Pediatric RESEARCH

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REVIEW ARTICLE

Role of zinc in neonatal growth and brain growth: review and scoping review

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This manuscript includes (1) a narrative review of Zinc as an essential nutrient for fetal and neonatal growth and brain growth and development and (2) a scoping review of studies assessing the effects of Zinc supplementation on survival, growth, brain growth, and neurodevelopment in neonates. Very preterm infants and small for gestational age infants are at risk for Zinc deficiency. Zinc deficiency can cause several complications including periorificial lesions, delayed wound healing, hair loss, diarrhea, immune deficiency, growth failure with stunting, and brain atrophy and dysfunction. Zinc is considered essential for oligodendrogenesis, neurogenesis, neuronal differentiation, white matter growth, and multiple biological and physiological roles in neurobiology. Data support the possibility that the critical period of Zinc delivery for brain growth in the mouse starts at 18 days of a 20–21-day pregnancy and extends during lactation and in human may start at 26 weeks of gestation and extend until at least 44 weeks of postmenstrual age. Studies are needed to better elucidate Zinc requirement in extremely low gestational age neonates to minimize morbidity, optimize growth, and brain growth, prevent periventricular leukomalacia and optimize neurodevelopment.

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IMPACT:

- Zinc is essential for growth and brain growth and development.
- In the USA, very preterm small for gestational age infants are at risk for Zinc deficiency.
- Data support the possibility that the critical period of Zinc delivery for brain growth in the mouse starts at 18 days of a 20–21-day pregnancy and extends during lactation and in human may start at 26 weeks' gestation and extend until at least 44 weeks of postmenstrual age.
- Several randomized trials of Zinc supplementation in neonates have shown improvement in growth when using high enough dose, for long duration in patients likely to or proven to have a Zinc deficiency.
- Studies are needed to better elucidate Zinc requirement in extremely low gestational age neonates to minimize morbidity, optimize growth and brain growth, prevent periventricular leukomalacia and optimize neurodevelopment.

INTRODUCTION

Insufficient growth in preterm infants, diagnosed by excessive postnatal decreases in *Z*-scores of weight, length, and fronto-occipital circumference (FOC), but not by percentiles at 36 weeks postmenstrual age (PMA) or discharge, is associated with neurodevelopmental impairment.[1] Nutritional factors for brain development include appropriate delivery and uptake of energy, protein, fat, carbohydrate, iron, copper (Cu), zinc (Zn), iodine, thiamine, folate, selenium, choline, vitamins A, B_{12}, C, D, and optimal proportions of long-chain polyunsaturated fatty acids.[2,3] Several studies have shown that the developing brain has critical growth periods; however, the critical period for Zn delivery for brain growth has not been established.[4–6]

This manuscript includes (A) a narrative review of the role of Zn as an essential nutrient for fetal and neonatal growth and brain growth and development and (B) a scoping review of the effects of Zn supplementation on survival, growth, brain growth, and neurodevelopment in neonates.

NARRATIVE REVIEW

Zinc as an essential nutrient

Role and distribution of Zn. Zn is an essential nutrient. Zn deficiency is an important cause of morbidity and stunting (short length for age and sex) in developing countries worldwide.[7–9] Zn is one of the most important trace elements in the body as ~10% of the proteins in the human proteome are Zn-dependent. Zn is a component of transcription factors, structural proteins, and enzymes including metalloproteases, nitric oxide synthase, and superoxide dismutase.[10–12] Most Zn in the body is bound to metallothioneins (MT), a class of proteins important for metal chelation, antioxidant protection, cellular repair processes, nutritional immunity, growth, and differentiation.[13] In adults, ~60% of Zn is stored in skeletal muscle, 30% in bone, 5% in liver, and skin.[14] Zn is absorbed in the duodenum and jejunum and distributed to all organs, tissues, fluids, and secretions.[10] The two families of Zn transporters, Zrt- and Irt-like protein (ZIP) transporters (which increase Zn uptake into the cytoplasm) and ZnT transporters

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(which reduce cytoplasmic Zn by exporting cellular Zn or by moving it into intracellular organelles or extracellular space) are ubiquitous.[14]

Assessing body Zn content. Assessing total body Zn content is challenging because Zn is primarily intracellular.[15] The Biomarkers of Nutrition for Development (BOND) Zn Expert Panel recommends three measurements for estimating Zn status: dietary Zn intake, plasma Zn concentration, and height-for-age of growing infants and children.[15] The amount of dietary Zn intake is higher in diets rich in meat and lower in strict vegetarian or vegan diets and in the breast milk of women with SLC30A2/ZnT2 (ZnT transporter) mutation.[10,11] Factors affecting enteral Zn absorption include gastrointestinal diseases, products interfering with Zn absorption (uncooked cereals, geophagy, Cu, iron, and calcium), and mutations of ZIP-4 (Zn transporter protein causing acrodermatitis enteropathica).[10,11] A meta-analysis in infants showed a significant relationship between the population mean Zn serum or plasma concentration and Zn intake.[16]

Most Zn (80%) in the blood is in red blood cells (RBCs) and 87% of RBC Zn is in carbonic anhydrase.[17–19] In serum, most Zn is bound to albumin and alpha-2 macroglobulin, and a smaller amount is bound to amino acids.[20] Serum Zn concentration may decrease with hypoalbuminemia, systemic steroids, infection, acute stress, increased nutritional intake, and growth rate and may be elevated with hemolysis or catabolic state.[20,21] Thus, serum Zn concentration is not a gold standard to assess total body Zn content. Potential and emerging biomarkers include hair Zn, urinary Zn, nail Zn, neurobehavioral function, Zn-dependent proteins, oxidative stress, inflammation, and DNA integrity, Zn kinetics, and taste acuity.[8,22,23] Zn depletion may occur with only a minimal decrease in hair Zn concentration.[23]

Role of Zn in growth (Fig. 1)

Zn deficiency limits linear growth, weight gain, and lean body mass accretion. This may be in part related to a reduction in circulating insulin-like growth factor 1 (IGF-1) concentration.[11] In a randomized control trial (RCT) in stunted children <2 years of age, Zn supplementation yielded catch-up growth and increased serum concentration of IGF-1.[24] However, in neonatal RCTs, Zn supplementation may increase growth without increasing IGF-1 and there is no direct correlation between Zn-related growth response and serum IGF-1 concentration.[25–27] Zn is required for phosphorylation of the IGF-1 receptor, which is essential for the transduction of the effects of IGF-1. Zn is also required for the activity of deoxythymidine kinase, which converts deoxythymidine into deoxythymidine 5′-monophosphate, a precursor of deoxythymidine triphosphate, which is needed for DNA, protein, and collagen synthesis in rats.[11]

