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# Iron and Calcium Supplementation for Reducing Blood Lead Levels:
## A Systematic Review and Meta-Analysis

Lee Crawfurd and Theo Mitchell


## Abstract

Approximately half of children in low- and middle-income countries have elevated blood lead levels. The WHO recommends calcium and iron supplementation for lead-exposed individuals with nutritional deficiencies, but acknowledges this is based on "very low-certainty evidence." We conducted a systematic review and meta-analysis of 11 randomized controlled trials (n=3,666 enrolled). Across all 7 calcium studies, the pooled effect on blood lead was −1.33 µg/dL (95% CI: −2.87 to +0.21 ; p=.078 ), attenuating to −0.36 µg/dL when restricted to 4 low-risk-of-bias studies. Iron supplementation reduced blood lead by −0.31 µg/dL (95% CI: −0.61 to −0.02 ; p=.045 ). The three studies from settings with widespread calcium deficiency—which are also the three high-risk-of-bias studies—showed substantially larger effects. We rate certainty of evidence as very low for calcium and moderate for iron. These interventions offer modest potential benefits at low cost but cannot substitute for primary prevention.


WORKING PAPER 746 · MAY 2026

# Iron and Calcium Supplementation for Reducing Blood Lead Levels: A Systematic Review and Meta-Analysis

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Lee Crawfurd and Theo Mitchell. 2026. "Iron and Calcium Supplementation for Reducing Blood Lead Levels: A Systematic Review and Meta-Analysis." CGD Working Paper 746. Washington, DC: Center for Global Development. https://www.cgdev.org/publication/iron-and-calcium-supplementation-reducing-blood-lead-levels-systematic-review-and-meta

The Center for Global Development is grateful for contributions from Coefficient Giving in support of this work.

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## Research in Context

### Evidence before this study

We searched Google Scholar (January 15, 2025) and PubMed/MEDLINE (February 11, 2025) for randomized controlled trials published between 1995 and 2025 examining the effect of iron or calcium supplementation on blood lead levels, supplemented by reference list screening. The WHO recommends iron and calcium supplementation for lead-exposed individuals with nutritional deficiencies, but grades this as based on "very low-certainty evidence." Previous narrative reviews have described the biological mechanisms and observational associations, and one systematic review examined observational studies of dietary calcium and blood lead levels, but no prior systematic review had formally pooled the experimental evidence.

### Added value of this study

To our knowledge, this is the first systematic review and meta-analysis to quantify the effects of iron and calcium supplementation on blood lead levels from randomized controlled trials. We identified 11 trials (n=3,666 enrolled) and found that across all 7 calcium studies, the pooled effect was $-1.33$ $\mu$g/dL (95% CI: $-2.87$ to $+0.21$ ; p=.078 ). Restricting to the 4 low-risk-of-bias studies attenuated the estimate to $-0.36$ $\mu$g/dL (p=.123 ), because the studies most relevant to calcium-deficient populations are also those with the highest risk of bias—a critical confound that limits certainty. Iron supplementation showed a smaller but statistically significant effect of $-0.31$ $\mu$g/dL (95% CI: $-0.61$ to $-0.02$ ). We rate certainty of evidence as very low for calcium (downgraded for risk of bias, inconsistency, indirectness, and imprecision) and low for iron (downgraded for indirectness and imprecision).

### Implications of all the available evidence

The evidence supports supplementation as a low-cost complement to primary prevention for lead-exposed populations with nutritional deficiencies, consistent with WHO recommendations. However, no high-quality trials exist from the settings of greatest policy relevance—populations with both high lead exposure and widespread nutritional deficiency. Rigorous trials in these contexts, measuring cognitive outcomes directly, are urgently needed.

# Contents

# 1. Introduction

Lead exposure remains a major global public health challenge. An estimated 800 million children worldwide have blood lead levels exceeding 5 $\mu$g/dL, with approximately half of children in low- and middle-income countries (LMICs) affected (Ericson et al., 2021). Lead exposure causes irreversible cognitive impairment: a meta-analysis of prospective studies estimates that each 1 $\mu$g/dL increase in blood lead is associated with a 0.5–1.0 point reduction in IQ (Lanphear et al., 2005). The global economic burden of childhood lead exposure has been estimated at $977 billion annually in lost lifetime earnings (Attina and Trasande, 2013).

While primary prevention through eliminating lead sources is the priority, treatment options for those already exposed are limited. Chelation therapy is reserved for high-level exposures and is often unavailable in resource-limited settings (Mitchell and Bonnifield, 2025). Nutritional supplementation offers a potential complementary approach: iron and calcium share gastrointestinal absorption pathways with lead, meaning adequate nutritional status may reduce lead uptake (Goyer, 1995; Mahaffey, 1990). This mechanism is supported by observational evidence showing that iron deficiency and low dietary calcium are consistently associated with elevated blood lead levels (Bradman et al., 2001; Hernández-Avila et al., 1996).

The World Health Organization (WHO) recommends iron and calcium supplementation for lead-exposed individuals with nutritional deficiencies (World Health Organization, 2021). However, this recommendation is explicitly graded as based on "very low-certainty evidence," with the WHO noting that existing studies are few and show heterogeneous results.

To our knowledge, no prior systematic review has synthesized the experimental evidence on this question. Previous narrative reviews have summarized the biological mechanisms and observational associations (Mahaffey, 1990; Goyer, 1995), and one systematic review examined observational studies of dietary calcium and blood lead (Rajaee et al., 2022), but the experimental evidence has not been formally pooled. Given the policy relevance of this question—supplementation is often the first-line response when lead exposure is detected in resource-constrained settings—a

quantitative synthesis is warranted.

We conducted a systematic review and meta-analysis of randomized controlled trials examining the effect of iron and calcium supplementation on blood lead levels. We aimed to: (1) estimate pooled effect sizes for each intervention; (2) assess heterogeneity and potential sources of variation; and (3) evaluate the certainty of evidence using established frameworks.

# 2. Methods

This review follows PRISMA guidelines for systematic reviews (Page et al., 2021). The protocol was not pre-registered.

## 2.1. Search Strategy

We searched two databases for studies published between 1995 and 2025.

Google Scholar was searched on January 15, 2025, using the following search string:

> ("blood lead level*" OR "blood lead concentration*" OR "lead poison*" OR "lead expos*") AND ("calcium supplement*" OR "calcium therapy*" OR "iron supplement*" OR "iron therapy*") AND (experiment OR effect OR random*)

PubMed/MEDLINE was searched on February 11, 2025, combining MeSH terms and free-text keywords:

> ("blood lead level"[tiab] OR "blood lead concentration"[tiab] OR "lead poisoning"[MeSH] OR "lead exposure"[tiab] OR "Lead/blood"[MeSH]) AND ("calcium supplementation"[tiab] OR "Calcium, Dietary/administration and dosage"[MeSH] OR "Calcium/therapeutic use"[MeSH] OR "iron supplementation"[tiab] OR "Iron, Dietary/administration and dosage"[MeSH] OR "Iron/therapeutic use"[MeSH]) AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized"[tiab] OR "experiment"[tiab] OR "effect"[tiab] OR "trial"[tiab])

Google Scholar was included because it indexes a broader range of sources than PubMed, including regional journals not indexed in MEDLINE. Two of our

included studies, *Haryanto et al. (2015) and *Sofyani and Lelo (2017), published in Indonesian journals, were identified through Google Scholar but are not indexed in PubMed. We supplemented database searches by screening reference lists of included studies and relevant reviews.

## 2.2. Eligibility Criteria

We included randomized controlled trials with a comparison group, in any age group, that examined calcium and/or iron supplementation (including fortified foods) compared with placebo, no treatment, or lower-dose supplementation, and that measured blood lead levels before and after the intervention. We excluded observational studies without an intervention, studies examining chelation therapy, and studies not reporting blood lead as an outcome. Although included studies were restricted to randomized controlled trials, our search strings were not restricted to RCT terminology—the broad design clause ("experiment OR effect OR random*") would have surfaced quasi-experimental designs (difference-in-differences, regression discontinuity, instrumental variables, synthetic control, interrupted time series) had they existed. No such studies measuring blood lead as an outcome of iron or calcium supplementation or fortification were identified at full-text screening.

