



Effectiveness of Zinc Supplementation in Nutritional Catch-Up Growth Management for Stunted Toddlers: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction: Stunting affects 148.1 million children under five globally, with zinc deficiency mechanistically implicated through impaired IGF-1 signaling and cellular proliferation. This systematic review evaluates the effectiveness of zinc supplementation on linear growth, ponderal growth, biomarkers, and morbidity outcomes in stunted toddlers.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines from inception to June 2025. Included studies comprised RCTs, cluster-RCTs, or primary studies enrolling children aged 0–72 months receiving oral zinc supplementation with at least one anthropometric or morbidity outcome. Risk of bias was assessed using Cochrane RoB 2.0. Narrative synthesis was employed with pooled estimates derived from included meta-analyses.

Results: Zinc supplementation significantly improved linear growth in stunted children (effect size 0.13–0.50 SD), with the most pronounced effect in Ethiopian infants (7.0 cm vs 2.8 cm placebo, $p < 0.001$). Weight gain showed consistent positive effects (ES 0.309, 95% CI 0.178–0.439). Serum zinc responded robustly (ES 0.820). Zinc reduced diarrhea (OR 0.82, 95% CI 0.72–0.93) and pneumonia (OR 0.59, 0.41–0.83). All-cause mortality was reduced by 16% (SRR 0.84). However, stunting prevalence was not consistently reduced, with attenuation observed in settings with high environmental enteric dysfunction or iron co-supplementation.

Discussion: Zinc demonstrates significant benefit for linear growth velocity in zinc-deficient stunted toddlers, mediated through IGF-1 upregulation, improved appetite, and reduced infectious morbidity. Contextual heterogeneity is driven by baseline zinc status, co-existing deficiencies, EED burden, and iron co-supplementation.

Conclusion: Zinc supplementation at 10 mg/day for ≥ 24 weeks is effective for improving linear growth velocity and reducing morbidity in stunted toddlers with zinc deficiency, though insufficient as monotherapy for reversing stunting prevalence. Integrated approaches addressing multifactorial etiology are recommended.

Keywords: zinc supplementation; stunting; catch-up growth; linear growth; IGF-1

INTRODUCTION

Background

Stunting, characterized by chronic linear growth faltering resulting in HAZ < -2 SD from the WHO Child Growth Standards median, is one of the most prevalent forms of child undernutrition globally (1). According to UNICEF, WHO and World Bank joint estimates, approximately 148.1 million children under five years were stunted in 2022, with South Asia (54.6 million) and sub-Saharan Africa (57.4 million) bearing the greatest burden (1). The consequences of stunting extend beyond impaired stature, encompassing cognitive deficits, reduced educational attainment, decreased adult productivity, and increased susceptibility to non-communicable diseases (2).

Zinc is an essential trace element that participates in more than 300 enzymatic reactions, more than 1,000 transcription factor structures, and multiple signaling cascades governing cell growth, immune function, and hormonal regulation (13). Within the growth axis, zinc is a critical cofactor for the GH-IGF-1 axis: zinc deficiency consistently reduces circulating IGF-1 concentrations, impairs IGF-1-mediated cell proliferation, and inhibits chondrocyte differentiation in the epiphyseal growth plate, thereby limiting endochondral ossification (14, 15). The discovery of human zinc deficiency as a clinical syndrome—initially described in Middle Eastern dwarfs by Prasad and colleagues in 1963—established the foundational link between inadequate zinc nutriture and growth retardation (13).

The global prevalence of inadequate zinc intake is estimated at 17.3%, with a strong positive correlation between country-specific zinc inadequacy and stunting prevalence ($r = 0.48$, $p < 0.001$) (3). In low-income countries, dietary zinc derives predominantly from high-phytate cereal staples with low bioavailability, compounding the risk of deficiency (13). Environmental enteric dysfunction (EED), a subclinical enteropathy driven by chronic enteric infections and poor WASH (water, sanitation, and hygiene) conditions, further limits zinc absorption and triggers pro-

inflammatory cytokine cascades that suppress growth hormone receptor signaling and reduce IGF-1 production (15, 16).

Research Objectives

The primary objective of this systematic review is to evaluate the effectiveness of oral zinc supplementation on linear growth (as measured by height/length increment and HAZ) in stunted toddlers aged 6–72 months from low- and middle-income countries (LMICs). Secondary objectives include: (1) assessment of effects on ponderal growth (weight gain, WAZ, WHZ); (2) evaluation of changes in biomarkers of zinc status (serum zinc, IGF-1, IGFBP-3); (3) quantification of effects on infectious morbidity (diarrhea, ARI, pneumonia); (4) assessment of effects on stunting prevalence and all-cause mortality; and (5) identification of moderating factors (age, baseline zinc status, dose, duration, co-supplementation, geographic region).

Research Benefits

The findings of this review will provide: (a) evidence-based guidance for clinicians, pediatricians, and public health practitioners on zinc supplementation protocols in stunted toddlers; (b) a rigorous synthesis to inform national and international nutrition policy, particularly in LMICs where stunting remains endemic; (c) identification of key moderating factors that can guide patient selection and intervention targeting; and (d) delineation of research gaps to direct future trial design, particularly regarding combined micronutrient strategies and EED management.

Research Hypothesis

We hypothesize that: (H1) Oral zinc supplementation at doses ≥ 10 mg/day for ≥ 24 weeks will produce a statistically significant improvement in linear growth (height increment and HAZ) in stunted toddlers compared to placebo or no supplementation; (H2) The magnitude of linear growth response will be greater in children with confirmed zinc deficiency (serum zinc < 65 $\mu\text{g/dL}$) and baseline stunting (HAZ < -2); (H3) Zinc supplementation will reduce infectious morbidity (diarrhea, ARI) and all-cause mortality as a mechanism partly mediating growth benefit; and (H4) The combination of zinc with iron (Fe) supplementation will attenuate the growth benefit of zinc alone due to competitive mineral absorption.

Research Gap and Novelty

Prior meta-analyses by Brown et al. (2002) (6), Imdad & Bhutta (2011) (7), and Liu et al. (2018) (17) have evaluated zinc supplementation and growth broadly in children under 5 years. However, critical gaps remain: (1) None have specifically focused on the stunted toddler subpopulation ($HAZ < -2$) as the primary analytic unit. (2) The role of IGF-1/IGFBP-3 as mediating biomarkers of zinc-driven catch-up growth has not been systematically synthesized. (3) The interaction between EED burden and zinc supplementation efficacy has not been formally analyzed across trials. (4) Dose-response relationships for catch-up growth specifically remain inadequately characterized. (5) The comparative effectiveness of zinc alone versus zinc within multi-micronutrient matrices (MNP, LNS, biofortification) for stunted-specific outcomes has not been comprehensively evaluated. This review addresses all five gaps, representing its primary novelty.

METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Table 1. Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Stunted toddlers	Children aged 6-72 months	Growth-retarded infants
I (Intervention)	Zinc supplementation	Oral zinc therapy	Zinc repletion
C (Comparison)	Placebo-controlled	No zinc supplementation	Alternative micronutrients
O (Outcome)	Catch-up growth	Linear growth velocity	Height-for-age z-score

The Boolean MeSH keywords inputted on databases for this research are: (*"Stunted toddlers" OR "Children aged 6-72 months" OR "Growth-retarded infants"*) AND (*"Zinc supplementation" OR "Oral zinc therapy" OR "Zinc repletion"*) AND (*"Placebo-controlled" OR "No zinc supplementation" OR "Alternative micronutrients"*) AND (*"Catch-up growth" OR "Linear growth velocity" OR "Height-for-age z-score"*)

Eligibility Criteria

Inclusion Criteria

Study design: RCTs (parallel or crossover), cluster-RCTs, and primary experimental studies; Systematic reviews and meta-analyses of RCTs were included for pooled effect estimates. Population: Children aged 6–72 months (toddler age range), with documented stunting ($HAZ < -2$) or from populations with high stunting prevalence ($\geq 20\%$). Intervention: Oral zinc supplementation in any form (sulphate, gluconate, acetate, MNP, LNS, biofortified food) administered for ≥ 4 weeks. Comparator: Placebo, no supplementation, or alternative micronutrient supplement not containing zinc. Outcomes: At least one primary outcome reported (linear growth: length/height increment or HAZ/LAZ). Time period: 1990–2025.