Zn in pregnancy and fetus

Maternal status in pregnancy. Maternal serum Zn concentration normally decreases until 35 weeks' gestational age (GA), due to hemodilution, hormonal changes, increased urinary Zn excretion, increased Zn uptake by maternal tissues, and active maternal-fetal transfer of Zn.[28] In contrast, RBC Zn concentration increases during pregnancy in parallel with carbonic anhydrase.[28]

Maternal Zn deficiency. Women with Zn deficiency have lower serum Zn concentration compared to those without deficiency.[29] Risk factors for maternal Zn deficiency include digestive disease, bariatric surgery, sickle cell disease, chronic renal disease, smoking, alcoholism, and a vegetarian diet rich in cereals and phytate.[30–32] Zn deficiency in pregnancy may increase the risk for fetal malformations (e.g., neural tube defects), intrauterine growth restriction (IUGR), and fetal programming of cardiovascular and renal diseases in adult life.[33–35] However, meta-analyses of RCTs have shown that, while Zn supplementation in pregnancy reduced by 14% the risk of prematurity, it did not improve fetal growth.[36–40] The latter finding likely results from multi-nutrient deficiencies.[37,39,40]

Transplacental transport. Zn is transferred from the mother to the fetus by 2 mechanisms: endocytosis and saturable carrier-facilitated transport.[41,42] Zn is taken up against gradient from maternal blood into microvillous borders of human syncytiotrophoblast resulting in Zn storage in the placenta (reaching a concentration of 44 mcg g^{-1} tissue, ~60× that in plasma), followed by slow passive transfer either bidirectionally or preferentially towards fetal umbilical venous (UV) cord blood.[43–47] Adaptation of Zn placental uptake was shown in an in vitro study of microvillous membrane vesicles from preterm and term placentas of Brazilian women.[48] Zn uptake was higher in preterm (20–25 weeks GA) than term (>37 weeks) vesicles. In term vesicles, Zn uptake was higher in those from women in the lowest quartile of serum Zn concentration than in those from the highest quartile.[48] Placental Zn transport is upregulated in mice with a Zn-deficient diet, as shown by the fact that whole-body Zn fetal uptake in mice is similar to whether the diet in pregnancy is Zn-deficient or Zn-sufficient.[49] ZIP and ZnP transporters and MT are expressed in the placenta in mouse, rat, and human.[50,51] A RCT suggested the upregulation of ZIP-4 and ZIP-8 mRNAs in the placenta of Gambian women with unsupplemented vs. supplemented Zn.[52] However, this study was limited by a lack of assessment of maternal or cord Zn concentration and of ZIP protein expression.[52] Smoking in pregnancy results in the upregulation of MT expression in the placenta, which accumulates cadmium instead of Zn.[53] In summary, the placenta expresses Zn transporters, takes up Zn from maternal blood, and transports Zn towards the fetus; these processes appear to be upregulated in pregnancies with Zn deficiency.

Serum Zn concentration in the umbilical cord. No study has compared serum Zn concentration in maternal arterial blood and uterine vein with UV and umbilical arterial (UA) blood, which would be the comparisons of choice for analyzing uptake and release in the feto-placental unit.[54] All studies comparing maternal to UA and UV Zn concentrations have used peripheral venous maternal blood instead of arterial blood.[34] Many studies have shown that serum Zn UV concentration is higher than UA concentration.[55,56] However, results are inconsistent across studies. Serum Zn concentration in UA and UV blood or both may be affected by labor, preeclampsia, IUGR, and maternal diabetes and obesity;[55–60] no data are available in extremely low GA neonates (ELGANs). Cord blood Zn concentration is negatively correlated with GA in studies with many ELGANs, especially AGA infants.[61,62] Meta-analysis showed that cord blood serum Zn concentration is lower in small for GA (SGA) or IUGR neonates.[35] In summary, cord serum Zn concentration decreases with GA and is lower in SGA and IUGR than in AGA neonates.

Zn accretion in the fetus. Most of Zn accretion in utero occurs during the last trimester of pregnancy; therefore, preterm infants, especially ELGANs, are at risk for Zn deficiency. Accretion of Zn by the human fetus during the third trimester is believed to range between 211 and 270 mcg kg^{-1} d^{-1}.[63] The fetus accumulates Zn in the liver (mostly in MT) at very high concentration, which peaks at 200–1020 mcg g^{-1} of wet tissue (in US, Japan, and New Zealand) at 22–30 wks GA and later decreases to 140–380 mcg g^{-1} at term and 50–60 mcg g^{-1} in infants, children, and adults.[64–68] Liver expression of MT decreases during the third trimester of pregnancy and the first months postnatal.[64] In the baboon fetus, MT expression decreases progressively in response to increasing maternal estrogen concentration.[69] It appears that MT released from the liver may provide an endogenous source of Zn in early postnatal life, possibly up to 2 months postnatal in preterm