## 2.3. Study Selection and Data Extraction

Two reviewers (LC, TM) independently screened titles and abstracts, then assessed full texts of potentially eligible studies. Disagreements were resolved by discussion.

From each included study, we extracted: author, year, country, population characteristics (age, sex, baseline nutritional status), sample size, intervention details (supplement type, dose, duration, delivery method), comparator, baseline and follow-up blood lead levels (mean, SD or SE) for each arm, and information for risk of bias assessment.

When standard errors were not reported, we estimated them from confidence intervals, p-values, or sample sizes using standard formulae. When studies reported multiple outcomes (e.g., different time points or subgroups), we extracted all estimates and accounted for dependence in analysis. Seven studies contributed multiple effect

estimates. Five studies reported results at two follow-up time points: at 14 and 30 weeks in *Zimmermann et al. (2006); at 3 and 6 months in *Markowitz et al. (2004) and *Hernández-Avila et al. (2003); at 4 and 9 months in *Sargent et al. (1999); and at the 2nd and 3rd trimesters in *Ettinger et al. (2009). Two studies compared multiple intervention arms within the same trial: *Keating et al. (2011) (fish meal and calcium tablets) and *Haryanto et al. (2015) (250 and 500 mg/d calcium). All available estimates were included in the meta-analysis; forest plots display study-level mean effects averaged across estimates from the same study.

Blood lead was measured in venous blood samples in 9 of 11 studies, analyzed using graphite furnace atomic absorption spectrometry (GFAAS) or inductively coupled plasma mass spectrometry (ICP-MS) in certified laboratories. Two studies, *Keating et al. (2011) and *Haryanto et al. (2015), used capillary blood with a portable LeadCare analyzer, which may have lower precision. Details of measurement methods for each study are provided in Supplementary Table S3.

## 2.4. Risk of Bias Assessment

We assessed risk of bias using the Cochrane Risk of Bias tool (RoB 2). which is the recommended tool by Cochrane for use in reviews of randomized trials. The tool evaluates five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study was rated as low risk, some concerns, or high risk of bias overall.

## 2.5. Statistical Analysis

We calculated the mean difference in blood lead levels ($\mu$g/dL) between intervention and control groups at follow-up for each study. We pooled effects using random-effects meta-analysis with robust variance estimation (RVE), implemented via the `robumeta` package in Stata 18 (Hedges et al., 2010). RVE accounts for within-study correlation when studies contribute multiple effect estimates (e.g., different time points or subgroups). We assumed an intra-study correlation of $\rho = 0.8$ for our primary specification, following common practice for repeated measures within the same participants (Hedges et al., 2010). Sensitivity analysis across $\rho$ values from 0.2

to 1.0 showed results were virtually unchanged (calcium: $-1.33$ across all values; iron: $-0.31$ across all values), as expected given that most studies contribute a single primary estimate to the meta-analysis. We note that RVE inference relies on Satterthwaite degrees of freedom, which may be small with few studies, potentially affecting the reliability of confidence interval coverage; results should be interpreted with appropriate caution given the limited number of studies. We present separate pooled estimates for calcium and iron interventions.

RVE is our primary estimator; all pooled estimates, confidence intervals, and forest plot diamonds reported in this paper use RVE. We quantified heterogeneity using the $I^2$ statistic and Cochran's Q test, estimated via the `metan` package using DerSimonian–Laird (DL) random effects. We conducted sensitivity analyses: (1) excluding studies rated as high risk of bias; (2) leave-one-out analysis; (3) varying the assumed within-study correlation $\rho$. We examined potential publication bias visually using funnel plots; formal tests (e.g., Egger's test) were not conducted given the small number of studies.

### 2.6. Certainty of Evidence

We assessed certainty of evidence using the GRADE framework (Guyatt et al., 2011), considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence was rated as high, moderate, low, or very low certainty.

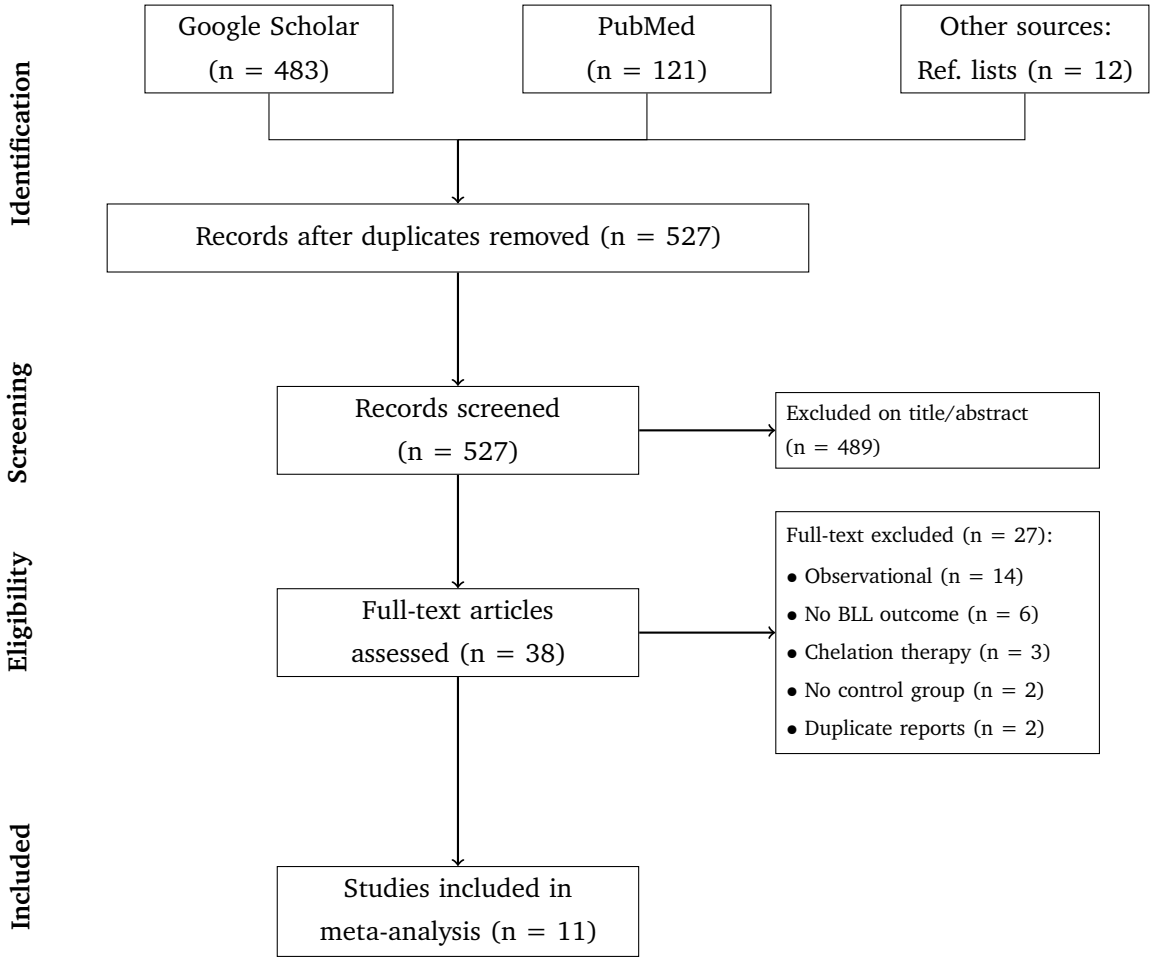
## 3. Results

### 3.1. Study Selection

Figure 1 shows the PRISMA flow diagram. Our database searches identified 483 records from Google Scholar and 121 records from PubMed, supplemented by 12 additional records from reference list screening. After removing 89 duplicates and screening titles/abstracts, we assessed 38 full-text articles for eligibility. We excluded 27 articles: 14 were observational studies without an intervention, 6 did not measure blood lead outcomes, 3 examined chelation rather than nutritional supplementation, 2 were duplicate reports of included studies, and 2 lacked a control group. Eleven

studies met inclusion criteria. The PubMed search did not identify any eligible studies beyond those already found through Google Scholar and reference list screening.

