

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Specific Care Question: Use of Supplemental Zinc in Children

Team Members:

Brandon Newell, MD; Margo Humenczuk, MA, RD, MBA; Barbara Warady, MS, RD and Facilitator Nancy Allen, MS, RD

Librarians: Benjy Stein MSLIS MEd. & Keri Swaggart, MLIS, Evidence Based Scholars: Kate Collum, RN, Sally Shubat MA, CCC-SPL, Nancy Allen, MS, MLS, RD, Jarrod Dusin, MS, RD, LD, CNSC, Daniela Pirvu, RN, Christina Gutierrez, RN

Inclusions criteria: The question specifically synthesized literature on zinc and absorption (of zinc), growth, failure to thrive, eczema, epidermolysis Bullosa (EB) and warts. Background information on assessing zinc status, harms of zinc supplementation, and contamination of zinc supplements were synthesized.

Exclusions criteria: This Question does not address zinc supplementation in children with ileostomies, burns or who participate in sports. Poor appetite is a basic and non-specific feature of zinc deficiency (National Academy of Science, 2001, p. 447) and is not included in this review ie studies were not identified.

Recommendations:

1. Based on moderate quality evidence, a strong recommendation is made not to obtain a serum zinc level to determine zinc deficiency in individuals. (Synopsis- Figure 1, [National Academy of Science \(2001\)](#) pp 452 & [DeBenoist 2007](#))
2. Based on high quality evidence a strong recommendation is made to treat zinc salts as equivalents. (Figure 9, Figure 10, Figure 11 and Figure 12)
3. The consideration of zinc supplementation is recommended for the following groups:
 - a. Based on strong evidence, strict vegetarians (major food staples are grains and legume AND dietary phytate:zinc molar ratio >15:1). [National Academy of Science \(2001\)](#) p. 480
 - b. Based on moderate evidence former preterm or small for gestational age infants (Figure 2)
4. Based on high quality evidence of upper limits to absorption rate a dose no greater than 15 mg elemental zinc/day is recommended. (Tran, 2004)
5. Based on practical issues with dosing (only forms available on CMH formulary are 15 mg & 50 mg tablets and 50 mg capsule) try to use an age appropriate multivitamin/multi-mineral supplement zinc. Based on the

	Infant		Children		Children		Adolescents	
	0-6 mo	7-12 mo	1-3 yrs	4-8 yrs	9-13 yrs		14-18 years	
					Boys	Girls	Boys	Girls
Dietary Reference Intake (DRI) (mg/d)	n/a	3	3	5	8	8	11	9
Tolerable Upper Limit (mg/d)	4	5	7	12	23	23	34	34

Table 1

*Tolerable Upper Limit is defined as the highest level of daily nutrient intake, from all sources, that is likely to pose no risk of adverse health effects for almost all individuals.

QA/QI on this topic will be a run chart of serum zinc levels drawn. I will request a quarterly report, by ordering service/ambulatory location.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Significance and importance of the question: Zinc is a known co-factor for the enzymes DNA and RNA polymerase. Deficiency, although not common, impairs growth. There is no good biological marker of an individual's zinc status. "Plasma and serum zinc concentrations do not seem to be sufficiently sensitive to serve as a subsidiary indicator" ([National Academy of Science \(2001\)](#), page 452). However, serum zinc appears to be indicator used by most, but it is influenced by the time of day, postprandial state and presence of stress (National Academy of Science, 2001). The Nutrition Department at Children's Mercy Hospital and Clinic in Kansas City(CMH&C) recommend supplemental zinc for children who have low serum zinc levels (<70 mcg/dl).

The recommendation for treatment (Lexicomp™, 2011) that is age based:

- 0-6 months – 3 mg/d
- 7-12 months 5 mg/d
- 1-10 years- 10 mg/d
- >10 years 15 mg/d

• **Treatment of Zinc deficiency: Oral:**

- Infants and Children: 0.5-1 mg elemental zinc/kg/day divided 1-3 times/day; somewhat larger quantities may be needed if there is impaired intestinal absorption or an excessive loss of zinc
- Adults: 110-220 mg zinc sulfate (25-50 mg elemental zinc)/dose 3 times/day

The Pharmacy at CMH&C stopped compounding zinc suspensions in July, 2008. Our pharmacy has two zinc supplements on formulary (a) 15mg elemental zinc (as gluconate) tablet and (b) and 50 mg elemental zinc (as sulfate) capsule. For inpatient use, a tablet/capsule is dispensed with instructions to make a slurry for administration for children who do not swallow. For children who are able to take a tablet/capsule instruction to split a tablet/capsule is provided for doses less than provide in the pill or capsule.

Here is an example, retrieved from PHRED for a child who was prescribed to take 15 mg of elemental zinc

Order Comments

"At home, patient was taking medication with the following details: Comments: Crush and or daily 1 tbl (abbreviation means tablet) and mix with 3 ml of water, five pt 1 ml of mixture" signed by APN

Product note

"Zinc Sulfate 220 mg is equivalent to 50 mg of Elemental Zinc. If GI upset occurs, take with food. If Necessary, Open capsule and dilute 50 mg of elemental zinc sulfate with 3 mLs sterile water. Give 1 ml to equal 16.7 mg. Product has 30 minute stability." signed by RPh.

