

# How Effective Are Secondary Interventions at Improving Health Outcomes in Children Exposed to Lead in Early Childhood?

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## Introduction

Environmental policies banning lead from products, including gasoline, paint, and plumbing, have been credited for the dramatic reduction in blood lead levels (BLLs) in the United States. Between 1976 and 2016, geometric mean BLLs in children between one and five years of age declined by more than 94 percent, from 15.2 micrograms per deciliter ( $\mu\text{g}/\text{dL}$ ; 1976–80) to 0.83  $\mu\text{g}/\text{dL}$  (2011–2016; Egan et al. 2021). Despite that progress, children continue to face exposure to lead from both new and legacy sources. For example, the US Department of Housing and Urban Development estimates that 19 percent of the US housing stock has a significant lead-based paint hazard (HUD 2021), and, in 2021, US manufacturers reported emissions of over 306,000 pounds of lead into the air.<sup>1</sup> Furthermore, the risk of lead exposure is not distributed equitably; non-Hispanic Black children and children in poverty have had persistently higher BLLs than other American children (Egan et al. 2021).

The developmental, behavioral, and neurological effects of lead on children are well documented, even at levels below what was considered “low” as recently as 2012 (BLL < 10  $\mu\text{g}/\text{dL}$ ). These effects can result in adverse long-term educational and labor market outcomes that are economically meaningful. Early childhood lead exposure can create educational deficits that

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<sup>1</sup><https://www.epa.gov/trinationalanalysis/lead>.

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persist at least through middle school (Shadbegian et al. 2019). Even later in adulthood, childhood lead exposure has been found to be associated with decreased socioeconomic outcomes (Reuben et al. 2017). A large study in Sweden found that lead exposure affected long-run cognitive and noncognitive outcomes and that a reduction in BLL from 10 to 5  $\mu\text{g}/\text{dL}$  increased earnings by 4 percent (Grönqvist et al. 2020). In-utero exposure to lead has been linked to significant decreases in lifetime earnings (Banzhaf and Banzhaf 2023).

No safe level of lead exposure has been identified, and the Centers for Disease Control and Prevention (CDC) has progressively lowered the BLL it recommends for children to receive follow-up actions to minimize exposure or mitigate adverse effects. In 2022, an estimated 560,000 children under the age of 6 had a BLL greater than the CDC's current blood lead reference value of 3.5  $\mu\text{g}/\text{dL}$ .<sup>2</sup> Between 2014 and 2018, state surveillance programs identified roughly 2,700 children annually with severely elevated BLLs above 20  $\mu\text{g}/\text{dL}$ , the level at which the CDC recommends more invasive interventions, including abdominal X-rays, chelation therapy, or gastrointestinal decontamination.<sup>3,4</sup>

Preventing childhood lead exposure has been at the forefront of environmental and public health policy in the United States. Estimates of the cognitive and other health effects of lead exposure suggest that primary prevention, particularly from reducing lead in air and dust, generates large net benefits. The net benefits of phasing out leaded gasoline have been estimated at billions of dollars annually (US EPA 1985, 1997). More recently, the US Environmental Protection Agency (US EPA) estimated that lowering the levels of lead in dust considered to be hazardous and allowable after abatements would result in a quantified annual net benefit between \$28 million and \$2.3 billion (US EPA 2019, 2020). Other estimates suggest that lead paint hazard control yields at least \$17 in benefits per dollar expended (Gould 2009).

When prevention fails and lead exposure occurs, secondary interventions are used to treat children with elevated BLLs. We review the literature on the effects of secondary lead interventions on children's BLLs and other health outcomes. Figure 1 depicts how different types of secondary interventions might directly or indirectly affect children's health. Our review discusses medical, nutritional, residential, educational, and combined interventions. Where possible, we not only focus on high-quality evaluations using randomized controlled trials (RCTs) but also discuss observational studies and studies deploying quasi-experimental methods.

We find that the literature on the effects of secondary lead interventions on children's BLL is small and dominated by studies whose results are not statistically significant or are inconclusive. There are even fewer studies examining the effects of these interventions on cognitive and behavioral outcomes that are the hallmarks of children's lead exposure and result in adverse long-term labor market and economic consequences. This means surprisingly little is known about what approaches can successfully mitigate or reverse the harm done to children already exposed to lead.

<sup>2</sup>The reference value is set to reflect the 97.5th BLL percentile for children between 1 and 5 years of age.

<sup>3</sup>CDC-recommended actions may be found at <https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm>.

<sup>4</sup>State surveillance data are available at <https://www.cdc.gov/lead-prevention/hcp/clinical-guidance/index.html>; <https://www.cdc.gov/lead-prevention/php/data/national-surveillance-data.html>.

