Food fortification with zinc seems to be an attractive public health strategy and a number of programs have been initiated, especially in developing countries

Ann Nutr Metab 2013;62(suppl 1):44–56

Systematic Review of Zinc Fortification Trials

by Jai K. Das et al.

Key insights

Food fortification is an effective public health strategy to address zinc deficiency in target populations, especially in developing countries. This systematic review was conducted in order to assess the efficacy of zinc fortification, and encompassed 11 studies with 771 participants.

Current knowledge

The World Health Organization (WHO) estimates that over 2 billion people are deficient in key vitamins and minerals, including zinc. Infants, young children, and pregnant and lactating women are especially vulnerable due to their greater physiological needs. Although food fortification programs are widespread, surprisingly few of these have been formally evaluated for the actual benefits on population health. Seven studies on infants, three studies on school age children and one study on women of reproductive age were included in the analysis. Food fortification resulted in significant improvements in plasma zinc concentrations, a functional indicator of zinc status. There were also positive trends for weight gain, as well as serum hemoglobin and copper concentrations.

Practical implications

Additional data is needed for vulnerable populations, particularly pregnant and lactating women. In order to determine whether large-scale fortification programs are able to address the zinc requirements of an entire population including all its vulnerable subgroups, impact assessment must be initiated. Uniform dosage, timing, type of food vehicle and proper sam-

Sources and functions of zinc. Please refer to the article for further details.

pling of serum zinc levels are key factors that should drive future studies designed to evaluate the efficacy of population-wide interventions.

Recommended reading

Brown KH, Hambidge KM, Ranum P, Zinc Fortification Working Group: Zinc fortification of cereal flours: current recommendations and research needs. Food Nutr Bull 2010;31(1 suppl):S62–S74.

Systematic Review of Zinc Fortification Trials

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Key Messages

- One third of the world population lives in countries with a high prevalence of zinc deficiency.
- The most vulnerable groups include infants, young children, and pregnant and lactating women because of their higher zinc requirements, as they are at critical stages of growth and physiological needs.
- Significant amounts of zinc reside in muscles and bones but are insufficient to provide a metabolic buffer, so serum zinc levels are totally dependent on intake.
- Food fortification with zinc is associated with significant improvements in the plasma zinc concentrations.
- The pooled analysis showed significant impact on height velocity for newborns with very low birth weight, whereas the effect was not significant for normal-weight newborns.
- Zinc fortification has no adverse effect on hemoglobin and serum copper levels.
- Zinc fortification as a strategy has the potential to alleviate zinc deficiency especially in children.

Key Words

Height velocity · Weight gain · Alkaline phosphatase · Serum copper levels · Fortification · Supplementation · Zinc · Children · Growth

Abstract

Zinc is one of the essential trace elements required by the human body as it is present in more than a hundred specific enzymes and serves as an important structural ion in transcription factors. Around one third of the world population lives in countries with a high prevalence of zinc deficiency. Food fortification with zinc seems to be an attractive public health strategy and a number of programs have been initiated, especially in developing countries. We conducted a systematic review to assess the efficacy of zinc fortification. A total of 11 studies with 771 participants were included in our analysis. Zinc fortification was associated with significant improvements in plasma zinc concentrations [standard mean difference (SMD) 1.28, 95% CI 0.56, 2.01] which is a functional indicator of zinc status. Significant improvement was observed for height velocity (SMD 0.52, 95% CI 0.01, 1.04); however, this finding was weak and based on a restricted analysis. Further subgroup analysis showed significant improvement in height velocity among very-low-birth-weight infants (SMD 0.70, 95% CI 0.02, 1.37), while for healthy newborns, the impact was insignificant. Zinc fortification had insignificant impacts on serum alkaline levels, serum copper levels, hemoglobin and weight gain. Although the findings highlight that zinc fortification is associated with an increased serum concentration of the micronutrient, overall evidence of the effectiveness of this approach is limited. Data on pregnant and lactating women is scarce. Large-scale fortification programs with robust impact assessment should be initiated to cover larger populations in all age groups. Mass fortification of zinc may be a cost-effective strategy to overcome zinc deficiency.

