five studies were conducted in the U.S. and one study each in Australia and Costa Rica. Mean age of study participants was 1.6 to 3.6 years and had balanced gender distributions in the three studies where gender was reported (44% to 58% female). One study

was rated good-quality, four fair-quality, and two were poor-quality. Poor-quality studies lacked descriptions of randomization methodology, allocation concealment, and masking and one study had poor followup. Results of poor-quality studies were included when no fair or good-quality studies were identified.

Chelation

One fair- and one good-quality trial evaluated effects of DMSA chelation therapy on blood lead concentrations in asymptomatic children with blood lead concentrations of 20 to 45 mcg/dL at baseline.[64,67,68,70,71] Although the good-quality trial found chelation therapy associated with lower blood lead concentrations versus placebo at 1 week, 6 months, and 1 year, it found no differences at 4-5.6 years. The fair-quality trial found no effect 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 12–33-month-old children with blood lead concentration between 20-44 µg/dL.[64,67,68,71] 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 3 times with a goal blood lead concentration of <15 µg/dL. DMSA was associated with a blood lead concentration at 1 week that was 11 µg/dL lower than children in the placebo group. However, blood lead concentrations increased once DMSA was discontinued, and at 52 weeks the treatment group's blood lead concentration was 2.7 µg/dL lower than the placebo group (95% CI, 1.9–3.5 µg/dL).[71] In a followup study of 7-year-old participants (approximately 4.5–6 years after treatment), blood lead concentrations were identical in both groups (8.0 µg/dL).[67]

A small, fair-quality study (n=39)[70] randomized children aged 2.5 to 5 years with blood lead concentrations between 30-45 µg/dL to one course of DMSA or control. DMSA was dosed according to weight (≤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 differences in blood lead concentrations at 1 month (27.4 µg/dL [SD 7.5] v. 33.2 µg/dL [SD 10.3], p=0.16) or at 6 months (28.8 µg/dL [SD 6.4] v. 25.1 µg/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.[69,72] 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.[69] The other study evaluated effects of iron supplementation in Costa Rican children[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 decreased in lead concentration in iron-deplete kids and placebo was associated

with slightly increase in lead in iron-replete kids, but it is unclear how baseline iron levels may have impacted lead concentrations independent of iron supplementation. Further limiting the outcomes is that results are reported for oral iron in the iron depleted group but not the 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 blood lead concentrations at baseline.[65,66,73] None of the studies were included in the prior review. One trial (n=175) randomized children younger than 28 months of age in Rhode Island with blood lead concentrations 15–19 mcg/dL[66] (n=175) to a home intervention (five home visits that included testing samples, tailored education, and assessment of nutrition and parent–child interaction plus lead abatement strategies) or control intervention (1–2 standard educational visits from an outreach worker). Blood lead concentrations in both groups decreased overall, but there was no difference between the intervention and control groups at 3, 6, or 12 months after baseline.

Another fair-quality trial (n=90)[65] conducted in Australia randomized pairs of 12–60-month-old children with blood lead concentrations between 15-30 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, remediation was not associated with a reduction in blood lead concentrations and neither group experienced significant reductions in blood lead concentration after 1 year (−10% versus −10%, p=0.90).

A fair-quality trial (n=84)[73] conducted in Florida enrolled asymptomatic children from the Women, Infants, & Children and Head Start programs and the local health department with blood lead concentrations 3–10 µg/dL (mean 5.29 µg/dL, range 3.0–9.3 µg/dL). Participants were randomized to receive an educational brochure, a home cleaning kit or a formal home inspection and remediation. The educational brochure including information about dietary, cleaning, and habits to reduce lead exposure. The home cleaning kit included a HEPA 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. A passive control group received no intervention or information. All groups had a decrease in blood lead concentration of 2.26–2.99 µg/dL over 6–12 months, and there was no 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 Blood Lead Levels?

Summary

One good-quality randomized study found no differences between chelation therapy versus placebo on neuropsychological outcomes despite a decrease in blood lead concentrations 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 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, and found no studies on effects of environmental or nutritional interventions on health outcomes.

The "Treatment of Lead-Exposed Children"[67,68,71] trial of DMSA chelation therapy versus placebo (see Key Question 4 for study details) is 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 differences between chelation therapy and placebo in the WPPSI-R, the Developmental Neuropsychological Assessment (NEPSY), or the Conners' Parent Rating Scale—Revised (CPRS-R). In a followup study[67] of the same children at age 7 years (4.5–6 years after treatment), chelation was associated with slightly lower (worse) scores on the adjusted Attention and Executive Functions subscore of NEPSY (unadjusted difference −1.8 (95% CI −4.5–1.0), 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 Blood Lead Levels?

Summary

One good-quality and one 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 7 years of age (**Appendix B3, C2**).[67]

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.

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 included for these narrative findings is unclear. It also identified adverse effects after DMSA chelation 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. Data on harms came from one good-quality RCT, also included in this report.

The "Treatment of Lead-Exposed Children (TLC)" study compared DMSA chelation therapy to placebo in children aged 12–33 months with blood lead concentrations between 20-44 µg/dL.[71] DMSA was associated with a small but statistically significant decrease in height growth over 34 months (difference of 0.35 cm, 95% CI 0.05–0.72 cm). There were no significant differences in laboratory values, including neutrophil count, platelet count, aminotransferase concentrations, and alkaline phosphatase concentration.[64,71] Children treated with DMSA were more likely to have evidence of minor traumatic injuries on physical examination (14.9% versus 9.9%).[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 25–40 µg/dL.[74] Twenty-nine adverse events were reported in 37% of study participants, including leukopenia (11%, wbc <4,000/mm^3); rash (9%), low platelet count (9%, <300/mm^3), enuresis (4%), abdominal pain (3%), and hematuria (1%) (**Appendix C3**).

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

Understanding whether current methods for testing for elevated blood levels is reliable would be helpful for confirming that a standard, predictable measure of blood lead exists and 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 labs 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 Blood Lead Levels and Improved Health Outcomes in Asymptomatic Children With Elevated Blood Lead Levels?

One good-quality randomized study (in four publications) addressed the association between reduced blood lead levels and improved health outcomes in children with elevated BLL. The previously described "Treatment of Lead-Exposed Children" study of chelation therapy with DMSA[67,68,71] (n=780) found an inverse relationship between cognitive test scores and changes in blood level concentration, with a decrease in cognitive test scores of 3.2–3.3 points for every 10 µg/dL increase in blood lead. However, the short-term decrease in blood lead concentration in the DMSA group compared to placebo was not correlated with long-term cognitive test scores.[68]

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

Evidence to determine the clinical benefits and harms of screening versus no screening is limited. No evidence directly evaluated health benefits and harms of screening children for elevated blood lead levels compared with no screening. Important gaps in the indirect chain of evidence include poor diagnostic accuracy of instruments to identify children at higher risk of high BLLs to guide targeted screening and limited evidence and no clear effects of interventions on lowering elevated blood levels in affected children or improving neurodevelopmental outcomes.

Given the decreased prevalence of elevated blood levels, targeted screening strategies have been suggested. 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 blood levels, with likelihood ratios that are not informative.[3] In addition, the CDC questionnaire was created in 1991, and no study on its accuracy has been published since 1997, limiting applicability of currently available evidence to contemporary clinical practice. Accurate risk assessment instruments would facilitate improved targeted screening strategies. 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 diagnostic accuracy, or ability to predict children at risk for elevated blood lead.[51,53,55,58] In lieu of accurate screening instruments for identifying children to screen, alternative strategies to universal screening[52,57] or screening targeted at communities with high prevalence of elevated lead levels could be effective.[60]

A recent systematic review[75] of screening questionnaires for elevated blood levels reported sensitivities that ranged from 0.25 to 0.87 and specificity that ranged from 0.31 to 0.80, but included other questionnaires, did not report results for the CDC questionnaire separately, included studies that evaluated different cutoffs for a positive questionnaire, and did not use venous samples as the reference standard. Our findings regarding the poor accuracy of the CDC questionnaire are generally consistent with this recent systematic review on accuracy of screening questionnaires and with evidence from the prior review that found fair evidence for the screening questionnaire to identify children with elevated BLL.

Four studies evaluated the diagnostic accuracy of capillary blood lead testing compared with venous measurement.[27,61-63] Capillary sampling appears to be 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 blood levels. The question of diagnostic accuracy using venous blood as a reference standard was not part of the prior review, which included descriptive information of some diagnostic tests.

Evidence on the effectiveness of interventions for elevated blood levels on neurodevelopmental

outcomes and blood lead levels is limited. The strongest evidence was for DMSA chelation based on one trial that showed short-term (through 1 year) effects on lowering blood levels versus placebo in children with moderately elevated blood levels at baseline, but no clear effects on longer-term lead levels or neurodevelopmental outcomes, with some data indicating potential harms (hematological and other lab parameters and growth). A small, fair-quality trial found no effects of DMSA chelation on blood levels. No trial evaluated effects of chelation in children with blood lead levels <20 µg/dL, but chelation in children 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, and evidence on nutritional interventions (calcium or iron supplementation) was 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, with no sustained effect over longer periods.