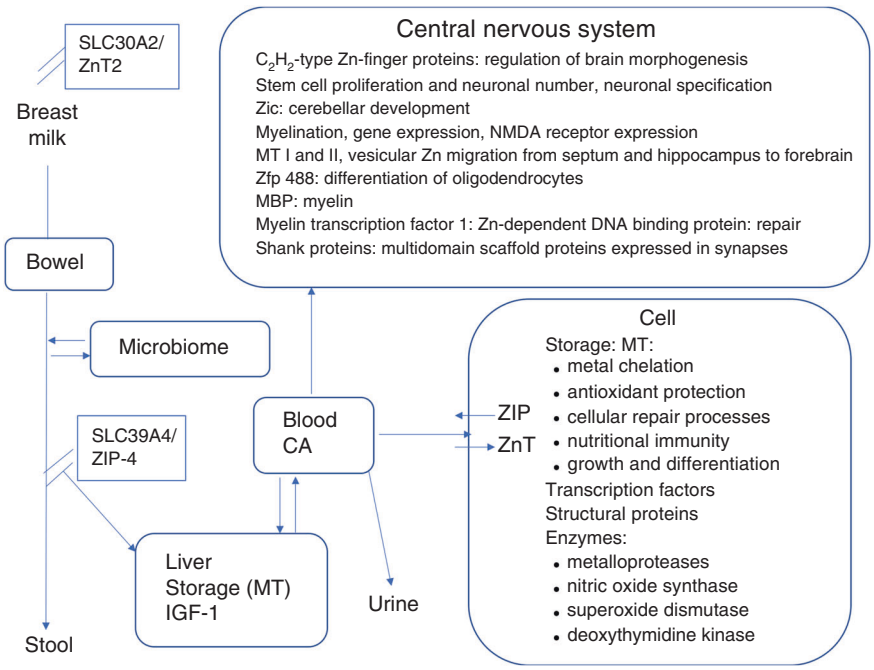

Fig. 1 Zinc role in growth and brain growth and development. Zn is the second most abundant metal in the body. Approximately 10% of the proteins in the human proteome are Zn-dependent. Zn is primarily intracellular, where it is stored in MT and is a component of multiple proteins. In the fetus, Zn is stored in liver MT-1, from which it can be released over the first months of postnatal life. Zn interacts with the gut microbiome, immunity, and inflammation. In the brain, Zn has multiple roles in growth, differentiation, and repair. Zn deficiency may result from[1] insufficient storage in pregnancy due to severe maternal Zn deficiency, smoking, extreme prematurity, and small size for age;[2] insufficient Zn intake due to low Zn concentration in breast milk due to SLC30A2/ZnT2 mutation or maternal Zn deficiency,[3] or decreased Zn absorption in the duodenum and jejunum due to SLC39A4/ZIP-4 mutation leading to acrodermatitis enteropathica, or to bowel resection. Zn deficiency may affect multiple transcription factors, storage and structural proteins, enzymes including deoxythymidine kinase, and may decrease the serum concentration of IGF−1 and phosphorylation of the IGF−1 receptor. CA carbonic anhydrase, IGF insulin-like growth factor, MT metallothionein, NMDA *N*-Methyl-D-aspartate, SLC30A2/ZnT2 mutation leading to lack of Zinc in breast milk, SLC39A4/ZIP-4 mutation leading to acrodermatitis enteropathica, ZIC Zinc finger proteins of the cerebellum, ZIP Zrt- and Irt-like protein, Zn Zinc, ZnT zinc transporter protein.

infants.[64,68] In Brazil, where Zn deficiency is prevalent, lower ranges of liver Zn concentration have been reported in autopsies (30–304 mcg g^{-1} at 26–38 weeks' gestation, 13–268 mcg g^{-1} at 40–41 weeks' gestation, and 3–299 mcg g^{-1} at <16 weeks post-delivery).[70] Smoking mothers have fetuses with lower liver MT expression, which could be due to competition of cadmium with Zn.[71] In summary, most Zn accretion by the fetus takes place in the third trimester. Liver Zn concentration peaks at 22–30 weeks and presumably provides an endogenous source of Zn.

Zn in the neonatal period

Zn as an essential nutrient in neonates. There is no consensus about Zn requirements in neonates.[12] Using a factorial method taking into account, endogenous liver Zn supply, Klein estimated Zn requirements in preterm infants as 1.5–2 mg kg^{-1} d^{-1} for those <1 kg, 1.2–1.7 mg kg^{-1} d^{-1} at 1–2 kg, and 1.0–1.3 mg kg^{-1} d^{-1} at 2–3 kg.[65] Griffin reviewed 11 studies on Zn retention and showed that Zn retention was significantly higher at higher Zn intakes, and higher in formula-based diets than in human milk-based diets.[72] Zn intakes of 1.8–2.4 mg kg^{-1} d^{-1} (from formula-based diets) and 2.3–2.4 mg kg^{-1} d^{-1} (from human milk-based diets) were required to achieve adequate Zn retention to maintain normal growth in preterm infants.[72] Intestinal absorption of Zn in preterm infants follows saturable kinetics similar to the adult.[73] Zn concentration in breast milk decreases over the early months postpartum, therefore unsupplemented pooled donor breast milk in the USA is not expected to meet Zn requirements for preterm infants.[74–76] Total parenteral Zn requirement in preterm infants is estimated as 450 mcg kg^{-1} d^{-1};[77] however, this may be insufficient, especially after bowel resection and enterostomy.

Zn deficiency in neonates. In countries where Zn deficiency is endemic, Zn deficiency at birth is more frequent in SGA especially preterm neonates.[78] In the US, Zn deficiency is more likely in SGA ELGANs.[79] Zn deficiency has been reported in some breastfed neonates because of very low Zn concentration in breast milk, due to deficiency in ZnT2 transporter.[10,80,81] In one study the frequency of significant ZnT2 polymorphisms was 8 among 750 or 1%.[82] Low Zn concentration in breast milk can also be secondary to maternal Zn deficiency. In one case, Zn deficiency was reported in a baby born to a mother with Zn deficiency with low breast milk Zn concentration. The baby improved with enteral Zn supplementation and maternal serum and breast milk concentrations improved with enteral Zn supplementation.[83]

Postnatal Zn deficiency has multiple potential complications including periorificial lesions, delayed wound healing, hair loss, diarrhea, immune deficiency, growth failure with stunting, decreased head growth, and cognitive impairment, which may improve with Zn supplementation.[7,11,26,80–88] Zn deficiency may contribute to abnormal gut-brain signaling by altering gut physiology and microbiota composition and by triggering an increase of inflammatory markers.[89]

Assessing Zn deficiency in the neonate. Normal serum Zn concentration in preterm infants decreases during the first weeks postnatal.[12] The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommends a normative Zn concentration of 0.74–1.46 mcg ml^{-1}.[77] Hair Zn concentrations in term neonates are correlated with maternal hair Zn concentrations.[90] In one cohort study in 29 wks preterm infants, hair Zn concentrations decreased by ~40% within 6 months postnatal

compared with term infants.[90] More data are needed for hair Zn concentrations.[15]

Zn role in brain growth, differentiation, and repair after injury

Zn role in brain growth and differentiation. Zn affects neuronal differentiation and white matter growth.[91] C_2H_2-type Zn finger proteins are transcription factors that contribute to the regulation of brain morphogenesis, influencing the proliferation, migration, and cell fate of stem cells and neural progenitor cells and their differentiation into neuronal cells.[92] The concentration of free Zn in oligodendrocytes decreases from the preoligodendrocyte stage to the mature oligodendrocyte.[93] This decrease in Zn concentration may mediate differentiation by modulating transcription factors, enzyme activities, and signaling pathways. mRNA expression of ZnP and ZIP transporters in oligodendrocytes is developmentally regulated in the mouse.[94] Expression of ZnT1 protein was shown in oligodendrocytes.[95] Saturable Zn uptake was demonstrated in oligodendrocyte progenitors.[96] Among those, an oligodendrocyte-specific Zn finger protein (Zfp 488) functions as a transcriptional co-regulator important for oligodendrocyte differentiation.[97]