At discharge families have to be able to

- Read supplement labels and discern between elemental zinc and zinc salt on the label.
- For children who do not swallow, crush and mix the zinc tablet with water and administer the correct fraction
- For children who do swallow, cut or separate the zinc tablet/capsule and administer the correct fraction

However, see the attached summary of the IOM report that establishes the requirements of zinc as a nutrient. Zinc is a dietary supplement and not a drug. It is not dispensed by most outpatient pharmacies, although it is sold in "drugstores" grocery stores and health food stores. It is not a covered by insurance: either private, Medicare or Medicaid. Families have to choose the appropriate product from the dietary supplement aisle. Zinc is poorly water soluble and readily precipitates out of the slurry created in this fashion.

The Nutrition Department desired to update the handout that was created to assist prescribers and families to be consistent with current dosing

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

constraints. To do so, the following questions arose:

- Which zinc salt is best absorbed?
- What is the best test to show zinc deficiency?
- Does supplemental zinc improve growth in:
 - Failure to thrive (FTT)
 - Epidermolysis Bullosa
 - Eczema
 - Warts

The goal of this Specific Clinical Care question is to understand how supplemental zinc is prescribed at our hospital, and to evaluate evidence that supports the zinc supplementation. For the first goal, data was pulled from the EMR at CMH&C (PHRED) for the Jan 2010 to Jan 2011. MRN, Zinc Order (only Inpatient) and Result of laboratory test for serum zinc (Inpatient and Ambulatory) was obtained.

Orders:

A summary of orders for supplemental zinc (timeframe Jan2010- Jan 2011)

- 101 unique MRNs were identified
- 176 orders were written for supplemental zinc
- 75 orders were duplicates on the same patients changing form of zinc supplement(i.e. from suspension to tablet, from 15 mg tablet to 50 mg tablet/capsule)
- The range of ordered zinc doses were 2 mg/d to 150 mg/d.

The Graph 1 is a representation of the number of CMH in-patients who had physician orders to receive zinc supplements by inpatient team. The Chart 1 is a representation of the various doses ordered for the patients who had zinc supplements ordered. See Graph "Range of Zinc Doses".

Laboratory

A summary of orders for serum zinc levels (timeframe Jan 2010-Jan 2011)

Graph 2

See Graph "Range of Serum Zinc Level (mcg/dl)"

- 59 unique MRNs had at least one serum zinc level ordered during the inpatient or observation stay.
- The range of serum zinc was from 30 mcg/dl to 121 mcg/dl. (Median s. zinc was 60 mcg/dl).
- 25% of the labs were drawn after 0600.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Graph 1