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Fig. 1. Sources and function of zinc in humans. LH = Luteinizing hormone; FSH = follicle-stimulating hormone.

Background

Vitamins and minerals are essential for growth and metabolism. The World Health Organization (WHO) estimates that more than 2 billion people are deficient in key vitamins and minerals, particularly vitamin A, iodine, iron and zinc [1]. Zinc is one of the essential trace elements required by the human body [2] as it is present in more than a hundred specific enzymes and serves as an important structural ion in transcription factors [3]. It is widely distributed across different tissues including the brain, muscles, bones, liver and kidney, with exceedingly large quantities present within the prostate and parts of the eye [4, 5]. It has a key role in reproductive physiology, immune modulation, growth and development [6]. In blood plasma, zinc is bound to and transported by albumin (60%, low-affinity) and transferrin (10%) [7], which also transports iron and copper; thus, an excessive concentration of these can reduce zinc absorption, and vice-versa. The physiology of zinc metabolism and functions and dietary sources are outlined in figure 1.

Zinc deficiency was recognized as a health concern for the first time in 1961 [6]. Since then, zinc has become a major focus of attention. It is estimated that one third of the world population lives in countries with a high prevalence of zinc deficiency [8]. The vulnerable populations include infants, young children, and pregnant and lactating women because of their higher zinc requirements, as they are at critical stages of growth and physiological needs [9, 10]. An estimated 82% of pregnant women worldwide also have an inadequate zinc intake to meet the normative needs of pregnancy [11]. Dietary zinc dependence in infants is greatest when the prenatal liver stores have been exhausted and subsequent transient zinc deficiency can occur as mother's milk has an exceptionally low concentration of zinc [12]. The Lancet series on maternal and childhood undernutrition estimated that zinc deficiency is responsible for approximately 4% of deaths and disability-adjusted life years among under-5 children in lower-income countries [10]. A recent meta-analysis of supplementation trials has shown that zinc

Fig. 2. Results of the search strategy.

supplementation has been associated with a reduced mortality due to diarrhea and pneumonia [13].

Evaluation of the impact of zinc fortification trials is challenging because of the lack of adequate biomarkers of individual zinc status. Nevertheless, recent analyses indicate that the mean serum zinc concentration of a population responds consistently to zinc supplementation, regardless of the population's baseline mean serum zinc concentration [14]. Additionally, morbidity reduction and growth [15] could be used as reliable indicators of successful zinc fortification. Notwithstanding the documented evidence of benefits of zinc supplementation, few large-scale fortification programs have been initiated in this regard, possibly due to the scarcity of data on the success of zinc fortification programs. Mass zinc fortification programs started in China and Mexico, where cereal flour was fortified. These programs were initiated so that populations match their recommended daily intakes of zinc. Several compounds of zinc have been found to be safe for human consumption. Zinc oxide is the most widely used as it is the cheapest, while zinc sulfate is used in formulas. Zinc losses during storage and transportation are also minimal for this compound, thus validating its use.

Food fortification with zinc seems to be an attractive public health strategy and a number of programs have been initiated, especially in developing countries. Surprisingly, relatively few of these have been formally evaluated to assess their impact on population health [16]. Much of the putative benefits of fortification are derived from supplementation trials, hence extrapolation to ben-

efits through fortification strategies where the vehicle and dosage differs greatly is difficult. As a result, we undertook a systematic review of the current evidence to assess impact of food fortification with zinc on the health and nutrition of women and children.

Zinc deficiency is responsible for approximately 4% of deaths and disability-adjusted life years among under-5 children in lower-income countries.

Methods

Search Strategy

All available evidence for the impact of fortification interventions was systematically retrieved and analyzed (fig. 2). A comprehensive search was done for key words including MeSH and free text terms on the Cochrane Library, Medline, PubMed, Popline, LILACS, CINAHL, and British Library for Development Studies (BLDS), the WHO regional databases as well as the IDEAS database of unpublished working papers, Google and Google Scholar. Detailed manual searches were undertaken including cross-references and bibliographies of available data and publications to identify additional sources of information. In particular, this search was also extended to review the gray literature in non-indexed and non-electronic sources. The bibliographies of books with relevant sections were also searched manually to identify relevant reports and publications. The date of last search was October 8, 2012.

