Functional indicators for assessing zinc deficiency

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Abstract

Zinc is an essential micronutrient for growth and proper immune function. There is currently no simple recommendation for the assessment of population-level zinc deficiency. Trials of zinc supplementation have shown positive effects of supplementation on clinical outcomes and growth. We reviewed the results of randomized trials of zinc supplementation and correlation studies that assessed infectious diseases, growth, and development outcomes among children under 5 years of age. The results indicate that zinc supplementation decreases the incidence and prevalence of diarrhea and pneumonia, but the use of trial data to make population-level estimates of zinc deficiency is not practical and is difficult to quantify. The data also indicate that zinc supplementation increases growth, especially among children who are stunted. Stunting rates are commonly estimated and can be used to estimate zinc deficiency. Previous recommendations suggest that stunting rates at or above 20% should be indicative of zinc deficiency among children under 5 years of age. This review provides additional data and analysis to support the current recommendation.

Key words: Zinc, supplementation, growth, morbidity

Introduction

Since the 1960s [1], severe zinc deficiency has been recognized as a major cause of growth retardation and delayed sexual maturation. Although these signs are easily recognizable when zinc deficiency is severe, the diagnosis becomes more difficult in young children who are moderately deficient and in children who have multiple nutritional deficiencies. Serum zinc is the most commonly assessed individual indicator of zinc status; however, it is not widely accepted as an accurate measure of true zinc status because its value is influenced by recent dietary intake and infection [2, 3]. On a population level, it has been proposed that assessing potential zinc intake based on food-balance sheets may be a way to assess the zinc status of a population [4], but this method generalizes for the entire population and does not allow for variation according to subgroup of the population.

Reports of trials assessing the effects of zinc given as a daily or weekly supplement have shown benefits when it is given short-term for diarrhea treatment [5], potential benefits when it is given short-term for pneumonia treatment [6], and positive effects of ongoing supplementation for the prevention of infectious diseases and improved growth in some populations [7, 8]. Enrollment in these studies was not dependent upon a biochemical assessment of individual zinc status, and many trials have observed positive effects of supplementation on the functional indicator assessed. Given that there is currently no simple method for assessing zinc status, we sought to determine if zinc deficiency could be assessed by measuring functional indicators such as basic rates of diarrhea and pneumonia infection, growth, and development.

In this review we present the results from randomized, controlled trials of zinc supplementation for the prevention and treatment of infectious diseases, growth retardation, and developmental delays, and nonrandomized studies demonstrating a correlation of biochemical zinc status with one of the functional indicators of interest. We conducted a literature search of PubMed using the key word phrases *zinc and diarrhea*; *zinc and pneumonia*; *zinc and malaria*; *zinc and growth*; and *zinc and development.* We searched only for studies of children and only for studies published in English.

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Studies of all children under 18 years of age were considered for growth outcomes, because prior meta-analysis of these data included all children. Otherwise we limited the studies to those conducted on children under 5 years of age. For randomized trials, only those where a direct comparison between children receiving zinc and those not receiving zinc could be assessed were included; i.e., the zinc group was different from the control group by only zinc, and all other micronutrients were consistent in study groups. Trials with multiple comparison groups were included, but only the zinc and control groups are presented here.

We present a brief summary and a more detailed table of the findings for each functional indicator. In conclusion, we discuss the practicality and effectiveness of using functional indicators to assess individual- and population-level zinc deficiency.

Treatment of infectious diseases

Acute diarrhea

There are 14 trials assessing zinc supplementation for the treatment of diarrhea [9–21]* (**table 1**). Thirteen of these trials were conducted in South Asia and one was conducted in Brazil. Outcomes assessed included diarrhea duration, stool frequency, stool volume, antibody response, percentage developing persistent diarrhea, weight loss during the episode, fluid intake, and need for an intravenous drip. In all but one trial, zinc supplementation had a positive effect on diarrhea: this trial was unique in that it is the only published study of zinc supplementation for diarrhea treatment in infants under 6 months of age [13]. The treatment dose in all studies was at least two times the recommended dietary allowance (RDA) for children under 5 years of age [22]. In two of the five studies in which serum zinc was measured at baseline, zinc had a greater effect among children who were deficient at baseline [18, 19].

Persistent diarrhea

Five trials have assessed zinc supplementation in children with persistent diarrhea [23–27] (**table 1**). One trial was conducted in Peru, and four were conducted in South Asia. Outcomes assessed were diarrhea duration, stool frequency, stool weight, and stool volume. Zinc-supplemented children had better diarrhea outcomes in three of the five trials [23, 24, 26]. All zinc-supplemented children received at least two times the RDA during the treatment period. Serum zinc was measured in all studies at baseline, but there were no reported differences according to baseline zinc status. One study reported a benefit of zinc supplementation only among boys or those children who were underweight at baseline [26].

Pneumonia

Zinc has been investigated as an adjunct treatment for pneumonia in three trials [6, 28, 29] (**table 1**), all of which were conducted in South Asia. Outcomes assessed were time to recovery from pneumonia symptoms, time to complete recovery, respiratory rate, hospitalization time, oxygen saturation, and difficulty feeding. Children receiving zinc recovered faster from pneumonia than those receiving placebo in two of the three trials [6, 28]. All treatment doses were at least two times the RDA and were given for 5 or 6 days or until the child recovered. Serum zinc was measured at baseline in all studies, and no differences in the effect of treatment according to baseline zinc status were reported.

Malaria

One multisite study assessed the effect of zinc supplementation as adjunct therapy for the treatment of malaria [30]. This study included four sites in Africa and one in Ecuador. Time until fever reduction, time until parasitemia reduction, and hemoglobin concentration were assessed as outcome measures. The zinc dose was at least two times the RDA and was given for 4 days in addition to standard malaria treatment. There was no overall effect of the added zinc on recovery from malaria. Serum zinc was measured at baseline, and no differences according to baseline zinc status were reported.

Prevention of infectious diseases

Short-course trials

Zinc supplementation, when given for 10 to 14 days during a diarrhea episode, has proven to be an effective treatment (**table 2**). Several studies have conducted follow-up visits for 2 to 3 months following this treatment to evaluate the effect of a short course of zinc, given at a treatment dose of at least two times the RDA, on the incidence and prevalence of infectious diseases after treatment [11, 31, 32]. In all three studies, zinc-supplemented children had fewer episodes of diarrhea during the months following and mixed results for incidence of pneumonia. One study only saw a benefit of zinc supplementation among children who were stunted or underweight at baseline [32].

* Roy SK. Zinc supplementation in malnourished Bangladeshi children with cholera (Abstract). In: 10th Asian Conference on Diarhhoeal Disease and Nutrition, 2005.

TABLE 1. Zinc (Zn) supplementation for the treatment of diarrhea, pneumonia, and malaria

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences ($p < .05$)
Acute diarrhea						
Sachdev et al. 1988 [19]	India	Randomized 20 mg Zn 2×/day vs. placebo until recovery	6–18 mo with acute diarrhea ($N = 50$)	Baseline: Zn 0.86, placebo 0.87 Recovery: Zn 0.92, placebo 0.76 mg/L	Diarrhea duration, stool frequency	Among those with low serum Zn at baseline, Zn decreased mean diarrhea duration (65.5 vs. 97.1 h) and stool frequency (6.7 vs. 10.0/d)
Sazawal et al. 1995 [20]	India	Randomized 20 mg Zn vs. placebo daily until recovery	6–35 mo with diarrhea < 7 days ($N = 935$)		Diarrhea duration, proportion of acute diarrhea episodes that progressed past 7 days	Zn-supplemented children had 23% shorter episodes of diarrhea than controls. Among acute diarrhea episodes, Zn-supplemented children had 39% fewer episodes > 7 days and 21% overall shorter duration of diarrhea than controls
Hidayat et al. 1998 [16]	Indonesia	Randomized 4–5 mg/kg Zn vs. placebo daily until recovery	< 3 yr with diarrhea < 7 days ($N = 2,279$)		Diarrhea duration	Zn-supplemented children had 11% reduction in risk of continued diarrhea
Roy et al. 1997 [18]	Bangladesh	Randomized 20 mg Zn + multiple micronutrients vs. multiple micronutrients alone daily for 14 days	3–24 mo with acute diarrhea ($N = 111$)	Baseline: Zn 11.2, placebo 12.6 Final: Zn 13.6, placebo 12.3 μmol/L	Weight, stool output, diarrhea duration	Zn-supplemented children maintained weight whereas controls lost weight. Among Zn-supplemented children, stool output was less in those who were shorter (239 vs. 326 g) or had low serum Zn at baseline (279 vs. 329 g). Among those with low serum Zn, Zn-supplemented children had higher weight gain than controls (1,209 vs. 309 g)
Faruque et al. 1999 [15]	Bangladesh	Randomized 14.2 mg (or 40 mg) Zn vs. placebo daily for 15 days	6 mo–2 yr with acute diarrhea and some dehydration ($N = 690$)		Diarrhea duration, proportion lasting > 16 days	Zn-supplemented children had 13% shorter episodes and were 43% less likely to have prolonged diarrhea than controls
Dutta et al. 2000 [14]	India	Randomized 40 mg Zn vs. placebo daily during hospitalization	3–34 mo boys with < −2 weight-for-length Z score, some dehydration, and acute diarrhea ($N = 80$)		Diarrhea duration, stool weight	Zn-supplemented children had shorter duration of diarrhea (70.4 vs. 103.4 h) and less stool (1.5 vs. 2.4 kg)