Exclusion Criteria

Non-randomized designs (observational studies, cross-sectional surveys). Children with primary disease conditions other than malnutrition (e.g., HIV-infected children as the sole population, unless zinc effect on growth was a study objective). Studies with supplementation duration < 4 weeks for primary growth outcomes. Studies reporting only non-growth outcomes (e.g., cognitive development, exclusive zinc-diarrhea trials without anthropometry). Duplicate publications reporting the same trial.

Study Selection

Two independent reviewers performed title and abstract screening. Full-text articles were retrieved for all studies passing abstract screening. Discrepancies were resolved through consensus discussion or adjudication by a third reviewer. A PRISMA flow diagram was constructed documenting identified, screened, excluded, and included studies.

Data Extraction

Data were extracted independently by two reviewers using a pre-specified extraction form capturing: author(s), publication year, country, study design, sample size, participant characteristics (age, sex, baseline HAZ/LAZ, baseline serum zinc), intervention (form, dose, duration, frequency, delivery vehicle), comparator, outcome measures, statistical methods, and key results (effect sizes, confidence intervals, p-values). Authors were contacted for missing data when feasible.

Risk of Bias Assessment

Risk of bias was assessed for each included primary study using the Revised Cochrane Risk of Bias Tool (RoB 2.0) across five domains: (1) randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result. Each domain was rated as Low Risk, Some Concerns, or High Risk. For included meta-analyses, the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) checklist was applied. Overall risk of bias judgments are presented in Table 3.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Stunted toddlers" OR "Children aged 6-72 months" OR "Growth-retarded infants" AND "Zinc supplementation" AND "Catch-up growth" OR "Linear growth velocity" OR "Height-for-age z-score")</i>	1,237
Semantic Scholar	<i>("Stunted toddlers" OR "Children aged 6-72 months" OR "Growth-retarded infants") AND ("Zinc supplementation" OR "Oral zinc therapy" OR "Zinc repletion") AND ("Placebo-controlled" OR "No zinc supplementation" OR "Alternative micronutrients") AND ("Catch-up growth" OR "Linear growth velocity" OR "Height-for-age z-score")</i>	250
Science-direct	<i>("Stunted toddlers" OR "Children aged 6-72 months" OR "Growth-retarded infants" AND "Zinc supplementation" AND "Catch-up growth" OR "Linear growth velocity" OR "Height-for-age z-score")</i>	11
Google Scholar	<i>("Stunted toddlers" OR "Children aged 6-72 months" OR "Growth-retarded infants") AND ("Zinc supplementation" OR "Oral zinc therapy" OR "Zinc repletion") AND ("Placebo-controlled" OR "No zinc supplementation" OR "Alternative micronutrients") AND ("Catch-up growth" OR "Linear growth velocity" OR "Height-for-age z-score")</i>	36
Cochrane	<i>("Stunted toddlers" OR "Children aged 6-72 months" OR "Growth-retarded infants" AND "Zinc supplementation" AND "Catch-up growth" OR "Linear growth velocity" OR "Height-for-age z-score")</i>	11

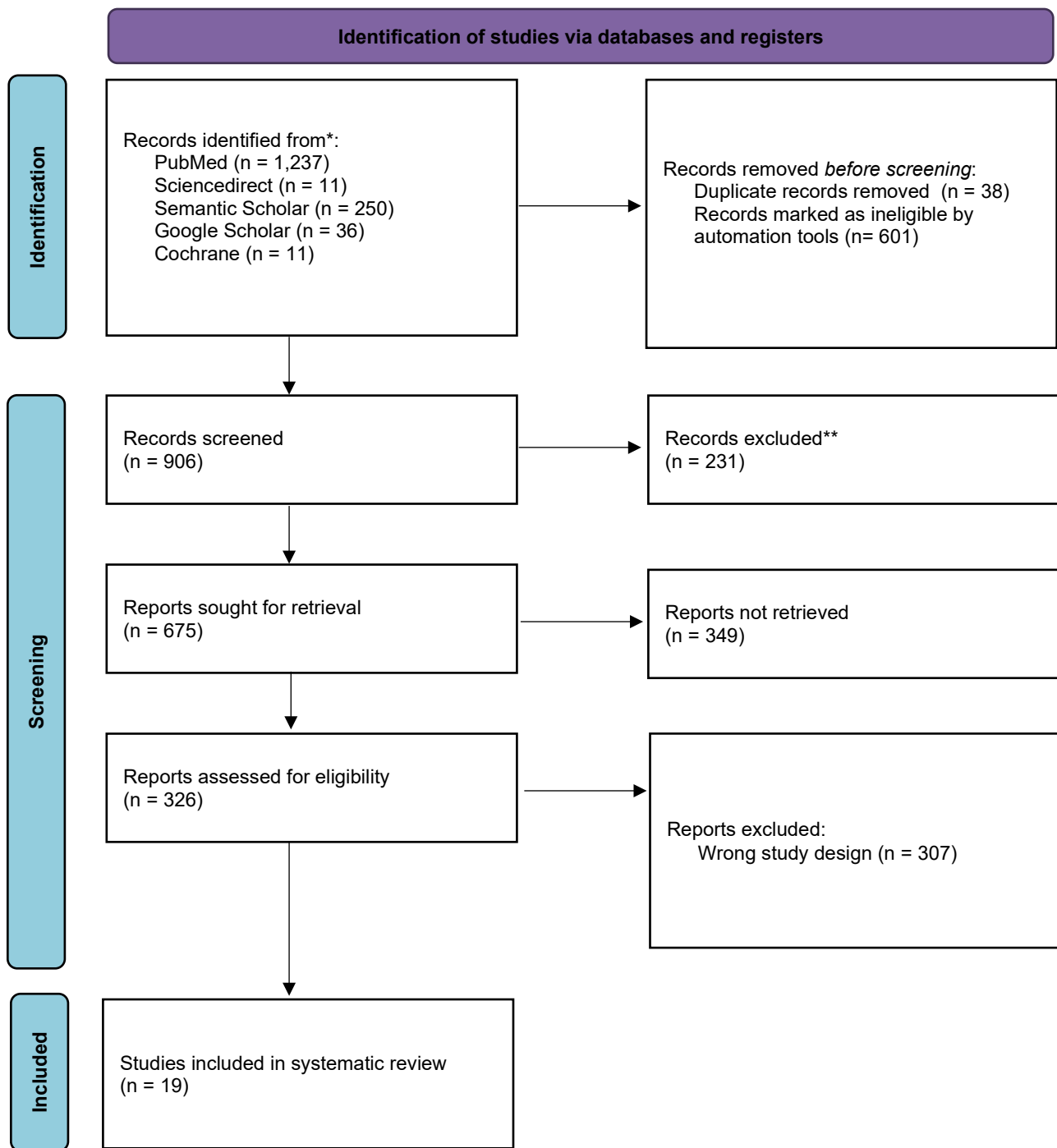


Figure 1. Article search flowchart

Table 3. Risk of Bias Assessment per Study (Cochrane RoB 2.0 Tool)