Table 1. Characteristics of the selected studies

First author	Year	Country	Study design	Target population and age groups	Fortification compound and carrier	Amount of zinc used in fortification (amount of zinc in control group)	Duration of intervention	Participants total n
Badii [27]	2012	Iran	RCT	zinc-deficient women aged 19–49 years	zinc sulfate in bread	50 and 100 mg/kg	1 month	75
Brown [17]	2007	Peru	RCT	infants aged 6–8 months with a risk of stunting	zinc sulfate in porridge	150 mg/kg dry weight	6 months	178
Diaz-Gomez [18]	2003	Spain	RCT	VLBW preterm infants	zinc sulfate in formula feed	10 mg/l (5 mg/l)	6 months	36
Friel [19]	1993	Canada	RCT	VLBW newborns	zinc sulfate in formula feed	11 mg/l (6.7 mg/l)	6 months	50
Hambidge [24]	1979	USA	RCT	2- to 7-year-old healthy children	zinc oxide in cereals	3.75 mg/oz	9 months	96
Kiliç [25]	1998	Turkey	RCT	7- to 11-year-old school children with asymptomatic zinc deficiency	zinc acetate in bread	400 mg/loaf	3 months	24
Matsuda [20]	1984	Japan	quasi	full-term newborns	formula feed	3.2 mg/l (1.0 mg/l)	5 months	39
Ohiokpehai [26]	2009	Kenya	quasi	6- to 9-year-old school children	porridge	5 mg/100 g	3 months	134
Salmenpera [21]	1994	Finland	RCT	full-term newborns	formula feed	5.2 mg/l, 1.1 mg/l	12 months	32
Schlesinger [22]	1992	Chile	RCT	malnourished infants	zinc chloride in formula feed	15 mg/l (3.2 mg/l)	3.5 months	39
Walravens [23]	1976	USA	RCT	full-term newborns	zinc sulfate in formula feed	5.8 mg/l (1.8 mg/l)	6 months	68

RCT = Randomized controlled trial; quasi = quasi-RCT.

Types of Studies

Types of studies included in our review were randomized controlled trials and quasi-randomized controlled trials. In addition, other less rigorous study designs like observational (cohort and case-control) studies, food fortification program evaluations and descriptive studies have been reviewed to understand the context in which these interventions were implemented.

Inclusion Criteria

Studies were included if

- Food was fortified with zinc as the only micronutrient.
- The food vehicles chosen for fortification were staples, condiments or processed foods.
- Effects of fortification were analyzed with respect to the health outcomes of women and children.
- Randomized controlled trials or quasi-randomized trials were considered for this review if the control group was no intervention group, with a regular diet or unfortified foods.
- Studies were not considered for inclusion if they focused on home fortification with micronutrient powders, food contents, intake levels, bioavailability, comparisons between different food vehicles or comparisons among compounds of the same micronutrient, comparisons between fortification and supplementation, biofortification and studies evaluating the sensory impacts of fortification.

Data Analysis

All the available studies underwent triage with standardized criteria for evaluating outputs from primary screening. Following

an agreement on the search strategy, the abstracts and full texts were screened by two independent abstractors to identify studies meeting the inclusion criteria. Any disagreements between the two primary abstractors were resolved by the third reviewer. After retrieval of the full texts of all studies that met the inclusion criteria, each study was double-data abstracted into a standardized form. We performed a meta-analysis of all the outcomes with more than one study. For dichotomous data, we presented results as summary risk ratio and odds ratios with 95% confidence intervals (CI). For continuous data, we used the standard mean difference (SMD), where the units of measurement were not uniform, between trials to denote if specific outcomes were comparable and in the right direction. SMDs were interpreted to be significant if the CI did not include 0; hence, SMDs >0 indicate improvement, whereas those <0 show deterioration.