Baqui et al. 2002 [11]	Bangladesh	Community effectiveness, 20 mg Zn daily for 14 days vs. not available	3–60 mo, living in participating communities		Diarrhea duration	Communities with Zn supplements available had 24% reduction in diarrhea duration
Strand et al. 2002 [21]	Nepal	Randomized 15 mg (or 30 mg depending on age) Zn vs. placebo daily for 10 days	6–35 mo with diarrhea < 96 h (N = 1,792)	Change in serum Zn: Zn 3.7, placebo 0.2 μmol/L	Diarrhea duration, stool frequency	Zn-supplemented children had a 43%–47% lower risk of prolonged diarrhea than controls
Bahl et al. 2002 [10]	India	Randomized 15 mg (or 30 mg depending on age) Zn syrup daily, same quantity of Zn premixed in syrup, or placebo	6–35 mo with acute diarrhea, not hospitalized (N = 1,219)		Stool output, proportion with watery stools, diarrhea duration	Zn syrup group had shorter duration (RR, 0.89) and less stool output (RR, 0.73) than placebo
Al-Sonboli et al. 2003 [9]	Brazil	Randomized 22.5 mg Zn vs. vitamin C daily until recovery	3–60 mo with diarrhea < 7 days (N = 81)	Baseline: Zn 9.1, placebo 9.2 μmol/L	Diarrhea duration, stool frequency	Duration less in Zn group (1.1 vs. 2.6 days)
Bhatnagar et al. 2004 [12]	India	Randomized 15 mg (or 30 mg depending on age) Zn daily for 14 days	3–36 mo boys with acute diarrhea (N = 287)		Stool output, diarrhea duration	Zn-supplemented children had decreased diarrhea duration (RR, 0.76), lower proportion with diarrhea > 5 days (OR, 0.49), and reduced total stool output (GM, 0.69) and stool output per day (GM, 0.76)
Brooks et al. 2005 [13]	Bangladesh	Randomized 5 mg or 20 mg Zn or placebo daily until recovery	1–6 mo boys hospitalized with diarrhea and some dehydration (N = 275)	Baseline: Zn (5 mg) 67.0, Zn (20 mg) 68.6, placebo 69.9 Final: Zn (5 mg) 84.1, Zn (20 mg) 101.0, placebo 69.1 μg/dL	Fluid intake, need for intravenous rehydration, diarrhea duration, stool volume, weight gain	No effect
Rahman et al. 2005 [17]	Bangladesh	Randomized 20 mg Zn + multiple micronutrients vs. multiple micronutrients alone daily for 14 days	12–35 mo with shigella (N = 506)		Proportion with shigella antibody response, antibody titer, inflammation, and histopathologic factors	Zn-supplemented children had higher proportion with shigella antibody response at day 30 than controls (73% vs. 36%)

continued

TABLE 1. Zinc (Zn) supplementation for the treatment of diarrhea, pneumonia, and malaria *(continued)*

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences ($p < .05$)
Roy et al.[1]	Bangladesh	Randomized 30 mg Zn vs. placebo daily until recovery	3–14 yr with cholera < 24 h ($N = 164$)		Diarrhea duration, stool volume	Overall, diarrhea duration was 14% shorter in Zn-supplemented children than controls, and among malnourished children (< 75% WAZ) it was 22% shorter in Zn-supplemented children than controls. Among children with < –2 WHZ, Zn-supplemented children passed 36% less stool than controls
Persistent diarrhea						
Sachdev et al. 1990 [27]	India	Randomized 20 mg Zn (2×/day) vs. placebo daily until recovery	6–18 mo with persistent diarrhea ($N = 40$)	Baseline: Zn 0.73, placebo 0.75 Recovery: Zn 0.80, placebo 0.67 mg/L	Diarrhea duration, stool frequency	No effect
Bhutta et al. 1999 [25]	Pakistan	Randomized 3 mg/kg Zn vs. placebo daily for 14 days in hospital and 14 days at home	3–60 mo hospitalized with diarrhea > 14 days ($N = 87$)	Baseline: Zn 78, placebo 70.3 µg/dL	Stool volume, stool frequency, diarrhea duration, weight gain	No effect
Penny et al. 1999 [24]	Peru	Randomized 20 mg/day Zn for diarrhea treatment	6–36 mo with persistent diarrhea ($N = 274$)	Baseline: Zn 74, placebo 72 Final: Zn 38, placebo 4 µg/dL	Diarrhea duration, weight, length	Zn decreased diarrhea duration by 28% after controlling for number of stools prior to enrollment and dysentery
Khatun et al. 2001 [23]	Bangladesh	Randomized 20 mg Zn + multiple micronutrients vs. multiple micronutrients alone daily for 7 days	6 mo–2 yr with diarrhea ≥ 14 days ($N = 48$)	Baseline: Zn 15.0, placebo 15.0 µmol/L	Stool weight, diarrhea duration, weight gain	Zn-supplemented children had lower stool weight (39% less after 2–7 days of diarrhea) and 46% higher weight gain
Pneumonia						
Mahalanibis et al. 2002 [29]	India	Randomized 40 mg Zn vs. placebo daily for 6 days	9 mo–15 yr with measles and pneumonia ($N = 85$)	Baseline: Zn 10.74, placebo 8.86 Final: Zn 12.97, placebo 11.67 µmol/L	Time to recovery: anorexia, fever, tachypnea. Time until cured	No effect

Brooks et al. 2004 [6]	Bangladesh	Randomized 20 mg Zn vs. placebo daily until discharge	2–23 mo hospitalized with pneumonia (N = 270)	Baseline: Zn 10.1, placebo 10.1 Discharge: Zn 14.5, placebo 11.2 µmol/L	Pneumonia duration, respiratory rate, duration of hospital stay, oxygen saturation	Zn-supplemented children had 30% shorter duration of severe pneumonia, 26% less time at regular respirations > 50/min, and 25% shorter duration of hospital stay
Mahalanabis et al. 2004 [28]	India	Randomized 20 mg Zn vs. placebo daily for 5 days	2–24 mo hospitalized with severe ALRI (N = 153)	Baseline: Zn 9.91, placebo 9.27 Final: Zn 16.79, placebo 11.28 µmol/L	Time to recovery: very ill status, fever, tachypnea, feeding difficulty	Zn-supplemented children recovered from illnesses 2.6× faster and from fever 3.0× faster than controls
Malaria						
Zinc Against Plasmodium Study Group, 2002 [30]	Ecuador, Ghana, Tanzania, Uganda, Zambia	Randomized 20 mg Zn (40 mg for older children) vs. placebo for 4 days	6 mo–5 yr with fever and ≥ 2,000 asexual forms of *Plasmodium falciparum*/µl (N = 1,087)	Baseline: Zn 8.54, placebo 8.34 Final: Zn 10.95, placebo 10.16 µmol/L	Time to reduction of fever, reduction of parasitemia, hemoglobin concentration	No effect

ALRI, acute lower respiratory infection; GM, ratio of geometric means; OR, odds ratio; RR, relative risk; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score

[1] Roy SK. Zinc supplementation in malnourished Bangladeshi children with cholera (Abstract). In: 10th Asian Conference on Diarhhoeal Disease and Nutrition, 2005.