**Figure 1.** PRISMA 2020 flow diagram of study selection.




## 3.2. Study Characteristics

Table 1 summarizes characteristics of the 11 included studies, comprising 3,666 enrolled participants (1,287 mothers, 2,379 children); analyzed samples are smaller due to dropout and, for studies contributing multiple time points to the meta-analysis, reflect participants measured at each time point. Four studies examined iron supplementation, seven examined calcium. Studies were conducted in the United States (n=2), Mexico (n=4), Morocco (n=1), India (n=1), Indonesia (n=2), and Nigeria

(n=1).

**Table 1.** Characteristics of Included Studies

| Study | Population | Intervention | Duration | N | RoB |
|---|---|---|---|---|---|
| *Iron supplementation* | | | | | |
| Rosado (2006) | Children, Mexico | Iron 30 mg/d | 6 mo | 517 | Low |
| Alatorre Rico (2006) | Children, Mexico | Iron 30 mg/d + Zinc | 4.5 mo | 266 | Low |
| Zimmermann (2006) | Children, India | Fortified food 15 mg/d | 16 wk | 134 | Some |
| Bouhouch (2016) | Children, Morocco | Fortified biscuits 8 mg | 28 wk | 457 | Low |
| *Calcium supplementation* | | | | | |
| Markowitz (2004) | Children, USA | Ca 1,800 mg/d | 3 mo | 88 | Low |
| Sargent (1999) | Infants, USA | High-Ca formula | 9 mo | 103 | Low |
| Ettinger (2009) | Pregnant, Mexico | Ca 1,200 mg/d | Pregnancy | 670 | Low |
| Hernández-Avila (2003) | Lactating, Mexico | Ca 1,200 mg/d | 6 mo | 617 | Low |
| Keating (2011) | Toddlers, Nigeria | Ca 400 mg/d | 12–18 mo | 358 | High†‡ |
| Haryanto (2015) | Children, Indonesia | Ca 250–500 mg/d | 3 mo | 400 | High |
| Sofyani & Lelo (2017) | Children, Indonesia | Ca 800 mg/d | 3 mo | 56 | High† |

*Note:* RoB = Risk of Bias. †Randomisation was conducted at the village level (cluster randomisation); the original papers analysed outcomes at the individual participant level. ‡All participants in *Keating et al. (2011), including controls, received vitamin A supplementation as part of the study protocol; calcium supplementation was the only differential treatment.

Iron interventions ranged from 8–30 mg/day, delivered as supplements or fortified foods, over 3–7 months. Calcium interventions ranged from 400–1,800 mg/day over 3–18 months. Baseline blood lead levels ranged from 2.8 to 25 $\mu$g/dL across studies.

## 3.3. Risk of Bias

Table 2 presents the risk of bias assessment. Seven studies were rated as low risk of bias overall: four calcium studies (*Markowitz et al., 2004; *Sargent et al., 1999; *Ettinger et al., 2009; *Hernández-Avila et al., 2003) and three iron studies (*Rosado et al., 2006; *Alatorre Rico et al., 2006; *Bouhouch et al., 2016). One study (*Zimmermann et al., 2006) was rated as having some concerns. Three studies (*Keating et al., 2011; *Haryanto et al., 2015; *Sofyani and Lelo, 2017) were rated as high risk of bias due

to concerns about randomisation procedures. *Keating et al. (2011) also had high attrition, leading to incomplete outcome data.

**Table 2.** Risk of Bias Assessment

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| *Iron supplementation* | | | | | | |
| Rosado (2006) | + | + | + | + | + | Low |
| Alatorre Rico (2006) | + | + | + | + | + | Low |
| Zimmermann (2006) | ? | + | + | + | + | Some |
| Bouhouch (2016) | + | + | + | + | + | Low |
| *Calcium supplementation* | | | | | | |
| Markowitz (2004) | + | + | + | + | + | Low |
| Sargent (1999) | + | + | + | + | + | Low |
| Ettinger (2009) | + | + | + | + | + | Low |
| Hernández-Avila (2003) | + | + | + | + | + | Low |
| Keating (2011) | − | ? | − | + | ? | High |
| Haryanto (2015) | − | ? | ? | + | ? | High |
| Sofyani & Lelo (2017) | − | ? | ? | + | ? | High |

*Note:* D1 = Randomization; D2 = Deviations from intervention; D3 = Missing data; D4 = Outcome measurement; D5 = Selective reporting. + = low risk; ? = some concerns; − = high risk.

Seven studies reported adequate randomization procedures (computer-generated sequences or random number tables with allocation concealment) and were rated low risk on D1. These studies also performed well across remaining domains: participants and personnel were blinded or deviations were unlikely to affect outcomes (D2: low risk), attrition was adequately handled or balanced between arms (D3: low risk), blood lead was measured objectively using standardized laboratory methods (D4: low risk), and outcomes were reported as pre-specified (D5: low risk). *Zimmermann et al. (2006) was rated "some concerns" because the method of sequence generation was not described, though baseline characteristics were balanced. Three calcium studies were rated high risk of bias overall.

*Keating et al. (2011) used alternating assignment rather than a random sequence (D1: high risk), had 43% attrition with differential dropout between arms (D3: high

risk), and could not blind participants given the food-based intervention (D2: some concerns). Blood lead was measured using capillary samples with a portable LeadCare analyzer rather than venous blood in a certified laboratory (D4: low risk, but lower precision). *Haryanto et al. (2015) did not describe the randomization procedure (D1: high risk), had 26% attrition that was evenly distributed between arms and attributable to equipment failure and school exam scheduling rather than treatment-related factors (D3: some concerns), and did not report blinding of outcome assessors (D5: some concerns). *Sofyani and Lelo (2017) was described as a quasi-experimental randomized clinical trial using simple random sampling (D1: high risk due to unclear allocation concealment), the small sample (n=56) raises concerns about baseline balance, 10% of enrolled participants dropped out with no information on whether dropout was related to treatment (D3: some concerns), and the calcium compound was not specified, limiting reproducibility.

Notably, these three high-risk studies were conducted in Nigeria and Indonesia—the only studies from settings with widespread calcium deficiency. The four low-risk calcium studies were all from the United States and Mexico, where baseline dietary calcium intake is substantially higher.

## 3.4. Meta-Analysis Results

Table 3 summarizes the pooled estimates. Figure 2 shows all individual effect estimates entering the RVE analysis, stratified by risk of bias; studies with multiple arms or time-point assessments appear as separate rows.

### 3.4.1. Calcium Supplementation

Across all 7 calcium studies, the pooled effect of calcium supplementation on blood lead was $-1.33$ $\mu$g/dL (95% CI: $-2.87$ to $+0.21$ ; p=.078 ; $I^2$=83 %). The three studies from settings with widespread calcium deficiency showed substantially larger study-mean effects: $-1.10$ $\mu$g/dL in *Keating et al. (2011), $-4.95$ $\mu$g/dL in *Haryanto et al. (2015), and $-2.78$ $\mu$g/dL in *Sofyani and Lelo (2017).

When restricted to the 4 low-risk-of-bias studies (all from US/Mexico), the pooled estimate attenuated to $-0.36$ $\mu$g/dL (95% CI: $-1.11$ to $+0.38$ ; p=.123 ; $I^2$=0

%). This sensitivity analysis excludes the three high-risk-of-bias studies (*Keating et al., 2011; *Haryanto et al., 2015; *Sofyani and Lelo, 2017), which are also the only studies from calcium-deficient populations; the attenuation therefore reflects the removal of both higher-bias and potentially higher-effect studies, and the resulting confidence interval crosses zero.