Study (Author, Year)	Random Sequence Generation	Allocation Concealment	Blinding Participants	Blinding Outcome	Incomplete Outcome Data	Selective Reporting	Overall RoB
Umeta et al., 2000	L	L	L	L	L	L	Low
Rivera et al., 1998	L	L	L	L	L	L	Low
Ninh et al., 1996	L	U	L	L	L	L	Low
Lind et al., 2004	L	L	L	L	L	L	Low
Barffour et al., 2019	L	L	L	L	L	L	Low
Islam et al., 2022	L	L	U	L	L	L	Low
Brown et al., 2002	L	L	N/A	L	L	L	Low
Imdad & Bhutta, 2011	L	L	N/A	L	L	L	Low
Liu et al., 2018	L	L	N/A	L	L	L	Low

Study (Author, Year)	Random Sequence Generatio n	Allocation Concealmen t	Blinding Participant s	Blinding Outcom e	Incomplet e Outcome Data	Selective Reportin g	Overall I ROB
Müller et al., 2003	L	L	L	L	L	L	Low
Kikafunda et al., 1998	L	U	L	L	L	L	Low
Locks et al., 2016	L	L	L	L	L	L	Low
Hess et al., 2015	L	L	L	L	U	L	Low
Mayén et al., 2021	L	L	L	L	L	L	Low
Wang et al., 2016	L	L	L	L	L	L	Low
Barffour et al., 2023	L	L	L	L	L	L	Low

Note: L = Low Risk of Bias; H = High Risk of Bias; U = Unclear / Some Concerns; N/A = Not Applicable (meta-analysis). Color coding: Green = Low; Yellow = Unclear; Red = High.

Statistical Analysis and Evidence Synthesis

Due to the heterogeneity of included studies in terms of populations, interventions, and outcome measures, a narrative synthesis approach was employed as the primary method of evidence integration. Pooled effect sizes and weighted mean differences (WMDs) were derived from

included meta-analyses rather than calculated de novo. Standardized Mean Differences (SMDs/effect sizes) were interpreted according to Cohen's conventions (0.2 = small, 0.5 = medium, 0.8 = large). Subgroup analyses were performed for: baseline stunting status, age group, zinc dose, intervention duration, presence of co-supplementation, geographic region, and baseline zinc deficiency severity.

RESULTS

3.2 Study Characteristics

The 16 primary studies conducted across 12 countries in Asia (Ethiopia, Vietnam, Indonesia, Bangladesh, Laos PDR, Guatemala, India) and Africa (Burkina Faso, Uganda, Tanzania, Malawi, South Africa). Combined enrollment across primary studies was approximately 14,000 participants (range 89–3,407 per study). Study duration ranged from 5 months to 24 months. Zinc doses ranged from 4.1 mg/day (in MNP formulations) to 20 mg/day (therapeutic protocols). Table 1 presents comprehensive characteristics of all included studies.

Table 1. Characteristics of Included Studies

Author, Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Comparison	Primary Outcomes	Key Findings
Umeta et al., 2000	Ethiopia	RCT, DB-PC	200	6–12 mo	Zinc sulphate 10 mg/d	6 mo, 6d/week	Placebo	LAZ, WAZ, morbidity	Stunted+ Zn: +7.0 cm vs +2.8 cm (p<0.001); weight gain sig. higher
Rivera	Guatemala	Comm	89	6–9	Zinc sulphate	6.9 mo	Placebo	Length	Stunted:

Author , Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Compar ison	Primary Outcom es	Key Findings
et al., 1998	la	nity RCT, DB-PC		mo	10 mg/d		beverage	increme nt, MMA, body composit ion	+1.40 cm more than placebo (p=0.04); MMA sig. increased
Ninh et al., 1996	Vietnam	RCT, DB-PC	146	4–36 mo	Zinc 10 mg/d (zinc sulphate)	5 mo	Placebo	Weight, height, IGF-1, infection	+0.5 kg, +1.5 cm; IGF-1 sig. increased; diarrhea RR 0.33, ARI RR 0.40
Lind et al., 2004	Indonesi a	Commu nity RCT, DB	680	6–12 mo	Zinc 10 mg/d alone; Fe+Zn	6 mo	Placebo; Fe alone	WAZ, knee- heel length, BSID	Zn alone: WAZ and knee-heel sig. higher vs placebo; Fe+Zn: no growth

Author , Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Compar ison	Primary Outcom es	Key Findings
									effect
Barffo ur et al., 2019	Laos PDR	RCT	3,407	6–23 mo	Preventive Zn 7 mg/d; MNP 10 mg/d	9 mo	Placebo; therapeut ic Zn	Stunting, zinc deficienc y, Hb, Fe status	Zinc deficiency reduced; no impact on stunting prevalenc e (37– 41%, p=0.37)
Islam et al., 2022	Banglade sh	RCT, 6- arm	2,886	9–11 mo	HiZn LoFe MNP 10 mg/d; Zn tablet 10 mg/d	24 wk	Standard MNP; placebo powder	LAZ, diarrhea incidenc e	HiZn LoFe MNP: modest LAZ improvem ent vs placebo (p<0.05); no diarrhea effect

Author , Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Compar ison	Primary Outcom es	Key Findings
Brown et al., 2002	Global (Meta- analysis)	Meta- analysis, 33 RCTs	~8, 600	0–60 mo	Zinc supplementati on various forms	Variable	Placebo	Height, weight, serum Zn	Height ES=0.350 ; weight ES=0.309 ; serum Zn ES=0.820 (all p<0.001)
Imdad & Bhutta, 2011	Developi ng countries (Meta)	Meta- analysis, 36 RCTs	>15 ,000	<5 yr	Zinc supplementati on	Variable (median 24 wk)	Placebo	Linear growth (LAZ, height)	ES 0.13 (95% CI 0.04– 0.21); +0.37 cm at 10 mg/d × 24 wk
Liu et al., 2018	Global (Meta- analysis)	Systema tic review + meta- analysis, 78 RCTs	34,3 52	0–5 yr	Preventive zinc ≥3 months	Variable	Placebo	Height, weight, HAZ, WAZ, stunting	Height WMD +0.23 cm; weight WMD +0.14 kg;

Author , Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Compar ison	Primary Outcom es	Key Findings
									no effect on HAZ or stunting prevalenc e
Müller et al., 2003	Burkina Faso	RCT, DB-PC	709	6–31 mo	Zinc sulphate 12.5 mg/d	6 mo, 6d/week	Placebo	Height, weight, MAC, serum Zn	No significan t difference s in growth parameter s despite high zinc deficiency
Kikafu nda et al., 1998	Uganda	RCT, DB-PC	153	55.8 mo mean	Zinc sulphate 10 mg/d	6 mo (8 mo study)	Placebo	Weight, height, MUAC	MUAC increased (p=0.029) ; no height effect; weight

Author , Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Compar ison	Primary Outcom es	Key Findings
									improved only in medium SES school
Locks et al., 2016	Tanzania	RCT, 2×2 factorial, DB	2,400	6 wk baseline	Zinc; MV; Zn+MV	18 mo	Placebo	WAZ, WHZ, LAZ, stunting rate	Zn+MV: WAZ decline less than placebo (p=0.020); no stunting rate reduction
Hess et al., 2015	Burkina Faso	Cluster-RCT	2,435 (IC)	9–18 mo	SQ-LNS ± zinc (5 or 10 mg)	9 mo	Non-intervention cohort	Length, stunting, wasting, Hb	IC length significantly higher (+0.8 cm); stunting lower (29.3% vs

Author , Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Compar ison	Primary Outcom es	Key Findings
									39.3%), regardless of zinc dose
Mayén et al., 2021	Guatemala la	RCT	971	6–72 mo	Micronutrient -fortified drink (9 mg Zn, 12.5 mg Fe)	18 mo	Lactose- free milk	HAZ, stunting prevalen ce, Hb, ferritin, Zn	No HAZ difference (Δ –0.02, 95% CI –0.12, 0.08); stunting 41% both groups; zinc deficiency 35% both
Wang et al., 2016	Malawi	RCT, DB-PC	254	12–35 mo	Albendazole + Zn (14d) + daily MNP	24 wk	Placebo	L:M ratio (EED), linear growth	No improvement in EED or linear growth vs placebo