The data were incorporated using a generic inverse variance method in which logarithms of risk ratio estimates were used along with the standard error. The level of attrition was noted for each study and its impact on the overall treatment effect was explored by using sensitivity analysis. Heterogeneity between trials was assessed using the I^2 statistic, a p value of <0.1 (on χ^2) and by visual inspection of forest plots. Mantel-Haenszel pooled relative risk and corresponding 95% CI were reported, or the DerSimonian-Laird pooled relative risk and corresponding 95% CI where there was an unexplained heterogeneity. All analyses were conducted using the software Review Manager 5.1.

Table 2. Risk of bias of the selected studies

First author	Sequence allocation	Allocation concealment	Blinding	Incomplete outcome data addressed	Selective reporting
Badii [27]	unclear	unclear	unclear	no	yes
Brown [17]	yes	unclear	yes	yes	yes
Friel [19]	yes	yes	yes	yes	yes
Diaz-Gomez [18]	yes	yes	yes	yes	yes
Hambidge [24]	unclear	unclear	yes	no	yes
Kiliç [25]	unclear	unclear	yes	no	yes
Matsuda [20]	unclear	unclear	unclear	yes	yes
Ohiokepehai [26]	no	no	no	yes	yes
Salmenpera [21]	unclear	unclear	unclear	no	yes
Schlesinger [22]	unclear	unclear	yes	no	yes
Walravens [23]	no	unclear	yes	no	yes

Results

Our search strategy, including manual search, identified eleven studies, seven of which were on infants [17–23] where infant formula feeds or milk were fortified, three were on school children where porridge or bread was fortified [24–26], while one study was on women of reproductive age [27]. Nine of the studies were randomized controlled trials while two [20, 26] were quasi-experimental designs. The studies varied in the duration of intervention, ranging from 1 to 12 months. Five studies [17–19, 23, 27] employed zinc sulfate as the fortification compound. Other compounds used were zinc oxide [24], zinc chloride [22] and zinc acetate [25]. All included studies compared zinc-fortified food with control groups with no fortification. Four studies were conducted in developing countries, while the rest were from the developed part of the world. The characteristics of the studies are summarized in table 1 and risk of bias assessment is presented in table 2. The most commonly reported outcomes were serum zinc concentration [17–22, 24–26], hemoglobin level [18, 22, 25], alkaline phosphatase [21, 23, 25], serum copper concentration [20, 22, 23, 25], weight gain [17, 18, 20, 22–24] and linear growth or height velocity (growth in mm/day) [17, 18, 20–24]. The study by Brown et al. [17] also looked at the effect of zinc fortification on episodes of diarrhea, flu-like symptoms, pneumonia and other illness during the period of intervention. The results of the study by Badii et al. [27] were not included in the pooled analysis as it was done on women of reproductive age, while all others were on children, including infants and school age children. A summary of the results is presented in table 3.

Effect on Serum Zinc Concentration

Results from nine trials [17–22, 24–26] showed that there was a significant impact of zinc fortification on serum zinc concentration, with individual impacts ranging from 0.08 (95% CI –0.65, 0.81) to 5.51 (95% CI 3.91, 7.11) and a combined SMD of 1.28 (95% CI 0.56, 2.01). The heterogeneity was high ($p < 0.00001$; $I^2 = 89\%$), hence a random effect model was used. The study by Badii et al. [27] showed a significant change in serum zinc concentration in women of reproductive age when compared to controls with a SMD of 1.82 (95% CI 1.52, 2.40). Subgroup analysis showed that there was no significant difference among the various compounds of zinc. Further subgroup analysis for the duration of intervention showed positive trends with a SMD of 1.48 (95% CI 0.57, 2.39) and 1.51 (95% CI 0.13, 2.89) for <6 and >6 months, respectively. The subgroup analysis of different study populations is presented in figure 3.