### 3.4.2. Iron Supplementation

Across 4 studies, the pooled effect of iron supplementation on blood lead was $-0.31$ $\mu$g/dL (95% CI: $-0.61$ to $-0.02$ ; p=.045 ). Heterogeneity was low ($I^2=0$ %). Although *Zimmermann et al. (2006) reported a substantially larger effect ($-2.10$ $\mu$g/dL), it received only 1.6% of the total weight in the inverse-variance pooled estimate due to its large standard error (n=134, SE=0.53), which is why $I^2$ remains near zero.

### 3.4.3. Summary of Pooled Results

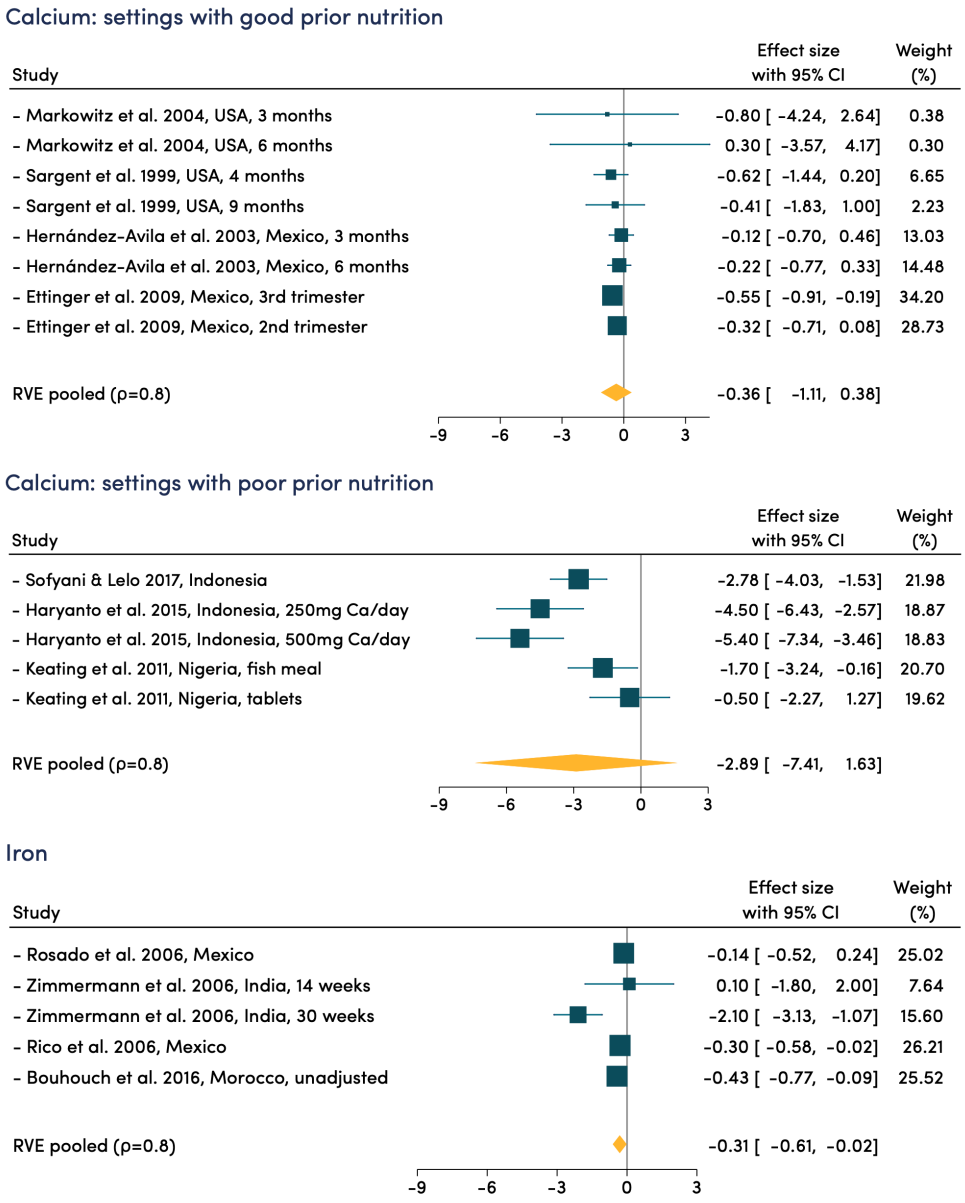
Because compliance was imperfect in all studies (ranging from 60% to 97%; see Table S4), Table 3 also reports Wald IV-adjusted estimates that scale the intent-to-treat effects by mean study-level compliance rates, providing an illustrative estimate of the per-protocol effect on compliers. Compliance-adjusted effects were modestly larger: $-1.71$ $\mu$g/dL for calcium (all studies; 95% CI: $-3.69$ to $+0.28$ ), $-0.46$ $\mu$g/dL for calcium (low RoB only; 95% CI: $-1.53$ to $+0.60$ ), and $-0.34$ $\mu$g/dL for iron (95% CI: $-0.64$ to $-0.04$ ).

**Table 3.** Summary of Meta-Analysis Results

| Analysis | Studies | ITT ($\mu$g/dL) | 95% CI | IV-adjusted | IV 95% CI | $I^2$ |
|---|---|---|---|---|---|---|
| Calcium (all studies) | 7 | −1.33 | −2.87 , +0.21 | −1.71 | −3.69 , +0.28 | 83 % |
| Calcium (low RoB only) | 4 | −0.36 | −1.11 , +0.38 | −0.46 | −1.53 , +0.60 | 0 % |
| Calcium (high RoB only) | 3 | −2.89 | −7.41 , +1.63 | −3.83 | −8.87 , +1.21 | 77 % |
| Iron (all studies) | 4 | −0.31 | −0.61 , −0.02 | −0.34 | −0.64 , −0.04 | 0 % |

*Note:* Negative values indicate reduction in blood lead. RoB = Risk of Bias. ITT = intent-to-treat estimate from RVE. IV-adjusted = Wald estimate dividing ITT by mean study-level compliance rate, with SE scaled analogously. IV confidence intervals assume the compliance rate is measured without error and should be treated as illustrative; they do not account for uncertainty in compliance measurement. $I^2$ values refer to the ITT analysis. Compliance rates ranged from 60% to 97% across studies (see Table S4). For two studies (*Haryanto et al., 2015; *Keating et al., 2011), compliance rates were not directly reported as summary statistics and were estimated from study descriptions; see Table S4 for details.

**Figure 2.** Forest plot of all primary effect estimates (stratified by supplement type and risk of bias).




*Note:* Each row is one effect estimate; studies with multiple arms or time-point assessments appear as separate rows. Square size reflects inverse-variance weight. Pooled diamonds show **RVE** estimates (Hedges et al., 2010, $\rho = 0.8$). Negative values indicate reduction in blood lead.

## 3.5. Sensitivity Analyses

Leave-one-out analysis for calcium showed that the pooled DL estimate ranged from $-0.80$ $\mu$g/dL when excluding *Haryanto et al. (2015) to $-1.66$ $\mu$g/dL when excluding *Hernández-Avila et al. (2003), with *Haryanto et al. (2015) exerting the greatest individual influence. Excluding any single study left the overall direction unchanged. We note that the DL leave-one-out confidence intervals exclude zero for most single-study exclusions (see Table S5), whereas the primary RVE confidence interval for all calcium studies does not exclude zero; this discrepancy arises because RVE produces wider confidence intervals that account for within-study clustering of multiple time-point estimates. For iron, results were highly stable: the pooled estimate ranged from $-0.26$ $\mu$g/dL when excluding *Bouhouch et al. (2016) to $-0.37$ $\mu$g/dL when excluding *Rosado et al. (2006), remaining statistically significant in all cases. Full leave-one-out results are reported in Appendix Table S5.