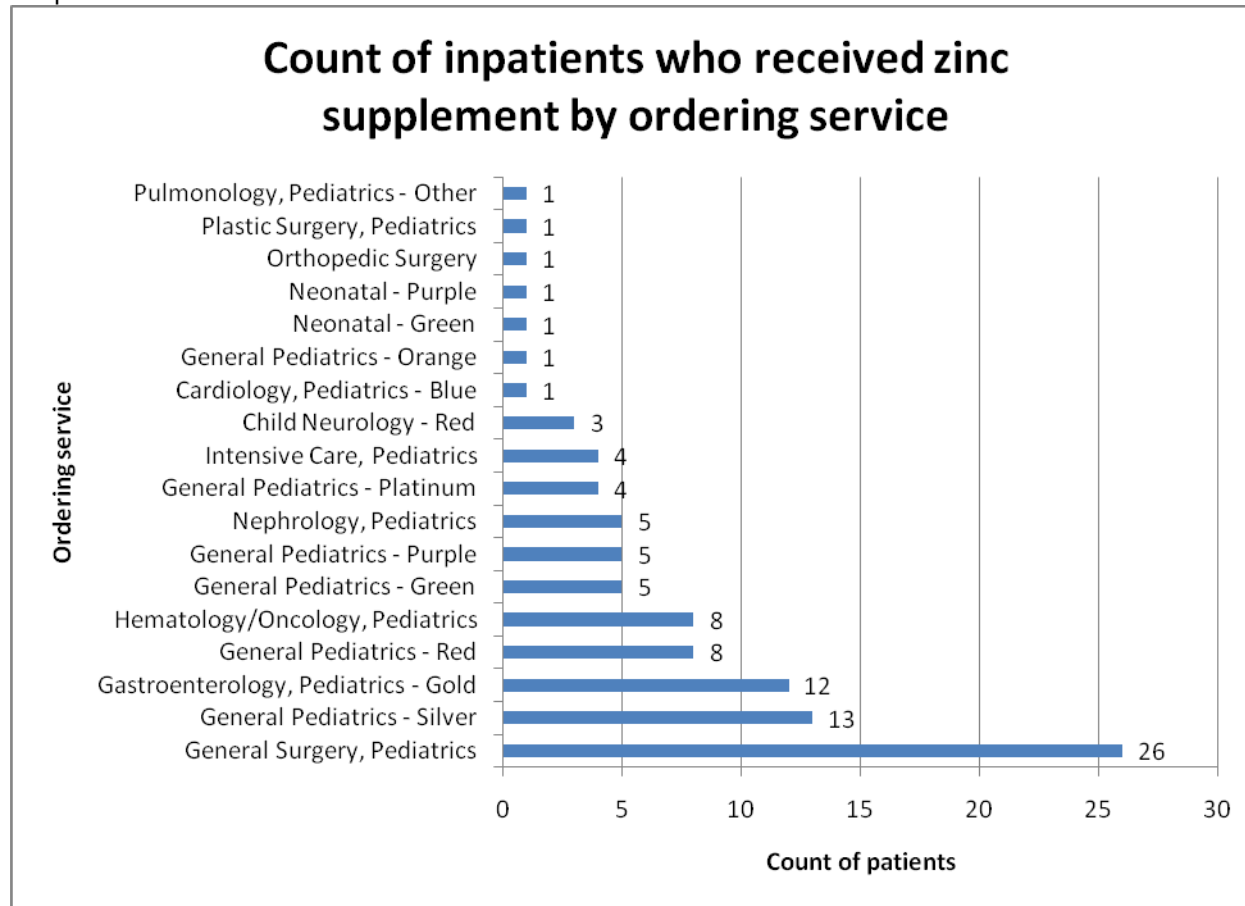


Chart 1. Count of various supplemental zinc doses:

Dose (mg)	Count	Dose (mg)	Count	Dose (mg)	Count
2	4	5.5	1	15	21
2.5	1	6	1	17.5	1
3.75	4	7	5	22.5	1
4	1	7.5	11	25	8
4.3	3	8	2	30	1
4.7	1	10	4	50	13
5	12	12.5	1	150	1

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Peach highlight denotes the amount of elemental zinc in either the zinc tablet or capsule on CMH formulary. Doses not in peach are manipulated by Nursing to achieve the ordered dose.

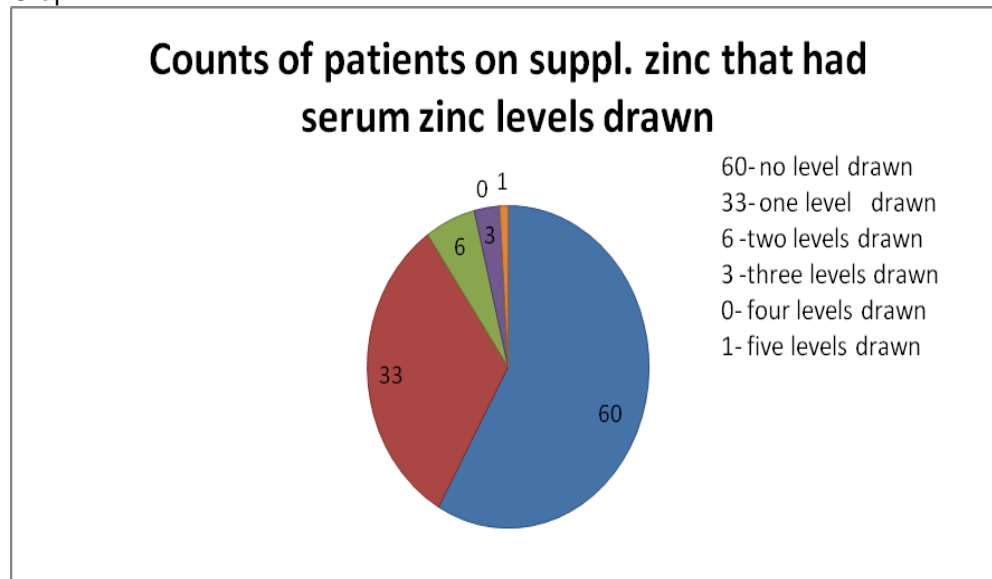
Chart 2 Origin of orders for serum zinc

<u>Origin of Order</u>	<u>Count of zinc levels ordered</u>	
Inpatient		
4 Sutherland Tower	1	
5 Henson Tower	1	
5 Sutherland Tower	5	10
5 West Observation	1	
6 Henson Tower	2	
Outpatient		
Allergy Clinic		
SC Allergy Clinic	3	9
	6	
Altered Nutrition Clinics		
BC Ready Set Grow	2	12
SC Eating Disorders Clinic	10	
Dermatology Clinic		
SC Dermatology	5	7
	2	
Dialysis Clinic		
Kidney Center	1	2
	1	
Endocrine Clinic		
NC Endocrine Clinic	3	6
SC Endocrine Clinic	2	
	1	
Gastroenterology Clinic		
GI Procedure Room	3	7
SC Gastroenterology Clinic	1	
	3	
Hematology Oncology Clinic		
Bone Marrow Transplant Clinic	1	4
Sickle Cell Clinic	1	
	2	
Other Clinics		11

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Down Syndrome Clinic	3	
Rehabilitation Clinic	2	
SC Ophthalmology Clinic	1	
Genetics Clinic	4	
BC Pediatric Care Clinic - Yellow	1	
Unable to Classify		
Outpatient Infusion Services	1	
Radiology Outpatient	1	
SC Lab Outreach	4	
SC Occupational Therapy	2	18
LAB Outpatient	2	
NC Lab Outpatient	2	
SC Lab Outpatient	6	

Graph 2.