Effect on Linear Growth and Height Velocity

Seven trials [17, 18, 20, 21, 23, 24] comprising 451 children showed that there was an insignificant change in height velocity (mm/day) with a SMD of 0.08 (95% CI –0.53, 0.69). On visual inspection of the forest plot, the study by Salmenpera et al. [21] was an outlier, and after removing this particular study, the impact on height velocity became significant with a SMD of 0.52 (95% CI 0.01, 1.04) (fig. 4). The subgroup analysis showed significant improvement in height velocity among newborns with very low birth weight (VLBW) with a SMD of 0.70 (95% CI 0.02, 1.37), while for the healthy newborns the impact was insignificant with a SMD of –0.48 (95% CI –2.45, 1.48).

Table 3. Summary of the study outcomes

Outcome	Studies n	Countries	Participants total n	SMD (95% CI)
<i>Biological (serum) markers</i>				
Serum zinc levels [17–22, 24–26]	9		683	1.28 (0.56, 2.01)
Healthy newborns [20, 21]	2	Japan, Finland	71	3.49 (–0.36, 7.33)
Newborns with VLBW [18, 19]	2	Spain, Canada	64	0.51 (–0.32, 1.34)
Infants at risk of stunting [17]	1	Peru	147	0.09 (–0.24, 0.41)
Malnourished infants [22]	1	Chile	35	0.12 (–0.55, 0.78)
School children with asymptomatic zinc deficiency [25]	1	Turkey	19	2.77 (1.43, 4.11)
School children [24, 26]	2	USA, Kenya	347	1.12 (–0.21, 2.46)
Serum hemoglobin [18, 22, 25]	3	Spain, Turkey, Chile	92	–0.11 (–0.52, 0.31)
Zinc sulfate for fortification [18]	1	Spain	34	0.00 (–0.67, 0.67)
Zinc chloride for fortification [22]	1	Chile	39	–0.39 (–1.03, 0.24)
Zinc acetate for fortification [25]	1	Turkey	19	0.28 (–0.62, 1.19)
Serum copper [20, 22, 23, 25]	4	Turkey, Japan, Chile, USA	161	0.29 (–0.96, 1.54)
Serum alkaline phosphatase [21, 23, 25]	3	Turkey, Finland, USA	119	0.94 (–0.29, 2.17)
<i>Anthropometric markers</i>				
Height growth velocity [17, 18, 20, 22–24]	6		451	0.52 (0.01, 1.04)
Healthy newborns [20, 21, 23]	3	Japan, Finland, USA	112	–0.48 (–2.45, 1.48)
Newborns with VLBW [18]	1	Spain	36	0.70 (0.02, 1.37)
Infants at risk of stunting [17]	1	Peru	176	0.05 (–0.25, 0.35)
Malnourished infants [22]	1	Chile	39	0.16 (–0.47, 0.79)
School children [24]	1	USA	88	0.31 (–0.11, 0.74)
Weight gain velocity [17, 18, 20, 22–24]	6		419	0.50 (–0.12, 1.11)
Healthy newborns [20, 23]	2	Japan, USA	80	1.48 (–1.49, 4.45)
Newborns with VLBW [18]	1	Spain	36	0.33 (–0.33, 0.99)
Infants at risk of stunting [17]	1	Peru	176	0.00 (–0.30, 0.30)
Malnourished infants [22]	1	Chile	39	–0.10 (–0.73, 0.52)
School children [24]	1	USA	88	0.25 (–0.17, 0.67)

Effect on Weight Gain

Six trials [17, 18, 20, 22–24] comprising 419 children showed that food fortification with zinc had an insignificant impact on weight gain (g/day) when compared to the control group, although the trend was positive with a SMD of 0.50 (95% CI –0.12, 1.11) (fig. 5). Results of a further subgroup analysis did show a positive trend in weight gain among newborn infants, infants with VLBW, infants at risk of stunting and growing school children, but not in malnourished infants. These results were all statistically insignificant and are summarized in table 3.

Effect on Alkaline Phosphatase Levels

Serum alkaline phosphatase levels may be responsive to zinc supplementation and increase in serum concentration has been used as an indirect biomarker of effect. Three studies with a total of 119 children evaluated the

impact of zinc fortification on the alkaline phosphatase activity; two studies examined healthy infants [21, 23], while one study had asymptomatic zinc-deficient school children as a study population [25]. The pooled analysis had a net SMD of 0.94 (95% CI –0.29, 2.17) (fig. 6).