## 3.6. Publication Bias

Funnel plots for calcium and iron studies are presented in Appendix Figure 3. With only 7 calcium studies and 4 iron studies, these plots have limited interpretive value—at least 10 studies are typically recommended for meaningful visual assessment of publication bias. The calcium funnel plot shows possible asymmetry, with smaller studies (higher standard errors) showing larger effects, though this pattern could also reflect true heterogeneity by setting rather than publication bias. The iron funnel plot with only 4 studies is essentially uninterpretable. Formal statistical tests (e.g., Egger's test) were not conducted given the small number of studies. Publication bias cannot be ruled out.

## 3.7. Certainty of Evidence (GRADE)

Tables 4 and 5 present the GRADE assessment.

**Table 4.** GRADE Summary of Findings — Calcium Supplementation

| **Calcium supplementation vs. placebo for reducing blood lead levels**<br>*Setting:* US, Mexico, Indonesia, Nigeria (mixed high- and low-income) | |
|---|---|
| **Studies (participants)** | 7 RCTs (980 calcium, 979 placebo/control) |
| **Risk of bias** | ↓ Serious[a] |
| **Inconsistency** | ↓ Serious[b] |
| **Indirectness** | ↓ Serious[c] |
| **Imprecision** | ↓ Serious[d] |
| **Publication bias** | Not downgraded[e] |
| **Absolute effect (95% CI)** | $-1.33$ $\mu$g/dL (95% CI: $-2.87$ to $+0.21$ ) |
| **Overall certainty** | $\oplus\circ\circ\circ$ **Very low** |

[a]Three of seven studies were rated high risk of bias and contributed disproportionately to the pooled estimate; excluding them reduced the effect from 1.33 to 0.36 $\mu$g/dL. [b]Substantial heterogeneity ($I^2$ = 83 %), with study-level means ranging from 0.17 to 4.95 $\mu$g/dL. [c]Blood lead is a surrogate outcome; no study measured cognitive function or other patient-relevant endpoints. [d]95% CI crosses zero ($-2.87$ to $+0.21$ $\mu$g/dL); a null effect cannot be excluded. [e]Too few studies for formal assessment; concern partially captured by imprecision and risk-of-bias downgrades.

**Table 5.** GRADE Summary of Findings — Iron Supplementation

| **Iron supplementation vs. placebo for reducing blood lead levels**<br>*Setting:* Mexico, India, Morocco | |
|---|---|
| **Studies (participants)** | 4 RCTs (432 iron, 420 placebo/control) |
| **Risk of bias** | Not serious |
| **Inconsistency** | Not serious |
| **Indirectness** | ↓ Serious[a] |
| **Imprecision** | ↓ Serious[b] |
| **Publication bias** | Not downgraded |
| **Absolute effect (95% CI)** | $-0.31$ $\mu$g/dL (95% CI: $-0.61$ to $-0.02$ ) |
| **Overall certainty** | $\oplus\oplus\infty$ **Low** |

[a]Blood lead is a surrogate outcome; no study measured cognitive function or other patient-relevant endpoints. [b]Only four studies; optimal information size not met. While the pooled CI excludes zero ($-0.61$ to $-0.02$ $\mu$g/dL), the sparse evidence base limits confidence.

We rate certainty of evidence as **very low** for calcium and **low** for iron.

**Calcium.** Starting from "high" (RCT evidence), we downgraded four times, reaching the floor of "very low." First, for *risk of bias*: three of seven studies were rated high risk, and these three contributed disproportionately to the pooled estimate due to their large effect sizes; excluding them reduced the estimate from 1.33 to 0.36 $\mu$g/dL. Second, for *inconsistency*: heterogeneity was substantial ($I^2 = 83$ %), with study-level mean point estimates ranging from 0.17 to 4.95 $\mu$g/dL. Third, for *indirectness*: blood lead level is a surrogate outcome; no included study directly measured cognitive function or other patient-relevant endpoints. Fourth, for *imprecision*: the 95% CI crosses zero ($-2.87$ to $+0.21$ $\mu$g/dL); we cannot exclude the possibility of no effect. We did not downgrade for publication bias (too few studies to formally assess, and this concern is already reflected in the imprecision and risk-of-bias downgrades).

**Iron.** Starting from "high," we downgraded twice, yielding "low" certainty. First, for *indirectness*: as with calcium, blood lead level is a surrogate outcome and no

included study measured cognitive function or other patient-relevant endpoints directly. Second, for *imprecision*: only four studies contribute to the pooled estimate and the optimal information size has not been met; while the pooled CI excludes zero ($-0.61$ to $-0.02$ $\mu$g/dL), the sparse evidence base limits confidence in the precision of the effect. We did not downgrade for risk of bias (three of four studies were low risk), inconsistency ($I^2 = 0$ %), or publication bias.

# 4. Discussion

## 4.1. Summary of Evidence

This systematic review and meta-analysis of 11 experimental studies finds that pooling all 7 calcium studies yields an effect of 1.3 $\mu$g/dL, which attenuates to 0.4 $\mu$g/dL when restricted to the 4 low-risk-of-bias studies; neither estimate achieves conventional statistical significance with robust variance estimation. The attenuation reflects the exclusion of three studies from calcium-deficient populations that also carry the highest risk of bias—a confound that substantially reduces certainty. Iron supplementation shows a smaller but statistically significant effect (0.3 $\mu$g/dL). These findings are consistent with the biological mechanism whereby calcium and iron compete with lead for gastrointestinal absorption.

## 4.2. Comparison with Prior Evidence

Our findings align with observational evidence. A systematic review of 28 studies found consistent inverse associations between calcium intake and blood lead levels (Rajaee et al., 2022). Similarly, iron deficiency has been repeatedly associated with elevated blood lead in observational studies (Bradman et al., 2001; Wright et al., 2003). The experimental evidence synthesized here provides causal support for these associations, though effect sizes are modest.

The WHO's characterization of the evidence as "very low certainty" (World Health Organization, 2021) is broadly supported by our analysis: we rate calcium evidence as very low and iron evidence as low. The use of blood lead as a surrogate outcome rather than a direct cognitive endpoint represents an additional source of uncertainty

not captured in prior assessments. For calcium, the two main sources of downgrade—high risk of bias in key studies and substantial heterogeneity—are interrelated. The studies showing the largest effects are precisely those with the highest risk of bias, making it difficult to determine whether the pooled estimate of 1.3 $\mu$g/dL reflects a genuine effect or is inflated by methodological weaknesses. The sensitivity analysis restricted to low-risk-of-bias studies (0.4 $\mu$g/dL) provides a lower bound, but these studies are all from higher-calcium settings (US/Mexico) and may underestimate effects in calcium-deficient populations.

## 4.3. Interpretation of Heterogeneity

The correlation between study quality and setting creates an identification problem. The high-risk studies (*Keating et al., 2011; *Haryanto et al., 2015; *Sofyani and Lelo, 2017) are the only studies from populations with widespread calcium deficiency. It is biologically plausible that effects are larger where deficiency is more prevalent—supplementation can only help if there is a deficit to correct. However, we cannot rule out that methodological weaknesses biased these estimates upward.

This pattern points to a critical evidence gap: there are no high-quality studies from the settings where benefits would be expected to be largest—populations with both high lead exposure and widespread nutritional deficiency.

Several potential effect modifiers warrant discussion, though we cannot fully disentangle biological from methodological explanations given the small number of studies and confounding between study quality and setting. First, baseline blood lead level may matter: studies with higher baseline BLLs, particularly *Haryanto et al. (2015) (14.2 $\mu$g/dL) and *Keating et al. (2011) (8.9 $\mu$g/dL), showed larger effects, consistent with a greater scope for reduction at higher levels. However, this pattern is not uniform: *Markowitz et al. (2004) had the highest baseline BLL (25.0 $\mu$g/dL) but showed a modest, non-significant effect, suggesting baseline level alone does not determine response. Second, baseline nutritional status is a plausible moderator: the three calcium-deficient populations (*Keating et al., 2011; *Haryanto et al., 2015; *Sofyani and Lelo, 2017) showed the largest calcium effects, which is biologically consistent with the absorption-competition mechanism—supplementation can only

reduce lead uptake if there is a nutritional deficit to correct. Third, dose and duration varied substantially across studies (calcium: 400–1,800 mg/d for 3–18 months; iron: 8–30 mg/d for 4–7 months), but with only 7 calcium and 4 iron studies, formal meta-regression of these moderators is not feasible.