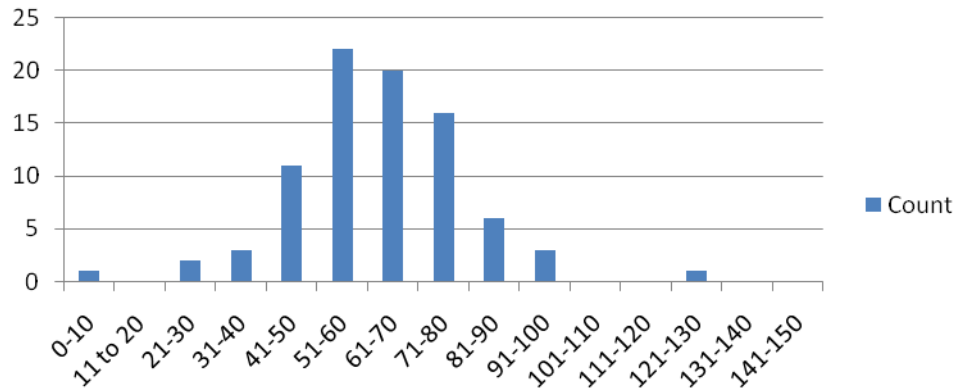


25 % of the s. zinc labs were drawn after 0600

Graph 3.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Count of s. zinc level per range of value in mcg/dl



Normal s. zinc is 70-150
mcg/dl in CMH lab

Search Strategy and Results:

Question 1- Zinc and Absorption: (February 14, 2011)

("zinc gluconate glycine "[Substance] OR "zinc lozenge"[All Fields] OR "Zinc Sulfate"[Mesh] OR "zinc salt"[All Fields] OR "zinc-histidine complex "[Substance]) AND ("Absorption"[Mesh] OR "Pharmacokinetics"[Mesh] OR "Intestinal Absorption"[Mesh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Review[ptyp] OR Case Reports[ptyp]) AND English[lang]

MEDLINE- PubMed (((("Phosphorus, Dietary"[Mesh] OR "Calcium"[Mesh] OR "Phytic Acid"[Mesh])) AND "Zinc/therapeutic use"[Mesh]) AND ("Absorption"[Mesh] OR "Pharmacokinetics"[Mesh] OR "pharmacokinetics" [Subheading] OR "absorption"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]))

Question 2- Zinc Deficiency- (January 10, 2011)

("Deficiency Diseases/diagnosis"[Mesh] AND "Zinc"[Mesh]) OR (("Biological Markers/blood"[Mesh] OR "Biological Markers/urine"[Mesh] OR "Diagnosis"[Mesh]) AND "Zinc/deficiency"[Majr]) AND ("humans"[MeSH Terms] AND English[lang] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) AND ((systematic[sb] OR "Cohort Studies"[Mesh]) OR (Meta-Analysis[ptyp] OR Practice Guideline[ptyp] OR Randomized Controlled Trial[ptyp]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp])))

Question 3 Zinc and Failure to Thrive: (January 10, 2011)(January 10, 2011)

("Zinc"[Mesh] AND "Failure to Thrive"[Mesh]) AND ("humans"[MeSH Terms] AND English[lang] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]))
5 citations

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Question 4- Zinc and Epidermolysis Bullosa- (January 10,2011)

("Zinc"[Mesh] AND "Epidermolysis Bullosa"[Mesh]) AND ("humans"[MeSH Terms] AND English[lang] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]))

Question 5 Zinc and Eczema: (January 10, 2011)

((("zinc gluconate glycine "[Substance] OR "zinc lozenge"[All Fields] OR "Zinc Sulfate"[Mesh] OR "zinc salt"[All Fields] OR "zinc-histidine complex "[Substance] OR "Zinc"[Mesh]) AND "Eczema"[Mesh]) AND ("humans"[MeSH Terms] AND English[lang] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]))

Question Zinc and Harm- (2/14/2011)

1.) Medline - PubMed ("Zinc/administration and dosage"[Major] OR "Zinc/adverse effects"[Major] OR ("Dietary Supplements/adverse effects"[Major] AND zinc[tiab])) AND ((odds AND ratio) OR benefi* OR harm* OR "Risk"[mesh]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp]) - limited to last 10 years

2.) MEDLINE- PubMed- search #2-(((("Heavy Metal Toxicity" [Supplementary Concept]) OR "Metals, Heavy/poisoning"[Mesh]) AND "Zinc"[Mesh]) AND ("Dietary Supplements"[Mesh] OR supplement*))