Contextual Issues

Evidence on the intra-individual and interlaboratory reliability of blood lead level 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.[76] Notably, precision is expected to decrease as the concentration gets closer to the limit of detection. 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 where relatively low levels of exposure exist.[77] The association between reduced blood lead levels and improved health outcomes was addressed in one treatment trial that found that short-term decreases in blood lead concentrations induced by DMSA did not correlate with long-term cognitive test scores.[68]

Limitations

The major limitation of this review was the lack of evidence to address all key questions. Other limitations of this review include restriction to English-language articles, which could result in language bias. However, we did not identify non–English-language studies in our searches that otherwise met inclusion criteria. Despite searching for updated data, the available studies evaluating the effectiveness of the risk-based questionnaires were published between 1994 and 2003 and may assess risk factors that are not as relevant today. Further, a BLL >5 µg/dL is the reference value used in current clinical practice based on updated CDC guidance. Importantly, several of the studies that were included for this review reflect an outdated 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 the measures of the continuous BLLs, as these are prone to miscategorization due to the dichotomization of results. We included nonrandomized studies

to evaluate the effectiveness of interventions for elevated blood levels. Such studies are more susceptible to confounding and bias, as reflected in the quality ratings assigned. Furthermore, direct correlation of environmental exposures with longer-term health outcomes is difficult to study and characterize since these exposures often have subtle clinical effects. We did not attempt meta-analysis, given small numbers of studies and clinical and methodological diversity within the studies, and were unable to formally assess for publication bias due to the small number of studies.

Evidence for Priority Populations, Particularly Racial/Ethnic Minorities

Elevated lead levels predominantly impact socioeconomically disadvantaged and minority children. Different sources of lead exposure than have been previously considered are emerging in these children, yet research on screening and prevention in these populations remains limited.[78-80] 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 U.S., 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 (FDA) and are more common in Hispanic and Asian populations.[79,80] 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 common sources of lead exposure also often live in areas with a higher risk for housing-related source exposures.[78] The dual risk associated with minority communities calls for a more focused strategy to deal with population-specific risks.

Future Research

Elevated blood lead levels are associated with serious health consequences. Additional research is needed to better inform decisions regarding screening for elevated blood levels in children. Effective screening could identify lead-contaminated residential environments and abate them, not only to improve the health of the individual child but also for siblings and others in the household. While remediation of lead exposures in a specific residence may be too late for an individual child who already is exposed, the downstream effect is to prevent exposure for subsequent generations of children who may reside in that residence. Development of questionnaires that incorporate current risk factors for elevated lead levels with validation in contemporary populations of children in the U.S. is necessary. Research is needed to evaluate the effectiveness of treatments for elevated lead levels 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 lead levels 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 are not entirely appropriate for screening or some interventions of environmental health exposures due to ethical issues. Research on newer methods for testing for elevated blood, such as point-of-care testing, and on the intra-individual and interlaboratory reliability of blood lead level testing would be helpful for informing testing strategies.

Conclusions

Evidence on the benefits and harms of screening children for lead poisoning is lacking. Studies of the 1991 CDC questionnaire and alternative screening questionnaires indicate poor accuracy for identifying children with elevated lead levels. Capillary blood testing is slightly less accurate than venous blood levels for identification of elevated blood levels. Treatment studies of chelating agents, often combined with environmental or household interventions, demonstrate short-term reductions in blood lead levels in children that are not sustained over longer periods and are associated with short- and longer-term harms.

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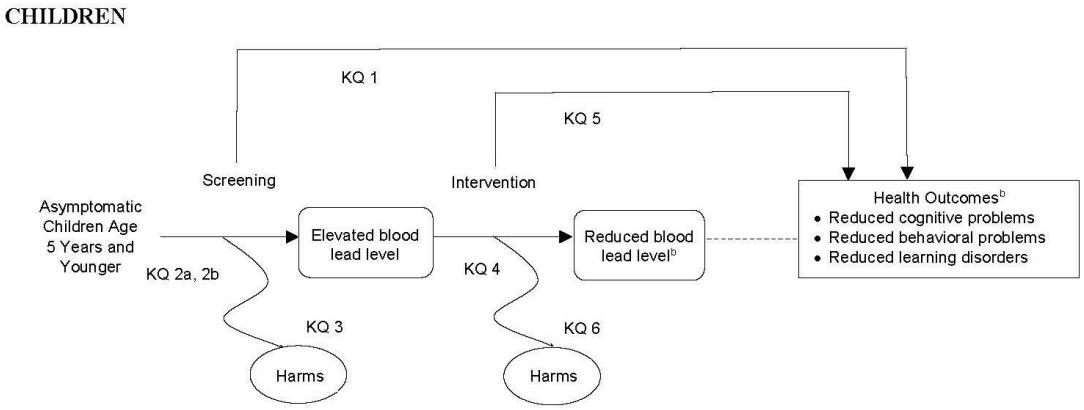
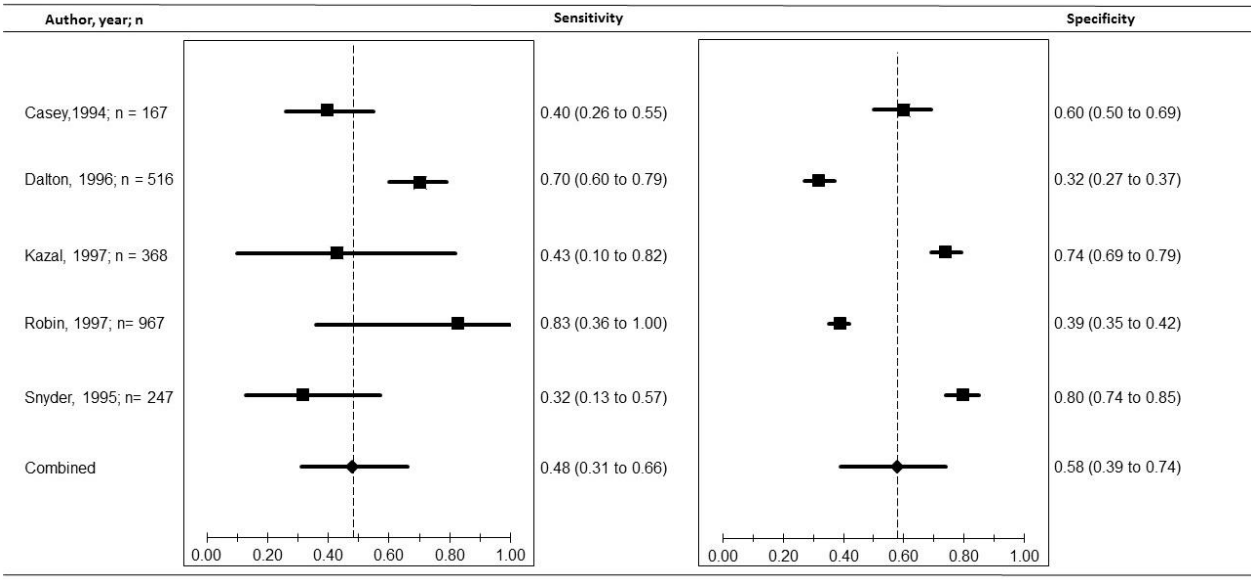
Figure 1. Analytic Framework and Key Questions



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

Abbreviation: KQ=Key Question.

Figure 2. Sensitivity and Specificity of CDC Screening Questionnaire*



* One or more positive answers and >10 µg/dL venous baseline lead level.

Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control and Prevention.

Table 1. Current Recommendations From Other Organizations

Organization, Year	Screening Recommendation
American Academy of Family Physicians (AAFP) 2006 [36]	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 blood levels in asymptomatic children ages 1 to 5 years who are at average risk.
American Academy of Pediatrics (AAP) 2016 [37]	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 12 to 24 months of age living in communities with ≥25% of housing built before 1960 or a prevalence of children's blood lead concentrations ≥5 µg/dL of ≥5%; children who live in or visit a home or child care facility with an identified lead hazard; children living in a home built before 1960 in poor repair or renovated in the past 6 months.
American Academy of Pediatrics (AAP)/Bright Futures [35] 2012	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.
American College of Preventive Medicine (ACPM) 2001 [33]	Screening for elevated lead levels via venous or capillary blood lead testing should be conducted for children 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 CDC in their 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 6 years of age.
Centers for Disease Control and Prevention (CDC) 2010 [23]	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.
Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) 2012 [4]	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.

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=United States Preventive Services Task Force.