Expressing effects as percentage change from each study's own baseline blood lead level offers a complementary perspective on this heterogeneity (Table S5). The pooled percentage change is $-18.07$ % for calcium (95% CI: $-38.54$ to $+2.41$ ; p=.073 ) and $-3.62$ % for iron (95% CI: $-10.73$ to $+3.49$ ; p=.161 ). This framing may be more biologically interpretable across studies with widely differing baseline exposures: the same absolute reduction represents a very different biological burden at 4 $\mu$g/dL versus 14 $\mu$g/dL. Notably, the high-risk-of-bias calcium studies—with higher baseline BLLs in *Haryanto et al. (2015) (14.2 $\mu$g/dL) and *Keating et al. (2011) (8.9 $\mu$g/dL)—show large percentage reductions, while the low-risk studies from the US and Mexico, where baselines are lower (3–5 $\mu$g/dL), show more modest percentage changes. The pattern of heterogeneity therefore persists on a relative scale, consistent with the hypothesis that supplementation is more impactful when baseline BLLs are higher, though the confound with study quality remains.

## 4.4. Limitations

This review has several important limitations. The protocol was not prospectively registered, which limits transparency regarding any analytical decisions made after data collection. We searched Google Scholar and PubMed but not Embase or the Cochrane Central Register of Controlled Trials (CENTRAL). While our PubMed search did not identify any additional eligible studies beyond those found through Google Scholar and reference screening, Embase may index additional trials, particularly from European and non-English-language journals. Two included studies from Indonesian journals were not indexed in PubMed and were identified only through Google Scholar, highlighting the value of broad search coverage. With only 11 studies (4 on iron, 7 on calcium), we had limited power to explore heterogeneity by study characteristics such as baseline exposure, dose, or duration. As discussed, the studies showing largest effects have highest risk of bias, and these are the only studies from

high-deficiency settings, which precludes strong conclusions about effects in priority populations. Blood lead is a biomarker, not a final health outcome; calcium may reduce neurotoxicity through mechanisms beyond absorption (e.g., competition at synaptic receptors), meaning blood lead may underestimate total benefits, while if the relationship between blood lead and cognition is not fully causal, blood lead may overestimate benefits. We are aware of no quasi-experimental evaluations of large-scale iron or calcium fortification programs that measured blood lead as an outcome; such studies, if they emerge from existing fortification rollouts, would be a valuable complement to the trial evidence. Finally, with few studies showing mostly positive effects, publication bias is plausible but could not be formally assessed.

## 4.5. Implications for Policy and Research

To contextualize effect magnitudes relative to a common reference: average blood lead in LMICs is approximately 5 $\mu$g/dL (Ericson et al., 2021), so a 0.3 –1.3 $\mu$g/dL reduction represents a 6 –26 % decrease from that reference. When effects are instead expressed as a percentage of each study's own baseline BLL, the estimates vary more widely across studies (see Table S5 and the discussion of heterogeneity above), reflecting the fact that included populations span a wide range of baseline exposures (2.8–25.0 $\mu$g/dL). This would still leave most individuals above the 3.5 $\mu$g/dL reference value used in the United States, indicating that supplementation alone cannot adequately address lead exposure. However, even modest reductions may yield meaningful cognitive benefits: each 1 $\mu$g/dL reduction in blood lead corresponds to approximately 0.5–1.0 IQ points (Lanphear et al., 2005), implying cognitive gains on the order of 0.2 –1.3 IQ points. We caution that this translation involves substantial uncertainty: the lead-cognition dose-response is derived from observational studies that may overestimate causal effects, may be non-linear at lower exposure levels, and the calcium estimate itself does not reach statistical significance with RVE.

Despite these limitations, the evidence is broadly consistent with current WHO recommendations for supplementation in lead-exposed populations with nutritional deficiencies, though the evidence base remains thin. The rationale is twofold: (1) the experimental evidence, while uncertain, consistently shows effects in the expected

direction; and (2) supplementation has independent benefits for anemia and bone health that strengthen the case even if lead-reduction benefits are modest. Iron and calcium supplementation is inexpensive—less than $1 per person per year for iron (GiveWell, 2021)—and cost-effectiveness analyses suggest benefit-cost ratios exceeding 6:1 in high-exposure settings even excluding anemia benefits (World Bank, 2025). Food fortification may be more sustainable than individual supplementation, as it changes defaults rather than requiring ongoing behaviour change.

We emphasize that supplementation is a complement to, not substitute for, primary prevention. Lead exposure is entirely preventable through elimination of sources (leaded paint, fuel, cookware, industrial emissions), and source reduction must remain the priority.

The most important research gap is the absence of high-quality trials in settings with both high lead exposure and widespread nutritional deficiency. Such trials should use rigorous randomization and blinding, measure cognitive outcomes directly rather than only blood lead, be adequately powered for subgroup analyses by baseline nutritional status, examine dose-response relationships, and include longer follow-up to assess sustainability of effects.

## 5. Conclusion

This meta-analysis finds consistent but statistically non-significant effects of calcium supplementation on blood lead levels. Pooling all 7 eligible studies yields an effect of 1.3 $\mu$g/dL; restricting to the 4 low-risk-of-bias studies attenuates the estimate to 0.4 $\mu$g/dL. Certainty is very low because the studies most relevant to low-income, calcium-deficient settings—where supplementation is most likely to be deployed and where biological effects may be largest—are also the studies with the highest risk of bias. Iron supplementation shows a smaller but statistically significant effect (0.3 $\mu$g/dL). The evidence base is thin, with only 11 studies, and certainty of evidence is very low for calcium and low for iron, due to risk of bias concerns, substantial heterogeneity, indirectness (use of blood lead as a surrogate outcome), and imprecision.

Critically, no high-quality evidence exists from the settings of greatest policy

relevance: populations with both high lead exposure and widespread nutritional deficiency. Future research should prioritize rigorous trials in these contexts, examining cognitive outcomes directly rather than relying solely on blood lead as an intermediate biomarker.

Despite these limitations, the existing evidence supports supplementation as a low-cost intervention that may provide modest benefits for lead-exposed populations with nutritional deficiencies. However, supplementation cannot substitute for primary prevention—eliminating sources of lead exposure must remain the priority.

## Funding

Support for this work was gratefully received from Coefficient Giving.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Author Contributions

LC and TM designed the study. LC and TM conducted the search and data extraction. LC and TM conducted statistical analysis. LC and TM drafted the manuscript. Both authors revised and approved the final version.

## Data Availability

The data extraction spreadsheet and analysis code are available at https://github.com/Center-for-Global-Development/Iron-and-Calcium-Supplementation-for-Reducing-Blood-Lead-Levels.

## Registration and Protocol

This review was not prospectively registered. No review protocol was prepared prior to conducting the review.

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*Note:* References marked with an asterisk (*) are studies included in the meta-analysis: **Bouhouch et al. (2016), **Ettinger et al. (2009), **Haryanto et al. (2015), **Hernández-Avila et al. (2003), **Keating et al. (2011), **Markowitz et al. (2004), **Alatorre Rico et al. (2006), **Rosado et al. (2006), **Sargent et al. (1999), **Sofyani and Lelo (2017), **Zimmermann et al. (2006).