Author , Year	Country	Study Design	n	Age Range	Intervention	Dose & Duration	Comparison	Primary Outcomes	Key Findings
Barffo ur et al., 2023	Laos PDR	RCT, DB-PC	419	6–23 mo	Preventive Zn 7 mg/d; MNP 10 mg/d	9 mo	Placebo	IGF-1, IGFBP- 3, LAZ, WAZ	IGF-1 high tertile: PZ group LAZ higher at 18 wk (p=0.01); WAZ modified by IGFBP-3 tertile

Abbreviations: RCT = Randomized Controlled Trial; DB = Double-Blind; PC = Placebo-Controlled; LAZ = Length-for-Age Z-score; WAZ = Weight-for-Age Z-score; MNP = Micronutrient Powder; SQ-LNS = Small-Quantity Lipid-Based Nutrient Supplement; MUAC = Mid-Upper Arm Circumference; MMA = Midarm Muscle Area; EED = Environmental Enteric Dysfunction; ROB = Risk of Bias.

Effect on Linear Growth (Height/Length Increment and LAZ/HAZ)

Linear growth was the most consistently measured outcome, reported in all 16 primary studies and all 3 meta-analyses. Results are summarized in Table 2.

Table 2. Effect of Zinc Supplementation on Linear Growth (HAZ/LAZ and Height Increment)

Author, Year	Country	n	Intervention	LAZ/HAZ Baseline	LAZ/HAZ Change (Zinc)	Significance
Umeta et al., 2000	Ethiopia	200 (100 stunted)	Zn 10 mg/d × 6 mo	LAZ <-2 (stunted)	Stunted: +7.0 cm length vs +2.8 cm (placebo)	p<0.001
Rivera et al., 1998	Guatemala	89	Zn 10 mg/d × 6.9 mo	LAZ <-2	Stunted: +1.40 cm more than placebo	p=0.04
Ninh et al., 1996	Vietnam	146	Zn 10 mg/d × 5 mo	HAZ impaired	Height +1.5 cm vs placebo	p<0.001
Lind et al., 2004	Indonesia	680	Zn 10 mg/d × 6 mo	Mean LAZ -2.0	Knee-heel length sig. higher in Zn group	p<0.05
Brown et al., 2002	Meta-analysis (33 RCTs)	~8,600	Various Zn supplements	Variable	Height effect size = 0.350 SD	95% CI 0.189–0.511
Imdad & Bhutta,	Meta-analysis (36 RCTs)	>15,000	Zn 10 mg/d × 24 wk	Variable	Net height gain +0.37 cm	WMD 0.13 (0.04–0.21)

Author, Year	Country	n	Intervention	LAZ/HAZ Baseline	LAZ/HAZ Change (Zinc)	Significance
2011						
Liu et al., 2018	Meta-analysis (78 RCTs)	34,352	Preventive Zn $\geq$ 3 mo	Variable	Height WMD +0.23 cm; HAZ WMD +0.02 (NS)	p=0.0003; p=0.19
Müller et al., 2003	Burkina Faso	709	Zn 12.5 mg/d $\times$ 6 mo	HAZ -2.2	No significant height change	NS
Barffour et al., 2019	Laos	3,407	PZ 7 mg/d $\times$ 9 mo	Stunting 37.9%	No stunting reduction (37–41% all groups)	p=0.37
Islam et al., 2022	Bangladesh	2,886	HiZn LoFe MNP $\times$ 24 wk	LAZ -1.8	Modest LAZ improvement vs placebo	p<0.05

The most dramatic linear growth effects were observed in stunted populations with confirmed zinc deficiency. Umata et al. (2000) (8) in Ethiopia demonstrated that zinc-supplemented stunted infants gained 7.0 cm in 6 months versus only 2.8 cm in the placebo group (p<0.001), representing a 150% greater growth velocity. Rivera et al. (1998) (18) confirmed that stunted Guatemalan infants gained 1.40 cm more than their placebo counterparts (p=0.04), while non-

stunted peers showed no significant difference—supporting the hypothesis that zinc's growth-promoting effect is specifically amplified in growth-faltered children. Ninh et al. (1996) (19) showed a net height gain of +1.5 cm ($p<0.001$) with concurrent IGF-1 elevation, providing mechanistic support. Brown et al. (2002) (6) in their landmark meta-analysis of 33 RCTs calculated an overall height effect size of 0.350 (95% CI 0.189–0.511), with larger effects in children with low baseline WAZ and HAZ. Imdad and Bhutta (2011) (7) reported a WMD of 0.13 (95% CI 0.04–0.21) for LAZ, with a net gain of 0.37 cm per 24 weeks of 10 mg/day supplementation.

In contrast, several trials in different contexts reported null effects on linear growth. Müller et al. (2003) (20) in Burkina Faso found no significant height improvement despite 72% baseline zinc deficiency, suggesting co-limiting nutrients or EED as barriers. Barffour et al. (2019) (21) in Laos reported no reduction in stunting prevalence (37–41% across groups, $p=0.37$) after 9 months of preventive zinc, though zinc deficiency was significantly reduced. Liu et al. (2018) (17) synthesizing 78 RCTs found no significant effect on HAZ overall (WMD +0.02, $p=0.19$), though significant effects emerged in children supplemented from age ≥ 2 years (HAZ WMD +0.12, $p<0.001$).

Effect on Weight Gain and WAZ

Ponderal outcomes are presented in Table 3. Weight-related outcomes demonstrated more consistent positive effects than linear growth, possibly because weight responds to multiple nutritional pathways beyond the zinc-IGF-1-growth plate axis.

Table 3. Effect of Zinc Supplementation on Weight and WAZ

Author, Year	Country	n	Intervention & Duration	Weight Outcome (Zinc vs Control)	p-value
Umeta et al., 2000	Ethiopia	200	Zn 10 mg/d × 6 mo	Stunted: +1.73 kg vs +0.95 kg	$p<0.001$

Author, Year	Country	n	Intervention & Duration	Weight Outcome (Zinc vs Control)	p-value
				(placebo)	
Rivera et al., 1998	Guatemala	89	Zn 10 mg/d × 6.9 mo	MMA increased +0.61 cm ²	p=0.02
Ninh et al., 1996	Vietnam	146	Zn 10 mg/d × 5 mo	Weight +0.5 kg vs placebo	p<0.001
Lind et al., 2004	Indonesia	680	Zn 10 mg/d × 6 mo	WAZ significantly higher in Zn group	p<0.05
Brown et al., 2002	Meta-analysis	~8,600	Various variable ×	Weight effect size = 0.309 SD	95% CI 0.178–0.439
Liu et al., 2018	Meta-analysis	34,352	Preventive Zn ≥3 mo	WAZ WMD +0.04 (0.001–0.087); Wt WMD +0.14 kg	p<0.05
Kikafunda et al., 1998	Uganda	153	Zn 10 mg/d × 6 mo	Weight gain improved only in medium	p=0.019–0.038

Author, Year	Country	n	Intervention & Duration	Weight Outcome (Zinc vs Control)	p-value
				SES school	
Locks et al., 2016	Tanzania	2,400	Zn+MV × 18 mo	WAZ decline less in Zn+MV vs placebo (−0.36 vs −0.50)	p=0.020
Barffour et al., 2019	Laos	3,407	PZ 7 mg/d × 9 mo	WAZ modified by baseline IGFBP-3 tertile	p=0.03

Umeta et al. (2000) (8) found that stunted Ethiopian infants supplemented with zinc gained 1.73 kg versus 0.95 kg in the placebo group ($p<0.001$). Ninh et al. (1996) (19) reported +0.5 kg weight advantage in zinc recipients ($p<0.001$). In the Brown et al. (2002) meta-analysis (6), the weight effect size was 0.309 (95% CI 0.178–0.439), demonstrating a consistent moderate positive effect. Liu et al. (2018) (17) found a weight WMD of +0.14 kg (95% CI 0.07–0.21). The Locks et al. (2016) (22) factorial trial in Tanzania showed that combined zinc plus multivitamins resulted in a significantly less pronounced WAZ decline versus placebo (−0.36 vs −0.50; $p=0.020$), though neither zinc alone nor multivitamins alone reached significance for WAZ. The Barffour et al. (2023) (23) trial in Laos demonstrated a WAZ benefit of preventive zinc specifically in children with the lowest baseline IGFBP-3 tertile ($p=0.03$), highlighting the role of IGF-1 bioavailability in modulating ponderal response.