3.) search #3- MEDLINE - PubMed- ("Zinc Compounds/adverse effects"[Mesh] OR "Zinc Compounds/poisoning"[Mesh] OR "Zinc Compounds/toxicity"[Mesh] OR "Zinc/adverse effects"[Mesh] OR "Zinc/poisoning"[Mesh] OR "Zinc/toxicity"[Mesh]) AND zinc[tiab] NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp])

4.) Heavy metal/contaminants MEDLINE - PubMed – (February 14, 2011) "Zinc/adverse effects"[MAJR] OR (("poisoning" [Subheading] OR "toxicity" [Subheading]) AND zinc[ti]) AND (ingest* OR administration OR supplement*)

Method Used for Appraisal and Synopsis:

28 articles read are included in this review:

RevMan and Grade Pro were used to appraise and synthesize the studies. Meta analysis was performed using RevMan. For studies that did not report data that is used in meta analysis, a Critically Appraised Topic chart was prepared.

A narrative report on for the "harm" question is included in the summary.

Results: Of the 28 studies read, all but 5 had major limitations in the study design. See Risk of Bias Summary Chart. It is difficult to group studies for meta analysis because (a) varied age range of subjects studied, (b) varied dose of zinc supplement, (c) varied time between assessments, (d) varied methods used for assessment (serum v. plasma of zinc level and (e) varied outcomes studied varied among groups. However, sub groups were created to remove the variability due to age.

- To asses changes in zinc blood level there was high heterogeneity ($I^2 > 95\%$) when studies could be grouped, except for children aged 3-6 years old. In general, the standard mean difference for blood zinc level showed no difference between supplemented subjects and those who received placebo. The strongest effect was seen in infants, but heterogeneity was high. (Figure 1)
- Wuehler (2008) demonstrated zinc supplementation as low as 3 mg/d increased plasma zinc concentrations ($p > 0.001$).
- To asses change in weight gain there was high heterogeneity. For the total group, the standard mean difference showed no difference between supplemented subjects and those who received placebo. Infants who were born small for gestational age had the greatest weight gain in response to zinc supplementation. (Figure 2)
- To assess change in height (length) gain for age there was high heterogeneity. For the total group, the standard mean difference showed no difference between supplemented subjects and those who received placebo. Infants who were born small for gestational age had the greatest gain in linear growth in response to zinc supplementation. (Figure 3)

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

- The strongest relationship was found in change in weight for height (length) between those who received zinc supplement and those who received placebo. Five studies included this measure. The I^2 statistic was 0%. (Figure 4)
- There was one study that showed no difference in IQ at 9 years of age in subjects who received zinc supplementation as infants (Figure 5)
- In a study that compared zinc absorption in children on either a high or low phytate diet, dietary phytate did not appear to have an effect on plasma zinc or fecal zinc. (Figures 6 & 7)
- One study (Al-Gurairi, 2002) assessed the effect of supplemental zinc in the treatment of viral warts. There was high risk of bias for selection, detection, attrition bias. It is not clear if the study zinc dose was based on elemental zinc or zinc salt. 43% of subjects in the treatment group dropped out of the study and 50% of subjects in the placebo group dropped out. The study is included on the request of the team leaders. (Figure 8)
- It is difficult to assess harm, most reports are case reports. A summary follows:
 - Boreiko (2010) gives an overview of the difficulties of determining dietary/supplemental intake for adequate Zn nutrition. However he reports acute problems arise from a large single dose of >400mg elemental Zn per day is likely to cause nausea, vomiting and diarrhea. Chronic exposure of > 100 mg/d elemental zinc has a detrimental effect on Cu metabolism. He states “the risks of Zn deficiency are given higher priority than the risk of alterations in Cu metabolism”
 - DeOliveira (2009) report plasma iron and copper levels decreased when 22 mg/d elemental Zn was given over 12 weeks (healthy soccer players)
 - Dekker (2010) reported no change in hemoglobin when children aged 0-15 years were supplemented with 10-20 mg/d elemental zinc for 4-15 months.
 - Broun (1990) reported nonspecificity of sideroblastic anemia d/t bone marrow suppression in a person who ate zinc containing coins over a period of 12 years, and another person who took supplemental zinc for 2 years. No doses were given.
 - Finally, Wuehler (2008) stated no ill effects in children 12-30 months who took 10 mg/d zinc for 5 months.