Effect on Hemoglobin Levels

We evaluated the possible concerns in relation to negative effect of zinc fortification on iron absorption and anemia. Three trials comprising 92 children [18, 22, 25] showed that zinc fortification of foods had an insignificant impact on the mean hemoglobin levels. Pooled results had a SMD of –0.11 (95% CI –0.52, 0.31). There was no significant heterogeneity (χ^2 : $p = 0.45$; $I^2 = 0\%$), hence a fixed model was used (fig. 7). Subgroup analysis of the various types of zinc compound used for fortification showed a decrease in hemoglobin level as compared to control with zinc chloride [22] (SMD –0.39, 95% CI

Fig. 3. Forest plot showing the effect of zinc fortification on serum zinc levels.

-1.03, 0.24). There was a positive trend for an influence of zinc acetate [25] on the hemoglobin levels (SMD 0.28, 95% CI -0.62, 1.19), while zinc sulfate [18] did not have any significant effect (SMD 0.00, 95% CI -0.67, 0.67), although all these results were not statistically significant.

Effect on Serum Copper Concentration

Zinc supplementation may be associated with a concomitant reduction in serum copper concentration. Four trials [20, 22, 23, 25] with a combined study population of 161 measured the impact of zinc fortification on serum

Fig. 4. Forest plot showing the effect of zinc fortification on height velocity.

copper concentration. The SMD for individual studies ranged from -0.88 (95% CI -1.54, -0.22) to 1.97 (95% CI 1.38, 2.55). The pooled results showed no net effect on serum copper concentration with a SMD of 0.22 (95% CI -1.14, 1.59) (fig. 8). Subgroup analysis between healthy infants [20, 23] and malnourished infants [22] did not reveal significant differences between the two groups with a SMD of 0.75 (95% CI -1.65, 3.16) and 0.21 (95% CI -0.46, 0.87), respectively.

Discussion

This systematic review was undertaken to evaluate the effects of zinc fortification on the biochemical indicators and health outcomes. Most of the studies were done on infants and the food most commonly fortified was infant formula. Food fortification with zinc was associated with significant improvements in the plasma zinc concentrations (SMD 1.28, 95% CI 0.56, 2.01) which are a functional indicator of zinc status. Also, significant differences were observed for height velocity (SMD 0.52, 95% CI

Fig. 5. Forest plot showing the effect of zinc fortification on weight gain.

0.01, 1.04); however, this finding was weak and based on a restricted analysis. Pooled estimates for other outcomes, such as hemoglobin levels, weight gain, alkaline phosphatase levels and serum copper concentrations, were statistically insignificant, although they showed positive trends.

It has been previously shown that zinc fortification may be associated with increased zinc availability and absorption [28]; however, a few studies have reported otherwise. These differences between fortification studies may be attributable to the varying concentrations of zinc used and the presence of components other than zinc in

the foods fortified. In addition to that, the type of food may also have affected the absorption and its bioavailability, as different food vehicles (milk, bread, infant formulae and porridge) were used.

Significant amounts of zinc are stored in muscles and bones but are insufficient to provide a metabolic buffer, so serum zinc levels are totally dependent on intake. There has been considerable debate in establishing whether serum zinc concentrations are a reliable indicator of zinc status, as a few studies have shown that zinc supplementation in zinc-deficient children may show improve-

Fig. 6. Forest plot showing the effect of zinc fortification on serum alkaline phosphatase.