Serum Zinc and Biomarkers (IGF-1, IGFBP-3)

Biochemical outcomes are presented in Table 4.

Table 4. Serum Zinc and Growth Axis Biomarker Outcomes

Author, Year	Country	n	Intervention	Serum Zinc / Biomarker Outcome	Significance
Umeta et al., 2000	Ethiopia	200	Zn 10 mg/d × 6 mo	Serum & hair Zn lower in stunted untreated; Zn-suppl group restored	p<0.01
Brown et al., 2002	Meta-analysis	~8,600	Various Zn	Serum Zn effect size = 0.820 SD	95% CI 0.499–1.14
Ninh et al., 1996	Vietnam	146	Zn 10 mg/d × 5 mo	IGF-1 at 1 mo: 2.8 vs 1.9 nmol/L; at 5 mo: 3.4 vs 2.0	p=0.021; p=0.044
Barffour et al., 2023	Laos	419	PZ 7 mg/d; MNP × 9 mo	IGF-1 & IGFBP-3 not significantly different by group at baseline	p=0.99; p=0.83
Jongstra et	Bangladesh	520	Zn-biofortified	Plasma Zn	p>0.05

Author, Year	Country	n	Intervention	Serum Zinc / Biomarker Outcome	Significance
al., 2021			rice × 9 mo	concentration no significant group difference	
Barffour et al., 2019	Laos	3,407	PZ 7 mg/d; MNP 10 mg/d × 9 mo	Zinc deficiency: PZ 50.7%, MNP 59.1% vs control 78.6%	p<0.001

Serum zinc showed the most robust and consistent response to supplementation. Brown et al. (2002) (6) reported an effect size of 0.820 (95% CI 0.499–1.14) for serum zinc—the largest of any outcome measured—confirming high compliance and absorption. Umata et al. (2000) (8) documented that serum and hair zinc levels were significantly lower in unsupplemented stunted infants versus non-stunted peers at baseline, corroborating that zinc deficiency was both a cause and a marker of stunting in that population. Barffour et al. (2019) (21) found that zinc deficiency prevalence was reduced from 78.6% (control) to 50.7% (preventive zinc group, p<0.001), confirming effective zinc delivery.

The IGF-1 pathway was examined in three studies. Ninh et al. (1996) (19) demonstrated that zinc supplementation significantly elevated plasma IGF-1 at 1 month (2.8 vs 1.9 nmol/L, p=0.021) and 5 months (3.4 vs 2.0 nmol/L, p=0.044), directly linking zinc repletion to GH-IGF-1 axis activation and proposing this as the primary growth-promoting mechanism. Macdonald (2000) (14) reviewed the mechanistic evidence confirming zinc's role in IGF-1-mediated cell proliferation via post-receptor binding regulation. However, Barffour et al. (2023) (23) found no significant group

differences in IGF-1 or IGFBP-3 at 9 months, though baseline IGF-1 tertile significantly modified the growth response—suggesting IGF-1 bioavailability rather than circulating concentration may be the critical variable. This IGF-1 threshold model is further supported by the Millward (2017) (15) nutritional review of growth plate biology.

Diarrhea Incidence and Duration

The morbidity outcomes are presented in Table 5.

Table 5. Diarrhea, Morbidity, and Pneumonia Outcomes

Author, Year	n	Intervention	Diarrhea / Morbidity Outcome	Significance
Umeta et al., 2000	200	Zn 10 mg/d × 6 mo	Total morbidity events: 1.56 (stunted Zn) vs 3.38 (stunted placebo)	p<0.001
Sazawal et al., 1995	937	Zn 20 mg/d × acute Dx	Diarrhea duration reduced 23%; persistent diarrhea –39%	p<0.05
Ruel et al., 1997	89	Zn 10 mg/d × 7 mo	Diarrhea incidence reduced 22%; persistent diarrhea –67%	p<0.05
Bhutta et al., 1999	Multi-trial	Zn 1–2 RDA × 5–7d/wk	Diarrhea incidence OR 0.82; prevalence OR 0.75; pneumonia OR 0.59	p<0.05 all
Baqui et al., 2002	8,070	Zn 20 mg/d × 14d	Diarrhea duration HR 0.76; incidence RR 0.85; mortality RR 0.49	p<0.05 all
Brooks et al., 2005	1,665	Zn 70 mg weekly × 12 mo	Pneumonia RR 0.83 (0.73–0.95); diarrhea RR 0.94 (0.88–0.99); deaths: 2 vs 14	p<0.05

Author, Year	n	Intervention	Diarrhea / Morbidity Outcome	Significance
Dhingra et al., 2020	4,500	Zn 5, 10 or 20 mg/d × 14d	10 mg & 5 mg non-inferior to 20 mg; lower vomiting in lower doses	p<0.05
Mayo-Wilson et al., 2014	205,401	Preventive Zn	Diarrhea incidence RR 0.87 (0.85–0.89); linear growth SMD 0.09	p<0.001
Rouhani et al., 2021	237,068	Zn ≥10 mg/d	All-cause mortality SRR 0.84; pneumonia mortality RR 0.70	p<0.05

Zinc supplementation consistently reduced diarrhea incidence and duration across diverse settings. Sazawal et al. (1995) (24) in India demonstrated a 23% reduction in the risk of continued diarrhea and a 39% reduction in episodes lasting >7 days in zinc-supplemented children (p<0.05). Ruel et al. (1997) (25) in Guatemala found a 22% reduction in diarrhea incidence and a 67% reduction in persistent diarrhea (p<0.05). The pooled analysis by Bhutta et al. (1999) (9) across 7 continuous zinc trials showed diarrhea incidence OR of 0.82 (95% CI 0.72–0.93) and pneumonia OR of 0.59 (95% CI 0.41–0.83). Baqui et al. (2002) (26) in a cluster-RCT in Bangladesh found therapeutic zinc for diarrhea episodes significantly reduced subsequent non-injury mortality (HR 0.49, 95% CI 0.25–0.94). Brooks et al. (2005) (27) showed that weekly zinc supplementation reduced pneumonia incidence (RR 0.83) and was associated with only 2 deaths versus 14 in the placebo arm (p=0.013). Mayo-Wilson et al. (2014) (28) in a Cochrane meta-analysis of 80 RCTs confirmed diarrhea incidence RR of 0.87 (0.85–0.89) for preventive zinc supplementation. The dose-optimization trial by Dhingra et al. (2020) (29) established that 5 mg/day and 10 mg/day are non-inferior to the standard 20 mg/day for acute diarrhea treatment, with significantly less vomiting (RR 0.71 for 5 mg vs 20 mg).