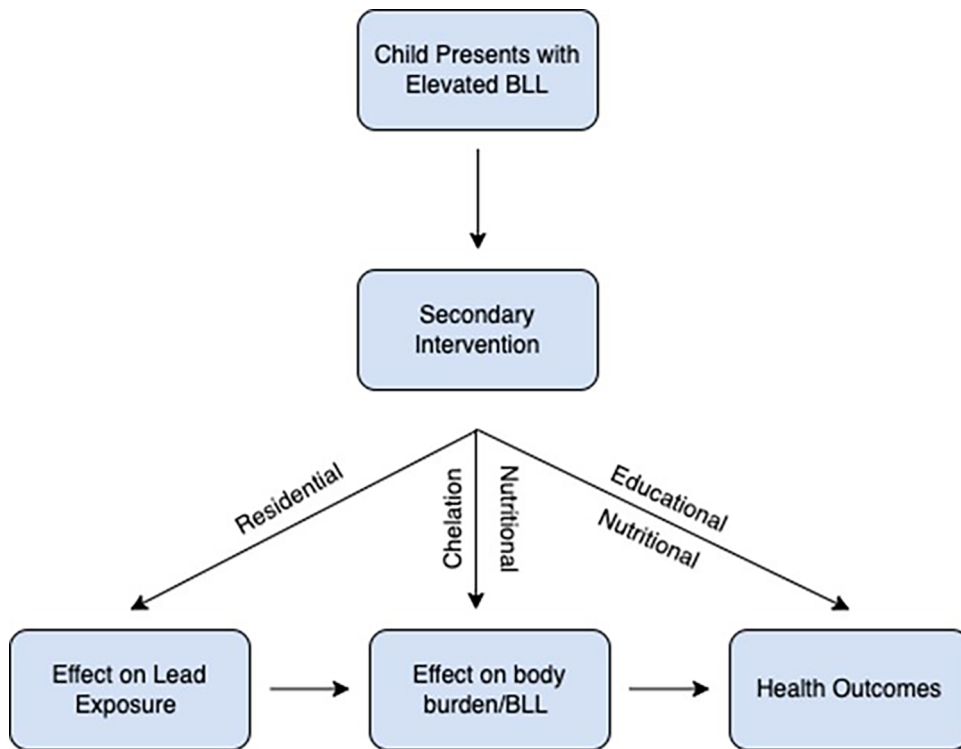


Figure 1 Direct and indirect effects of secondary interventions.

## Medical Interventions

Chelation therapy is a medical intervention used in cases of extreme lead exposure.<sup>5</sup> It consists of an oral or injected chemical agent that binds with lead in the blood and soft tissue to create a compound that is naturally excreted from the body. Chelation does not reduce the amount of lead to which a child is exposed—rather, it has the potential to reduce the amount of lead in the body by promoting excretion (see figure 1).

The most rigorous evidence on the effectiveness of chelation therapy comes from the Treatment of Lead-Exposed Children (TLC) Trial, an RCT to assess the effects of chelation in 780 young children with BLLs of 20–44  $\mu\text{g}/\text{dL}$  in four US cities in the 1990s. Results showed that chelation caused short-term (<1 year) decreases in BLL but no longer-term (>1 year) effects on BLL, IQ, or other measures of cognition and behavior up to age 7 (Rogan et al. 2001; Dietrich et al. 2004). Children in both the treatment and control groups also received in-home lead hazard reduction and nutritional interventions on study entry, which was thus prior to chelation therapy in the treatment group. Researchers did not assess the effects of these other interventions on BLL or neurobehavioral outcomes because of the lack of an appropriate counterfactual group.

<sup>5</sup>In 1995, the American Academy of Pediatrics recommended chelation for children with  $\text{BLL} \geq 45 \mu\text{g}/\text{dL}$ . The CDC noted that at BLLs below 45  $\mu\text{g}/\text{dL}$ , “no evidence exists that chelation avoids or reverses neurotoxicity” (American Academy of Pediatrics Committee on Drugs 1995).

A smaller RCT of 39 US children with initial BLLs of 30–45 µg/dL showed similar results: no statistically significant differences between the treatment and control groups in the drop in mean BLLs after 6 months (O'Connor and Rich 1999). Similar to the TLC trial, both groups were provided home lead inspections, remediation, and iron supplements.

In contrast, a 2016 RCT by Bouhouch et al. (2016) examined the effectiveness of iron, ferric sodium EDTA (a chelator), and iron × EDTA-fortified wheat biscuits on 457 children in Morocco with an initial mean BLL of 4.3 µg/dL.<sup>6</sup> Note that this sample of children had a much lower mean BLL than the earlier stated studies. Bouhouch et al. (2016) found that after a 28-week intervention, children receiving EDTA-fortified biscuits had a statistically significantly lower BLL relative to those receiving the placebo biscuits. No effect, however, was found on cognitive outcomes.