Table 2. Summary of Evidence

Key Question[a]	Main Findings from Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Strength of Evidence[b]
1	No studies	0	No studies	No studies	Not applicable	No studies	Insufficient
2a	Not previously reviewed[c]	10 cross-sectional studies	All studies conducted from 1994 to 2003; studies used the 1991 CDC questionnaire or a modified version of this survey.	Consistent	Moderate	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%).	Moderate
2b	Not previously reviewed[c]	4 observational studies	None	Consistent	Moderate	Four studies conducted in U.S. urban areas found capillary BLL testing associated with sensitivity of 87% to 91% and specificity >90% (92% to 99%) for identification of elevated BLL compared with venous sampling.	Moderate
3	No studies	0	No studies	No studies	Not applicable	No studies	Insufficient
4	Not previously reviewed[c]	7 RCTs or observational studies (in 10 publications)	Poor-quality studies of nutritional interventions do no provide adequate data to assess treatment effects.	Consistent	Low to moderate	One large RCT found chelation therapy with DMSA in children with mean BLL of 20 to 45 µg/dL associated with decreased BLL vs. placebo at 1 week, 6 months, and 1 year, but there were no effects at longer-term follow up 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 two studies to determine effects of nutritional supplementation. Three studies of residential lead hazard control techniques found no difference in BLL between intervention and control groups.	Moderate

Table 2. Summary of Evidence

Key Question[a]	Main Findings from Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Strength of Evidence[b]
5	No clear evidence to support a clinical benefit from chelation therapy in children with elevated BLL at baseline, based on one trial; no studies on effects of environmental or nutritional interventions on health outcomes	1 RCT (in 3 publications)	Based on one 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.	Consistent	Moderate	One randomized study found no differences between chelation therapy versus 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.	Moderate
6	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 hyperphosphatasemia, neutropenia, eosinophilia, and elevations in serum aminotransferases.	1 RCT (in 3 publications) and 1 observational study	One poor-quality study reported intermediate outcomes associated with adverse effects of treatment.	Consistent	Moderate to high for harms	One good-quality and ne 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 7 years of age. 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.	Moderate

[a] Key Question 1. Is there direct evidence that screening for elevated blood lead levels 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 blood lead levels?
Key Question 2b. What is the accuracy of capillary blood lead testing in children?

Table 2. Summary of Evidence

Key Question 3. What are the harms of screening for elevated blood lead levels (with or without screening questionnaires) in children?
Key Question 4. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy reduce blood lead levels in asymptomatic children with elevated blood lead levels?
Key Question 5. Do counseling and nutritional interventions, residential lead hazard control techniques, or chelation therapy improve health outcomes in asymptomatic children with elevated blood lead levels?
Key Question 6. What are the harms of interventions in asymptomatic children with elevated blood lead levels?
[b] EPC Assessment of Strength of Evidence is based on new evidence identified for this update and relevant evidence from the prior report.
[c] 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; GI=gastrointestinal; RCT=randomized controlled trial; U.S.=United States.

Table 3. Characteristics and Results for Studies of Screening Questionnaires

Study, Year Setting Quality	Screening Test Definition of a Positive Screening Exam	Sample Size Proportion with Condition Population Characteristics	Sensitivity (95% CI)	Specificity (95% CI)
Casey, 1994 [57] United States Urban general pediatric department Fair	CDC Risk Assessment Questionnaire ≥1 positive answer	n=167 Elevated BLL: overall ≥10 ug/dL: 29% (48/165) 10-14 ug/dL: 22% (36/165) 15-19 ug/dL: 4% (7/165) 20-44 ug/dL: 2.5% (4/165) 46 ug/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	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%	Overall: 60% (70/117, 95% CI 50.36 to 68.78%) By screening question: Peeling paint: 76% Renovation: 75% Sib with Pb: 99% Adult's job with Pb: 97% Live near Pb industry: 98%
Dalton, 1996 [60] United States Medical center Fair	CDC Risk Assessment Questionnaire Additional behavioral risk factor questions ≥1 positive or equivocal answer	n=516 Elevated BLL: overall ≥10 ug/dL: 22% (101/463) ≥15 ug/dL: 6% (28/463) Mean age, months: NR, range: 6 to 72 Female: NR Ethnicity: NR	<u>CDC Risk Factors</u> Overall: 70.3% (95% 60.39 to 78.98) <u>Behavioral Risk Factors</u> Playing near outside of house: 74.2% (95% 64.60 to 82.44)	<u>CDC Risk Factors</u> Overall: 31.8% (95% CI 27.00 to 36.84) <u>Behavioral Risk Factors</u> Playing near outside of house: 54.1% (95% CI 28.05 to 37.98)
France, 1996 [51] United States Multisite primary care network Fair	CDC Risk Assessment Questionnaire Additional risk factor questions ≥1 positive or equivocal answer	n=2978 Mean BLL: 4.19 ug/dL Elevated BLL ≥10 ug/dL: 2.9% (85/2978) Mean age, months: NR, range: 5 months to 6.5 years Female: NR Ethnicity: NR	CDC + additional questions: 59.7% (95% CI 48 to 72) CDC alone: 57% (95% CI 45 to 69)	CDC + additional questions: 36% (95% CI 34 to 38) CDC alone: 51% (95% CI 49 to 53)

Table 3. Characteristics and Results for Studies of Screening Questionnaires

Study, Year Setting Quality	Screening Test Definition of a Positive Screening Exam	Sample Size Proportion with Condition Population Characteristics	Sensitivity (95% CI)	Specificity (95% CI)
Holmes, 1997 [58] United States Continuity clinic at a children's hospital Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n=754 Elevated BLL ≥10 ug/dL: 3.1% (25/801)	68% (95% CI 46.50 to 85.05)	58% (95% CI 53.93 to 61.23)
Kazal, 1997 [52] United States Rural clinic, Navajo Reservation Fair	CDC Risk Assessment Questionnaire Additional risk factor questions Unclear definition of positive screening exam	n=368 Elevated BLL ≥1 0ug/dL: 2.2% (8/368) Mean age, months: 30.5 months Female: 49% Ethnicity: 98% Navajo	CDC questions: 42.9% (95% CI 9.90 to 81.59) CDC + additional questions: 42.9% (95% CI NR)	CDC questions: 68.52% (95% CI 68.52 to 78.50) CDC + additional questions: 66.1% (95% CI NR)
Muniz, 2003 [53] United States Rural clinic Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n=171 Elevated BLL ≥10 ug/dL: 2.3% (4/171) Mean age: NR, range 9 to 24 months Female: NR Ethnicity: NR	CDC questions: 25% (95% CI NR) CDC + additional questions: 50.0% (95% CI 6.76 to 93.24)	CDC questions: 49% (95% CI NR) CDC + additional questions: 49.70 (95% CI 41.88 to 57.53)
Robin, 1997 [54] United States Urban and Rural Medicaid recipients Fair	Modified Health Care Financing Administration questionnaire	n=967 Elevated BLL ≥10 ug/dL: 0.6% (6/967) Mean age: NR, range 2-6 years Female: 51.3% Ethnicity: Alaska native: 60% White: 28% Black: 5%	83.3% (95% CI 35.88 to 99.58)	38.6% (95% CI 35.50 to 41.77)

Table 3. Characteristics and Results for Studies of Screening Questionnaires

Study, Year Setting Quality	Screening Test Definition of a Positive Screening Exam	Sample Size Proportion with Condition Population Characteristics	Sensitivity (95% CI)	Specificity (95% CI)
Schaffer, 1996 [55] United States Rural clinic Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n=705 Elevated BLL ≥10 ug/dL: 8.4% (59/705) Mean age: NR, range 6 to 72 months Female: NR Ethnicity: NR	CDC + additional questions: 75% (95% CI NR) Condensed questionnaire from 4 most likely to correctly identify patients: 88% (95% CI NR)	CDC + additional questions: NR Condensed questionnaire from 4 most likely to correctly identify patients: NR
Snyder, 1995 [59] United States Public clinics Fair	CDC Risk Assessment Questionnaire Additional risk factor questions	n= 247 Elevated BLL ≥10 ug/dL: 7.7% (19/247) Mean age: NR, range 6 to 72 months Female: NR Ethnicity: NR	CDC questions: 31.6% (95% CI 12.58 to 56.55) Additional questions: 89.5% (95% CI 66.86 to 98.70) CDC + additional questions: 89.5% (95% CI 66.6 to 98.70)	CDC questions: 79.8 (95% CI 74.02 to 84.83) Additional questions: 37.3% (95% CI 30.99 to 43.91) CDC + additional questions: 31.6% (95% CI 25.6 to 38.0)

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

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)") (1028)
10 exp pregnancy/
11 exp pregnancy complications/
12 exp fetus/
13 exp prenatal care/
14 exp Prenatal Exposure Delayed Effects/
15 exp Prenatal Injuries/
16 exp "Embryonic and Fetal Development"/
17 10 or 11 or 12 or 13 or 14 or 15 or 16
18 8 and 17
19 9 or 18
20 ((test* or assay* or sampl* or detect* or surveil* or screen* or questionnair* or survey* or (risk* adj3 (assess* or predict* or determin* or measur* or calculat*))) adj5 (lead or pb) adj7 (infan* or fetus or fetal* or prenat* or pregnan* or baby or babies or child* or toddler*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
21 19 or 20
22 exp diagnosis/
23 3 and 22
24 17 and 23
25 limit 24 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
26 24 or 25
27 ((test* or assay* or sampl* or detect* or surveil* or screen* or questionnair* or survey* or (risk* adj3 (assess* or predict* or determin* or measur* or calculat*))) adj5 (lead or pb) adj7 (infan* or fetus or fetal* or prenat* or pregnan* or baby or babies or child* or toddler*)).mp.
28 17 and 27
29 limit 27 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)") (538)
30 28 or 29
31 26 or 30
32 21 or 31
33 limit 32 to humans
34 limit 33 to english language
35 limit 33 to abstracts
36 34 or 35