In rats, gestational Zn deficiency may cause neural tube defects and other brain malformations and affect brain development (e.g., stem cell proliferation and neuronal number, neuronal specification, myelination, gene expression, *N*-methyl-D-aspartate [NMDA] receptor expression) and impairs learning and memory into adulthood.[91,98–101] In a model of differentiation of human pluripotent stem cells into motor neurons, mRNA expression of ZnTs and Shank proteins (multidomain scaffold proteins expressed in synapses) was highly regulated during neuronal differentiation.[102] In that model, low Zn concentration in the media was associated with increased apoptosis and decreased cell survival, altered neuronal differentiation, and, in particular, synaptic function.[102] In summary, Zn may regulate brain ontogeny, neuronal and oligodendrocyte proliferation, differentiation, and function.

In patients with acrodermatitis enteropathica, homozygous or compound loss-of-function mutations in the SLC39A4/ZIP-4 gene result in Zn depletion by blocking gut absorption of Zn; in one case report diffuse cortical atrophy seen on computerized tomography resolved following Zn repletion.[103]

Critical period of Zn intake for brain growth and differentiation. The critical period of Zn delivery for human brain growth has not been defined.[4,6] In the rat, distribution of MT I and II is limited to the septum and hippocampus at birth and progressively involves all forebrain postnatally; vesicular Zn has a similar pattern of development.[104] In mice, Zn deprivation starting at 18 days of pregnancy and continuing during lactation reduces weights of pup body, whole brain, and cerebellum during the suckling period when compared with pups from dams fed a diet adequate in Zn.[105] In contrast, Zn restriction only in pregnancy or only during the lactational period resulted in smaller changes.[105,106] In summary, data in the mouse provides evidence showing that the critical period of Zn delivery for brain growth starts at 18 days of pregnancy and extends during lactation.

In the human brain, MT I and II containing glial cells appear in the subventricular and periventricular zones at 21 weeks of GA and migrate progressively, reaching the entire white and gray matter by 35 weeks GA.[107,108] A minor population of late oligodendrocyte progenitors is present in the white matter at 18–27 weeks' GA, i.e., months before these cells commit to myelinogenesis.[109] Starting at 28 weeks GA, the number of immature oligodendrocytes increases, followed by an increase in myelin-binding protein (MBP) and myelin sheets in the periventricular area; this process coincides with the developmental window of vulnerability for periventricular white matter injury.[109,110] Limited data suggest that Zn concentration in the human brain progressively decreases from 8 mcg g^{-1} (wet tissue) at 12 weeks GA to 3–5 mcg g^{-1} at 23–26 weeks and then increases again to 9 (range 17–22) mcg g^{-1} at term and in early infancy.[67,111–113] These data suggest that the critical period of Zn delivery for brain growth is species-specific, i.e., starts at 18 days of pregnancy and extends during lactation in the mouse and could start at 26 weeks and extend until at least 35 weeks of PMA in the human.

Zn role in cerebellar development. Zinc finger proteins of the cerebellum (Zic) may mediate cerebellar developmental control via regulation of neuronal progenitor proliferation-differentiation and the patterning of the cerebellar primordium.[114] Zic proteins interact with sonic hedgehog signaling, retinoic acid signaling, and TGFβ signaling during mouse cerebellar development.[115] Heterozygous deficiency in Zic1 and Zic4 is associated with Dandy–Walker malformation.[115]

Zn role in brain injury, degeneration, and repair. Zn has roles in DNA repair, protection against oxidation injury, and repair after ischemia.[116,117] Experimental models of ischemic and excitotoxic death acutely alter Zn distribution and increase free Zn concentrations in brain tissue.[118–120] A block in oligodendrocyte differentiation into MBP-expressing cells is a central problem in periventricular leukomalacia (PVL).[121,122] In the chronic stage of PVL cells expressing myelin transcription factor 1, a Zn-dependent DNA binding protein, are significantly increased around necrotic foci and some of the regions are coincident with increasing MBP immunoreactivity.[123]

Vela et al.[124] have reviewed the literature suggesting a possible link between bowel and brain development in autism spectrum disorders. In summary, Zn repletion is important in repair in the chronic phase after brain injury, but not during the acute phase because of increased free Zn concentration in the brain immediately after an ischemic insult.

SCOPING REVIEW: ZINC SUPPLEMENTATION FOR NEONATAL SURVIVAL, GROWTH, BRAIN GROWTH, AND NEURODEVELOPMENT

Method

On August 28, 2020, we conducted a PubMed search using the following search words: Zinc supplementation neonate. The Pubmed search engine translated these words into the following strings: ("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND ("supplemental"[All Fields] OR "supplementating"[All Fields] OR "supplementation"[All Fields] OR "supplementation s"[All Fields] OR "supplementations"[All Fields] OR "supplemention"[All Fields]) AND ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonate"[All Fields] OR "neonates"[All Fields] OR "neonatality"[All Fields] OR "neonatals"[All Fields] OR "neonate s"[All Fields]).

We selected neonatal studies assessing one or more of four outcomes: survival, growth, brain growth, and neurodevelopment. We excluded case reports and studies if they assessed the effects of antenatal Zn supplementation, initiation of Zn supplementation at >28 days (4 weeks) after due dates, and/or supplementation of other nutrients (except Cu to compensate for Zn and Cu competition for gastrointestinal absorption, or studies with factorial design).

Results

The search yielded 411 manuscripts, among which 33 were assessed on full-text copy and 22 studies met criteria (Fig. 2).