TABLE 2. Zinc supplementation for prevention of diarrhea, pneumonia, and malaria

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences ($p < .05$)
Short-course trials (daily for 14 days with longer-term follow-up)						
Roy et al. 1999 [32]	Bangladesh	Randomized 20 mg Zn + multiple micronutrients daily vs. multiple micronutrients alone for 14 days. Follow-up for 8 wk	3–24 mo with acute diarrhea ($N = 111$)	Baseline: Zn 11.2, placebo 12.6 Final: Zn 13.6, placebo 12.3 μmol/L	Incidence of diarrhea, ALRI Prevalence of diarrhea, ALRI	Among stunted children, Zn-supplemented had fewer episodes of diarrhea (0.07 vs. 0.6) and ALRI (1.0 vs. 2.4). Among underweight children, Zn-supplemented had fewer episodes of diarrhea (0.4 vs. 1.0) and shorter duration of diarrhea (1.0 vs. 3.0 days)
Rahman et al. 2001 [31]	Bangladesh	Randomized 20 mg Zn daily for 14 days vs. placebo. Follow-up for 6 mo	12–35 mo ($N = 506$)		Incidence of diarrhea, ALRI, dysentery Prevalence of diarrhea, ALRI, dysentery	Zn groups had 11% decreased incidence of diarrhea, but increased risk of ALRI (RR, 1.62) and increased prevalence of pneumonia (RR, 2.07)
Baqui et al. 2002 [11]	Bangladesh	Community effectiveness, 20 mg Zn daily for 14 days vs. not available	3–60 mo, living in participating communities		Incidence of diarrhea, ALRI Hospital admissions Mortality	Zn groups had 15% reduction in diarrhea incidence, 24% reduction in hospital admission for diarrhea, and 51% reduction in mortality
Long-term daily supplementation (5–7×/wk)						
Castillo-Duran et al. 1987 [54]	Chile	Randomized 2 mg/kg Zn vs. placebo daily for 60 days	Marasmic 2–14 mo ($N = 32$)	Baseline: Zn 96, placebo 105 Final: Zn 102, placebo 102 μg/dL	Incidence of diarrhea, URTI, ALRI, pyoderma	Zn-supplemented children had lower incidence of total infections and lower incidence of pyoderma
Ninh et al. 1996 [53]	Vietnam	Paired and randomized 10 mg Zn vs. placebo daily for 5 mo	4–36 mo, < –2 WAZ and < –2 HAZ		Incidence of diarrhea, ALRI	Zn decreased percentage of children with 1 episode of diarrhea (30% vs. 36%), 2 episodes (14% vs. 40%) and > 2 episodes (12% vs. 40%)
Sempertegui et al. 1996 [52]	Ecuador	Randomized 10 mg Zn vs. placebo daily for 60 days	12–59 mo with WAZ and HAZ < 10th percentile ($N = 50$)	Baseline: Zn 88.5, placebo 84.6 After 60 days: Zn 118.6, placebo 83.1 μg/dL	Prevalence of cough, fever, URTI	Zn-supplemented children were 28% less likely to have URTI, 48% less likely to have cough, and 70% less likely to have fever than controls

Sazawal et al. 1997 [51]	India	Randomized 10 mg Zn daily + multiple micronutrients vs. multiple micronutrients for 6 mo	6–35 mo (N = 579)	Baseline: Zn 9.88, placebo 9.94 Final: Zn 13.4, placebo 9.76 μmol/L	Incidence and prevalence of diarrhea	Among children > 11 mo, Zn-supplemented had 26% lower incidence of diarrhea and 35% lower prevalence of diarrhea. Among children with < 9.18 μmol/L Zn at baseline, Zn-supplemented had 33% lower incidence of diarrhea
Rosado et al. 1997 [50]	Mexico	Randomized 20 mg Zn vs. placebo daily for 12 mo	18–35 mo (N = 109)	Baseline: Zn 13.2, placebo 14.2 Final: Zn 16.8, placebo 14.4 μmol/L	Incidence and duration of diarrhea, ALRI, all illnesses Incidence of fever	Zn-supplemented children had lower number of diarrhea episodes (0.7 vs. 1.1) and lower number of all illness episodes (3.9 vs. 4.6)
Ruel et al. 1997 [49]	Guatemala	Randomized 10 mg Zn vs. placebo daily for 7 mo	6–9 mo (N = 99)		Incidence and prevalence of diarrhea, persistent diarrhea, ALRI	Zn-supplemented children had 22% lower incidence of diarrhea, with bigger difference among boys and children with low weight-for-height at baseline. 67% fewer Zn-supplemented children had persistent diarrhea than controls
Meeks Gardner et al. 1998 [48]	Jamaica	Randomized 5 mg Zn vs. placebo daily for 12 wk	6–24 mo, < –2 LAZ (N = 61) and well-nourished babies (N = 24)		Incidence and duration of apathy, anorexia, dyspnea, cough, nasal discharge, ear infections, fever, diarrhea, vomiting, rashes, other Hospitalizations	Mean duration of skin rashes less in Zn-supplemented children (5.9 vs. 9 days). Rate of hospitalization lower in Zn-supplemented (0 vs. 5 children)
Lira et al. 1998 [47]	Brazil	Randomized 5 mg Zn, 1 mg Zn, or placebo daily for 8 wk	LBW infants enrolled at birth (N = 205)		Prevalence of diarrhea, cough Number and duration of hospitalizations Mortality	5 mg Zn-supplemented children had 28% lower diarrhea prevalence than controls. Duration of hospitalization shorter in 5 mg Zn-supplemented children (5.0 vs. 7.7 days)

continued

TABLE 2. Zinc supplementation for prevention of diarrhea, pneumonia, and malaria *(continued)*

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences ($p < .05$)
Sazawal et al. 1998 [46]	India	Randomized 10 mg Zn vs. placebo daily for 6 mo	6–35 mo ($N = 609$)	Serum Zn deficiency decreased in Zn-supplemented children (35.6% to 11.6%) but increased in controls (36.8% to 43.6%)	Incidence and prevalence of diarrhea, ALRI	Zn reduced ALRI episodes by 45% after correcting for within-subject correlation. Zn-supplemented had 0.19 diarrhea episodes/yr compared with 0.35 episodes/yr in controls
Kikafunda et al. 1998 [45]	Uganda	Randomized 10 mg Zn vs. placebo in juice daily for 6 mo (8 mo observation)	Mean age 55.8 ± 11.2 mo		Incidence of infections	No effect
Shankar et al. 2000 [44]	Papua New Guinea	Randomized 10 mg/day vs. placebo 6 days/wk for 46 wk	6–60 mo		Incidence of clinic-based malaria (parasitemia + fever)	Zn-supplemented children had 38% fewer episodes of clinic-based malaria for those with parasitemia ≥ 9,200/μL and 69% fewer episodes for those with parasitemia ≥100,000/μL
Umeta et al. 2000 [43]	Ethiopia	Randomized 10 mg Zn vs. placebo 6 days/wk for 6 mo	Breastfed infants 6–12 mo, 100 stunted (< –2 LAZ) and 100 matched nonstunted > –2 LAZ	Final serum Zn: Stunted infants—Zn 15.8, placebo 11.0 Non-stunted infants—Zn 17.9, placebo 14.5 μmol/L Final hair Zn: Stunted infants—Zn 1.38, placebo 1.16 Non-stunted infants—Zn 1.57, placebo 1.43 μmol/g	Incidence of anorexia, cough, diarrhea, fever, vomiting	Among stunted children, Zn-supplemented had fewer episodes of anorexia (3 vs. 15), cough (15 vs. 32), diarrhea (13 vs. 40), fever (27 vs. 41), and vomiting (12 vs. 24) than controls
Sazawal et al. 2001 [42]	India	Randomized 5 mg Zn vs. placebo daily from 90 days to 9 mo (additional arms of study given multiple micronutrients)	SGA full-term infants,< 10th percentile ($N =$ 1,154)		Mortality	68% decrease in mortality in all Zn groups (half given multiple micronutrients)