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

Treatment

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

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

Screening and Treatment

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

1 ((treat* or therap* or interven* or antidot* or remed* or cure or cured or curing or cures or chelat*) adj7 (lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*))).mp.
2 ((screen* or ((routin* or annual* or yearly) adj5 (test* or diagnos* or assay* or exam*))) adj7 ((lead or pb) adj5 (poison* or toxic* or intoxic* or ((high* or elevat*) adj3 level*)))).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 or 2

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

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

Appendix A2. Inclusion and Exclusion Criteria

	Include	Exclude
Populations	Asymptomatic children age ≤ 5 years	All other populations [a]
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	All other screening tests, including point-of-care blood lead level assays that are not approved by the U.S. Food and Drug Administration and are not available in the United States
Interventions	KQs 4–6: Studies assessing interventions aimed at reducing blood lead levels, including one or more of the following: counseling families to reduce lead exposure, nutritional interventions, residential hazard control techniques, and chelation therapy	Policies, laws, or community-based interventions focused on the primary prevention of lead exposure
Comparisons	KQs 1, 3: Screened vs. nonscreened groups KQ 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	All other comparisons, including head-to-head comparisons of two different interventions
Outcomes	KQs 1, 5: Validated measures of cognitive and neurobehavioral outcomes in children, including assessment of IQ or development [b] 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 [b] KQ 6: Anxiety or distress; inconvenience associated with intervention (e.g., school absenteeism associated with follow up testing); morbidity attributed to chelation therapy (e.g., renal toxicity, sensitivity reactions)	All other outcomes, including measures of household lead dust
Study designs	KQ 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	Systematic reviews,[c] case series, case reports, or comparison with historical controls
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	All other settings, including community health case-finding (e.g., blood lead level monitoring after known environmental exposure)
Country Setting	KQs 1-3: Research conducted in the United States or in populations similar to U.S. populations with services and interventions applicable to U.S. practice (i.e., countries with a United Nations Human Development Index of "very high" or "high" when no other evidence is available) KQs 4-6: Any country	KQs 1-3: Research not relevant to the United States or conducted in countries with a Human Development Index other than "very high"
Language	English language	Languages other than English

[a] Studies enrolling older children will be eligible if at least 50% of the sample is age ≤5 years, or if studies report outcomes separately for children ≤5 years.

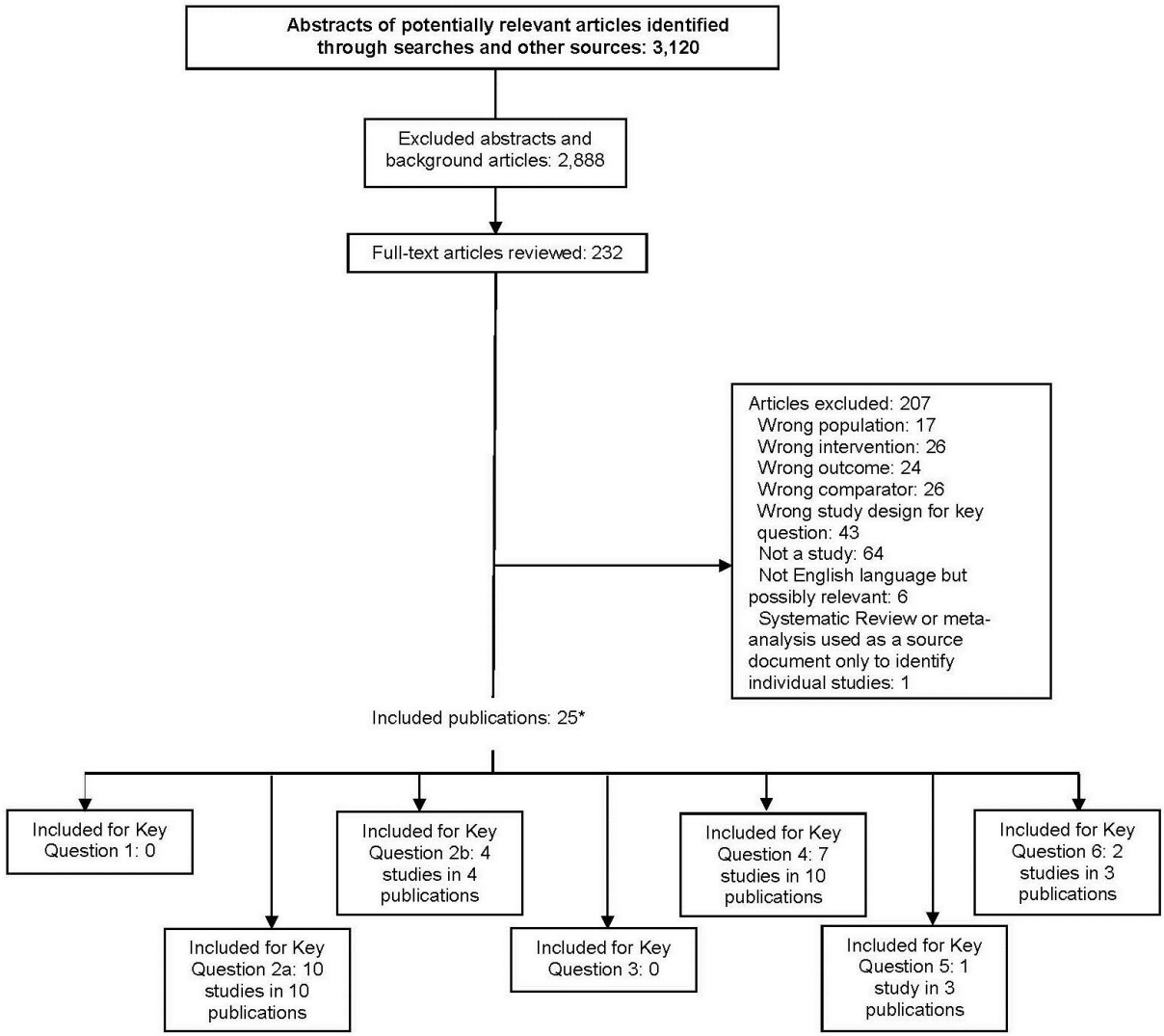
Appendix A2. Inclusion and Exclusion Criteria

[b] We will include outcomes measured in family members (e.g. siblings, pregnant women in the same household) who are subsequently identified as having elevated blood lead levels after the index family member was found to have an elevated blood lead level during screening.

[c] Systematic reviews are excluded from the evidence review. However, we will conduct 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 will describe any relevant systematic reviews in the Discussion section of the report.

Abbreviations: CC=controlled clinical trial; RCT=randomized controlled trial.

Appendix A3. Literature Flow Diagram



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

Appendix A4. List of Excluded Studies

1. Abendroth K. [Excellent effect of sodium-citrate-EDTA-combination therapy in severe lead poisoning during pregnancy]. Dtsch Gesundheitsw. 1971 Nov 04;26(45):2130-1. PMID: 5004297. Excluded: Not English language, but possibly relevant.
2. Alfaro C, Vincelet C, Lombrail P, et al. [Evaluation of the screening strategy for lead poisoning in 1-to-3-year-old children monitored in maternal-child welfare centers in Paris]. Rev Epidemiol Sante Publique. 1993;41(6):473-9. PMID: 8296033. Excluded: Not English language, but possibly relevant.
3. Alpert JJ. Screening for lead poisoning. Pediatrics. 1970 Apr;45(4):721-2. PMID: 5438185. Excluded: Not a study.
4. Altmann P, Maruna RF, Maruna H, et al. [Lead detoxication effect of a combined calcium phosphate and ascorbic acid therapy in pregnant women with increased lead burden (author's transl)]. Wien Med Wochenschr. 1981;131(12):311-4. PMID: 7293190. Excluded: Not English language, but possibly relevant.
5. Anderson MK, Amrich M, Decker KL, et al. Using state lead poisoning surveillance system data to assess false positive results of capillary testing. Matern Child Health J. 2007 Nov;11(6):603-10. doi: 10.1007/s10995-007-0196-1. PMID: 17340181. Excluded: Wrong study design for key question.
6. Andrews KW, Savitz DA, Hertz-Picciotto I. Prenatal lead exposure in relation to gestational age and birth weight: a review of epidemiologic studies. Am J Ind Med. 1994 Jul;26(1):13-32. PMID: 8074121. Excluded: Not a study.
7. Anonymous. The Treatment of Lead-exposed Children (TLC) trial: design and recruitment for a study of the effect of oral chelation on growth and development in toddlers. Paediatr Perinat Epidemiol. 1998 Jul;12(3):313-33. PMID: 9690266. Excluded: Not a study.
8. Arbuckle TE, Liang CL, Morisset AS, et al. Maternal and fetal exposure to cadmium, lead, manganese and mercury: The MIREC study. Chemosphere. 2016 Nov;163:270-82. doi: 10.1016/j.chemosphere.2016.08.023. PMID: 27540762. Excluded: Wrong study design for key question.
9. Aschengrau A, Beiser A, Bellinger D, et al. The impact of soil lead abatement on urban children's blood lead levels: phase II results from the Boston Lead-In-Soil Demonstration Project. Environ Res. 1994 Nov;67(2):125-48. doi: 10.1006/enrs.1994.1069. PMID: 7982389. Excluded: Wrong intervention.
10. Aschengrau A, Hardy S, Mackey P, et al. The impact of low technology lead hazard reduction activities among children with mildly elevated blood lead levels. Environ Res. 1998 Oct;79(1):41-50. doi: 10.1006/enrs.1998.3858. PMID: 9756679. Excluded: Wrong outcome.
11. Awasthi S, Awasthi R, Srivastav RC. Maternal blood lead level and outcomes of pregnancy in Lucknow, North India. Indian Pediatr. 2002 Sep;39(9):855-60. PMID: 12368533. Excluded: Wrong study design for key question.
12. Baghurst PA, Robertson EF, McMichael AJ, et al. The Port Pirie Cohort Study: lead effects on pregnancy outcome and early childhood development. Neurotoxicology. 1987 Fall;8(3):395-401. PMID: 2443882. Excluded: Wrong study design for key question.
13. Bajorek MM. Screening children for lead poisoning. West J Med. 1995 Jul;163(1):64. PMID: 7667984. Excluded: Not a study.
14. Baloh R, Sturm R, Green B, et al. Neuropsychological effects of chronic asymptomatic increased lead absorption. A controlled study. Arch Neurol. 1975 May;32(5):326-30. PMID: 1137507. Excluded: Wrong study design for key question.
15. Bartsocas CS, Grunt JA, Boylen GW, Jr., et al. Oral D-penicillamine and intramuscular BAL+EDTA in the treatment of lead accumulation. Acta Paediatr Scand. 1971 Sep;60(5):553-8. PMID: 4999890. Excluded: Wrong study design for key question.