Summary:

1. Based on guidance from the IOM and the [WHO/UNICEF/IAEA/IZINCG](#) serum and/or plasma zinc is not a sensitive indicator of zinc status for individuals. It is useful on a population level. Obtaining serum zinc of the assessment of adequacy of zinc status is not recommended.
2. There is great heterogeneity in the data on supplemental zinc effect on plasma or serum zinc, weight change, height change. New research is very likely to change confidence in the effect seen by giving supplemental zinc.
3. There is stronger data that supports the effect of supplemental zinc on increasing weight for height (length), primarily in infants aged 1-6 months (only one study in this comparison included children aged 2-6 years (Walravens, 1983). New research is likely to change confidence in the effect seen by giving supplemental zinc.
4. Based on one study included in this review, dietary phytate did not change zinc absorption. However from the IOM report, dietary phytate is the major factor affecting the variability of zinc absorption. There is great uncertainty about the estimate of the effect from this study.
5. Questions surrounding zinc tablets available and getting the correct dose, now that zinc suspension is not available should be resolved.
6. Although LexiComp recommends 0.5-1 mg/kg as the dose for treating zinc deficiency in children, there is no maximum dose noted. The IOM report gives a Tolerable Upper Intake Level (UL). The UL is defined as the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. The IOM used the activity of erythrocyte copper-zinc superoxide dismutase (ESOD) as a marker of an adverse effect of zinc intake. There was a consistent decrease in ESOD activity which is indicative of copper status.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

UL by age

- 0-6 months 4 mg/d of zinc
- 7-12 months 5 mg/d
- 1-3 years 7 mg/d
- 4-8 years 12 mg/d
- 9-13 years 23 mg/d
- 14-18 years 34 mg/d
- Adults (> 19 years of age) 40 mg/d of zinc

The U/L value is based on reduction in erythrocyte copper-zinc superoxide dismutase activity. The emetic dose is 225-450 mg elemental zinc (National Academy of Science, 2001). Wuehler (2008) showed significant increases in plasma zinc in 1-3 year old children with doses as low as 3 mg/d. From this information, an upper limit on maximum zinc dose per age should be considered.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

References Included studies

- Abdulhamid, I., Beck, F.W.J., Millalrd, S., Chen, X and Prasad, A. Effect of zinc supplementation on respiratory tract infections in children with cystic fibrosis. *Pediatric Pulmonology* 2008;43, 281-287.
- Al-Gurairi, R.T., Al-Waiz, M. & Sharquie, K.E. Oral zinc sulphate in the treatment of recalcitrant viral warts: Randomized placebo-controlled trial. *British Journal of Dermatology* 2002; 146:423-431.
- Bin, B., Prasad, A. S., Francis, W. J. B., Snell, D., Suneja, A., Sarkar, F. H., Doshi, N., Fitzgerald, J.T., & Swerdlow, P. Zinc supplementation decreases oxidative stress, incidence of infection, and generation of inflammatory cytokines in sickle cell disease patients. *Translational Research*. 2008: 152, 67-80.
- Berger, J., Ninh, N.X., Khan, N.C., Nhien, N.V., Lien, D.K., Trung, N.Q. & Khoi, H.H. Efficacy of combined iron and zinc supplementation on micronutrient status and growth in Vietnamese infants. *European Journal of Clinical Nutrition* 2006; 60: 443-454. [DOI: 10.1038/sj.ejcn.1602336]
- Boreiko, C.J.(2010) , Overview of health risk assessments of zinc. *Journal of Toxicology and Environmental Health, Part, A*, 73, 166-174.
- Bose, A., Coles, C. I., Gunavathi, H.J., Prabhakar, M., Raghupathy, P., Kirubakaran, C., Black, R. E., Brooks, W. A., Santosham, M. (2006). Efficacy of zinc in the treatment of severe pneumonia in hospitalized children < 2 years old. *American Journal of Clinical Nutrition*, 83, 1089-1096.
- Broun, E. R., Greist, A., Tricot, G., Hoffman, R. (1990). Excessive zinc ingestion: A reversible cause of sideroblastic anemia and bone marrow depression. *Journal of the American Medical Association*, 264, 1441-1443.
- Castillo-Duran, C., Rodriguez, A., Vanegas, G., Alvarez, P., & Icaza, G. Zinc supplementation and growth of infants born small for gestational age.. *Journal of Pediatrics* 1995;127:206-211.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Cole, C.R., Grant, F.K., Swaby-Ellis, E. D., Smith, J.L., Jacques, A., Northrop-Clewes, C.A., Caldwell, K.L., Pfeiffer, C.M. & Ziegler, T.R. Zinc and iron deficiency and their interrelations in low-income African American and Hispanic children in Atlanta. *American Journal of Clinical Nutrition* 2010;91:1027-1034.

Dekker, L. H., Villamor, E. (2010). Zinc supplementation in children is not associated with decreases in hemoglobin concentrations. *Journal of Nutrition*, 140,5,1035-1040.

deOliveira, K., Donangelo, C.M., deOliveira, A., deSilveira, C., Koury, J.C. (2009). Effect of zinc supplementation on the antioxidant, copper and iron status of physically active adolescents. *Cell Biochemistry and Function*, 27, 162-166. Doi: 10.1002/dbf.1550

Dijkhuizen, M.A., Winichagoon, P., Wieringa, F.T., Wasantwisut, E., Utoma, B., Ninh, N, X., Hidayat, A., & Berger, J. Zinc supplementation improved length growth only in anemic infants in a multi-country trial of iron and zinc supplementation in South-East Asia. *Journal of Nutrition* 2008;138:1969-1975.