Osendarp et al. 2002 [41]	Bangladesh	Randomized 5 mg Zn vs. placebo daily from 4 to 24 wk	4 wk (N = 301)	Baseline: Zn 11.9, placebo 11.7 Final: Zn 13.3, placebo 10.7 μmol/L	Incidence and prevalence of ALRI, diarrhea	Among those Zn-deficient at baseline, Zn-supplemented children had 70% decreased risk of ALRI
Bhandari et al. 2002 [39 ,40]	India	Randomized 10 mg Zn if infant, 20 mg Zn if older, vs. placebo daily for 4 mo (all get vitamin A)	6–30 mo (N = 2,482)	Baseline: Zn 62.0, placebo 62.0 After 4 mo: Zn 129.1, placebo 60.8 μg/dL	Proportion of children with ALRI, diarrhea, severe diarrhea, recurrent diarrhea Incidence of pneumonia, ALRI, diarrhea, severe diarrhea Prevalence of pneumonia, ALRI, diarrhea, severe diarrhea	Zn-supplemented children had 2.5% lower incidence of pneumonia after correction for multiple episodes (OR, 0.74). Zn decreased incidence of episodes lasting 7–13 days (OR, 0.79) and ≥ 14 days (OR, 0.69), stool frequency of 3–5/day (OR, 0.90), 6–9/day (OR, 0.87), and > 10/day (OR, 0.77). Zn decreased recurrent diarrhea (OR, 0.51)
Gupta et al. 2003 [38]	India	Randomized 10 mg Zn 5 days/wk vs. placebo for 16 wk	6–41 mo (N = 280)		Incidence of diarrhea, Duration of diarrhea episodes	Zn-supplemented children had fewer episodes of diarrhea than controls (0.68 vs. 1.67 episodes/yr). Zn-supplemented children less likely to develop any episode of diarrhea
Sur et al. 2003 [37]	India	Randomized 5 mg Zn in vitamin B complex vs. vitamin B daily for 1 yr	LBW infants at birth (N = 100)		Incidence of diarrhea	Zn-supplemented infants had 30% fewer episodes/yr
Lind et al. 2004 [36]	Indonesia	Randomized 10 mg Zn vs. placebo daily for 6 mo	6–12 mo (N = 326)		Incidence of diarrhea, ALRI Duration of diarrhea, ALRI	No effect
Penny et al. 2004 [35]	Peru	Randomized 10 mg Zn vs. placebo daily for 6 mo (originally for diarrhea treatment, but then for 6 mo)	6–35 mo with persistent diarrhea (N = 164)	Baseline: Zn 70.4, placebo 70.2 Final: Zn 97.7, placebo 76.3 μg/dL	Incidence of diarrhea, severe diarrhea, persistent diarrhea, ALRI, pneumonia Prevalence of fever, cough, diarrhea, anorexia	Zn-supplemented children had lower prevalence of cough (42% vs. 51% of days)
Meeks Gardner et al. 2005 [34]	Jamaica	Randomized 10 mg Zn vs. placebo daily for 6 mo	9–30 mo with < −1WAZ (N = 110)		Incidence and duration of diarrhea, apathy, fever, anorexia, nasal discharge, cough, rapid/difficulty breathing, vomiting, ear infections, skin problems	Zn-supplemented children had fewer episodes of diarrhea (0 vs. 0.8)

continued

TABLE 2. Zinc supplementation for prevention of diarrhea, pneumonia, and malaria *(continued)*

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences ($p < .05$)
Richard et al. 2006 [33]	Peru	Randomized 20 mg Zn vs. placebo daily for 7 mo	0.5–15 yr ($N = 855$)	Baseline: Zn 10.80, placebo 10.72 Final: Zn 13.82, placebo 10.36 μmol/L	Incidence of malaria, ALRI, diarrhea	Zn-supplemented children had lower risk of *Plasmodium vivax* malaria. Zn-supplemented children < 5 yr were 30% less likely to have a diarrhea episode
Long-term weekly supplementation (1–2 ×/wk)						
Bates et al. 1993 [55]	Gambia	Randomized 70 mg Zn vs. placebo 2×/ wk for 1.25 yr	0.57–2.3 yr ($N = 110$)		Incidence of diarrhea, malaria, ALRI, other infections	No effect
Baqui et al. 2003 [57]	Bangladesh	Randomized 20 mg Zn + 1 mg riboflavin vs. 1 mg riboflavin weekly for 6 mo	6 mo ($N = 318$)	Baseline: Zn 0.71, placebo 0.65 After 6 mo: Zn 0.79, placebo 0.69 mg/L	Incidence of diarrhea, severe diarrhea, ALRI	No effect
Gupta et al. 2003 [38]	India	Randomized 50 mg Zn 1 day/wk vs. placebo for 16 wk	6–41 mo ($N = 280$)		Incidence of diarrhea Duration of diarrhea episodes	Zn-supplemented children had fewer episodes of diarrhea than controls (0.67 vs. 1.67 episodes/yr). Zn-supplemented children less likely to develop any episode of diarrhea
Brooks et al. 2005 [56]	Bangladesh	Randomized 70 mg Zn vs. placebo weekly from 60 days to 12 mo	60 days ($N = 1,665$)	Baseline: Zn 9.9, placebo 9.7 After 10 mo: Zn 11.0, placebo 9.9 μmol/L	Incidence of diarrhea, pneumonia Mortality	Zn decreased incidence of pneumonia by 17% and diarrhea by 6%. Fewer overall deaths in Zn group (2 vs. 14) and fewer pneumonia deaths (0 vs. 10)

ALRI, acute lower respiratory infection; HAZ, height-for-age z-score; LAZ, length-for-age z-score; LBW, low birthweight; OR, odds ratio; RR, relative risk; SGA, small for gestational age; URTI, upper respiratory tract infection; WAZ, weight-for-age z-score

Long-term daily supplementation

Long-term daily zinc supplementation for the prevention of infectious illnesses has been assessed in 21 trials (**table 2**) [33–54]. Supplementation in these studies continued for at least 8 weeks, and doses ranged from 5 to 20 mg per day. Outcome measures assessed include incidence and prevalence rates of diarrhea, respiratory tract infections, pyoderma, fever, malaria, ear infections, vomiting, and rashes, as well as rates of hospitalizations and mortality. Nineteen of the 21 trials observed a positive effect of zinc supplementation on at least one outcome measure assessed [33–36, 38–44, 46–54]. Zinc supplementation decreased the incidence of diarrhea by approximately 18% and the prevalence of diarrhea by 25% [8]. For pneumonia, zinc supplementation decreased the incidence by 41% [8]. Ten of these trials assessed serum zinc at baseline, and one assessed hair zinc as well [8, 33, 35, 39–41, 43, 46, 50–52, 54]. Of these trials, two observed greater benefits among children who had lower serum zinc levels at baseline [41, 51], one study observed a lower prevalence and incidence of diarrhea among children older than 11 months [51], and one found a larger positive effect of zinc supplementation on the incidence of diarrhea among boys and children with low weight-for-length at baseline [49]. Rates of hospitalization and mortality were not often considered because of the large sample sizes required. However, two studies reported a smaller number of hospitalizations and a shorter duration of stay [47, 48], and one study reported an overall lower mortality rate in zinc-supplemented children [42].

Long-term weekly supplementation

Four trials assessed weekly zinc supplementation for at least 2 months for the prevention of infectious diseases (**table 2**) [38, 55–57]. Supplementation ranged from 20 to 70 mg, one or two times per week. One study was conducted in Gambia and three were conducted in South Asia. These studies reported the effect of zinc on the incidence of diarrhea, acute lower respiratory tract infections, malaria, the prevalence of diarrhea, and mortality rates. Two of the four trials observed a positive effect of zinc on diarrhea incidence (6% lower in zinc-supplemented children [56] and 40% lower in zinc-supplemented children [38]). One trial observed a decrease in pneumonia incidence by 17%, as well as fewer deaths among infants supplemented with zinc at a weekly dose of 50 to 70 mg [56]. No trial reported differences according to baseline serum zinc status.