Appendix A4. List of Excluded Studies

16. Batagol R. Australian Drug Evaluation Committee: Medicines in pregnancy-An Australian categorisation of risk of drug use in pregnancy, 4th. Australian Government Publishing Service, Canberra, Australia; 1999. Excluded: Not a study.

17. . Ultrastructural findings in fetal penicillamine syndrome. Presentation and abstract, March of Dimes 14th Annual Birth Defects Conference, San Diego, CA; 1981. Excluded: Wrong outcome.

18. Bellinger D. Prenatal/early postnatal exposure to lead and risk of developmental impairment. Birth Defects Orig Artic Ser. 1989;25(6):73-97. PMID: 2481518. Excluded: Not a study.

19. Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics. 1992 Dec;90(6):855-61. PMID: 1437425. Excluded: Wrong study design for key question.

20. Benson PF, Chisolm JJ, Jr. A reliable qualitative urine coproporphyrin test for lead intoxication in young children. J Pediatr. 1960 Jun;56:759-67. PMID: 13799015. Excluded: Wrong intervention.

21. Besunder JB, Super DM, Anderson RL. Comparison of dimercaptosuccinic acid and calcium disodium ethylenediaminetetraacetic acid versus dimercaptopropanol and ethylenediaminetetraacetic acid in children with lead poisoning. J Pediatr. 1997 Jun;130(6):966-71. PMID: 9202621. Excluded: Wrong comparator.

22. Bhattacharya A, Shukla R, Auyang ED, et al. Effect of succimer chelation therapy on postural balance and gait outcomes in children with early exposure to environmental lead. Neurotoxicology. 2007 May;28(3):686-95. doi: 10.1016/j.neuro.2007.03.007. PMID: 17499360. Excluded: Wrong outcome.

23. Binns HJ, Kim D, Campbell C. Targeted screening for elevated blood lead levels: populations at high risk. Pediatrics. 2001 Dec;108(6):1364-6. PMID: 11731660. Excluded: Not a study.

24. Binns HJ, LeBailly SA, Fingar AR, et al. Evaluation of risk assessment questions used to target blood lead screening in Illinois. Pediatrics. 1999 Jan;103(1):100-6. PMID: 9917446. Excluded: Wrong comparator.

25. Binns HJ, LeBailly SA, Poncher J, et al. Is there lead in the suburbs? Risk assessment in Chicago suburban pediatric practices. Pediatric Practice Research Group. Pediatrics. 1994 Feb;93(2):164-71. PMID: 8121725. Excluded: Wrong comparator.

26. Blanksma LA, Sachs HK, Murray EF, et al. Failure of the urinary delta-aminolevulinic acid test to detect pediatric lead poisoning. Am J Clin Pathol. 1970 Jun;53(6):956-62. PMID: 5515391. Excluded: Wrong intervention.

27. Blumenthal S, Davidow B, Harris D, et al. A comparison between two diagnostic tests for lead poisoning. Am J Public Health. 1972 Aug;62(8):1060-4. PMID: 5046445. Excluded: Wrong intervention.

28. Borja-Aburto VH, Hertz-Picciotto I, Rojas Lopez M, et al. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol. 1999 Sep 15;150(6):590-7. PMID: 10489998. Excluded: Wrong study design for key question.

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

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

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

Appendix A4. List of Excluded Studies

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

33. Briss PA, Rosenblum LS. Screening strategies for lead poisoning. JAMA. 1993 Dec 01;270(21):2556; author reply -7. PMID: 8230637. Excluded: Not a study.

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

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

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

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

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

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

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

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

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

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

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

45. Carpenter JW. Pediatric lead level screening. Alaska Med. 1993 Apr-Jun;35(2):173. PMID: 8238773. Excluded: Wrong study design for key question.

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

47. Centers for Disease Control and Prevention. Blood lead levels among children in a managed-care organization--California, October 1992-March 1993. MMWR. 1995 Sep 01;44(34):627-9, 35. PMID: 7643848. Excluded: Wrong outcome.

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

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

Appendix A4. List of Excluded Studies

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

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

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

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

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

55. Chisolm JJ, Jr. Management of increased lead absorption and lead poisoning in children. N Engl J Med. 1973 Nov 08;289(19):1016-8. doi: 10.1056/NEJM197311082891906. PMID: 4742201. Excluded: Not a study.

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

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

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

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

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

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

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

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

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

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

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

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

Appendix A4. List of Excluded Studies

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

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

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

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

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

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

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

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

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

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

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

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

80. Etchevers A, Glorennec P, Le Strat Y, et al. Screening for elevated blood lead levels in children: assessment of criteria and a proposal for new ones in France. Int J Environ Res Public Health. 2015 Dec 03;12(12):15366-78. doi: 10.3390/ijerph121214989. PMID: 26633457. Excluded: Wrong outcome.

81. Ettinger AS, Lamadrid-Figueroa H, Mercado-Garcia A, et al. Effect of calcium supplementation on bone resorption in pregnancy and the early postpartum: a randomized controlled trial in Mexican women. Nutr J. 2014 Dec 16;13(1):116. doi: 10.1186/1475-2891-13-116. PMID: 25511814. Excluded: Wrong outcome.

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

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

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

Appendix A4. List of Excluded Studies

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

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

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

88. Garza A. Screening strategies for lead poisoning. JAMA. 1993 Dec 01;270(21):2555; author reply 6-7. PMID: 8230634. Excluded: Not a study.

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix A4. List of Excluded Studies

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

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

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

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

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

107. Jacobziner H, Raybin HW. Lead poisoning treated with bal. N Y State J Med. 1964 Feb 01;64:441. PMID: 14118322. Excluded: Not a study.

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

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

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

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

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

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

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

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

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

Appendix A4. List of Excluded Studies

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

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

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

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

121. Knighton AJ, Payne NR, Speedie S. Lead Testing in a Pediatric Population: Underscreening and Problematic Repeated Tests. Journal of Public Health Management & Practice. 2016 Jul-Aug;22(4):331-7. doi: https://dx.doi.org/10.1097/PHH.0000000000000344. PMID: 26418307. Excluded: Wrong outcome.

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

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

124. Lanphear BP. The paradox of lead poisoning prevention. Science. 1998 Sep 11;281(5383):1617-8. PMID: 9767027. Excluded: Not a study.

125. Lanphear BP. Childhood lead poisoning prevention: too little, too late. JAMA. 2005 May 11;293(18):2274-6. doi: 10.1001/jama.293.18.2274. PMID: 15886384. Excluded: Not a study.

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

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

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

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

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

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

132. Mabry IR. Screening for elevated blood lead levels in children and pregnant women. Am Fam Phys. 2008 Nov 15;78(10):1201-2. PMID: 19035069. Excluded: Not a study.

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

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

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135. Marcus M, Hollander M, Lucas RE, et al. Micro-scale blood lead determinations in screening: evaluation of factors affecting results. Clin Chem. 1975 Apr;21(4):533-6. PMID: 1116287. Excluded: Wrong study design for key question.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

162. Rainey PM, Schonfeld DJ. Comparability of capillary and venous blood samples for lead screening. JAMA. 1994 Nov 16;272(19):1482. PMID: 7966831. Excluded: Not a study.

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

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

165. Raymond J, Wheeler W, Brown MJ, et al. Lead screening and prevalence of blood lead levels in children aged 1-2 years--Child Blood Lead Surveillance System, United States, 2002-2010 and National Health and Nutrition Examination Survey, United States, 1999-2010. MMWR Suppl. 2014 Sep 12;63(2):36-42. PMID: 25208256. Excluded: Wrong study design for key question.

Appendix A4. List of Excluded Studies

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

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

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

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

170. Ruff HA, Bijur PE, Markowitz M, et al. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. JAMA. 1993 Apr 07;269(13):1641-6. PMID: 8455297. Excluded: Wrong outcome.