Fig. 7. Forest plot showing the effect of zinc fortification on serum hemoglobin levels.

ments in clinical features of deficiency, but with only marginal or no increase in the plasma zinc levels. The study by Schlesinger et al. [22] showed that zinc fortification was associated with improvements in linear growth and immune function of malnourished children, while

the plasma zinc levels did not reflect the same findings. On the other hand, Salmenpera et al. [21], Diaz-Gomez et al. [18], Matsuda et al. [20] and Kiliç et al. [25] report improved zinc concentration with fortification. There may be reservations whether zinc status can be judged by

Fig. 8. Forest plot showing the effect of zinc fortification on serum copper levels.

increased zinc levels, but a low concentration of zinc clearly signifies deficiency. The increase in the serum zinc concentration is inversely related to the amount of zinc ingested, as it attains a plateau stage after an initial steep rise [28]. This was suggested by a study showing that supplementing 25 mg daily did improve zinc levels in the first month, but results were not consistent when compared to the 9 months post data [29]. Another possible explanation could be the different characteristics of the sample groups and the sampling techniques. A recent briefing published by the International Zinc Nutrition Consultative Group suggests the use of a standardized procedure for sampling and its interpretation, as the timing of sampling and contamination can affect the results significantly [30].

Zinc supplementation has been associated with increased linear growth. Walravens and Hambidge [23] and Hambidge et al. [24] have reported a significant increase in growth velocity, but studies by Matsuda et al. [20] and Salmenpera et al. [21] do not corroborate this. In fact, Salmenpera et al. [21] reported increased growth velocity for the non-supplemented group. This discrepancy could be due to the dose differences of zinc, as the concentration of zinc was higher in Walravens and Hambidge [23] and Hambidge et al. [24]. The pooled analysis showed significant impact on height velocity for newborns with VLBW, while the effect was not significant for normal-weight newborns. This could mean that newborns with low birth weight could benefit more from zinc fortification as compared to healthy newborns. This observation is contradicted by a study which showed no significant differences

between healthy term newborns and small-for-gestational-age newborns when supplemented with zinc [31]. This can be a potential area for future research to provide more consolidated evidence.

Zinc can interact with iron and reduce its absorption [32] when administered in large quantities; however, fortified foods do not have such high zinc concentrations [18]. This was also suggested by our review as the hemoglobin levels were not affected significantly. Zinc supplementation is also associated with a decrease in serum copper levels as they compete for the same receptors [33–35]. Our review provides mixed findings in relation to this parameter. Kiliç et al. [25] and Schlesinger et al. [22]

Although the findings highlight that zinc fortification is associated with an increased serum concentration of the micronutrient, overall evidence of the effectiveness of this approach is limited.

showed that zinc fortification had no negative effects on the concentration of copper, but Matsuda et al. [20] showed significantly reduced copper levels, while Walravens and Hambidge [23] showed that serum copper concentration in fact improved after zinc fortification. Only one study reported an effect of zinc fortification on morbidities during the intervention period [17], but conclud-

ed that there was no significant effect on prevalence of diarrhea, common cold, lower respiratory tract infections and fever.

Although the findings highlight that zinc fortification is associated with an increased serum concentration of the micronutrient, overall evidence of the effectiveness of this approach is limited. This could be attributable to multiple factors including paucity of studies, small size of the trials, the age group identified, zinc levels at baseline, zinc compound fortified and the food vehicles used. It is therefore necessary to identify the amount of zinc for fortification and the appropriate vehicle. This has been widely evaluated and certain recommendations have already been suggested [36].

Cost is important when planning mass food fortification programs. Since staples and condiments are widely consumed by most of the population, changes in prices can significantly affect a large group of people. It is now established that zinc oxide is one of the cheapest compounds available for mass fortification. It is estimated that the use of zinc costs USD 0.006–0.013 for a woman to receive her annual requirement [37].

As data on susceptible populations, notably pregnant and lactating women, are scarce, large-scale fortification programs with robust impact assessment should be initiated to cover larger populations in all age groups. Currently, data from mass fortification programs are not yet available; it will be crucial to look at the effect of mass fortification programs on serum zinc levels and growth parameters. This may be the critical evidence to answer the question whether zinc provided through food fortifications is the key to overcoming zinc deficiency. Future research using a targeted strategy should focus on the use of uniform levels of zinc content, duration of fortification and the vehicle employed with special focus on the proper sampling of serum zinc levels.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the paper. The writing of this article was supported by Nestlé Nutrition Institute.

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