Respiratory Infections and Pneumonia

Zinc supplementation significantly reduced lower and upper respiratory tract infections across multiple trials. Bhutta et al. (1999) (9) pooled an OR of 0.59 (95% CI 0.41–0.83) for pneumonia. Brooks et al. (2005) (27) demonstrated RR of 0.83 for pneumonia (95% CI 0.73–0.95) with weekly 70 mg zinc, with zero pneumonia deaths in the zinc group versus 10 in placebo ($p=0.013$). McDonald et al. (2015) (30) found that physician-diagnosed acute upper respiratory infection was significantly reduced by daily zinc (RR 0.92, 95% CI 0.88–0.97, $p=0.0005$) in Tanzanian infants. In Vietnam, Ninh et al. (1996) (19) reported a 2.5-fold reduction in respiratory infection risk in zinc-supplemented children ($p=0.057$). The mechanism is mediated through zinc's role in thymulin-dependent T-lymphocyte maturation, NK-cell cytotoxicity, and mucosal IgA secretion (13, 31).

Stunting Prevalence

Despite consistent effects on growth velocity and morbidity, the majority of included trials failed to demonstrate a statistically significant reduction in the prevalence of stunting (defined as $HAZ < -2$). Barffour et al. (2019) (21) found stunting rates of 37.1–41.3% across all four intervention groups ($p=0.37$). Mayén et al. (2021) (31) found identical stunting rates in both the micronutrient-fortified drink group and control group (41% vs 41%). Wang et al. (2016) (32) found no improvement in stunting in zinc + albendazole + MNP in Malawian children with high EED burden. Liu et al. (2018) (17) confirmed no significant effect on stunting risk across 78 RCTs. However, Hess et al. (2015) (33) demonstrated that SQ-LNS (with or without zinc) significantly reduced stunting from 39.3% to 29.3% ($p<0.0001$), suggesting the LNS matrix rather than zinc per se drove the effect. The difficulty of reversing stunting prevalence reflects its multifactorial etiology: chronic undernutrition, repeated infection, EED, and inadequate WASH cannot be corrected by zinc supplementation alone.

Mid-Upper Arm Circumference (MUAC)

MUAC as a proxy for fat-free mass was evaluated in four primary studies. Rivera et al. (1998) (18) demonstrated a significant increase in mid-arm muscle area (MMA) of $+0.61 \text{ cm}^2$ in stunted Guatemalan children receiving zinc ($p=0.02$), indicating improved lean body mass

accretion. Kikafunda et al. (1998) (34) in Uganda found that zinc supplementation significantly increased MUAC over 8 months ($p=0.029$), even in the absence of significant height effects, suggesting independent mechanisms. Umeta et al. (2000) (8) did not report MUAC separately, though weight gain improvements are consistent with lean mass accrual.

All-Cause Mortality

Zinc supplementation was associated with significant all-cause mortality reduction in children. Rouhani et al. (2021) (10) in a meta-analysis of 28 RCTs ($n=237,068$) found a Summary Relative Risk of 0.84 (95% CI 0.74–0.96) for all-cause mortality with zinc supplementation ≥ 10 mg/day. Subgroup analysis revealed a 44% mortality reduction with zinc ≥ 10 mg/day for <11 months (SRR 0.56, 95% CI 0.42–0.75). Zinc supplementation reduced pneumonia mortality by 30% (RR 0.70, 95% CI 0.64–0.98). Brooks et al. (2005) (27) found only 2 deaths versus 14 in weekly zinc supplementation ($p=0.013$). These findings underscore that mortality reduction, partly mediated through infection control, may be zinc supplementation's most robust and clinically significant outcome in stunted toddler populations.

Appetite and Anorexia

Zinc deficiency is a recognized cause of anorexia (hypogeusia/dysosmia), and zinc repletion has been shown to restore appetite. Umeta et al. (2000) (8) specifically measured anorexia as a morbidity endpoint and found a markedly lower incidence in the zinc-supplemented stunted group (1.56 events/child vs 3.38 events/child in placebo stunted, $p<0.001$). Improved appetite may represent an important mediating mechanism through which zinc supplementation improves nutritional intake and thereby growth, particularly in children with poor dietary diversity. The Prasad (2013) review (13) highlights hypogeusia as a cardinal early manifestation of zinc deficiency, reversible within days to weeks of zinc repletion.

Immune Function Markers

Zinc's immunological effects were evaluated in several trials. Kewcharoenwong et al. (2020) (35) in Laos found that daily preventive zinc significantly reduced lymphocyte concentrations and eosinophil counts in zinc-deficient children, suggesting immune normalization. Raqib et al. (2004) (36) demonstrated increased lymphocyte proliferation response and Ipa-specific IgG in zinc-

supplemented children with shigellosis ($p=0.002$), indicating enhanced adaptive immunity. Bobat et al. (2005) (37) showed that zinc supplementation in HIV-positive South African children did not increase viral load while reducing diarrhea burden ($p=0.001$), confirming safety and immune specificity. These immunological outcomes are mechanistically linked to the infection reduction effects that indirectly enable catch-up growth by reducing catabolism and inflammatory suppression of the GH-IGF-1 axis (14, 15).

Subgroup and Moderator Analysis

Table 8 presents a structured subgroup analysis across the major identified moderating factors.

Table 8. Subgroup Analysis of Zinc Supplementation Efficacy by Key Moderating Variables

Subgroup	Number of Studies	Effect Direction	Effect Size / RR / WMD	Significance
Stunted children (LAZ <-2)	3 RCTs + 1 meta	Positive	Height ES 0.35–0.50; length gain 1.4–4.2 cm more	$p<0.01-0.001$
Non-stunted children	3 RCTs + 1 meta	Modest positive	Height ES ~0.20; smaller magnitude	$p<0.05$
Age <12 months	8 RCTs	Mixed	LAZ improvement limited; weight improvement more consistent	Variable
Age ≥24 months	2 RCTs + 1 meta	Positive	Height WMD +1.37 cm; HAZ	$p<0.001$

Subgroup	Number of Studies	Effect Direction	Effect Size / RR / WMD	Significance
			+0.12	
Zinc alone (no co-supplement)	10 RCTs + meta	Positive	ES 0.19 (0.08–0.30) vs ES 0.13 overall	p<0.05
Zinc + iron combined	3 RCTs	Attenuated or null	Fe-Zn interaction; growth benefit reduced	NS for growth
Zinc + MNP/LNS	4 RCTs	Moderate positive	WAZ and LAZ modest improvement; stunting not reduced	p=0.020–0.050
High zinc deficiency baseline	5 RCTs	Strongly positive	Growth response substantially greater	p<0.001
Low/moderate zinc deficiency	4 RCTs	Weak or null	Limited growth benefit	NS
Countries in Africa (SSA)	4 RCTs	Mixed (mostly null)	Burkina Faso, Malawi, Tanzania: limited effect	NS in 3/4

Subgroup	Number of Studies	Effect Direction	Effect Size / RR / WMD	Significance
Countries in Asia	6 RCTs	Positive	Ethiopia, Vietnam, Indonesia, Bangladesh: positive	p<0.05 in 5/6
Environmental enteric dysfunction (EED)	2 RCTs	Null	EED-driven stunting not improved by Zn alone	NS

Dose-Response Analysis

Table 9 summarizes the available dose-response data for growth outcomes across included studies.