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

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

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

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

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

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

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

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

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

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

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

Appendix A4. List of Excluded Studies

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

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

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

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

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

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

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

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

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

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

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

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

194. Triantafyllidou S, Le T, Gallagher D, et al. Reduced risk estimations after remediation of lead (Pb) in drinking water at two US school districts. Sci Total Environ. 2014 Jan 01;466-467:1011-21. doi: 10.1016/j.scitotenv.2013.07.111. PMID: 23988746. Excluded: Wrong outcome.

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

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

Appendix A4. List of Excluded Studies

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

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

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

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

201. Watt GC, Britton A, Gilmour WH, et al. Is lead in tap water still a public health problem? An observational study in Glasgow. BMJ. 1996 Oct 19;313(7063):979-81. PMID: 8892418. Excluded: Wrong study design for key question.

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

Systematic Reviews

Criteria:

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

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

Case-Control Studies

Criteria:

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

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

RCTs and Cohort Studies

Criteria:

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

- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Definition of ratings based on above criteria:

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

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

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

Diagnostic Accuracy Studies

Criteria:

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

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients

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

*Reference: U.S. Preventive Services Task Force Procedure Manual. December 2015. Accessed at https://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Appendix A6. Expert Reviewers of the Draft Report

Jennifer A. Lowry, MD, Chief, Section of Toxicology and Environmental Health, Children's Mercy

Suril Mehta, MPH, Health Scientist, Office of the Report on Carcinogens, U.S. National Toxicology Program, National Institute of Environmental Health Sciences

Matthew Strickland, PhD, MPH, Associate Professor of Epidemiology, School of University Health Sciences, University of Nevada, Reno

Federal Partners from the United States Environmental Protection Agency

- Ruth A. Etzel, MD, PhD, Director, Office of Children's Health Protection, United States Environmental Protection Agency

Additional Federal Partners from the Centers for Disease Control and Prevention

- Brandy Peaker, MD, MPH, CDC Liason, Centers for Disease Control and Prevention

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

Appendix B Table 1. Data Abstraction of Screening Questionnaire Studies

Study, Year	Screening Test	Definition of a Positive Screening Exam	Reference Standard	Type of Study	Country Setting	Population Characteristics	Sample Size Proportion with Condition
Casey, 1994 [57]	CDC Risk Assessment Questionnaire	≥1 positive answer	Venous	Cross-sectional	United States Urban general pediatric department	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	n=167 Elevated BLL, Overall ≥10 ug/dL: 29% (48/165) 10-14 ug/dL: 22% (36/165) 15-19 ug/dL: 4% (7/165) 20-44 ug/dL: 2.5% (4/165) 46 ug/dL: 0.5% (1/165)
Dalton, 1996 [56]	CDC Risk Assessment Questionnaire Additional behavioral risk factor questions	≥1 positive or equivocal answer	Venous	Cross-sectional	United States Medical center	Mean age, months: NR, range: 6 to 72 Female: NR Ethnicity: NR	n=516 Elevated BLL, Overall ≥10 ug/dL: 22% (101/463) ≥15 ug/dL: 6% (28/463)
France, 1996 [519]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive or equivocal answer	Venous	Cross-sectional	United States Multisite primary care network	Mean age, months: NR, range: 5 months to 6.5 years Female: NR Ethnicity: NR	n=2978 Mean BLL: 4.19 ug/dL Elevated BLL ≥10 ug/dL: 2.9% (85/2978)
Holmes, 1997 [58]	CDC Risk Assessment Questionnaire Additional risk factor questions	Unclear	Venous	Cross-sectional	United States Continuity clinic at a children's hospital	Mean age, months: 28.44, range 9 to 72 Female: 46% Ethnicity: 39% Hispanic, 39% Black, 18% white	n=754 Elevated BLL ≥10 ug/dL: 3.1% (25/801)

Appendix B Table 1. Data Abstraction of Screening Questionnaire Studies

Study, Year	Proportion Unexaminable by Screening Test	Analysis of Screening Failures	Proportion Who Underwent Reference Standard and Included in Analysis	Sensitivity (95% CI)	Specificity (95% CI)
Casey, 1994[57]	n=2	NR	98% (165/167)	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%	Overall: 60% (70/117, 95% CI 50.36 to 68.78%) By screening question: Peeling paint: 76% Renovation: 75% Sib with Pb: 99% Adult's job with Pb: 97% Live near Pb industry: 98%
Dalton, 1996[56]	n=0	NR	89.7% (463/516)	CDC Risk Factors Overall: 70.3% (95% 60.39 to 78.98) Behavioral Risk Factors Playing near outside of house: 74.2% (95% 64.60 to 82.44)	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)
France, 1996[51]	n=562 (19%)	Prevalence of elevated BLL did not differ for those who did not complete screening questionnaire: 3.2% (p=0.51)	81% (2416/2978)	CDC + additional questions: 59.7% (95% CI 48 to 72) CDC alone: 57% (95% CI 45 to 69)	CDC + additional questions: 36% (95% CI 34 to 38) CDC alone: 51% (95% CI 49 to 53)
Holmes, 1997[58]	n=47 (5.9%)	NR	94% (754/801)	68% (95% CI 46.50 to 85.05)	57361% (95% CI 53.93 to 61.23)

Appendix B Table 1. Data Abstraction of Screening Questionnaire Studies

Study, Year	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Quality Rating
Casey, 1994[57]	Overall: 1.0 (95% CI 0.65 to 1.49) Peeling paint: 0.625 Renovation: 1.24 Sibling with Pb: 6.0 Adults job: 0.67 Live near Pb: 3	Overall: 1.0 (95% CI 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	Overall: 29% (19/66, 95% CI 21.09 to 37.94) Peeling paint: 20% Renovation: 34% Sibling with Pb: 75% Adult's job: 25% Live near Pb: 60%	Overall: 71% (76/99, 95% CI 64.75 to 76.03) Peeling paint: 68% Renovation: 73% Sibling with Pb: 72% Adult's job: 71% Live near Pb: 72%	Fair
Dalton, 1996[56]	CDC risk factors: 1.03 (95% CI 0.89 to 1.19) Playing near outside of house: 1.62 (95% CI 0.97 to 1.27)	CDC risk factors: 0.93 (95% CI 0.67 to 1.31) Playing near outside of house: 0.78 (95% CI 0.54 to 1.13)	CDC risk factors: 22.33% (95% CI 19.91 to 24.94) Playing near outside of house: 23.58% (95% CI 21.23 to 26.12)	CDC risk factors: 79.31% (73.26 to 84.29) Playing near outside of house: 82.07% (95% CI 76.11 to 86.80)	Fair
France, 1996[51]	CDC + additional questions: 0.93 (95% CI NR) CDC alone: 1.16 (95% CI NR)	CDC + additional questions: 1.12 (95% CI NR) CDC alone: 0.84 (95% CI NR)	CDC + additional questions: 2.8 (95% CI NR) CDC alone: NR	CDC + additional questions: NR CDC alone: NR	Fair
Holmes, 1997[58]	1.60 (95% CI 1.21 to 2.13)	0.56 (95% CI 0.31 to 0.99)	5.21% (95% CI 3.98 to 6.80)	98.13% (95% CI 96.73 to 98.94)	Fair

Appendix B Table 1. Data Abstraction of Screening Questionnaire Studies

Study, Year	Screening Test	Definition of a Positive Screening Exam	Reference Standard	Type of Study	Country Setting	Population Characteristics	Sample Size Proportion with Condition
Kazal, 1997[52]	CDC Risk Assessment Questionnaire Additional risk factor questions	Unclear	Venous	Cross-sectional	United States Rural clinic, Navajo Reservation	Mean age, months: 30.5 months Female: 49% Ethnicity: 98% Navajo	n=368 Elevated BLL ≥10ug/dL: 2.2% (8/368)
Muniz, 2003[53]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive or equivocal answer	Venous	Retrospective cohort	United States Rural clinic	Mean age: NR, range 9 to 24 months Female: NR Ethnicity: NR	n=171 Elevated BLL ≥10 ug/dL: 2.3% (4/171)
Robin, 1997[54]	Modified Health Care Financing Administration questionnaire	≥1 positive answer	Venous	Cross-sectional	United States Urban and Rural Medicaid recipients	Mean age: NR, range 2–6 years Female: 51.3% Ethnicity: Alaska native: 60% white: 28% Black: 5%	n=967 Elevated BLL ≥10 ug/dL: 0.6% (6/967)
Schaffer, 1996[55]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive or equivocal answer to the CDC questions	Venous (approximately 6% were capillary)	Cross-sectional	United States Rural clinic	Mean age: NR, range 6 to 72 months Female: NR Ethnicity: NR	n=705 Elevated BLL ≥10 ug/dL: 8.4% (59/705)
Snyder, 1995[57]	CDC Risk Assessment Questionnaire Additional risk factor questions	≥1 positive answer	Venous	Cross-sectional	United States Public clinics	Mean age: NR, range 6 to 72 months Female: NR Ethnicity: NR	n= 247 Elevated BLL ≥10 ug/dL: 7.7% (19/247)