Growth

Zinc supplementation for enhanced growth in children has been widely studied in developing countries where there are high rates of stunting and widespread malnutrition. Twenty-eight trials of children from birth to 17 years of age have been summarized in **table 3** [34, 36, 37, 41, 43, 45, 47, 48, 50, 52–56, 58–71]. Growth outcomes assessed were weight, height, weight-for-age z-score (WAZ), height-for-age z-score (HAZ), weight-for-height z-score (WHZ), mean upper-arm circumference (MUAC), arm span, triceps skinfold thickness (TSF), arm muscle area for age, mid-arm muscle area [72], head circumference, knee–heel length, and chest circumference. Seven of these trials reported no effect of zinc on any measured indicator [34, 48, 50, 52, 60, 61, 70], yet all others reported a positive effect of zinc on at least one measured indicator. Seventeen of the trials assessed serum zinc at baseline, and of those, one reported positive effects only among children who were zinc-deficient at baseline [41].

Growth was previously assessed in a meta-analysis by Brown et al. [7], which included studies conducted in both developing and developed countries. This meta-analysis rigorously compiled data from both published and unpublished studies and also included several reports not available in English. This comprehensive meta-analysis reported statistically significant effect sizes for height increments (0.35; 95% confidence interval [CI], 0.189 to 0.511) and weight increments (0.309; 95% CI, 0.178 to 0.439) [7].

This analysis was recently updated for this review to compare the effect size of zinc on height observed in developed versus developing countries. In a separate analysis of only developing countries, the effect sizes for both height and weight were calculated. For these analyses, units were converted to effect size by calculating the "difference between the means of the zinc and control groups divided by their pooled standard deviation" [7]. **Figure 1** illustrates the change in effect size observed as the initial mean HAZ score changes. As initial HAZ score improves, the effect size decreases in both developing and developed country studies. This effect size is illustrated by country status and initial HAZ score for all children in **figure 2** [43, 45, 47, 48, 50, 52, 53, 55, 58, 59, 62–67, 69, 71, 73–83]. **Figure 3** [43, 45, 48, 52, 53, 55, 58, 59, 62–64, 66, 67, 71, 73–75, 79, 82] also illustrates the effect size of zinc on height but includes only children 6 months of age and older. These figures show that there is not an overall difference in effect size between developed countries and less-developed countries for all studies, or for those studies of only children 6 months of age and older. The effect of zinc is greatest among children with low HAZ scores at enrollment; this difference in effect according to HAZ score appears to be more dramatic in older children.

Developing countries: Change in height or length

There was a significant effect of zinc on change in

TABLE 3. Zinc supplementation for the acceleration of growth

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences ($p < .05$)
Mahloudji et al. 1975 [70]	Iran	Randomized 20 mg Zn + 20 mg Fe vs. Fe alone daily for 8 mo	6–12 yr ($N = 59$)		Weight, height	No effect
Castillo-Duran et al. 1987 [54]	Chile	Randomized 2 mg/kg Zn vs. placebo daily for 60 days	Marasmic 2–14 mo ($N = 32$)	Baseline: Zn 96, placebo 105 Final: Zn 102, placebo 102 µg/dL	Weight, length	Zn-supplemented children gained more weight-for-length than controls (9% vs. 3%)
Hong et al. 1992 [69]	China	Randomized 1.14–2.25 mg/kg Zn vs. regular formula diet for 6 mo	At birth ($N = 69$)	Change in serum Zn: Boys: Zn 3.45, placebo 1.51 Girls: Zn 3.14, placebo 1.28 µmol/L	Weight, length	Zn-supplemented children gained more weight
Cavan et al. 1993 [67]	Guatemala	Randomized 10 mg Zn vs. placebo daily for 25 wk	74.5–88.5 mo ($N = 162$)	Baseline: Zn 14.2, placebo 14.4 Final: Zn 16.2, placebo 14.9 µmol/L	Height, weight, TSF, MUAC z-scores	Zn-supplemented children had greater change in TSF z-score (0.50 vs. 0.38) and a smaller decline in MUAC z-score (−0.03 vs. −0.2)
Shrivastava et al. 1993 [68]	India	Randomized 5.625 mg Zn vs. placebo daily for 3 mo	8–24 mo with mild to moderate protein-energy malnutrition ($N = 30$)	Baseline: Zn 87.5. placebo 91.2 Final: Zn 121.0, placebo 91.0 µg/dL	Weight	Zn-supplemented children gained more weight (3.74 vs. 2.04 kg) than controls
Bates et al. 1993 [55]	Gambia	Randomized 70 mg vs. placebo 2×/wk for 1.25 yr	0.57–3.3 yr ($N = 110$)		MUAC, weight, length	Zn-supplemented children had 2% greater gain in arm circumference than controls
Castillo-Duran et al. 1994 [71]	Chile	Randomized 10 mg Zn vs. placebo daily for 12 mo	6–14 yr with low LAZ ($N = 80$)	Mean throughout 12 mo: Zn 106, placebo 114.1 µg/dL	Weight, height z-scores, arm span	Zn-supplemented boys had greater improvement in HAZ (−2.57 to −2.44 vs. −2.59 to −2.72) than controls
Dirren et al. 1994 [66]	Ecuador	Randomized 10 mg Zn vs. placebo daily 6 days/wk for 15 mo	12–50 mo ($N = 96$)	Baseline: Boys—Zn 78, placebo 77 Girls—Zn 68, placebo 71 µg/dL	Height, weight z-scores	Zn-supplemented boys grew 1 cm more than controls and had improved HAZ (0.32 vs. 014). Zn-supplemented children had less improvement in WHZ (0.02 vs. 0.34) than controls. Zn-supplemented girls had increased HAZ (0.20 vs. −0.02) and WAZ (0.25 vs. 0.04) compared with controls

Castillo-Duran et al. 1995 [65]	Chile	Randomized 3 mg Zn vs. placebo daily for 6 mo	SGA at birth (N = 68)	Baseline: Zn 12.6, placebo 12.1 Final: Zn 10.5, placebo 8.9 µmol/L	Weight, length z-scores, head circumference	Zn-supplemented children gained more weight (change in WAZ –2.05 to –0.24 vs. –2.06 to –1.07) and more length (LAZ –1.3 to –0.66 vs. –1.3 to –1.47) than controls
Sempertegui et al. 1996 [52]	Ecuador	Randomized 10 mg Zn vs. placebo daily for 60 days	12–59 mo with low WAZ and HAZ (N = 50)	Baseline: Zn 88.5, placebo 84.6 Final: Zn 118.6, placebo 83.1 µg/dL	Weight, height z-scores	No effect
Ninh et al. 1996 [53]	Vietnam	Randomized 10 mg Zn vs. placebo daily for 5 mo	4–36 mo with < –2 WAZ and < –2 HAZ		Length, weight	Zn-supplemented children had increased weight and height after 5 mo in multiple logistic regression analysis (0.5 kg and 1.5 cm, respectively)
Rosado et al. 1997 [50]	Mexico	Randomized 20 mg Zn vs. placebo daily for 12 mo	18–35 mo (N = 109)	Baseline: Zn 13.2, placebo 14.2 Final: Zn 16.8, placebo 14.4 µmol/L	Weight, length z-scores	No effect
Ruz et al. 1997 [63]	Chile	Randomized 10 mg Zn vs. placebo daily for 14 mo	27–50 mo (N = 98)	Serum Zn: Baseline—Zn 17.7, placebo 17.2 At 6 mo—Zn 17.6, placebo 17.7 µmol/L Hair Zn: Baseline—Zn 1.74, placebo 1.75 At 6 mo—Zn 2.23, placebo 2.14 nmol/kg	Weight, height z-scores, TSF, MUAC	Zn-supplemented boys gained 0.9 cm more than those who received placebo
Friis et al. 1997 [64]	Zimbabwe	Randomized 30 or 50 mg Zn vs. placebo on school days for 12 mo	6–17 yr (N = 313)	Change in serum Zn: After 3 mo of intervention— Zn 0.24, placebo 0.85 After 12 mo of intervention— Zn 0.09 placebo 1.11 µmol/L	Weight, height, MUAC, TSF, MMA-for-age z-scores	Zn-supplemented children gained more weight (change in WAZ –0.08 vs. –0.14) and had improved MMA-for-age z-scores (0.1 vs. 0.01) compared with controls over the first 3 mo of observation
Lira et al. 1998 [47]	Brazil	Randomized 5 or 1 mg Zn vs. placebo daily for first 8 wk	LBW infants (N = 205)		Weight, length	Infants receiving 5 mg Zn had increased weight at 17–26 wk compared with controls