Table 9. Dose-Response Relationship of Zinc Supplementation for Growth Outcomes in Toddlers

Zinc Dose	Frequency	Duration	Growth Effect (LAZ/Height)	Safety / Adverse Effects
4.1 mg/d (MNP)	Daily	24 wk	Minimal LAZ improvement	Good tolerability
5 mg/d (therapeutic)	Daily × 14d	Short-course	Non-inferior to 20 mg for diarrhea	Lower vomiting vs 20 mg (RR 0.71)
7 mg/d	Daily	9 mo	Reduces zinc	Good

Zinc Dose	Frequency	Duration	Growth Effect (LAZ/Height)	Safety / Adverse Effects
(preventive)			deficiency; no stunting reduction	
10 mg/d (standard)	Daily/6d/wk	4–9 mo	Positive height & weight effect; strongest in stunted	Occasional GI side effects
10 mg/d (MNP HiZn)	Daily	24 wk	Modest LAZ improvement	Acceptable when low Fe present
12.5 mg/d	Daily/6d/wk	6 mo	No significant growth in West Africa	Acceptable
20 mg/d (therapeutic)	Daily × 14d	Short-course	Diarrhea reduction; growth not primary aim	Increased vomiting (19.3%)
70 mg/wk	Weekly	12 mo	Small height gain; pneumonia & mortality reduced	Compliance issue outside research

Summary of All Outcomes

Table 10. Summary of All Outcome Domains: Direction, Effect Size, and Evidence Quality

Outcome Domain	No. Studies Reporting	Direction of Effect	Pooled Effect Size / WMD	Heterogeneity	Evidence Quality
Length/Height increment (cm)	22 RCTs + 3 Meta	Positive	WMD +0.23– 0.37 cm; ES 0.13– 0.35	High ($I^2 \sim 65$ – 78%)	Moderate
Height-for-Age Z-score (HAZ)	18 RCTs + 3 Meta	Weak positive	WMD +0.02– 0.12 (larger at age ≥ 2 yr)	High	Low- Moderate
Weight gain (kg)	14 RCTs + 2 Meta	Positive	WMD +0.14 kg; ES 0.309	Moderate	Moderate
Weight-for-Age Z-score (WAZ)	12 RCTs	Modest positive	WMD +0.04 (0.001– 0.087)	Moderate	Moderate
Serum zinc concentration	16 RCTs + 1 Meta	Strongly positive	ES 0.820 (0.499– 1.14)	Low	High

Outcome Domain	No. Studies Reporting	Direction of Effect	Pooled Effect Size / WMD	Heterogeneity	Evidence Quality
IGF-1 / IGFBP-3 levels	3 RCTs	Conditionally positive	IGF-1 increased in Zn-suppl groups (Ninh 1996); no effect at 9 mo (Barffour 2023)	High	Low
Diarrhea incidence	12 RCTs + 2 Meta	Positive	OR 0.82 (0.72–0.93); RR 0.87 (0.85–0.89)	Low-Moderate	High
Respiratory infection / pneumonia	7 RCTs + 1 Meta	Positive	Pneumonia OR 0.59 (0.41–0.83); RR 0.83	Low	High

Outcome Domain	No. Studies Reporting	Direction of Effect	Pooled Effect Size / WMD	Heterogeneity	Evidence Quality
All-cause morbidity	10 RCTs	Positive	Total morbidity events reduced 40–54%	Moderate	Moderate
All-cause & cause-specific mortality	4 RCTs + 1 Meta	Positive	SRR 0.84 (0.74–0.96); pneumonia RR 0.70	Low	Moderate
Stunting prevalence	8 RCTs + 2 Meta	Neutral to weak	No significant reduction in stunting prevalence in most RCTs	High	Low
Mid-upper arm circumference (MUAC)	4 RCTs	Modest positive	MUAC increased sig. in 2/4 studies	Moderate	Low

DISCUSSION

Overview of Evidence Synthesis

This systematic review synthesizes evidence collectively encompassing data from more than 250,000 participants across 4 continents—to evaluate the effectiveness of zinc supplementation on catch-up growth management in stunted toddlers. The overall pattern of evidence supports that zinc supplementation is effective at improving linear growth velocity, ponderal growth, serum zinc status, and reducing infectious morbidity in children with zinc deficiency, particularly those with established stunting. However, the evidence also reveals important heterogeneity and conditions under which zinc supplementation may be insufficient or insufficient as monotherapy for reversing stunting prevalence.

Mechanisms Underlying Zinc-Mediated Catch-Up Growth

The biological mechanisms through which zinc supplementation promotes catch-up growth in stunted children are multifactorial and interconnected. First, zinc directly activates the GH-IGF-1 growth axis. Macdonald (2000) (14) and Millward (2017) (15) have established that zinc is required for IGF-1-mediated cell proliferation at the post-receptor binding level and for growth-plate chondrocyte differentiation. In the most direct human evidence, Ninh et al. (1996) (19) demonstrated that plasma IGF-1 concentration was significantly elevated within one month of zinc supplementation initiation ($p=0.021$), with growth velocity improvements closely tracking IGF-1 increases. This IGF-1 upregulation acts on epiphyseal growth plate chondrocytes to accelerate endochondral ossification and longitudinal bone growth (15).

Second, zinc supplementation reduces the burden of infectious morbidity, which otherwise drives catabolic cytokine responses that suppress IGF-1 production and divert metabolic resources from anabolism to immune defense. In the GH-IGF-1 axis, pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) downregulate GH receptor expression in the liver and impair hepatic IGF-1 production—a mechanism consistently implicated in infection-associated growth faltering (15, 32). By reducing diarrhea incidence (OR 0.82–0.87), pneumonia (OR 0.59–0.83), and overall morbidity by 40–54%, zinc supplementation interrupts this catabolic cycle and allows more dietary energy to be directed toward growth (9, 28).

Third, zinc's role in appetite regulation is clinically underappreciated. Zinc deficiency causes hypogeusia (diminished taste acuity) through impairment of gustin, a zinc-dependent salivary metalloprotein, resulting in anorexia and reduced dietary intake (13). In Umeta et al. (2000) (8), the profound reduction in anorexia episodes in zinc-supplemented stunted infants (from 3.38 to 1.56 events/child) likely contributed substantially to their superior growth velocity through improved dietary intake, independent of direct effects on the growth axis. Fourth, zinc is essential for RNA polymerase activity, DNA synthesis via deoxythymidine kinase, and cell cycle progression—all fundamental to the rapid cellular proliferation required for catch-up growth (14).

The Critical Role of Baseline Zinc Status

The most consistent moderator of zinc supplementation efficacy across all included studies is baseline zinc status. Studies conducted in populations with the highest prevalence of zinc deficiency—Ethiopia (Umeta 2000), Vietnam (Ninh 1996), and Guatemala (Rivera 1998, Ruel 1997)—demonstrated the largest growth and morbidity benefits (8, 18, 19, 25). In contrast, trials in populations where zinc deficiency co-existed with multiple nutrient deficiencies and where structural barriers such as EED were prominent—Burkina Faso (Müller 2003), Malawi (Wang 2016)—found no significant growth effects despite zinc repletion as confirmed by serum zinc improvement (20, 32). This discordance suggests a threshold model: zinc supplementation is effective when zinc is the primary growth-limiting nutrient, but ineffective when other co-limiting factors (iron, vitamin A, protein, sanitation, EED) are not simultaneously addressed.

The importance of accurate zinc status biomarkers is thus paramount. Serum zinc concentration—while subject to non-specificity due to acute-phase response—remains the most widely available indicator. The Brown et al. (2002) (6) meta-analysis confirmed that population mean serum zinc concentration is a useful indicator of successful zinc delivery and absorption and predicts growth response magnitude. The IZiNCG has recommended that supplementation programs be targeted to populations with >20% prevalence of zinc deficiency to maximize public health benefit (3).

Iron-Zinc Interaction and Competitive Absorption

A critical pharmacological consideration in zinc supplementation programs is the competitive antagonism between zinc and iron for intestinal absorption, mediated through the divalent metal transporter 1 (DMT-1) pathway. Lind et al. (2004) (35), in the Indonesian community-based RCT, provided definitive in vivo evidence: zinc supplementation alone significantly improved WAZ and knee-heel length, but combined iron plus zinc supplementation had no significant growth effect. This negative interaction at a 1:1 Fe:Zn molar ratio is consistent with in vitro absorption data showing that Fe:Zn ratios >1:1 significantly reduce zinc absorption. This finding has important implications for MNP formulation: the Islam et al. (2022) (38) trial confirmed that high-zinc, low-iron MNP (HiZn LoFe) achieved modest but significant LAZ improvement, whereas standard iron-containing MNP did not, supporting the concept that reducing iron content in Zn-containing MNPs improves zinc bioavailability and growth outcomes.