# Appendix A: Supplementary Tables

## Table S1. Individual Study Results

| Study | Analyzed N | | Follow-up BLL | | Effect | SE |
|---|---|---|---|---|---|---|
| | Int | Ctrl | Int | Ctrl | | |
| | | | *mean (SD) μg/dL* | | *μg/dL* | |
| *Iron supplementation* | | | | | | |
| Rosado (2006) | 129 | 122 | — | — | −0.14 | 0.20 |
| Alatorre Rico (2006) | 138 | 128 | — | — | −0.30 | 0.14 |
| Zimmermann (2006) | | | | | | |
| *14 weeks* | 66 | 68 | 12.1 (5.8) | 12.0 (5.4) | +0.10 | 0.97 |
| *30 weeks* | 66 | 68 | 8.1 (4.7) | 10.2 (5.2) | −2.10 | 0.53 |
| Bouhouch (2016) | 99 | 102 | 3.3 (0.9) | 3.7 (1.0) | −0.43 | 0.17 |
| *Calcium supplementation* | | | | | | |
| Markowitz (2004) | | | | | | |
| *3 months* | 35 | 32 | 15.1 (6.3) | 16.6 (7.2) | −0.80 | 1.75 |
| *6 months* | 34 | 24 | 14.0 (7.2) | 14.4 (6.8) | +0.30 | 1.98 |
| Sargent (1999) | | | | | | |
| *4 months* | 44 | 45 | 3.5 (1.7) | 4.6 (2.3) | −0.62 | 0.42 |
| *9 months* | 40 | 41 | 4.8 (3.5) | 5.0 (2.7) | −0.41 | 0.72 |
| Ettinger (2009) | | | | | | |
| *2nd trimester* | 334 | 336 | — | — | −0.32 | 0.20 |
| *3rd trimester* | 334 | 336 | — | — | −0.55 | 0.18 |
| Hernández-Avila (2003) | | | | | | |
| *3 months* | 296 | 321 | — | — | −0.12 | 0.30 |
| *6 months* | 296 | 321 | — | — | −0.22 | 0.28 |
| Keating (2011) | | | | | | |
| *Fish meal* | 103 | 117 | 6.4 (4.8) | 7.5 (4.6) | −1.70 | 0.79 |
| *Tablet* | 138 | 117 | 9.8 (7.9) | 7.5 (4.6) | −0.50 | 0.90 |

| Study | Int | Ctrl | Int | Ctrl | Effect | SE |
|---|---|---|---|---|---|---|
| Haryanto (2015) | | | | | | |
| *250 mg Ca/d* | 92 | 102 | 8.7 (4.5) | 12.1 (6.8) | −4.50 | 0.98 |
| *500 mg Ca/d* | 103 | 102 | 7.1 (2.7) | 12.1 (6.8) | −5.40 | 0.99 |
| Sofyani & Lelo (2017)† | 30 | 26 | — | — | −2.78 | 0.64 |

*Notes:* Effect = mean difference (intervention − control); negative values indicate lower blood lead. SE = standard error. Analyzed N refers to sample sizes at each time point or arm and differs from enrolled N in Table 1 due to dropout. All estimates were included in the meta-analysis; within-study dependence was accounted for using robust variance estimation ($\rho = 0.8$). Forest plots show study-level mean effects. Studies without follow-up BLL columns (—) did not report post-intervention group means; effects were derived from reported summary statistics.

†This study appeared as a conference paper (*Sofyani and Lelo, 2017) and as a journal article (Sofyani et al., 2020). We use the 2017 version because it reports group means and standard errors, allowing difference-in-differences estimation. The 2020 article reports only medians.

## Table S2. Baseline Characteristics of Included Studies

| Study | Age | Baseline BLL | Nutritional Status | Lead Source |
|---|---|---|---|---|
| | | *μg/dL* | | |
| *Iron supplementation* | | | | |
| Rosado (2006) | 6–8 y | 9.4 | Mixed | Lead smelter |
| Alatorre Rico (2006) | 6–8 y | 11.5 | Mixed | Lead smelter |
| Zimmermann (2006) | 5–8 y | 6.8 | Iron deficient | Environmental |
| Bouhouch (2016) | 6–11 y | 4.8 | Mixed | Environmental |
| *Calcium supplementation* | | | | |
| Markowitz (2004) | 1–6 y | 25.0 | Not reported | Urban housing |
| Sargent (1999) | 0–9 mo | 3.5 | Not reported | Environmental |
| Ettinger (2009) | Pregnant | 4.5 | Not reported | Bone stores |
| Hernández-Avila (2003) | Lactating | 9.5 | Not reported | Bone stores |
| Keating (2011) | 12–24 mo | 8.9 | Ca deficient | Environmental |
| Haryanto (2015) | 9–11 y | 14.2 | Ca deficient | Environmental |
| Sofyani & Lelo (2017) | 9–12 y | 2.8 | Not reported | Environmental |

*Note:* BLL = Blood lead level. Baseline BLL shows mean value at study entry. Nutritional status refers to iron or calcium status as applicable. Lead source indicates primary suspected source of exposure in study population.

## Table S3. Blood Lead Measurement Methods

| Study | Sample Type | Analysis Method | Laboratory |
|---|---|---|---|
| Rosado (2006) | Venous | GFAAS | CINVESTAV, Mexico |
| Alatorre Rico (2006) | Venous | AAS | Not specified |
| Zimmermann (2006) | Venous | GFAAS | ETH Zurich |
| Bouhouch (2016) | Venous | ICP-MS | ETH Zurich |
| Markowitz (2004) | Venous | GFAAS | Montefiore Medical Center |
| Sargent (1999) | Venous | GFAAS | Dartmouth-Hitchcock |
| Ettinger (2009) | Venous | GFAAS | Harvard/INSP Mexico |
| Hernández-Avila (2003) | Venous | GFAAS | INSP Mexico |
| Keating (2011) | Capillary* | LeadCare | Field testing |
| Haryanto (2015) | Capillary* | LeadCare | Field testing |
| Sofyani & Lelo (2017) | Venous | AAS | Universitas Sumatera Utara |

*Note:* GFAAS = Graphite furnace atomic absorption spectrometry; ICP-MS = Inductively coupled plasma mass spectrometry; AAS = Atomic absorption spectrometry. **Keating et al. (2011) and *Haryanto et al. (2015) used capillary blood with LeadCare portable analyzers; all other studies used venous blood samples analyzed in certified laboratories.

## Table S4. Supplement Dosage, Delivery, and Uptake

| Study | Compound | Dose | Dur. | Delivery | Comp. (%) | Drop. (%) |
|---|---|---|---|---|---|---|
| *Iron supplementation* | | | | | | |
| Rosado | Fe fumarate | 30 mg Fe/d | 6 mo | Oral supplement | 90 | 14 |
| Alatorre Rico | Iron + zinc | 30 mg Fe/d | 4.5 mo | Oral, at school | 90 | <1 |
| Zimmermann | Fe pyrophosphate | 15 mg Fe/d | 16 wk | Fortified rice | 80 | <5 |
| Bouhouch | Fe sulphate | 8 mg Fe/d | 28 wk | Fortified biscuits | 97 | 10 |
| *Calcium supplementation* | | | | | | |
| Markowitz | Ca glubionate | 1,800 mg/d | 3 mo | Liquid, 3×/d | 80 | 24 |
| Sargent | Ca glycerophos. | 1,600–1,730 mg/d | 9 mo | Infant formula | 83 | 21 |
| Ettinger | Ca carbonate | 1,200 mg/d | Preg. | Oral tablet | 74 | 16 |
| Hernández-Avila | Ca carbonate | 1,200 mg/d | 6 mo | Oral tablet | 83 | 17 |
| Keating | Fish / $CaCO_3$ | 400–500 mg/d | 12–18 mo | Food / tablet | 60[a] | 43 |
| Haryanto | Ca carbonate | 250–500 mg/d | 3 mo | Chewable tablet | 80[b] | 26 |
| Sofyani & Lelo | Not stated | 800 mg/d | 3 mo | Oral, 2×/d | 82 | 10 |

*Notes:* Compliance = estimated rate among study completers. Dropout = percentage lost to follow-up. Doses are elemental calcium (Ca) or iron (Fe). Sargent used two dosage levels (1,600 and 1,730 mg Ca/d). Keating compared calcium-rich food (∼500 mg/d) and tablets (400 mg/d). Haryanto compared 250 and 500 mg Ca/d. Alatorre Rico also included an iron+zinc arm; both arms are pooled in the meta-analysis.