continued

TABLE 3. Zinc supplementation for the acceleration of growth *(continued)*

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences ($p < .05$)
Meeks Gardner et al. 1998 [48]	Jamaica	Randomized 5 mg Zn vs. placebo daily for 12 wk	6–24 mo, < –2 LAZ ($N = 61$) and well-nourished babies ($N = 24$)		Length, weight, head circumference	
Kikafunda et al. 1998 [45]	Uganda	Randomized 10 mg Zn vs. placebo in juice daily for 6 mo (+ 2 additional mo observation)	Mean age 55.8 + 11.2 mo		MUAC, weight, length	Zn-supplemented children increased MUAC (0.86 vs. –0.82 mm) and greater weight gain compared to those who received placebo in medium socioeconomic status schools
Rivera et al. 1998 [62]	Guatemala	Randomized 10 mg Zn vs. placebo daily for average 6.9 mo	6–9 mo ($N = 89$)		Weight, length, MUAC, HEAD circumference, TSF, MMA	Zn-supplemented infants grew longer by 0.75 cm, and among stunted infants those receiving Zn grew longer by 1.4 cm, than controls
Smith et al. 1999 [58]	El Salvador	Randomized 70 mg Zn vs. placebo weekly for 6 mo	28–72 mo ($N = 43$)	Final: Zn 12.1, placebo 11.7 µmol/L	Weight, height z-scores	Zn-supplemented children had greater change in HAZ than controls (posttreatment mean, –2.09 vs. –2.57)
Sayeg Porto et al. 2000 [59]	Brazil	Randomized 5 mg/kg Zn vs. placebo daily for 6 mo (follow–up 6 more mo)	7–10 yr, low height-for-age ($N = 18$)	Baseline: Zn 101.3, placebo 100.0 Final after 6 mo of supplementation: Zn 91.3, placebo 88.9 µg/dL	Weight, length	Zn-supplemented children had greater growth velocity during and after 6 mo of supplementation than those receiving placebo (5.99 vs. 5.05 cm/yr), but growth rates in both groups were equal during the follow-up, non-supplemented period
Umeta et al. 2000 [43]	Ethiopia	Randomized 10 mg Zn vs. placebo 6 days/wk for 6 mo	Breastfed infants 6–12 mo, 100 stunted (< –2 LAZ) and 100 matched nonstunted (≥ –2 LAZ)	Final serum Zn: Stunted infants—Zn 15.8, placebo 11.0 Nonstunted infants—Zn 17.9, placebo 14.5 µmol/L Final hair Zn: Stunted infants—Zn 1.38, placebo 1.16 Nonstunted infants—Zn 1.57, placebo 1.43 nmol/kg	Length, weight, knee–heel length, MUAC, TSF z-scores	Increase in length and weight was greater among Zn-supplemented infants than among controls for both stunted (7 vs. 2.8 cm, 1.73 vs. 0.95 kg) and non-stunted (6.6 vs. 5.0 cm, 1.19 vs. 1.02 kg) infants
Dijkhuizen et al. 2001 [60]	Indonesia	Randomized 10 mg Zn vs. placebo daily for 6 mo	4 mo ($N = 188$)	Final: Zn 16.1, placebo 13.0 µmol/L	Weight, length, knee–heel length z-scores	No effect

Castillo-Duran et al. 2001 [61]	Chile	Randomized 5 mg Zn vs. placebo daily for 12 mo	Full-term neonates (N = 150)		Weight, length	No effect
Osendarp et al. 2002 [41]	Bangladesh	Randomized 5 mg Zn vs. placebo daily from 4 to 24 wk	4–24 wk (N = 301)	Baseline: Zn 11.9, placebo 11.7 Final: Zn 13.3, placebo 10.7 µmol/L	Weight, length, head circumference, chest circumference, MUAC	Among those who were Zn-deficient at baseline, Zn-supplemented infants had greater weight gain (3.15 vs. 2.66 kg) than controls
Sur et al. 2003 [37]	India	Randomized 5 mg Zn in vitamin B complex vs. vitamin B alone daily from birth to 1 yr	LBW infants (N = 100)		Weight, length z-scores	Zn-supplemented infants gained more weight (6,084 vs. 5,280 g) and length (23.7 vs. 21.4 cm) only after 12 mo than controls
Lind et al. 2004 [36]	Indonesia	Randomized 10 mg Zn vs. placebo daily for 6 mo	6–12 mo (N = 326)		Length, weight z-scores	Zn-supplemented infants had higher WAZ than controls (–1.46 vs. –1.72)
Brooks et al. 2005 [56]	Bangladesh	Randomized 70 mg Zn vs. placebo weekly from 60 days to 12 mo	60 days (N = 1,665)	Baseline: Zn 9.9, placebo 9.7 Final: Zn 11.0, placebo 9.9 µmol/L	Length, weight	Zn-supplemented infants grew at a faster rate than controls (1.4 vs. 1.3 cm/mo)
Meeks Gardner et al. 2005 [34]	Jamaica	Randomized 10 mg Zn vs. placebo daily for 6 mo	9–30 mo with < –1 WAZ (N = 110)		Length, weight, z-scores	No effect

HAZ, height-for-age z-score; LAZ, length-for-age z-score; LBW, low birthweight; MMA, mid-arm muscle area; MUAC, mean upper-arm circumference; SGA, small for gestational age; TSF, triceps skinfold; WAZ, weight-for-age z-score

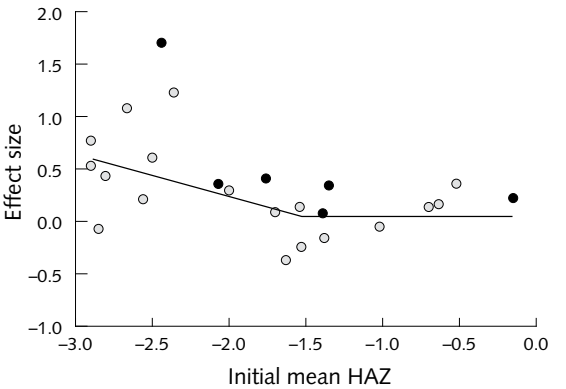

FIG. 1. Effect size of zinc on height according to baseline height-for-age z-score (HAZ). Solid circles represent studies conducted in developing countries and shaded circles studies conducted in developed countries

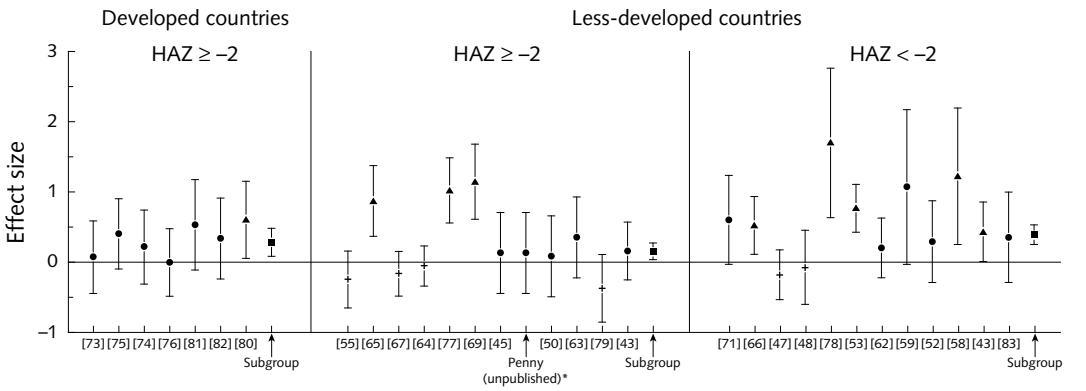

FIG. 2. Effect size of zinc on height according to country status and initial height-for-age z-score (HAZ) for all children. Circles represent nonsignificant positive effects, triangles significant positive effects, squares subgroup effects, and crosses nonsignificant negative effects. Vertical bars represent 95% confidence intervals. References to studies are given in square brackets