## Nutritional Interventions

As early as 1985, the CDC advocated for nutritional intervention in children with high BLLs, emphasizing the importance of iron and calcium (CDC 1985). These recommendations were based on “generally accepted nutritional principles” rather than evidence from clinical trials. This was because of the lack of high-quality RCTs examining the relationship between nutritional deficiencies or supplements and BLL (Roberts and Reigart 2002). Instead, animal research, observational studies, and clinical studies with small sample sizes comprised most of the evidence on nutritional supplements and BLL at that time.

As with chelation therapy, and as shown in figure 1, the intent of nutritional interventions is to reduce the burden of lead in the body by limiting absorption or promoting excretion. Animal studies suggest that iron deficiency may increase lead absorption, predisposing the body to lead poisoning (Six and Goyer 1970; Barton et al. 1978). Higher lead retention rates have also been found in animals fed a low-calcium diet (Six and Goyer 1970; Barton et al. 1978; Roberts and Reigart 2002). Calcium, however, interferes with the absorption of iron, which may complicate how it interacts with BLLs, particularly in iron-deficient children. Vitamin C aids the body's ability to absorb iron (Kordas 2017) and has chelating properties that promote excretion of lead.

Cross-sectional studies of children with BLLs ranging from below 5 µg/dL to above 60 µg/dL show mixed associations between BLLs and either consumption of or deficiencies in calcium, iron, and vitamin C (Yip, Norris, and Anderson 1981; Clark, Royal, and Seeler 1988; Wasserman et al. 1992; Hammad, Sexton, and Langenberg 1996; Wright et al. 1999; Ballew and Bowman 2001; Bradman et al. 2001; Kordas 2017; Kordas et al. 2018; Gulson et al. 2019; Desai et al. 2021). We did not identify any RCTs or other rigorous studies evaluating the causal effect of vitamin C supplements on BLLs in children.<sup>7</sup> However, researchers have used RCTs to investigate the effects of iron and calcium supplements on BLLs in children. We identified three RCTs examining iron supplements. A study in Mexico of over 500 children

<sup>6</sup>See the nutrition section for more information on the effectiveness of the iron-supplemented biscuits.

<sup>7</sup>Studies from the 1970s administering vitamin C supplements to children and adults found large decreases in BLL, but these studies included no control groups. Sohler, Kruesi, and Pfeiffer (1977) studied adults and children with psychiatric disorders with BLLs between 3.8 and 53 µg/dL, with a mean of 15.6 µg/dL.

with a mean BLL of 11.4  $\mu\text{g}/\text{dL}$  found no statistically significant differences in the change in BLL across groups receiving an iron, zinc, iron and zinc, or placebo supplement for six months (Rosado et al. 2006). However, RCTs from both Morocco ( $N = 457$ , mean BLL = 4.3  $\mu\text{g}/\text{dL}$ ) and India ( $N = 134$ , mean BLL = 11.6  $\mu\text{g}/\text{dL}$ ) found that iron-fortified foods caused a significant reduction in BLL compared with children assigned to the placebo group (Zimmermann et al. 2006; Bouhouch et al. 2016). The prevalence of iron deficiency was higher among the Moroccan and Indian participants than the Mexican participants, raising the possibility that iron supplementation yields benefits only in situations with existing nutritional deficiencies. The Morocco study also assessed the effect of the intervention on several cognitive measures but found no significant effects (Bouhouch et al. 2016).

Turning to calcium supplementation, we are aware of three RCTs conducted in varying populations, including US infants with low BLL ( $N = 103$ , mean BLL = 2.5  $\mu\text{g}/\text{dL}$ ), US children with high BLL ( $N = 67$ , BLL = 10–45  $\mu\text{g}/\text{dL}$ ), and Nigerian children with high BLL ( $N > 300$ , mean BLL = 11.1  $\mu\text{g}/\text{dL}$ ; Sargent et al. 1999; Markowitz, Sinnett, and Rosen 2004; Keating et al. 2011). None of these studies found a significant effect of calcium supplements on BLL.