Observational studies. Four studies met the criteria (Table 1).[79,86,125,126] In one retrospective study of 60 preterm

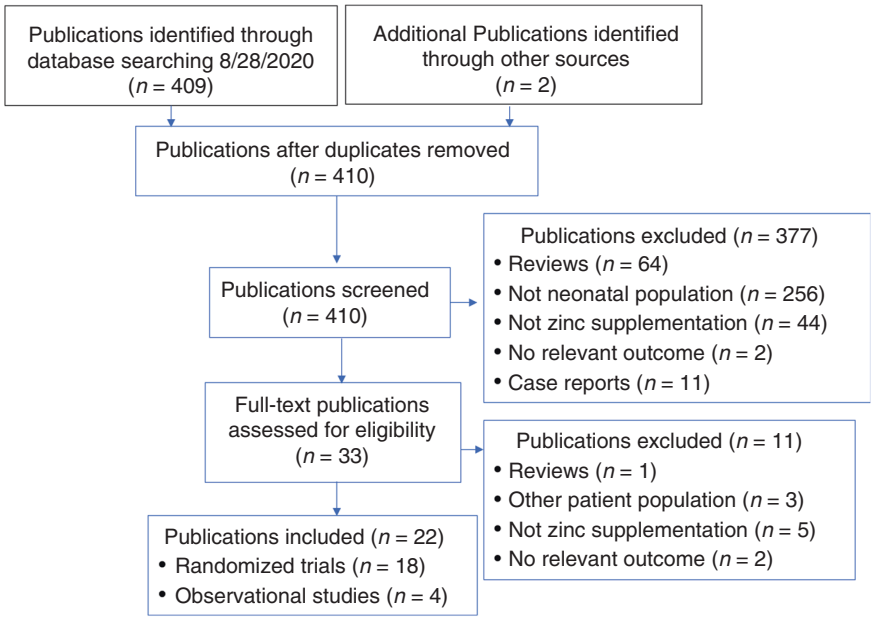

Fig. 2 Flow diagram of the scoping review. This diagram shows the number of manuscripts found by Pubmed search (using Zinc supplementation neonate) and other sources, as well as the process used to select manuscripts relevant to this review.

Table 1. Observational studies of Zinc supplementation started before or at 28 days after due dates ($44^{0/7}$ weeks PMA) assessing mortality, growth, head growth or brain function in neonates or preterm infants.

Study	Subjects	Design/intervention	Results
El Mashad et al.[125] $n = 60$ Egypt	Healthy preterm infants below 37 weeks of age Mean GA 35 ± 1 weeks	Retrospective cohort study Zn-supplemented group fed with breast milk and supplemented with Zn (2 mg kg^{-1} day^{-1}) since the first day of life, and a non-Zn-supplemented group fed with breast milk	Zn-supplemented infants had higher weight and length at the age of 6 months compared with unsupplemented controls
Shaikhkhalil et al.[126] $n = 52$ USA	ELBW with chronic lung disease (oxygen at 36 weeks PMA) Mean GA 25 ± 2 weeks	Retrospective cohort study Zn supplementation (1.7 ± 0.6 mg kg^{-1} day^{-1}) starting at 33 + 2 weeks PMA for a duration ranging between 9.3 and 43 weeks in infants who had poor weight gain	Weight gain increased from 10.9 g kg^{-1} day^{-1} before supplementation to 19.9 g kg^{-1} day^{-1} after supplementation Linear growth increased from 0.7 cm $week^{-1}$ before supplementation to 1.1 cm $week^{-1}$ after supplementation
Harris et al.[86] $n = 105$ USA	Infants born at 26–37 weeks GA (mean 31.8 ± 2.5 weeks GA, 1.8 ± 0.1 kg)	Prospective cohort study	Total enteral Zn intake positively associated with weight gain and FOC growth in NICU Higher Zn intake linked to weight gain after accounting for GA
Brion et al.[79] $n = 302$ USA	ELGANs born at 23–28 weeks GA	Prospective cohort study Serum Zn concentration was obtained in infants with poor linear growth after optimizing other nutrients. Zn supplementation to increase total Zn intake to 3–3.5 mg kg^{-1} day^{-1} (average supplementation 1.27±0.33 mg kg^{-1} day^{-1}) in infants with poor linear growth and serum Zn concentration <0.74 mcg/ml; Cu supplementation if needed to bring total daily intake to 300–350 mcg kg^{-1} day^{-1}	*Birth cohort*: $n = 302$: Zn deficiency (serum Zn concentration <0.74 mcg/ml) in 8 of 24 (33%) small for GA (SGA) vs. 35 of 278 (13%) non-SGA infants *Zn cohort*: $n = 64$: Zn deficiency in 52. In 41 Zn-deficient infants, Zn supplementation starting at 36 weeks PMA (range 32–44) in for >2 weeks (but not ≤2 weeks) increased FOC growth rate (assessed by change in *Z*-score over time) but not weight or length growth in the absence of simultaneous administration of systemic steroids

Pubmed search was conducted on 8/28/2020 using the following search strings: ("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND (((((("supplemental"[All Fields] OR "supplementating"[All Fields]) OR "supplementation"[All Fields]) OR "supplementation s"[All Fields]) OR "supplementations"[All Fields]) OR "supplemention"[All Fields]) AND ((((((("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields])) OR "newborn infant"[All Fields]) OR "neonatal"[All Fields]) OR "neonate"[All Fields]) OR "neonates"[All Fields]) OR "neonatality"[All Fields]) OR "neonatals"[All Fields]) OR "neonate s"[All Fields]). We excluded case reports and studies that assessed the effects of antenatal Zn supplementation, initiation of Zn supplementation at >28 days (4 weeks) after due dates, and/or multiple simultaneous interventions along with enteral Zn supplementation (except for a small amount of copper because Zn supplementation may inhibit the absorption of copper or studies with factoral design) or did not assess any of the pre-specified outcomes.
Cu copper, *ELBW* extremely low birth weight infant, *ELGAN* extremely low gestational age neonate, *FOC* fronto-occipital circumference, *GA* gestational age, *NICU* neonatal intensive care unit, *PMA* postmenstrual age, *SGA* small for GA, *Zn* zinc.

infants born at 35 ± 1 weeks GA in Egypt, those who received Zn since the first day of life had higher weight and length at the age of 6 months compared with unsupplemented controls.[125] The three studies done in the US included FOC measurements. In one retrospective cohort study of 52 ELBW infants (mean GA 25 ± 2 weeks) with chronic lung disease, weight gain increased by 83% and linear growth velocity increased by 57% after supplementing Zn starting at 33 ± 2 weeks PMA for a range of 9.3–43 weeks.[126] In a prospective cohort of 105 infants born at 26–37 weeks GA there was a direct relationship between Zn intake and FOC growth.[86]