Fischer Walker, C.L., Baqui, A.H., Ahmed, S., Zaman, K., El Arifeen, S., Begum, N., Yunus, M., Black, R.E., & Caulfield, L.E. Low-dose weekly supplementation of iron and/or zinc does not affect growth among Bangladeshi infants. *European Journal of Clinical Nutrition* 2009; 63:87-92. [DOI: 10.1038/sj.ejcn.1602905]

Hamadani, J.D., Fuchs, G.J., Osendarp, S.J.M., Khatun, F., Huda, S.N., & Grantham-McGregor, S.M. Randomized controlled trial of the effect of zinc supplementation on the mental development of Bangladeshi infants. *American Journal of Clinical Nutrition* 2001;74:381-6.

Heinig, M.J., Brown, K.H., Lönnerdal, B., & Dewey, K.G. Zinc supplementation does not affect growth, morbidity, or motor development of US term breast fed infants at 4-10 mo of age. *American Journal of Clinical Nutrition* 2006;84(3):594-601.

Henderson, L. M., Brewer, G. J., Dressman, J. B., Swidan, S. Z., DuRoss, D. J., Adair, C. H., Barnett, J. L., & Berardi, R. R. Effect of intragastric

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

pH on the absorption of oral zinc acetate and zinc oxide in young healthy volunteers. *Journal of Parenteral and Enteral Nutrition* 1995;19(5):393-397.

Hettiarachchi, M., Liyanage, C., Wickremashinghe, R., Hilmers, D. C. & Abrams, S. A.. The efficacy of micronutrient supplementation in reducing the prevalence of anaemia and deficiencies of zinc and iron among adolescents in Sri Lanka. *European Journal of Clinical Nutrition* 2008;62:856-865. [DOI: 10.1038/sj.ejcn.1602791]

Holtz, C., DeHaene, J., Woodhouse, L. R., Villalpando, S., Rivera, J. A. & King, J. C. Zinc absorption from zinc oxide, zinc sulfate, zinc oxide+EDTA, or Sodium-Zinc EDTA does not differ when added as fortificants to maize tortillas. *The Journal of Nutrition* 2005;135:1102-1105.

Hunt, J. R., Beiseigel, J. M., and Johnson, L. K. (2008). Adaptation in human zinc absorption as influenced by dietary zinc and bioavailability. *American Journal of Clinical Nutrition*, 87, 1336-1345.

Jalla, S., Krebs, N. F., Rodden, D., & Hambidge, K. M. (2004). Zinc homeostasis in premature infants does not differ between those fed preterm formula or fortified human milk. *Pediatric Research*, 56, 4, 615-620.

Kennedy, G., Hambidge, K.M., & Manary, M. A reduced phytate diet does not reduce endogenous fecal zinc in children on a habitual high-phytate diet. *Journal of Pediatric Gastroenterology and Nutrition* 2010; 51(5):678 - 679. [DOI: 10.1097/MPG.0b013e3181e536f7]

Keyzer, J.J., Oosting, E., Wolthers, B. G., & Muskiet, F. A. J. (1983). Zinc absorption after oral administration of zinc sulfate. *Pharmaceutisch Weekblan Scientific Edition*, 5, 252- 253.

Krone, C. A., Wyse, E. J. & Ely, J. T. A. (2001). *International Journal of Food Sciences and Nutrition*, 52, 379-382.

Mazariegos, M., Hambidge, K.M., Krebs, N.F., Westcott, J.E., Lei, S., Grunwald, G.K., Campos, R., Barahona, B., Raboy V ., Solomons, N. (2006). Zinc absorption in Guatemalan schoolchildren fed normal or low-phytate maize. *American Journal of Clinical Nutrition*, 83, 59-64.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Mazariegos, M., Hambidge, K. M., Westcott, J. E., Solomons, N. W., Raboy, v., Das, A., Goco, N., Kendem, M., Wright, L. L., & Krebs, N. F.

Neither a zinc supplement nor phytate reduced maize nor their combination enhance growth of 6- to 12 month old Guatemalan infants.

Journal of Nutrition 2010;140: 1041-1048.

McKenna, A. A., Ilich, J. Z., Andon, M. B., Wang, C., & Matkovic, V. (1997). Zinc balance in adolescent females consuming a low-or high-calcium

diet. American Journal of Clinical Nutrition, 65, 1460-1464.

Mehdizadeh, M., Zamani, G., & Tabatabaee, S. (2008). Zinc status in patients with major β -thalassemia. *Pediatric Hematology and Oncology*, 25,

49-54.

Mozaffari-Khosravi, H., Shakiba, M., Eftekhari, M.H & Fatehi, F. Effects of Zinc Supplementation on Physical Growth in 2–5-Year-Old Children.

Biological Trace Element Research 2009; 128:118-127. [DOI: 10.1007/s12011-008-8261-1]

Nakamura, T., Nishiyama, S., Futagoishi-Suginohara, Y, Matsuda, I., & Higashi, A. (1993). Mild to moderate zinc deficiency in short children: Effect

of zinc supplementation on growth velocity. *Journal of Pediatrics*, 123, 65-69.