Overall, there is suggestive evidence that iron supplementation can reduce BLLs in iron-deficient children, but there is little evidence that calcium or vitamin C supplementation can reduce BLLs. Conclusions drawn from the literature may be limited for several reasons. First, because of complex interactions among nutrients in the body, studies of single-nutrient supplements yield limited insights into how consumption of dietary nutrients might affect lead absorption and body burden. Second, as depicted in figure 1, comparisons of health outcomes may be confounded by the fact that nutritional interventions can affect health endpoints directly, irrespective of any effects on BLL and body burden. Third, several studies had small sample sizes and may lack the statistical power to identify a statistically significant effect, even in cases where there may be an actual effect from the intervention. Fourth, some RCTs evaluated the effects of nonfood nutritional supplements on BLL, even though recommendations typically promote the consumption of nutrient-rich foods (Kordas 2017). Although the CDC's guidance to promote healthy nutrition among children with elevated BLLs seems largely innocuous, Ballew and Bowman (2001, 71) have cautioned that "statements that diet can ameliorate the deleterious effects of environmental lead could provide a false sense of efficacy and divert efforts from lead abatement and from behavioral modifications that might have more impact."

## Residential Interventions

Since most childhood lead exposure is experienced in older homes with deteriorated lead paint and other legacy lead sources, another category of interventions targets residences. As depicted in figure 1, residential interventions are intended to reduce children's lead exposure. Residential interventions vary in type and intensity. Informational home interventions provide guidance or training for families regarding lead sources and how to clean the home to minimize exposure. They include home visits, classes, videos, and written materials. Residential interventions can also involve conducting lead hazard control or abatement. Hazard control refers to nonpermanent measures such as specialized cleaning, paint stabilization (i.e., scraping, and repainting surfaces covered with deteriorated lead-based paint), and installing window trough liners. Abatement refers to the permanent elimination of at-home

lead hazards, including replacing windows, removing lead paint, or removing and replacing contaminated soil.

The literature on residential interventions contains RCTs and observational analyses. Baseline BLLs vary considerably across studies and are sometimes well below thresholds that are considered elevated. Sample sizes for individual RCTs range from less than 100 to over 300 participants. Although systematic reviews of some of these studies have found no evidence of an effect or high uncertainty about the effect (Haynes et al. 2002; Nussbaumer-Streit et al. 2020; Dobrescu et al. 2022), the literature is mixed.

### Residential Information Interventions

A Cochrane systematic review conducted a meta-analysis of five RCTs evaluating the effect of information or information combined with cleaning supplies on children's BLL (Nussbaumer-Streit et al. 2020). The meta-analysis found no significant effect on either mean BLL or BLLs exceeding 10 or 15  $\mu\text{g}/\text{dL}$ , nor did any of the five studies individually find significant effects.<sup>8</sup> A sixth RCT identified by Nussbaumer-Streit et al. (2020) but excluded from the meta-analysis because of incomplete data found a significant decline in BLL from the intervention (central tendency BLL 15–19  $\mu\text{g}/\text{dL}$ ; Shen et al. 2004). One observational study found a statistically significant decline in BLL from informational home visits (baseline BLL = 20–24  $\mu\text{g}/\text{dL}$ ; Schultz, Pawel, and Murphy 1999).

### Residential Dust Control Interventions

Based on nine studies examining dust control measures alone or in combination with information, the Cochrane systematic review concluded that there is likely no effect on children's BLL (Nussbaumer-Streit et al. 2020).<sup>9</sup> Dust control measures evaluated in these studies sometimes just involved cleaning but in other cases included paint stabilization, contaminated soil removal, window replacement, and replacement of floor coverings. The only two studies that showed significant declines in BLLs included frequent professional cleaning for several months and studied children with mean BLL > 10  $\mu\text{g}/\text{dL}$  (Charney et al. 1983; Rhoads et al. 1999). Two other studies in the Cochrane review, however, shared the same features but did not find statistically significant effects (Hilts et al. 1998; Sterling et al. 2004).<sup>10</sup> The other five dust control studies included in the Cochrane review found no statistically significant effects from the interventions on children's BLLs. The Cochrane review did not identify any RCTs evaluating the effect of comprehensive abatement of all sources of lead in the home.

Observational studies on dust lead remediation over a wide range of BLLs (from below 3  $\mu\text{g}/\text{dL}$  to above 40  $\mu\text{g}/\text{dL}$ ) also show mixed results (Amitai et al. 1991; Staes et al. 1994; Rich

<sup>8</sup>A separate meta-analysis of just two of these studies also found no significant effect of the interventions on children's BLLs (Haynes et al. 2002).

<sup>9</sup>A meta-analysis of two of these studies also found no significant effect of the interventions on children's BLLs (Haynes et al. 2002).