Appendix B Table 1. Data Abstraction of Screening Questionnaire Studies

Study, Year	Proportion Unexaminable by Screening Test	Analysis of Screening Failures	Proportion Who Underwent Reference Standard and Included in Analysis	Sensitivity (95% CI)	Specificity (95% CI)
Kazal, 1997[52]	n=45 (12.2%)	NR	100%	CDC questions: 42.9% (95% CI 9.90 to 81.59) CDC + additional questions: 42.9% (95% CI NR)	CDC questions: 68.52% (95% CI 68.52 to 78.50) CDC + additional questions: 66.1% (95% CI NR)
Muniz, 2003[53]	n=0	NR	100%	CDC questions: 25% (95% CI NR) CDC + additional questions: 50.0% (95% CI 6.76 to 93.24)	CDC questions: 49% (95% CI NR) CDC + additional questions: 49.70 (95% CI 41.88 to 57.53)
Robin, 1997[54]	n= 0	NR	100%	83.3% (95% CI) 35.88 to 99.58)	38.6% (95% CI 35.50 to 41.77)
Schaffer, 1996[55]	n=1 (0.1%)	NR	99.2% (705/711)	CDC + additional questions: 75% (95% CI NR) Condensed questionnaire from 4 most likely to correctly identify patients: 88% (95% CI NR)	CDC + additional questions: NR Condensed questionnaire from 4 most likely to correctly identify patients: NR
Snyder, 1995[57]	n=0	NR	100%	CDC questions: 31.6% (95% CI 12.58 to 56.55) Additional questions: 89.5% (95% CI 66.86 to 98.70) CDC + additional questions: 89.5% (95% CI 66.6 to 98.70)	CDC questions: 79.8 (95% CI 74.02 to 84.83) Additional questions: 37.3% (95% CI 30.99 to 43.91) CDC + additional questions: 31.6% (95% CI 25.6 to 38.0)

Appendix B Table 1. Data Abstraction of Screening Questionnaire Studies

Study, Year	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Quality Rating
Kazal, 1997[52]	1.63 (95% CI 0.68 to 3.91) CDC + additional questions: 1.27 (95% CI NR)	0.77 (95% CI 0.41 to 1.48) CDC + additional questions: 0.79 (95% CI NR)	3.49% (95% CI 1.48 to 7.98) CDC + additional questions: 2.7 (95% CI NR)	98.31% (95% CI 96.83 to 99.11) CDC + additional questions: 98.1 (95% CI NR)	Fair
Muniz, 2003[53]	CDC + additional questions: 0.99 (95% CI 0.37 to 2.68)	CDC + additional questions: 1.01 (95% CI 0.37 to 2.71)	CDC + additional questions: 2.33% (95% CI 0.88 to 6.03)	CDC + additional questions: 97.65% (95% CI 93.90 to 99.11)	Fair
Robin, 1997[54]	1.36 (95% CI 0.95 to 1.95)	0.43 (95% 0.07 to 2.59)	0.84% (0.59 to 1.21)	99.73% (98.40 to 99.95)	Fair
Schaffer, 1996[55]	CDC + additional questions: NR Condensed questionnaire from 4 most likely to correctly identify patients: NR	CDC + additional questions: NR Condensed questionnaire from 4 most likely to correctly identify patients: NR	CDC + additional questions: NR Condensed questionnaire from 4 most likely to correctly identify patients: NR	CDC + additional questions: 98% Condensed questionnaire from 4 most likely to correctly identify patients: 98% (95% CI NR)	Fair
Snyder, 1995[57]	CDC questions: 1.57 (95% CI 0.77 to 3.19) Additional questions: 1.43 (95% CI 1.19 to 1.71) CDC + additional questions: 1.31 (95% CI 1.09 to 1.56)	CDC questions: 0.86 (0.63 to 1.17) Additional questions: 0.28 (95% CI 0.08 to 1.06) CDC + additional questions: 0.33 (95% CI 0.09 to 1.25)	CDC questions: 11.54% (95% CI 6.02 to 20.98) Additional questions: 10.6% (95% CI 9.00 to 12.5) CDC + additional questions: 9.83% (95% CI 8.36 to 11.52)	CDC questions: 93.33% (95% CI 91.11 to 95.03) Additional questions: 97.7% (95% CI 91.89 to 99.38) CDC + additional questions: 97.3 (95% CI 90.54 to 99.27)	Fair

Abbreviations: BLL=blood lead level; CDC=Centers for Disease Control and Prevention; CI=confidence interval; LRs=likelihood ratios; NR=not reported; Pb=lead.

Appendix B Table 2. Data Abstraction of Capillary Screening Studies

Study, Year	Screening Test	Definition of a Positive Screening Exam	Reference Standard	Type of Study	Country Setting	Population Characteristics	Sample Size Proportion with Condition	Proportion Unexaminable by Screening Test
Holtrop, 1998[61]	Capillary	≥10 ug/dL ≥15 ug/dL ≥20 ug/dL	Venous	Prospective cohort	United States Urban clinic	Mean age: NR Female sex: 41% Ethnicity: 97% Black	n=124 Elevated BLL, ≥10 ug/dL: 26% (31/120)	0%
Parsons, 1997[27]	Capillary	≥10 ug/dL ≥15 ug/dL ≥20 ug/dL ≥25 ug/dL	Venous	Prospective cohort	United States County Health Clinics and University Hospital	Mean age: NR (range, 0-12 years) Female sex: 43% Ethnicity: 38% white, 28% Black, 21% Hispanic, 6% Asian	n=499 Elevated BLL ≥10 ug/dL: 30.5% Elevated BLL ≥15 ug/dL: 16.7% Elevated BLL ≥20 ug/dL: 9.9% Elevated BLL ≥25 ug/dL: 6.6%	5% (29/533)
Sargent, 1996[62] See also: Sargent, 1996[81]	Capillary	≥8 ug/dL ≥10 ug/dL ≥12 ug/dL ≥15 ug/dL	Venous	Prospective cohort	United States Urban clinic	NR	n=513 Elevated BLL ≥10 ug/dL: 20.5% Elevated BLL ≥20 ug/dL: 2.3%	2.7% (16/586)
Schlenker, 1994[61]	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	≥20 ug/dL	Venous	Prospective cohort	United States Urban health department and clinics	Mean age: 3 years Female sex: 47% Ethnicity: 88% Black	n=295 Elevated BLL: NR	NR

Appendix B Table 2. Data Abstraction of Capillary Screening Studies

Study, Year	Proportion Who Underwent Reference Standard and Included in Analysis	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)	Quality Rating
Holtrop, 1998[61]	97% (120/124)	≥10 ug/dL: 94% (95% CI NR) ≥15 ug/dL: 75% (95% CI NR) ≥20 ug/dL: 78% (95% CI NR)	≥10 ug/L: 99% (95% CI NR) ≥15 ug/L: 98% (95% CI NR) ≥20 ug/L: 100% (95% CI NR)	≥10 ug/L: 94 ≥15 ug/L: 37.5 ≥20 ug/L: Not estimable	≥10 ug/L: 0.06 ≥15 ug/L: 0.26 ≥20 ug/L: 0.22	≥10 ug/L: 97% (95% CI NR) ≥15 ug/L: 86% (95% CI NR) ≥20 ug/L: 100% (95% CI NR)	≥10 ug/L: 98% (95% CI NR) ≥15 ug/L: 96% (95% CI NR) ≥20 ug/L: 98% (95% CI NR)	Poor
Parsons, 1997[27]	93.6% (499/533)	≥10 ug/dL: 87.5% (81.8 to 91.9%) ≥15 ug/dL: 83.0% (74.8 to 89.5%) ≥20 ug/dL: 81.8% (70.4 to 90.2%) ≥25 ug/dL: 82.5% (67.2 to 92.3%)	≥10 ug/dL: 93.2% (90.0-95.6%) ≥15 ug/dL: 95.3% (92.8 to 97.2%) ≥20 ug/dL: 97.3% (95.3 to 98.6%) ≥25 ug/dL: 98.5% (96.9 to 99.4%)	≥10 ug/dL: 12.9 (8.6 to 19.2) ≥15 ug/dL: 17.7 (11.4 to 27.7) ≥20 ug/dL: 30.3 (17.2 to 53.6) ≥25 ug/dL: 54.8 (25.9 to 115.9)	≥10 ug/dL: 0.13 (0.09 to 0.20) ≥15 ug/dL: 0.18 (0.12 to 0.27) ≥20 ug/dL: 0.19 (0.11 to 0.31) ≥25 ug/dL: 0.18 (0.09 to 0.35)	≥10 ug/dL: 87.5% (82.5% to 91.3%) ≥15 ug/dL: 83.0% (75.8 to 88.4%) ≥20 ug/dL: 81.8% (71.8 to 88.8%) ≥25 ug/dL: 82.5% (69.0 to 90.9%)	≥10 ug/dL: 93.2% (90.3 to 95.3%) ≥15 ug/dL: 95.3% (93.1 to 96.9%) ≥20 ug/dL: 97.3% (95.6 to 98.4%) ≥25 ug/dL: 98.5% (97.1 to99.2%)	Fair
Sargent, 1996[62] See also: Sargent, 1996[81]	88% (513/586)	≥8 ug/dL: 100% (95% CI NR) ≥10 ug/dL: 91% (95% CI NR) ≥12 ug/dL: 63% (95% CI NR)	≥8 ug/dL: NR ≥10 ug/dL: 92.2% (95% CI NR) ≥12 ug/dL: NR ≥15 ug/dL: NR	NR	NR	≥8 ug/dL: NR ≥10 ug/dL: 74.8% (95% CI NR) ≥12 ug/dL: NR ≥15 ug/dL: NR	NR	Fair
Schlenker, 1994[61]	100%	Method 1: 95% (95% CI NR) Method 2: 96% (95% CI NR) Method 3: 88% (95% CI NR) Method 4: 86% (95% CI NR)	Method 1: 94% (95% CI NR) Method 2: 96% (95% CI NR) Method 3: 100% (95% CI NR) Method 4: 91% (95% CI NR)	Method 1: 15.8 Method 2: 24.0 Method 3: Not estimable Method 4: 9.6	Method 1: 0.05 Method 2: 0.04 Method 3: 0.12 Method 4: 0.15	NR	NR	Poor

Abbreviations: CI=confidence interval; NR=not reported.