[a]Keating reported children consumed “about 50–60%” of intended doses; 60% is used. [b]Haryanto did not report a summary compliance statistic; estimated from monitoring description.

## Table S5. Study-Level Percentage Change in Blood Lead Level from Study-Specific Baseline

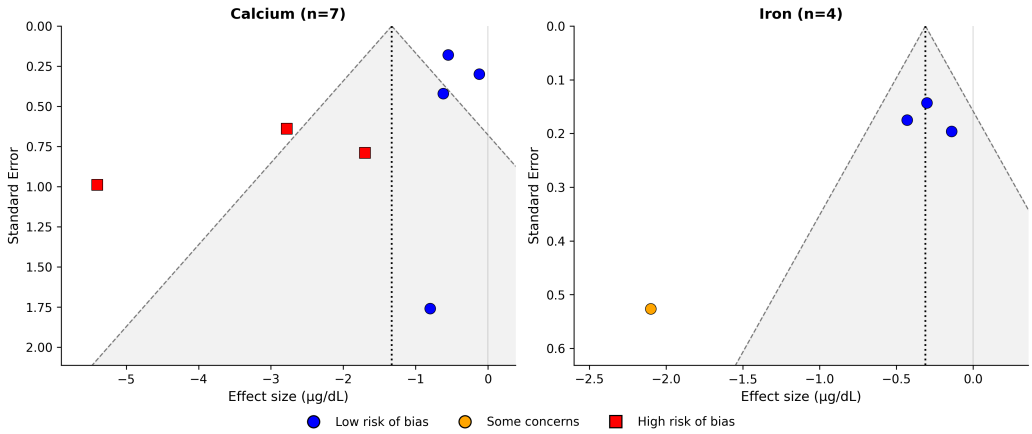
| Study | Baseline BLL ($\mu g/dL$) | Effect ($\mu g/dL$) | % Change |
|---|---|---|---|
| *Iron supplementation* | | | |
| Rosado (2006) | 11.6 | −0.14 | −1.2 % |
| Alatorre Rico (2006) | 11.5 | −0.30 | −2.6 % |
| Zimmermann (2006) | 12.1 | −1.00[a] | −8.3 % |
| Bouhouch (2016) | 4.1 | −0.43 | −10.6 % |
| *Calcium supplementation* | | | |
| Markowitz (2004) | 21.0 | −0.25[a] | −1.2 % |
| Sargent (1999) | 2.5 | −0.52[a] | −20.8 % |
| Ettinger (2009) | 4.0 | −0.44[a] | −11.0 % |
| Hernández-Avila (2003) | 9.3 | −0.17[a] | −1.8 % |
| Keating (2011) | 10.7 | −1.10[a] | −10.6 % |
| Haryanto (2015) | 14.1 | −4.95[a] | −35.2 % |
| Sofyani & Lelo (2017) | 2.8 | −2.78 | −98.7 % |

*Note:* Baseline BLL is the pooled (sample-weighted) whole-sample mean at study entry. % Change = (effect / baseline BLL) × 100; negative values indicate a reduction.

[a] Effect shown is the study-level mean averaged across multiple time points or arms (as used in the meta-analysis); individual estimates are shown in Table S1.

# Appendix B: Funnel Plots

**Figure 3.** Funnel plots for calcium and iron supplementation studies.




*Note:* Blue circles = low risk of bias; orange circles = some concerns; red squares = high risk of bias. Shaded region shows 95% pseudo-confidence interval centered on pooled estimate (dotted line). With <10 studies, these plots have limited interpretive value.

# Appendix C: Leave-One-Out Sensitivity Analysis

**Table S5.** Leave-One-Out Sensitivity Analysis

| Study excluded | Pooled effect ($\mu$g/dL) | 95% CI |
|---|---|---|
| *Calcium supplementation* | | |
| Ettinger et al. (2009) | −1.62 | −3.00, −0.24 |
| Haryanto et al. (2015) | −0.80 | −1.46, −0.13 |
| Hernández-Avila et al. (2003) | −1.66 | −2.94, −0.38 |
| Keating et al. (2011) | −1.37 | −2.38, −0.36 |
| Markowitz et al. (2004) | −1.38 | −2.33, −0.43 |
| Sargent et al. (1999) | −1.51 | −2.58, −0.44 |
| Sofyani & Lelo (2017) | −0.99 | −1.85, −0.13 |
| *Iron supplementation* | | |
| Bouhouch et al. (2016) | −0.26 | −0.49, −0.04 |
| Alatorre Rico et al. (2006) | −0.32 | −0.58, −0.06 |
| Rosado et al. (2006) | −0.37 | −0.58, −0.15 |
| Zimmermann et al. (2006) | −0.30 | −0.49, −0.11 |

*Note:* Each row shows the DerSimonian–Laird random-effects pooled estimate when the named study is excluded. Calcium estimates are from study-level means (7 studies); iron estimates are from country-level means (4 studies).

# Appendix D: PRISMA 2020 Checklist

| # | Item | Checklist Item | Location |
|---|---|---|---|
| **TITLE** | | | |
| 1 | Title | Identify the report as a systematic review | Title |
| **ABSTRACT** | | | |
| 2 | Abstract | Structured summary | Abstract |
| **INTRODUCTION** | | | |
| 3 | Rationale | Describe the rationale in context of existing knowledge | Introduction |
| 4 | Objectives | Provide explicit statement of objectives | Introduction |
| **METHODS** | | | |
| 5 | Eligibility criteria | Specify inclusion/exclusion criteria | Methods 2.2 |
| 6 | Information sources | Specify all databases searched with dates | Methods 2.1 |
| 7 | Search strategy | Present full search strategy | Methods 2.1 |
| 8 | Selection process | Specify selection methods | Methods 2.3 |
| 9 | Data collection | Specify data extraction methods | Methods 2.3 |
| 10 | Data items | List variables extracted | Methods 2.3 |
| 11 | Study risk of bias | Describe RoB assessment methods | Methods 2.4 |
| 12 | Effect measures | Specify effect measure(s) | Methods 2.5 |
| 13 | Synthesis methods | Describe synthesis methods | Methods 2.5 |
| 13a | | Criteria for meta-analysis | Methods 2.5 |
| 13b | | Heterogeneity methods | Methods 2.5 |
| 13c | | Software used | Methods 2.5 |
| 13d | | Sensitivity analyses | Methods 2.5 |
| 14 | Reporting bias | Publication bias assessment methods | Methods 2.5 |
| 15 | Certainty assessment | GRADE or similar methods | Methods 2.6 |

| # | Item | Checklist Item | Location |
|---|---|---|---|
| **RESULTS** | | | |
| 16 | Study selection | Flow diagram and numbers | Results 3.1, Fig 1 |
| 17 | Study characteristics | Characteristics table | Results 3.2, Table 1 |
| 18 | Risk of bias in studies | Present RoB assessments | Results 3.3, Table 2 |
| 19 | Individual results | Data for each study | Results 3.4, Fig 2, Table S1 |
| 20 | Synthesis results | Pooled results with CI and heterogeneity | Results 3.4, Table 3 |
| 21 | Reporting biases | Publication bias assessment | Results 3.5, Fig 3 |
| 22 | Certainty of evidence | GRADE assessment | Results 3.6, Table 4 |
| **DISCUSSION** | | | |
| 23 | Discussion | Interpretation, limitations, implications | Discussion |
| **OTHER INFORMATION** | | | |
| 24 | Registration | Registration information | PROSPERO section |
| 25 | Protocol | Protocol access | N/A |
| 26 | Amendments | Protocol amendments | N/A |
| 27 | Support | Funding sources | Funding |
| 28 | Competing interests | Declarations | Conflicts of Interest |
| 29 | Data availability | Data/code access | Data Availability |