<sup>10</sup>We are aware of one additional, small ( $N = 37$ ) study (Tohn et al. 2003) finding that a one-time professional, low-cost cleaning reduced dust lead levels immediately after the intervention. This study did not focus on child outcomes and was excluded from the Cochrane systematic review due to its before-after study design with no control group. The authors noted that by 6 months after intervention, dust lead returned to precleaning levels, raising concerns about reaccumulation of dust lead hazards without frequent cleaning.

et al. 2001; Leighton et al. 2003; Berg et al. 2012). Two studies found significant *increases* in BLL after abatement, presumably because the remediation activities released dust lead onto household surfaces (Farfel and Chisholm 1990; Aschengrau et al. 1997). Because of the non-randomized research designs, the results of these studies could be confounded by unobservable factors correlated with willingness to participate in home inspections and remediations. In contrast to studies relying on data from individual children, Jones (2012) investigated census tract-level effects of remediation on the prevalence of children with BLLs  $\geq 10$   $\mu\text{g}/\text{dL}$ . Jones found a significant decrease in the prevalence of elevated BLLs resulting from an increase in the number of remediated pre-1978 properties.

We are aware of only one study, an RCT, estimating the effect of lead hazard control on cognitive and health outcomes (Braun et al. 2018). One to two years after the intervention, the treatment group had significantly lower dust lead levels in the home, but children's BLLs were not significantly different from the control group. The treatment group performed slightly better than the control group across several neurobehavioral measures, but the differences were generally not statistically significant. Homes in both groups had mean pre-intervention dust lead levels well below US federal standards, and children in both groups had mean BLLs below 2  $\mu\text{g}/\text{dL}$ .

### Residential Soil Abatement Interventions

The Cochrane review included two RCTs studying soil abatement and found they provided insufficient evidence to draw a conclusion. One of the studies found significant declines in BLL for children at properties receiving soil abatement ( $N = 152$ , mean BLL = 12.5  $\mu\text{g}/\text{dL}$ ; Weitzman et al. 1993). The other found declines that were not statistically significant ( $N = 408$ , mean BLL = 11  $\mu\text{g}/\text{dL}$ ; Farrell et al. 1998). Another systematic review including these two RCTs plus four additional nonrandomized studies concluded that soil remediation can reduce children's BLLs but that there is high uncertainty given the available evidence (Dobrescu et al. 2022). In addition, a recent study using a difference-in-difference-like analysis of BLL data for almost 75,000 children living in residential areas of the Omaha Lead Superfund site showed statistically significant decreases in the probability of BLL  $>5$   $\mu\text{g}/\text{dL}$  and  $>10$   $\mu\text{g}/\text{dL}$  from soil remediation (Ye et al. 2022).<sup>11</sup>

In sum, the existing literature provides some evidence that sustained professional cleaning and soil abatement can reduce BLLs, but the overall evidence is mixed. Dust control interventions have less evidence supporting their effectiveness, but studies vary in the activities involved and children's baseline lead exposure levels. The effectiveness of lead paint abatement depends on the paint removal method; when done improperly, it could even release lead into the air. Several of the interventions evaluated were conducted prior to EPA's 2001 regulations setting the allowable lead dust levels after residential abatement activities and may not be representative of exposure reductions from current practices.

<sup>11</sup>Ye et al. (2022) did not provide statistics on mean BLL but reported that 19 percent of observations in the pre-remediation group had BLLs  $> 5$   $\mu\text{g}/\text{dL}$ .

## Educational Interventions

Although the adverse effects of childhood lead exposure on IQ and academic performance are well established (US EPA 2013), there is scant evidence on the effect of educational interventions for lead-exposed children. As illustrated in figure 1, educational interventions may directly improve cognitive outcomes, countering the adverse effects of lead.

Special education services for children under age three with a disability are available through a federally funded, state-run program called the Individuals with Disabilities Education Act, Part C.<sup>12</sup> States are responsible for determining eligibility criteria for the early intervention programs. Several states have used Part C to provide services to children with elevated BLL. As of 2023, 25 states include lead exposure as a qualifying condition for eligibility. The eligibility cut-offs range from the CDC reference value of 3.5–45 µg/dL. Several other states reference lead or toxic substances more generally. Nine states make no reference to lead as a qualifying condition (see table 1).

We identified one observational study but no RCTs evaluating the effects of educational services on cognitive outcomes for children with elevated BLLs. Stingone et al. (2022) studied children with a BLL of at least 4 µg/dL, using a propensity score matching approach to compare those who received early intervention services such as occupational therapy, physical therapy, or speech therapy with those who did not receive services ( $N = 10,917$ ). Children who received services scored significantly higher on third-grade standardized test scores. These results were amplified among children with higher BLLs ( $\geq 10$  µg/dL).