* Penny ME, Peerson JM, Marin RM. Unpublished observations.1998

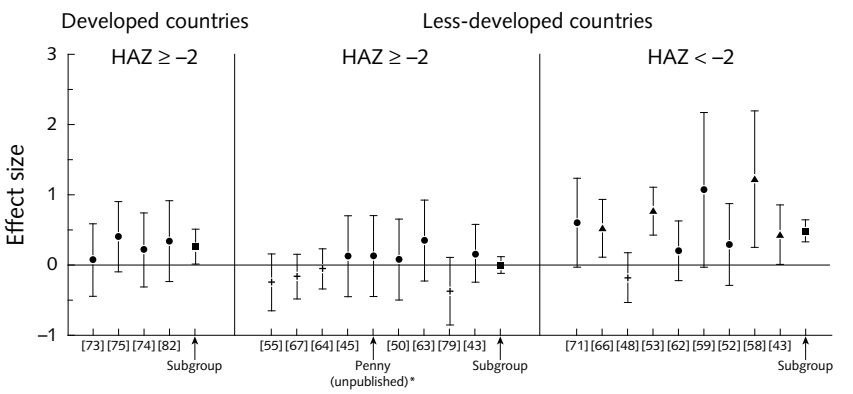

FIG. 3. Effect size of zinc on height according to country status and initial height-for-age z-score (HAZ) for children 6 months of age or older. Circles represent nonsignificant positive effects, triangles significant positive effects, squares subgroup effects, and crosses nonsignificant negative effects. Vertical bars represent 95% confidence intervals. References to studies are given in square brackets

* Penny ME, Peerson JM, Marin RM. Unpublished observations.1998

height or length in this meta-analysis ($p < .0001$) (**fig. 4**) [43, 45, 47, 48, 50, 52, 53, 55, 58, 59, 62–67, 69, 71, 77, 79, 84]. The weighted average effect size was 0.281 (95% CI, 0.195 to 0.367) for the fixed model and 0.355 (95% CI, 0.142 to 0.568) for the random-effects model. Numerous variables were included in bivariate analyses to assess the correlation with the effect size (**table 4**). Studies that did not monitor dosing and those with more frequent doses had larger effect sizes; but no variable was significant in the backward stepwise random-effects meta-regression.

Developing countries: Change in weight

There was a significant effect of zinc on change in weight in this meta-analysis ($p < .0001$) (**fig. 5**) [43, 45, 47, 48, 50, 52, 53, 55, 58, 62–67, 69, 71, 77, 79, 84]. The weighted average effect size was 0.302 (95% CI, 0.216 to 0.389) for the fixed model and 0.316 (95% CI, 0.151 to 0.482) for the random-effects model. Selected variables were included in bivariate analyses assessing the relation of these with the effect size of zinc on weight (**table 5**). As was observed with the analyses of height or length described above, studies that did not monitor dosing and those that used more frequent dosing had larger effect sizes. When variables were removed from

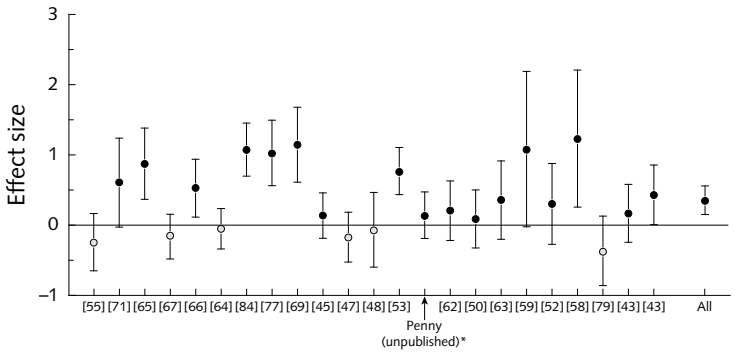

FIG. 4. Effect size for the change in height or length in all studies and overall. References to studies are given in square brackets
* Penny ME, Peerson JM, Marin RM. Unpublished observations.1998

TABLE 4. Correlation of selected trial and patient characteristics with effect size of zinc on height/length

Variable	Correlation with effect size	*N*	*p* value
Units	—	23	.47
Form of zinc (sulfate, gluconate, acetate)	—	23	.31
Initial mean age	–0.39	23	.191
Monitored	–0.66	22	.001
Dose	–0.28	21	.479
Frequency	0.56	23	.043
Weekly dose	–0.27	21	.159
Duration of study	–0.07	23	.706
Total dose	–0.19	21	.295
% male	0.29	23	.062
Initial mean height-for-age	–0.08	22	.659
Initial mean height-for-age < –2 z-scores	0.25	22	.238
Initial mean weight-for-age	0	21	.896
Initial mean weight-for-age < –2 z-scores	0.42	21	.100
Initial mean weight-for-height	–0.1	20	.944
Initial mean serum Zn	–0.23	16	.518
Initial mean serum Zn < 80 μg/dL	0.1	16	.660
Rural	–0.16	22	.314

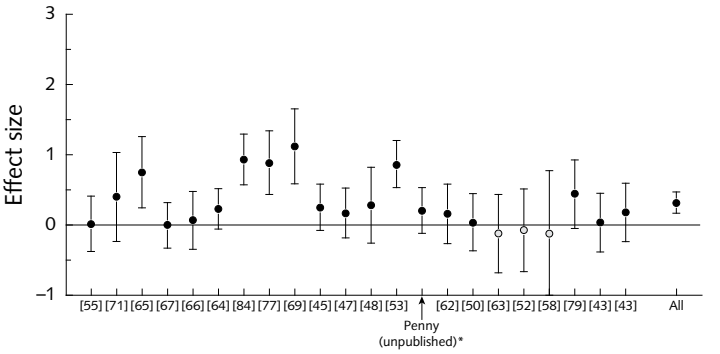

FIG. 5. Effect size for the change in weight in all studies and overall. References to studies are given in square brackets
* Penny ME, Peerson JM, Marin RM. Unpublished observations.1998

TABLE 5. Correlation of selected trial and patient characteristics with effect size of zinc on weight

Variable	Correlation with effect size	*N*	*p* value without outlier
Units	—	22	.066
Form of zinc (sulfate, gluconate, acetate)	—	2	.80
Initial mean age	–0.24	22	.259
Monitored	–0.81	21	< .001
Dose	–0.27	21	.182
Frequency	0.49	22	.028
Weekly dose	–0.16	21	.378
Duration of study	–0.37	22	.090
Total dose	–0.31	21	.148
% male	–0.13	22	.694
Initial mean height-for-age	0.05	21	.669
Initial mean height-for-age < –2 z-scores	0.05	21	.916
Initial mean weight-for-age	–0.07	20	.905
Initial mean weight-for-age < –2 z-scores	0.46	20	.061
Initial mean weight-for-height	–0.32	19	.194
Initial mean serum zinc	–0.33	15	.288
Initial mean serum zinc < 80 μg/dL	0.05	15	.894
Rural	–0.13	21	.477

a multivariate model in stepwise fashion, no predictor variable remained in the model. However, underweight status was marginally significant (p = .06), with a weighted average effect size of 0.204 (95% CI, 0.051 to 0.356) for those studies in which the initial mean WAZ was greater than –2, and a weighted average effect size of 0.532 (95% CI, –0.028 to 1.093) for those studies in which the initial mean WAZ was less than –2.

Development

Child development indicators have been assessed in seven trials of zinc supplementation [34, 61, 85–89] (**table 6**). The studies were conducted in Latin America and South Asia. Zinc supplements were given for at least 8 weeks, with doses ranging from 1 to 10 mg per day, and one trial giving 20 mg once weekly. The studies assessed infants under 1 year of age for basic development indicators, including the Bayley Scales of Infant Development (BSID), Psychomotor Development Index (PDI), and Motor Development Index [90]. Five out of seven trials showed some benefit of zinc on at least one measured indicator [34, 61, 86–88], one trial observed a negative effect of zinc on the mental development index of the BSID [89], and one trial observed no effect [85].