In a prospective cohort study of 302 ELGANs who received recommended Zn intake, a serum Zn concentration was obtained in 52 who had insufficient linear growth; Zn deficiency (serum concentration <0.74 mcg/ml) was diagnosed in 43 infants.[79] The odds of Zn deficiency increased in SGA infants and with decreasing GA. In a model including postnatal variables, the odds of Zn deficiency increased with decreasing GA, severe bronchopulmonary dysplasia (BPD), and longer duration of parenteral nutrition.[79] In the absence of Zn supplementation, the change in FOC Z-score from time of Zn concentration to discharge or 50 weeks PMA was lower in infants with Zn concentration <0.74 mcg ml^{-1} than in those with Zn concentration >0.74 mcg ml^{-1}. In Zn-deficient infants, Zn supplementation started at 36 weeks PMA (range 32–44) for >2 weeks but not ≤2 weeks increased FOC growth rate, but not weight or length growth, in the absence of systemic steroids. The change in FOC *Z*-score in response to Zn supplementation increased[1] with a duration of Zn supplementation (>2 weeks vs. ≤2 weeks),[2] lower change in FOC *Z*-score in response to prior supplementation of protein and[3] severe co-morbidity (defined as either severe BPD, gastrointestinal perforation, necrotizing enterocolitis, or severe organ failure). The FOC response to Zn was not affected by PMA at the initiation of therapy. This latter data suggest that the critical period of Zn delivery for brain growth could extend longer than suggested by basic sciences data, i.e., until at least 44 weeks PMA.

Randomized controlled trials. Eighteen studies met the criteria (Table 2).[25–27,127–141] Most studies had some risk of bias limiting the level of evidence (right column, Table 2) and seven studies had no documented sample size analysis. Inclusion criteria were[1] SGA, LBW, or IUGR,[2] prematurity,[3] clinical sepsis,[4] or low socioeconomic status. There was substantial heterogeneity in country, duration (10 days–1 year), and a dose of Zn supplementation, type, and timing of assessment tools, and documented or possible confounding variables (micronutrient deficiencies, severe comorbidities, systemic steroids). This heterogeneity limited the validity of a meta-analysis.

Among LBW or preterm neonates in countries where Zn deficiency is prevalent or has been reported in association with stunting (India, Iran, Egypt), prolonged Zn supplementation improved weight in 7/9 studies, length in 6/9, and FOC in 3/5; in other countries (Spain, Italy, USA), respective numbers were 1/4, 2/3, and 0/3.

Five studies assessed the effect of Zn supplementation for at least 8 weeks in SGA or IUGR term infants (studies 1–5, Table 2). Among two studies using a low dose of Zn (1 mg day^{-1}), one showed no effect on growth and no effect on Bayley scores at 6–12 months; the other one, conducted in India, showed that Zn supplementation reduced diarrhea and mortality. Among three studies using higher dose Zn (3–5 mg day^{-1}), 1/3 showed increased weight gain and linear growth.

Among 8 studies enrolling LBW or VLBW infants that were mostly or exclusively preterm (studies 7–14, Table 2), prolonged Zn supplementation improved weight gain in 4/8 studies, linear growth in 5/7, FOC in 3/7, and 2/2 studies showed improved neurologic assessment (one in the NICU and one at 12 months). One Italian RCT using high dose Zn supplementation in VLBW infants showed decreased mortality and composite morbidity (composite of late-onset sepsis, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity) and increased weight at discharge.[84]

Three studies assessed short (10 days or until discharge) Zn supplementation (1 or 6 mg kg^{-1} day^{-1}) for neonates with clinical sepsis (studies 15–17, Table 2). Two of three studies showed no improvement in mortality and one showed no improvement in developmental assessment at 1 year of age. None of these studies assessed growth.

The single study assessing Zn supplementation for low economic status in Chile (study 18, Table 2) showed no effect on growth and showed improvement in Bayley score at 6 months but not at 1 year.

In summary, Zn supplementation was most likely to increase growth in preterm infants in countries where Zn deficiency is prevalent. Zn supplementation may reduce mortality in selected populations. None of the studies assessed important long-term (at least 18 months postnatal age corrected for prematurity) neurodevelopmental outcomes.

Summary

Available data in the mouse provide evidence showing that the critical period of Zn delivery for brain growth starts at 18 days of pregnancy and extends during lactation. Based on limited available data in the human we speculate that the critical period could be from 26 weeks GA until at least 44 weeks PMA.

In countries where Zn deficiency is prevalent, Zn supplementation may help growth in preterm infants and survival in LBW infants. In the US, Zn deficiency is associated with ELGAN, SGA, poor postnatal growth, severe BPD, and prolonged need for parenteral nutrition. Much less frequently, Zn deficiency results from genetic mutations or from maternal Zn deficiency.

Zn deficiency in neonates is best identified with a serum concentration <0.74 mcg/ml and should be treated with Zn supplementation for >2 weeks. Variability in growth response to Zn supplementation depends on several factors:[1] patient selection and accuracy of serum level in the detection of Zn deficiency;[2] sufficiency of dose and duration of supplementation;[3] comorbidities (nutritional, systemic, and medications).

Research gaps

Data are needed to assess markers of total body and brain Zn content in neonates. More data are needed to assess the validity of serum and hair Zn concentration and other biomarkers for this purpose.

No RCT of Zn supplementation was focused on ELGANs or ELBW infants starting before 29 weeks PMA and no RCT has assessed the effect of Zn supplementation on long-term neurodevelopment. Studies are urgently needed to determine the optimal dose, timing, and duration of supplemental Zn in ELGANs that will minimize morbidity, optimize growth and brain growth, prevent periventricular leukomalacia, and optimize neurodevelopment. However, Zn supplementation may not result in optimized growth and brain growth if co-existing nutritional deficiencies exist. Since growth failure is ELGANs is often multifactorial, precision medicine approach may be the best method, requiring a systems biology approach that could include metallomics (assessing trace elements), metabolomics (snapshots of multiple biochemical compounds), and microbiome.[89,142–144]

Table 2. Randomized controlled trials of Zinc supplementation* started before or at 28 days after due dates ($44^{0/7}$ weeks PMA) assessing mortality, growth, head growth, or brain function in neonates or preterm infants.