## Combined Interventions under State and Local Programs

Interventions for children with elevated BLLs are typically implemented by state and local public health programs. Although states and municipalities vary in the BLL thresholds triggering various actions,<sup>13</sup> they generally follow the CDC guidance on the types of interventions offered. The CDC recommends a home investigation, dietary information, and testing for and treating iron deficiency for all children with confirmed BLLs above the CDC reference value. Residential lead hazard control activities may be implemented when investigations identify lead hazards. At higher BLLs, the CDC recommends additional interventions, such as a physical exam and abdominal X-rays for children with  $BLL \geq 20$  µg/dL. State and local programs can also refer qualifying households to federally funded nutrition assistance programs. This means that in real-world settings outside the context of a tightly controlled RCT, children with higher BLLs may receive multiple interventions, making it difficult to ascertain the effectiveness of any single intervention.

<sup>12</sup> Available services include (1) assistive technology; (2) audiology services; (3) family training, counseling, and home services; (4) health services; (5) medical services; (6) nursing services; (7) nutrition services; (8) occupational therapy; (9) physical therapy; (10) psychological services; (11) service coordination; (12) sign language; (13) social work; (14) special instruction; (15) speech-language pathology; (16) transportation; and (17) vision.

<sup>13</sup> As of 2023, different states used different values as the action level triggering environmental investigations, ranging from 3.5 to 20 µg/dL (National Center for Healthy Housing 2023).

**Table I** Individuals with Disabilities Education Act: Part C State Eligibility Criteria for Early Intervention (EI) (2023)

Elevated BLL Qualifies for Automatic Eligibility in EI Program (Specific BLL or Definition)	Elevated BLL as a “Risk Factor” That Does NOT Automatically Qualify for EI Program	Lead Mentioned without Specified BLL as Criterion for Eligibility in EI Program	“Disorders Secondary to Exposure to Toxic Substances” as EI Eligibility Criteria	No Mention of Lead
Colorado (lead poisoning)	New York (BLL $\geq$ 15 $\mu\text{g}/\text{dL}$ ) requires referral to EI for further evaluation	Kansas	Alabama <sup>a</sup>	Alaska
Connecticut (BLL $\geq$ 10 $\mu\text{g}/\text{dL}$ )		New Mexico	Arizona <sup>a</sup>	California
Delaware (BLL $\geq$ 5 $\mu\text{g}/\text{dL}$ )			Arkansas <sup>a</sup>	Georgia
Florida (lead poisoning)			Hawaii	Kentucky
Illinois (BLL $\geq$ 5 $\mu\text{g}/\text{dL}$ )			Indiana <sup>a</sup>	North Carolina
Idaho (lead poisoning)			Maine <sup>a</sup>	Oklahoma
Iowa (BLL $\geq$ 20 $\mu\text{g}/\text{dL}$ )			Maryland <sup>a</sup>	Pennsylvania
Louisiana (lead intoxication requiring chelation)			Mississippi <sup>a</sup>	South Dakota
Massachusetts (BLL $\geq$ 5 $\mu\text{g}/\text{dL}$ )			Nebraska <sup>a</sup>	Texas
Michigan (BLL $\geq$ CDC reference value)			New Jersey <sup>a</sup>	
Minnesota (BLL $\geq$ 45 $\mu\text{g}/\text{dL}$ )			North Dakota <sup>a</sup>	
Missouri (BLL $\geq$ 10 $\mu\text{g}/\text{dL}$ )			South Carolina	
Montana (lead encephalopathy)			Vermont <sup>a</sup>	
New Hampshire (lead poisoning)			Virginia <sup>a</sup>	
Ohio (BLL $\geq$ 5 $\mu\text{g}/\text{dL}$ )			Washington <sup>a</sup>	
Oregon (BLL $\geq$ 5 $\mu\text{g}/\text{dL}$ )			Wyoming <sup>a</sup>	
Rhode Island (BLL $\geq$ 15 $\mu\text{g}/\text{dL}$ )				
Tennessee (BLL $\geq$ 5 $\mu\text{g}/\text{dL}$ )				
Utah (BLL $\geq$ 10 $\mu\text{g}/\text{dL}$ )				
West Virginia (BLL $\geq$ 15 $\mu\text{g}/\text{dL}$ )				
Wisconsin (BLL $\geq$ 10 $\mu\text{g}/\text{dL}$ )				

<sup>a</sup>Does not include “lead” in the wording.

One approach for studies that use observational data is to estimate the average effect of combined interventions on children with elevated BLLs. This methodology was used by Billings and Schnepel (2018) to estimate the *intent-to-treat* effect of interventions, offered by the North Carolina Childhood Lead Poisoning Prevention Program, on the academic and behavioral outcomes among children with elevated BLLs ( $N = 301$ , mean BLL = 12.09–17.85  $\mu\text{g}/\text{dL}$ ). The authors found significant reductions in school absenteeism, suspensions, and crime but modest (and largely insignificant) improvements in educational outcomes for children who were eligible for lead interventions in early childhood compared to those who narrowly missed the cutoff.