Appendix B Table 3. Data Abstraction of Childhood Treatment Trials

Author, Year	Study Design	Setting Country	Study Duration Mean Followup	Interventions (N)	Inclusion Criteria	Patient Characteristics	Loss to Followup	Adjusted Variables for Statistical Analysis (for observational studies)
Boreland, 2009[65]	RCT	Lead-mining neighbor-hood Australia	Duration: mean 13 months	A. Immediate lead home remediation (n=45) B. Delayed lead home remediation (n=45)	Children aged 12-60 months with BLL 15–29 ug/dL	Age: 3.5 years Race: NR Sex: 58% female BLL: 15-19 ug/dL: 28% BLL: 20-24 ug/dL: 23% BLL: 25-29 ug/dL: 37% BLL: >30 ug/dL: 12%	Loss to follow up: 2% (1/45) vs. 2% (1/45)	Sex, location, lead loading, lead paint, dust proofing, soil lead, yard dust potential, general environment, and age at remediation
Brown, 2006[66]	RCT	Rhode Island Department of Health United States	Duration: 1 year	A. 5 home visits from a nurse (n=92) B. Usual care, including educational outreach about lead poisoning (n=83)	Children <28 months of age with BLL 15–19 ug/dL	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 ug/dL	Loss to follow up: 13% (22/175)	NR
Nicholson, 2017[73]	RCT	Urban children's hospital United States	Duration: 6 months	A. Professional lead inspection and cleaning kit B. Professional lead inspection C. Cleaning kit D. EPA lead exposure pamphlets	Low income families with children <6 years and BLL 3 to 9.9 ug/dL	Age: 3.94 years Race: Not reported Sex: Not reported BLL, ug/d (A vs. B vs. C vs. D): 5.18 vs. 5.75 vs. 5.25 vs. 5.02	Loss to follow up: 8.3%	NR
O'Connor, 1999[70]	RCT	Urban children's hospital United States	Duration: 6 months	A. DMSA chelation 100-200 mg three times daily (dose weight-dependent) (n=19) B. Placebo (n=20)	Children aged 2.5-5 years with BLL 30–45 ug/dL	A vs. B Age: 39.8 vs. 40.8 months Race: NR Sex: 68% vs. 35% female Mean BLL: 34.9 vs. 33.0 ug/dL	Loss to follow up: 5% (2/39)	NR
Treatment of Lead-Exposed Children (TLC) Trial Group, 2000[62] See also: Rogan, 2001[71]; Liu, 2002[68]; Dietrich, 2004[67]	RCT	Multiple urban clinics United States	Duration: 3 years	A. Succimer, dose dependent on body surface area (n=396) B. Placebo (n=384)	Children aged 12-33 months with BLL between 20 and 44 ug/dL	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 ug/dL	Loss to follow up: 17% (69/396) vs. 15% (59/384)	NR

Appendix B Table 3. Data Abstraction of Childhood Treatment Trials

Author, Year	Intermediate Outcomes	Clinical Health Outcomes	Adverse Events	Quality Rating	Funding Source
Boreland, 2009[65]	BLL: 17.5 vs. 17.9 ug/dL; mean change 1% (95% CI -11% to 11%)	NR	NR	Fair	Australian Department of Health and Ageing
Brown, 2006[66]	BLL did not differ between groups at 3, 6, or 12 months (data only reported in a figure) Last available BLL test >10 ug/dL: 51% vs. 51%; p=NS Any BLL test >20 ug/dL: 8% vs. 11%; p=NS	NR	NR	Fair	Maternal and Child Health Bureau of the Centers for Disease Control and Prevention
Nicholson, 2017[73]	Change in BLL at 6 months: −2.54 vs. −2.99 vs. −2.46 vs. −2.26, no significant differences	NR	NR	Fair	Grant funding
O'Connor, 1999[70]	1 month BLL, mean: 27.4 vs. 33.2 ug/dL; p=NS 6 months BLL, mean: 28.8 vs. 25.1 ug/dL; p=NS	NR	NR	Fair	Case Western University
Treatment of Lead-Exposed Children (TLC) Trial Group, 2000[62] See also: Rogan, 2001[71]; Liu, 2002[68]; Dietrich, 2004[67]	6 months BLL: mean difference −4.5 (95% CI −3.7 to -5.3) ug/dL 12 months BLL: mean difference −2.7 (95% CI −1.9 to −3.5) ug/dL 7 years of age BLL >10 ug/dL: 25% vs. 27%; p=NS	36 months No differences in WPPSI-R, NEPSY, or CPRS neurodevelopment scales or any of their subscales[71] No difference or change in WPPSI-R or Bayley Scale of Infant Development cognitive scale scores[68] No differences in WISC-III, NEPSY, or WLPB-R cognition scales; BASC behavior scales; CVLT-C learning and memory scales; CPT attention scale; or CPT or NESS neuromotor scales[67]	3 months Hospitalizations: 5.6% vs. 3.9%; p=NS No differences in rates of any adverse event 36 months No difference between groups in any category of adverse events (data not reported in paper but available online) [68] Height at 7 years of age shorter in succimer-treated patients by 1.17 (95% CI 0.41 to 1.93) cm	Good	National Institute of Environmental Health Sciences, National Institutes of Health, and Centers for Disease Control and Prevention

Abbreviations: BASC=Behavior Assessment System for Children; BLL=blood lead level; CI=confidence interval; CPRS=Connors Parent Rating Scale; CPT=Connors 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-third edition; WLPB-R=Woodcock Language Proficiency Battery-Revised; WPPSI-R=The Wechsler Preschool and Primary Scale of Intelligence—Revised.

Appendix C Table 1. 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?	Were the Index Test Results Interpreted Without Knowledge of the Results of the Reference Standard?	If a Threshold Was Used, Was It Pre-specified?	Is the Reference Standard Likely to Correctly Classify the Target Condition?	Were the Reference Standard Results Interpreted Without Knowledge of the Results of the Index Text?	Was There an Appropriate Interval Between Index Test 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[57]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	Fair
Dalton, 1996[60]	No	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	No	Fair
France, 1996[51]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Holmes, 1997[58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Fair
Holtrop, 1998[59]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Kazal, 1997[52]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes	No	Fair
Muniz, 2003[53]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	Yes	Yes	Fair
Parsons, 1997[27]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
Robin, 1997[54]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Sargent, 1996[62]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Schaffer, 1996[55]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	No	No	No	Fair
Schlenker, 1994[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Snyder, 1995[59]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Fair
Tejeda, 1994[564]	No	Yes	Yes	Unclear	Yes	Yes	Unclear	No	Yes	Yes	No	Poor

Appendix C Table 2. Quality Assessment of Childhood Trials

Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup Differential/ High?	Analyze People in the Groups in Which They Were Randomized?	Quality Rating
Boreland, 2009[65]	Unclear	Unclear	Yes; matched	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
Brown, 2006[66]	Yes	Yes	Yes	Yes	Yes	No; not for the intervention group	No	Yes	No/No	Yes	Fair
Markowitz, 2004[69]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes (34% overall)	Yes	Poor
Nicholson, 2017[73]	No (shuffled envelopes)	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
O'Connor, 1999[68]	Unclear	Unclear	No; not sex	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Fair
Treatment of Lead-Exposed Children (TLC) Trial Group, 2000[62] See also: Rogan, 2001[71]; Liu, 2002[68]; Dietrich, 2004[67]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Wolf, 2003[72]	Unclear	Unclear	Unclear; only BLL reported	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair

Appendix C Table 3. Quality Assessment of Childhood Cohort Studies

Author, Year	Did the Study Attempt to Enroll All (or a Random Sample of) Patients Meeting Inclusion Criteria, or a Random Sample (Inception Cohort)?	Were the Groups Comparable at Baseline on Key Prognostic Factors?	Did the Study Use Accurate Methods for Ascertaining Exposures and Potential Confounders?	Were Outcome Assessors and/or Data Analysts Blinded to the Exposure Being Studied?	Did the Article Maintain Comparable Groups?	Did the Study Perform Appropriate Statistical Analyses on Potential Confounders?	Is There Important Differential Loss to Followup or Overall High Loss to Followup?	Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods?	Quality Rating
Shannon, 1988[74]	Yes; all	Unclear	Unclear	Unclear	Unclear	No	No/No	Yes	Poor