Number	Study and country	Subjects	Intervention	Results	Risk for potential sources of bias
Term infants SGA or LBW					
1	Castillo-Durán et al.[127] $n = 68$ Chile	SGA term infants	3 mg of Zn acetate per day vs. placebo from time of Zn level after 3 days of life until 6 months of life	Improved weight gain and change in weight *Z*-score at 2 months Improved linear growth and change in length *Z*-score at 6 months Additive effect on weight increase: Zn supplementation, exclusive breastfeeding after 4 months and gender	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): none Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: not provided
2	Ashworth et al.[128]; Lira et al.[129] $n = 134$ Brazil	Singleton SGA term 1500–2499 g	All 134 neonates born Jan 1993–Jan 1994 were randomized to either Zn supplementation 1 mg day^{-1} for 8 weeks or placebo. All 71 neonates born Feb 1994–Aug 1994 were not randomized and received 5 mg day^{-1}.	No change in weight gain or linear growth with 1 mg day^{-1} until 26 weeks (randomized) Increased weight gain (weeks 17–26) with 5 mg day^{-1} (not randomized) Less diarrhea with 5 mg day^{-1} (not randomized) No difference in Bayley scores at 12 months	Sequence generation (selection bias): no information Allocation concealment (selection bias): no information Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 20%: 14% moved out; 6% died* Selective reporting (reporting bias): low Any other bias: There was a mistake in drug manufacture. All 71 born Feb 1994–Aug 1994 were not randomized and received 5 mg day^{-1}. *Data reported on attrition bias are merged for randomized and non-randomized groups. Sample size analysis: not provided
3	Sazawal et al.[130] $n = 1154$ India	Full-term SGA	Factorial design: (1) riboflavin and zinc vs. riboflavin (2) riboflavin, calcium, phosphorus, folate, iron with zinc vs. without zinc Dose of zinc: day 15–29: 1 mg day^{-1} as sulfate; days 30–284: 5 mg day^{-1} as sulfate	Reduced mortality and diarrhea Mortality also reduced with breastfeeding	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): Unclear (see below) Selective reporting (reporting bias): 96 died, moved or withdrew before starting follow-up Any other bias: N/A Sample size analysis: yes
4	Bueno et al.[25] $n = 38$ Spain	IUGR and asymmetric growth 38–41 weeks	Zn supplementation (3 mg day^{-1} elemental Zn as Zn sulfate) vs. placebo for 6 months	No change in weight, length or FOC at 1 month, 2 months, 4 months, 6 months No change in serum IGF-1	Sequence generation (selection bias): no information Allocation concealment (selection bias): no information Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low

Table 2. continued

Number	Study and country	Subjects	Intervention	Results	Risk for potential sources of bias
					Incomplete outcome data (attrition bias): 2 lost to follow-up Selective reporting (reporting bias): 4 for discontinued intervention; 1 for metabolic disorder Any other bias: N/A Sample size analysis: yes
5	Taneja et al.[131] $n = 2052$ India	Hospital-born full-term infants ≤2500 g	5 mg day^{-1} for those infants between ages 2 weeks and 6 months and 10 mg day^{-1} for those infants aged >6 months	No change in weight or length at 1, 2, 3, 4 months No change in diarrhea, lower respiratory tract infections	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias):141/2052 (7%) Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes
LBW, GA not available					
6	Sur et al.[132] $n = 100$ India	LBW irrespective of GA GA not available	1 ml daily dose of 5 mg of elemental Zn as Zn sulfate in vitamin B complex-based syrup vs. placebo from birth up to 1 completed year of age	Increased linear growth from birth to 1 year (but no difference until 10 months of age) Increased difference in weight *Z*-score from birth to 10 months Decreased frequency of diarrhea	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): no Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes
LBW, predominantly or exclusively preterm					
7	Friel et al.[133] $n = 52$ USA	VLBW, mean GA 29 ± 3 weeks	Zn supplement in formula 4.4 mg L^{-1}. A small amount of copper was started when tolerating a 20 cal oz^{-1} formula (~1 month before discharge, 37 ± 1 weeks PMA) and continued for 6 months	Increased change in *Z*-score of length but not weight or FOC from birth to 12 months Improved motor development (Griffiths Mental Developmental Scales) up to 12 months of age	Sequence generation (selection bias): some concern* Allocation concealment (selection bias): some concern* Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 14/52 (weight): 27% Selective reporting (reporting bias): high: 28/52 have no motor scale reported; no information about Griffiths scores Any other bias: N/A *Random number tables operated by a technician not associated with follow-up Sample size analysis: not provided

Table 2. continued

Number	Study and country	Subjects	Intervention	Results	Risk for potential sources of bias
8	Díaz-Gómez et al.[26] $n = 36$ Spain	1000–2500 g, preterm <37 weeks AGA GA 32.2 ± 2.3 weeks	Zn supplementation in formula at final concentration of 5 mg L^{-1} vs. same formula without supplementation started at 36 weeks postconceptional age until 6 months corrected age	Increased linear growth rate but not weight or FOC growth at 3 months and 6 months corrected age Increase length but not weight or FOC at 3 months and 6 months corrected age. Less frequent diarrhea No change in serum IGF-1 concentration	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 1 parental refusal Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: not provided
9	Islam et al.[134] $n = 100$ India	1000–2499 g AGA <37 weeks	Zn supplementation 2 mg kg^{-1} day^{-1} for 6 weeks started at 7–21 days of age, before discharge	Increased weight and length but not FOC after 6 weeks of supplementation and 6 weeks afterwards FI No significant change in diarrhea (4/50 vs. 8/50)***	Sequence generation (selection bias): high (lottery of selection cards) Allocation concealment (selection bias): high Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 15/100 (15%) lost to follow-up Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes
10	Aminisani et al.[135] $n = 76$ Iran	LBW Average 34 weeks; Mostly preterm	5 ml day^{-1} of liquid with vs. without 5 mg elemental Zn (Zn sulfate) between 4 weeks (28 days) and 24 weeks of age	Increased weight gain and linear length and FOC growth from 4 weeks to 24 weeks	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 16% did not complete the study (refused, moved) Selective reporting (reporting bias): low Any other bias: N/A Sample size based on available funds
11	Kumar et al.[136] $n = 91$ India	VLBW Average: 1300 g, 35 weeks, predominantly SGA	Zn supplementation (10 mg elemental Zn) daily for 60 days	Increased weight at 52 weeks postconceptional age Increased length at 40 weeks and 52 weeks Increased FOC at 52 weeks Increased linear growth velocity No change in mortality	Sequence generation (selection bias): low Allocation concealment (selection bias): low (opaque envelopes) Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 6/91 (7%) Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes

Table 2. continued

Number	Study and country	Subjects	Intervention	Results	Risk for potential sources of bias
12	Terrin et al.[84] $n = 193$ Italy	VLBW 401–1500 g or GA 24–32 weeks,	Vitamin with Zn sulfate (9 mg day^{-1} elemental Zn) vs. vitamin without Zn from 7th day of life until discharge	Increased weight at discharge. No change in weight gain until discharge Length and FOC not reported Reduced composite morbidity (composite of late-onset sepsis, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity) Reduced mortality	Sequence generation (selection bias): no information Allocation concealment (selection bias): no information Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 5 lost to follow-up Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes
13	El-Farghali et al. [27] $n = 200$ Egypt	LBW 1500–2499 g, 28–40 weeks GA (71 SGA; 129 AGA)	Zn supplementation 10 mg day^{-1} started immediately for 6 months	Increased percentage of SGA infants with length >10th centile at 3 months; weight & length >10th centile at 6 months; weight, length and FOC >10th centile at 1 year. Increased weight but not length or FOC at 3 months Increased weight, length and FOC at 6 and 12 months Increased weight, linear and FOC growth to 1 year Increased serum IGF-1 at 6 months; however, no correlation between IGF-1 concentration and anthropometric measurements	Sequence generation (selection bias): some concern Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 30 of 200 (15%) Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: not provided
14	Mahtur et al.[137] $n = 100$ India	Preterm breastfed infants GA 33.5 ± 2.2 weeks	Zn gluconate (2 mg kg^{-1} day^{-1}) supplementation until 3 months corrected age	No change in weight, length and FOC at 3 months corrected age No difference in mortality Improved alertness and attention at term corrected age (Amiel-Tilson neurologic assessment), decreased hyperexcitability at term and 3 months corrected age	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): high Blinding of outcome assessment (detection bias): high Incomplete outcome data (attrition bias): 7/100 (7%) Selective reporting (reporting bias): low Any other bias: N/A Sample size: based on convenience
Neonates with clinical signs of sepsis					
15	Mehta et al.[138] $n = 614$ Nepal	Neonates with probable neonatal sepsis based on the tenth revision of the International Classification of Diseases (ICD)	Oral or nasogastric Zn 1 mg kg^{-1} day^{-1} until discharge or death	No difference in mortality or duration of hospital stay	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 86 Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes

Table 2. continued

Number	Study and country	Subjects	Intervention	Results	Risk for potential sources of bias
16	Newton et al.[139] $n = 88$ India	Inborn with clinical signs of sepsis ≥32 weeks and <28 days, on significant enteral feeds (>50 % feeds), with at least two screening tests positive among microESR, CRP, and band cell count or positive blood culture	Oral Zn 3 mg kg^{-1} twice a day for 10 days	No change in mortality Less frequent abnormal neurological signs at 1 month	Sequence generation (selection bias): some concern Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): no Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes
17	Banupriya et al.[140] $n = 150$ India	Neonates with clinical signs of sepsis, ≥32 weeks, microESR >15 mm h^{-1}, CRP >6 mg L^{-1} and cell count >20% or positive blood culture	Oral Zn sulfate 3 mg kg^{-1} twice a day for 10 days	Decreased mortality (5/75 vs. 13/75, $P = 0.04$) No significant change in mental development quotient (Developmental Assessment Scale for Indian Infants [DAS II])** or motor development quotient at 12 months	Sequence generation (selection bias): low Allocation concealment (selection bias): low Blinding of participants and personnel (performance bias): high: no placebo Blinding of outcome assessment (detection bias): high Incomplete outcome data (attrition bias): 15 lost to follow-up Selective reporting (reporting bias): low Any other bias: N/A Sample size analysis: yes
Term neonates of low socioeconomic status					
18	Castillo-Durán et al.[141] $n = 150$ Chile	Term neonates of low socioeconomic status initially breastfed	Supplemental Zn 5 mg day^{-1} vs. lactose placebo started before 20 days until 12 months	No difference in weight or length at 6 and 12 months No difference in *Z*-score of weight for age No difference in mean PDI and MDI on Bayley scales at 1 year Lower proportion scoring <100 on MDI and PDI at 6 months	Sequence generation (selection bias): no information Allocation concealment (selection bias): no information Blinding of participants and personnel (performance bias): low Blinding of outcome assessment (detection bias): low Incomplete outcome data (attrition bias): 5 lost to follow-up, 3 incomplete psychomotor evaluation Selective reporting (reporting bias): high: 24 for poor compliance, 3 for congenital malformation, 4 for anemia, 2 for fortified formula Any other bias: N/A Sample size analysis: yes

We excluded case reports and studies that assessed the effects of antenatal Zn supplementation, initiation of Zn supplementation at >28 days (4 weeks) after due dates, and/or multiple simultaneous interventions along with enteral Zn supplementation (except for a small amount of copper because Zn supplementation may inhibit the absorption of copper or studies with factoral design) or did not assess any of the pre-specified outcomes.

AGA appropriate for gestational age, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *FOC* fronto-occipital circumference, *GA* gestational age, *IGF-1* insulin-like growth factor 1, *IUGR* intrauterine growth restriction, *LBW* low birth weight, *MDI* Mental Developmental Index, *PDI* Psychomotor Developmental Index, *PMA* postmenstrual age, *SGA* small for gestational age, *VLBW* very low birth weight, *Zn* zinc.

*Pubmed search was conducted on 8/28/2020 using the following search strings: assessed antenatal Zn supplementation, initiation of ("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND (((((("supplemental"[All Fields] OR "supplementating"[All Fields]) OR "supplementation"[All Fields]) OR "supplementation s"[All Fields]) OR "supplementations"[All Fields]) OR "supplemention"[All Fields]) AND ((((((("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields])) OR "newborn infant"[All Fields]) OR "neonatal"[All Fields]) OR "neonate"[All Fields]) OR "neonates"[All Fields]) OR "neonatality"[All Fields]) OR "neonatals"[All Fields]) OR "neonate s"[All Fields]).

$P = 0.05$ in the original publication; $P = 0.054$ calculated using SPSS version 25 (IBM, Inc., Armonk, NY) with the data provided; * listed as significant in the original publication, $P = 0.54$ by Fisher's exact test with the data provided.

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AUTHOR CONTRIBUTIONS

L.P.B. wrote the first draft of the manuscript, critically reviewed the revisions, and approved the final manuscript as submitted. R.H. and C.S.L. critically reviewed the revisions and approved the final manuscript as submitted.

ADDITIONAL INFORMATION

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