TABLE 6. Zinc supplementation for improved development

Author, date	Country	Study design	Population	Serum zinc	Indicators assessed	Significant differences
Bentley et al. 1997 [87]	Guatemala	Randomized 10 mg Zn vs. placebo daily for 7 mo	6–9 mo ($N = 85$)		Motor development, time in various positions, time playing, time crying	Zn-supplemented infants were observed sitting up on more days than controls and played more than controls
Ashworth et al. 1998 [88]	Brazil	Randomized 1 or 5 mg Zn vs. placebo 6 days/wk for 8 wk	LBW infant at birth, follow-up at 6 and 12 mo		BSID at 6 and 12 mo. 5-point behavior rating system used at 12 mo (responsiveness, emotional tone, activity level, cooperation, vocalization)	At 12 mo, infants receiving 5 mg Zn had highest score for all 5 ratings compared with both 1 mg Zn and placebo groups
Hamadani et al. 2001 [89]	Bangladesh	Randomized 5 mg Zn vs. placebo daily for 5 mo	1 mo of age ($N = 212$), follow-up at 7 and 13 mo		BSID	Zn-supplemented infants had lower mental development index of the BSID than controls
Castillo-Duran et al. 2001 [61]	Chile	Randomized 5 mg Zn vs. placebo daily for 12 mo	Full-term neonates ($N = 150$)		PDI, MDI, BSID	Fewer Zn-supplemented infants scored < 100 in MDI (42/57 vs. 46/52) and had low motor quality factor at 6 mo (2/57 vs. 8/52) than controls
Black et al. 2004 [86]	Bangladesh	Randomized 20 mg Zn vs. 1 mg riboflavin weekly for 6 mo	6 mo ($N = 318$)	Baseline: Zn 0.71, placebo 0.65 After 6 mo: Zn 0.79, placebo 0.69	Orientation engagement, MDI, PDI, emotional quality percentile, motor quality percentile	Benefit of zinc on orientation and engagement
Black et al. 2004 [85]	India	Randomized 5 mg Zn vs. placebo daily from 90 days to 9 mo (additional arms of study given multiple micronutrients)	SGA full-term infants (< 10th percentile) ($N = 200$)		Temperament, mental development, weight, length, emotional regulation	No effect
Meeks Gardner et al. 2005 [34]	Jamaica	Randomized 10 mg Zn vs. placebo daily for 6 mo	9–30 mo with < –1 WAZ ($N = 68$ for development)		Hand–eye coordination, motor development, hearing, speech, performance	Zn-supplemented infants had increased hand–eye coordination. There were significant interactions between Zn supplementation and stimulation

BSID, Bayley Scales of Infant Development; LBW, low birthweight; MDI, Motor Development Index; PDI, Psychomotor Development Index; SGA, small for gestational age; WAZ, weight-for-age z-score

TABLE 7. Nonrandomized studies assessing correlation between serum zinc and functional indicators

Author, date	Country	Study design	Population	Zinc indicators assessed	Significant differences ($p < 0.05$)
Cohort studies					
Bahl et al. 1998 [92]	India	Cohort	12–59 mo, recovering from acute diarrhea ($N = 125$)	Serum Zn, follow-up morbidity for 90 days	Children with low plasma Zn at baseline (≤ 8.4 μmol/L) had more episodes of diarrhea (RR, 1.47) and severe diarrhea (RR, 1.70) than those with higher plasma Zn. Prevalence associated with fever 4× higher in Zn-deficient group. Prevalence of ALRI 3.5× higher in Zn-deficient group
Hautvast et al. 2000 [91]	Zambia	Cohort	6–9 mo ($N = 108$), 14–20 mo ($N = 102$), followed-up 9 and 21 mo later	Weight, length, serum Zn	Micronutrient status did not show a significant relation with later HAZ
Cross-sectional studies					
Gibson et al. 1991 [93]	Papua New Guinea	Cross-sectional	24–120 mo ($N = 123$)	Weight, length z-scores, hair Zn, presence of malaria	Correlation among boys (24–95.5 mo) between HAZ and hair Zn concentration
Brown et al. 1993 [94]	Peru	Cross-sectional	11–19 mo ($N = 153$)	Serum Zn, clinical signs of infection	Nonsignificant trend for children with infection to have lower serum Zn than those without infection
Strand et al. 2004 [2]	Nepal	Cross-sectional	6–35 mo ($N = 1,757$)	Serum Zn	Factors associated with low serum Zn: fever (0.59 μmol/L increase per degree increase C); dysentery and high C-reactive protein associated with low plasma zinc. Dehydration linked with higher serum Zn
Case–control studies					
Castillo-Duran et al. 1988 [97]	Chile	Case–control	3–14 mo infants with acute diarrhea and age-matched controls ($N = 29$)	Fecal Zn, urine Zn, serum Zn	Fecal loss higher in diarrhea group than in controls (159.4 vs. 47.4 μg/kg/day) for 48 h, but not after 6–7 days. Plasma Zn lower at 48 h and day 6 than in controls (57.7, 101.4 vs. 123.6 μg/dL)
Chaudhary et al. 1996 [98]	India	Case–control	Children with diarrhea and age-matched controls ($N = 50$)	Serum Zn	Plasma Zn lower in children with persistent diarrhea and acute diarrhea than in controls (79.4, 135.4 vs. 151.87 μg/dL)
Demirci et al. 2003 [96]	Turkey	Case–control	Children with chronic giardiasis ($N = 34$) and controls	Serum Zn	Serum Zn lower in children with chronic giardiasis than in controls (109 vs. 136 μg/dL)
Shakur et al. 2004 [95]	Bangladesh	Case–control	6–60 mo with ALRI ($N = 35$) and healthy children ($N = 38$)	Serum Zn, hair Zn	Serum Zn (90 vs. 176 μg/dL) and hair Zn (158 vs. 247 μg/g) lower in children with ALRI than in controls; low serum Zn associated with ALRI in multiple logistic regression analysis

ALRI, acute lower respiratory infection; HAZ, height-for-age z-score; RR, relative risk

Correlation studies

We included studies with cohort, cross-sectional, or case–control designs that assessed a biochemical measure of zinc status and one of the functional indicators we have included in this review (**table 7**). Two cohort studies assessed serum zinc at baseline, and one found that lower serum zinc status was associated with increased infection rates during the 90 days of follow-up [91, 92]. Three cross-sectional studies assessed correlations of serum zinc status and presence of infection and/or anthropometric indicators [2, 93, 94]. Four studies assessed serum zinc levels among children with diarrhea and matching controls [95–98]. The studies found that serum zinc was lower among children with an active infection than among control children.

Summary and discussion

Zinc deficiency is now widely recognized as a leading risk factor for morbidity and mortality; however, accurately assessing individual zinc deficiency remains challenging [4, 99]. The results of zinc supplementation trials show positive effects of zinc on functional outcomes, including infectious disease morbidity, growth, and development. These data are important for the treatment and prevention of illnesses in young children and should lead to interventions that include zinc in supplementation or food-based interventions.

Evaluating the therapeutic response to zinc supplementation as assessed by randomized trials would be useful to determine population-level zinc deficiency. However, continuing trials with a policy for supplementation during contemporaneous diarrhea treatment would be unethical, and therefore, additional data will not be available. Zinc deficiency can lead to increased rates of diarrhea and pneumonia, but the rates of these diseases are variable between and within individual countries. The effect of zinc deficiency on the incidence and prevalence rates of diarrhea is not so great that it could be used to distinguish populations or groups likely to be deficient. However, it is possible to expect that populations with the highest rates of diarrhea would be more likely to have higher rates of zinc deficiency because of losses of zinc in the stools. The effects of zinc deficiency on child development are not consistent and are too difficult to measure to be useful as a population indicator.

It is well known that zinc deficiency can lead to growth retardation [1]. Brown et al. previously showed that children receiving zinc supplementation responded positively, especially when they were underweight or stunted at baseline [7]. Additional analysis of the results from growth trials confirms that we will expect to see the greatest response to supplementation in populations with the highest rates of stunting. Stunting rates of 20% and higher are considered a public health concern by the World Heath Organization [100], and this value was recommended as a realistic cutoff to estimate problematic zinc deficiency within a population [4]. The additional investigation presented in this review supports these findings and recommendations for using stunting rates as the best approximation for estimating zinc deficiency at the population level for children under 5 years of age.

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