## Discussion

When primary prevention fails and a child is exposed to lead, one policy objective may be to mitigate or reverse the harm done. Understanding the effectiveness of secondary interventions is critical for the development of appropriate public health responses. However, an examination of the literature reveals shortcomings in existing knowledge. We highlight the following four issues: measurement of lead body burden, difficulties in defining appropriate counterfactual groups, lack of information about the environmental justice implications of lead interventions, and uncertainty about how interventions affect the health outcomes caused by lead exposure.

### Measurement Error and the Precision of Estimated Effects

Assessing the effectiveness of a lead intervention policy by its effect on BLL is imperfect. BLL does not reflect total body burden; it measures lead circulating in the bloodstream at a given moment, where it has a half-life of approximately one month (Dignam et al. 2008). Lead is stored for longer in the bones, teeth, and organs, from which it may be rereleased into the bloodstream under certain conditions.

In addition, measurement error may be introduced through pre- and postsampling factors and contamination of blood samples (NRC 1993; Caldwell et al. 2017).<sup>14</sup> In studies estimating the effect of BLL on health and academic outcomes, if the measurement error is uncorrelated with BLL or other covariates, then it biases the estimated effect of BLL toward zero (Aizer and Currie 2019). When BLL is instead the outcome variable, as in most of the studies in this review, measurement error does not bias the estimated effect of an intervention on BLL. However, inference about the statistical significance of the effect can be biased because measurement error in a dependent variable inflates the standard errors of the regression, possibly leading to erroneous null results in the presence of a true effect.

Furthermore, many of the RCTs cited have relatively small sample sizes of a few hundred observations. Similar to the issues introduced by imprecisely measuring lead exposure, studies with small samples may lack the statistical power to identify effects distinguishable from zero, even when there is a true improvement from a secondary intervention.

<sup>14</sup>Measurement error may be particularly pronounced at BLLs below 10  $\mu\text{g}/\text{dL}$  (Caldwell et al. 2017).

## Constructing the Appropriate Counterfactual

RCTs are the gold standard in medical research. However, ethical considerations to ensure lack of harm to study participants, along with the multitiered approach to addressing children with elevated BLLs, make it difficult to undertake an RCT to evaluate single interventions without confounding effects from additional activities. For example, RCTs evaluating chelation therapy also provided nutritional supplements and home remediation to children in both the treatment and control groups (O'Connor and Rich 1999; Rogan et al. 2001; Dietrich et al. 2004). In one case, an RCT provided home-specific information on lead sources and contamination levels to the treated group, but households in the control group received standard educational materials on lead poisoning and prevention (Brown et al. 2006). Braun et al.'s (2018) study of residential lead hazard reduction provided households in the control group with a home intervention to reduce the risk of injury, an intervention that is unrelated to lead exposure but could potentially improve children's health and cognitive outcomes.

Such interventions given to the control group can confound the estimation of the effect of the intervention of interest. At the same time, researchers have an ethical duty to not harm study participants. This tradeoff between a rigorous experimental design and ethical concerns was discussed by Rosner and Markowitz (2012), who highlighted a 2001 legal case brought against Johns Hopkins University for conducting research that actively assigned different levels of partial lead abatement interventions to homes. BLLs of children who subsequently lived in these homes were measured and compared with BLLs of children in two control groups—those who lived in fully abated homes and those who lived in newer homes where lead paint was not used. Although partially abated homes generally reduced BLLs, two children experienced increased BLL. The Maryland Court of Appeals ruled that although partial abatement was generally an improvement, the researchers knowingly let children reside in homes with a remaining risk of exposure and did not fully inform participants of this risk.

Well-crafted quasi-experimental designs using observational data are one way to circumvent the confounding effects and ethical concerns that surround study designs where researchers actively intervene. Quasi-experiments are “natural” experiments that exploit different “treatments” of otherwise similar groups as a result of natural, political, or other nonexperimental occurrences. Quasi-experiments attempt to mimic classical experimental designs and can provide evidence of causal relationships (Angrist and Pischke 2009; Greenstone and Gayer 2009; Billings and Schnepel 2018; Clay, Hollingsworth, and Severnini 2024).

## Environmental Justice

Some studies we reviewed controlled for characteristics such as race and ethnicity, parental education, and/or household income across treatment and control groups. These considerations are important because the use of interventions may differ across demographic groups. However, few studies have investigated the systematic differences in the *application* and *effectiveness* of interventions across demographic groups. One exception is Braun et al. (2018), who examined the effects of residential remediations separately by race. The intervention demonstrated significantly larger decreases in floor dust lead levels and BLLs for non-Hispanic Black children than for non-Hispanic White children. However, effects on neuro-behavioral outcomes were small and largely insignificant for all demographic groups.