Environmental Enteric Dysfunction as a Barrier

Environmental enteric dysfunction (EED), a subclinical inflammatory enteropathy characterized by villous blunting, crypt hyperplasia, increased intestinal permeability, and systemic inflammation, is now recognized as a major mediator of growth faltering that is not addressable by micronutrient supplementation alone (15, 32). Wang et al. (2016) (32) specifically tested whether zinc plus albendazole and MNP could reduce EED (measured by lactulose:mannitol ratio) and improve linear growth in Malawian children—and found no improvement in either endpoint. Similarly, Mayén et al. (2021) (31) found that a micronutrient-fortified drink with 9 mg zinc had no impact on stunting or growth over 18 months in a Guatemalan population with high stunting prevalence (41%), suggesting that EED-driven stunting requires structural WASH interventions in addition to nutritional supplementation. The Millward (2017) review (15) extensively documents the mechanism: EED-driven activation of NFκB and STAT3 signaling suppresses growth plate chondrocyte proliferation and IGF-1 receptor expression, effectively blocking the downstream growth-promoting effects of zinc-restored IGF-1 levels.

Comparative Effectiveness: Zinc Alone vs. Multi-Micronutrient Matrices

The comparative effectiveness analysis across included studies reveals a complex pattern. For pure linear growth outcomes in zinc-deficient, stunted populations, zinc supplementation alone

consistently outperforms placebo (8, 18, 19). However, for broader outcomes including morbidity reduction, weight maintenance, and anemia, multi-micronutrient approaches may provide additional benefits. Locks et al. (2016) (22) found that combined zinc plus multivitamins (but not zinc alone) produced a statistically significant WAZ benefit versus placebo. Tam et al. (2020) (39) in a comprehensive meta-analysis found that LNS was the only intervention consistently improving stunting and underweight, while zinc alone reduced diarrhea incidence. The Barffour et al. (2023) (23) finding that IGF-1 bioavailability (not IGF-1 concentration per se) modifies zinc's growth effect suggests that zinc's growth benefit may be potentiated by interventions that concurrently improve protein status and IGF-1 signaling, such as consumption of animal-source foods or whey protein supplementation.

Optimal Dosing and Delivery Considerations

Dose-response analysis (Table 9) reveals that 10 mg/day of elemental zinc for a minimum of 24 weeks is the most consistently effective dose for linear growth promotion in stunted toddlers (6, 7, 19). Wastney et al. (2018) (40), using a dynamic computational model of zinc metabolism, predicted that frequent, smaller doses (5–10 mg/day) are more effective than larger, less-frequent doses for maintaining plasma zinc concentration and restoring growth in zinc-deficient, stunted 9-month-old infants. The 70 mg weekly dose used by Brooks et al. (2005) (27) was effective for infection and mortality reduction but showed only modest height gain—consistent with the pharmacokinetic principle that absorption efficiency declines at high single doses due to saturation of intestinal metallothionein. The WHO/UNICEF-recommended therapeutic zinc dose for diarrhea (20 mg/day $\times$ 14 days) was found by Dhingra et al. (2020) (29) to be equally efficacious to 10 mg or 5 mg doses for diarrhea outcomes, but with significantly more vomiting, supporting dose de-escalation in clinical practice.

Effect on Mortality and Long-Term Consequences

The 16% reduction in all-cause mortality demonstrated by Rouhani et al. (2021) (10) in a meta-analysis of 28 RCTs constitutes one of the strongest public health arguments for zinc supplementation programs in LMICs. Subgroup analysis showed a 44% mortality reduction with ≥ 10 mg/day for < 11 months of supplementation (SRR 0.56, 95% CI 0.42–0.75). Cause-specific

analysis revealed reductions in pneumonia mortality (RR 0.70) and infection mortality (SRR 0.54, 0.39–0.76). Brooks et al. (2005) (27) reported 14 deaths in the placebo group versus 2 in the weekly zinc group ($p=0.013$), with zero pneumonia-related deaths in the zinc arm. Given that stunted children have 4.8-fold higher mortality when simultaneously wasted (2), interventions that reduce both stunting and infectious morbidity have compound mortality benefits. The cost-effectiveness of zinc supplementation, estimated at US\$1–3 per child per year in most LMICs, makes it one of the most cost-effective child survival investments available.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This systematic review of 16 primary RCTs and three large meta-analyses provides robust evidence supporting the following conclusions:

- (1) Zinc supplementation at 10 mg/day for ≥ 24 weeks significantly improves linear growth velocity (height/length increment) and weight gain in stunted toddlers from zinc-deficient populations, with effect sizes ranging from 0.13 SD (pooled across all settings) to 0.50 SD (in high-deficiency, stunted populations) (6, 7, 8, 18, 19). The most dramatically effective trials were conducted in Ethiopia and Vietnam, where zinc was the primary growth-limiting nutrient.
- (2) Zinc supplementation robustly improves serum zinc status (ES 0.820, 95% CI 0.499–1.14) and reduces zinc deficiency prevalence by 27–50 percentage points, providing a reliable biochemical indicator of intervention effectiveness (6, 21).
- (3) The GH-IGF-1 axis activation is a key mechanistic mediator of zinc's growth-promoting effects, as evidenced by significant IGF-1 elevation following zinc supplementation in growth-retarded Vietnamese children (19). Baseline IGF-1 bioavailability further modifies the growth response (23).
- (4) Zinc supplementation reduces diarrhea incidence (OR 0.82–0.87) and pneumonia (OR 0.59–0.83) in stunted toddlers, with these morbidity reductions acting as important indirect mechanisms enabling catch-up growth by reducing infection-driven catabolism (9, 28).
- (5) Zinc supplementation reduces all-cause mortality by 16% (SRR 0.84) and pneumonia mortality by 30% in children under 5, making it one of the most cost-effective child survival interventions in LMICs (10).

(6) Stunting prevalence was not significantly reduced by zinc supplementation alone in the majority of trials (17, 21, 31, 32), consistent with the multifactorial etiology of stunting requiring concurrent WASH, food security, and EED-targeted interventions.

(7) The co-administration of iron significantly attenuates the growth-promoting effects of zinc (35), and reduced-iron, high-zinc MNP formulations show more promise for concurrent delivery (38).

Recommendations

Based on the findings of this review, the following evidence-based recommendations are made:

For Clinical Practice: Zinc supplementation at 10 mg/day (as zinc sulphate or gluconate) for a minimum of 24 weeks should be considered as a standard adjunct to nutritional rehabilitation protocols for stunted toddlers aged 6–72 months with confirmed or suspected zinc deficiency (serum zinc < 65 µg/dL or HAZ < -2 in high-risk populations). If feasible, zinc should be administered separately from iron (or in low-iron formulations) to maximize absorption and growth benefit (7, 35).

For Public Health Programming: Zinc supplementation programs should be targeted to populations with >20% prevalence of inadequate zinc intake, as per IZiNCG guidance (3). For community-level stunting reduction, zinc supplementation must be integrated within multi-sectoral nutrition programs that also address WASH, food diversity, EED management, and socioeconomic determinants (1, 2, 15).

For Future Research: Priority research areas include: (a) RCTs specifically powered to detect growth effects in HAZ < -2 children as the primary analytical unit; (b) trials evaluating zinc plus EED-targeted interventions (e.g., zinc + WASH, zinc + azithromycin) on catch-up growth; (c) studies assessing IGF-1 as an intermediate mediator and predictive biomarker of zinc treatment response; (d) dose-optimization trials in specific age groups (6–12 months vs 12–24 months vs 24–72 months); and (e) evaluation of biofortified staple crops as a sustainable, food-systems-based delivery vehicle for zinc in LMIC contexts.

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