Environmental justice implications of lead interventions are further highlighted by Zierold, Havlena, and Anderson (2007), who conducted an observational study of the time to completion of residential lead paint remediations during 1996–1999 ( $N = 382$ , initial BLL = 20–40  $\mu\text{g}/\text{dL}$ ). Black children were twice as likely as other children to live in homes that took more than 6 months to be remediated. Girls, White children, and children with BLLs  $>35 \mu\text{g}/\text{dL}$  were more likely than other children to live in homes remediated in less than 6 months.

### Cognitive and Health Outcomes

Most studies examining secondary lead interventions focus on BLL as the outcome. There is an assumption that reduced BLL will translate into improved health outcomes, based on existing evidence on the association between BLL and health. Interventions, however, may have both direct and indirect effects on health outcomes (CDC 1991), as illustrated in figure 1. The true outcome of interest is whether the intervention improves a child's physical, mental, and social health.

Empirical evidence is needed to determine whether the effects of secondary interventions—which are not directly related to lead exposure—are positive or negative. For example, RCTs evaluating micronutrient interventions for children with iodine and iron deficiencies have consistently found improvements in cognitive performance (Lam and Lawlis 2017), independent of any association with BLL. Evidence suggests that preschool programs and other early intervention programs unrelated to environmental exposures improve long-term health and economic outcomes (Currie and Almond 2011; Conti, Heckman, and Pinto 2016). In contrast, chelation therapy can cause adverse side effects such as skin rashes and can also leach nonlead minerals from the body, since it operates by binding with metals (Bradberry and Vale 2009). The TLC study of chelation in highly lead-exposed children measured children's height at age 7 and found that treated children were significantly *shorter* on average than children in the control group (Dietrich et al. 2004). Educational activities are not generally intended to affect BLL or lead exposure at all, but rather they attempt to directly improve cognitive and behavioral outcomes.

Relatively few studies have assessed cognitive, behavioral, or other health outcomes of secondary interventions. These few exceptions include the TLC chelation study (Rogan et al. 2001; Dietrich et al. 2004), the RCT of iron- and chelator-fortified biscuits in Morocco (Bouhouch et al. 2016), one residential hazard reduction RCT (Braun et al. 2018), the observational study of early educational interventions (Stingone et al. 2022), and the intent-to-treat quasi-experimental study of combined interventions (Billings and Schnepel 2018). The nutritional supplement study found no significant effect of treatment on cognitive or behavioral outcomes. The lead hazard reduction intervention found lower anxiety levels among the treatment group, but there were no significant differences in effects on other neurobehavioral measures (Braun et al. 2018).

The two studies that found significant improvements in cognitive and/or behavioral measures were both observational studies employing quasi-experimental approaches to try to establish causal inference. The educational intervention study, which used propensity score matching to reduce the potential for confounding effects, found significant increases in third-grade academic test scores (Stingone et al. 2022). The study of combined interventions

in North Carolina found significant declines in school suspensions and crime among students eligible to receive early interventions, though the improvements in educational outcomes were largely not statistically significant (Billings and Schnepel 2018).

In addition, follow-up observational analysis of children participating in the TLC chelation trial found that cognitive and behavioral outcomes at ages 5 and 7 were more strongly associated with concurrent BLL than with BLL at age 2. This finding occurred in both the treatment *and* control groups and suggests that declines in BLL later in childhood are associated with neurodevelopmental benefits, even though chelation was not responsible for the decline in BLL (Liu et al. 2002; Chen et al. 2005). The observational nature of this follow-up analysis does not yield any insights into the causal mechanisms resulting in improved outcomes or whether unobserved factors including parental caregiving quality are responsible for the changes in both BLL and cognitive and behavioral metrics.

## Conclusion

The use of secondary interventions to address lead poisoning in children is standard procedure; however, their effectiveness at reducing BLL and improving health outcomes has not been established. The existing literature is thin in many respects and consists of many null and inconclusive results. Relatively few studies focus on the relationship between interventions and health outcomes in children, even though these are the primary outcomes of interest. RCTs, typically considered the gold standard in causal inference, are limited by ethical considerations and may often lack sufficient statistical power. The construction of a pure, unconfounded control group may not be possible.

The recent emergence of studies employing quasi-experimental methods on observational data provides a promising path to potentially overcome both confounding factors and statistical power issues. Furthermore, methods to better target interventions to high-risk populations may also help determine whether interventions result in improved health outcomes (Callendar et al. 2024). Together, they can help build a robust body of evidence on whether there are interventions that work to reverse or mitigate the damage experienced by lead-exposed children.

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