Nève, J., Hanocq, M., Peretz, A., Khalil, F. A., & Pelen, F. (1991). Absorption and metabolism of oral zinc gluconate in humans in fasting state,

during and after a meal. Biological Trace Element Research, 32, 201-201.

Oksel, F., Köksyo, H., Taneli, B. (1996). Zinc tolerance test patterns in normal children and in moderate and severe zinc deficiency states. *Indian*

Journal of Pediatrics, 63, 655-658.

Pongcharoen, T., DiGirolamo, A.M., Ramakrishnan, U., Winichagoon, P., Flores, R., & Martorell, R. Long-term effects of iron and zinc

supplementation during infancy on cognitive function at 9 y of age in northeast Thai children: A follow-up study. American Journal of

Clinical Nutrition 2011;93:363-643. [DOI: 10.3945/ajcn.110.002]

Prasad, A. S., Beck, W. J. B., Kaplan, J., Chandrasekar, P. H., Ortega, J., Fitzgerald, J. T., & Swerdleo, P. Effect of zinc supplementation on

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

incidence of infections and hospital admission in sickle cell disease (SCD). *American Journal of Hematology* 61:194-202. [Other: FDA #FD-U-000457]

Ramakrishnan, U., Nguyen, P., & Martorell, R. (2009). Effects of micronutrients on growth of children under 5 y of age: Meta-analysis of single and multiple nutrient interventions. *American Journal of Clinical Nutrition*, 89, 191-203.

Spencer, H., Rubio, N., Kramer, L., Norris, C., & Osis, D. (1987). Effect of zinc supplements on the intestinal absorption of calcium. *Journal of the American College of Nutrition*, 6, 1. 47-51.

Taneja, S., Bhandari, N., Rongsen-Chandola, T., Mahalanabis, D., Fontaine, O., Bhan, K., and Other Members of the Study Group. Effect zinc supplementation on morbidity and growth in hospital born, low-birth-weight infants. *American Journal of Clinical Nutrition* 2009;90:385-391. [ClinicalTrials.gov: NCT00272142]

Tran, C. D., Miller, L. V., Krebs, N. F., Lei, S., & Hambidge, K. M. Zinc absorption as a function of the dose of zinc sulfate in aqueous solution. *American Journal of Clinical Nutrition* 2004;80:1570-1573.

Tran, C. D., Katsikeros, R., Manton, N., Krebs, N. F., Hambidge, K. M., Butler, R. N., & Davidson, G.P. (2011). Zinc homeostasis and gut function in children with celiac disease. *American Journal of Clinical Nutrition*, [DOI: 10.3945/ajcn.111.018093]

Walravens, P. A., Krebs, N.F., and Hambidge, K.M. Linear growth of low income preschool children receiving a zinc supplement. *American Journal of Clinical Nutrition* 1983;38:195-201.

Wasantwisut, E., Winichagoon, P., Chitchumroonchokchai, C., Yamborisut, U., Boonpradern, A., Pongcharoen, T., Sranacharoenpong, K. & Russameessaphorn, W. Iron and zinc supplementation improved iron and zinc status, but not physical growth of apparently healthy, breast fed infants in rural communities of northeast Thailand. *Journal of Nutrition* 2006;136:2405-2411.

Wuehler, S.E., Sempértegui, F. & Brown, K.H. Dose-response trial of prophylactic zinc supplements, with or without copper, in young Ecuadorian

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

children at risk of zinc deficiency. American Journal of Clinical Nutrition 2008;87:723-33.

Yip, R., Reeves, J.D., Lönnerdal, B., Keen, C., & Dallman, P.R. Does iron supplementation compromise zinc nutrition in healthy infants? American Journal of Clinical Nutrition 1985;42:683-687.

Zemel, B.S., Kawchak, D.A., Fung, E.B., Ohene-Frempong, K., & Stallings, V.A. Effect of zinc supplementation on growth and body composition in children with sickle cell disease. American Journal of Clinical Nutrition 2002;75:300-7.

Characteristics of excluded studies

- López de Romaña, D., Lönnerdal, B., & Brown, K.H. (2003). Absorption of zinc from wheat products fortified with iron and either zinc sulfate or zinc oxide. American Journal of Clinical Nutrition, 78, 279-283.

Reason for exclusion: Used geometric means to compare data that cannot be used in meta analysis.

Silva, A.P.R., Vitola, M.R., Zara, L.F., & Castro, C. F. Effects of zinc supplementation on 1- to 5 year old children. Jornal de Pediatria (RioJ) 2006; 82(3):227-231. [DOI: 10.2223/JPED.1480]

Reason for exclusion: 40% of subjects dropped out of the study. Drop outs were not described, not certain to which group they were assigned.

Other References

DeBenoist, B., Darnton-Hill, I., Devidsson, L., Fontaine, O., & Hotz, C. (2007). Conclusions of the Joint WHO/UNICEF/IAEA/IZiNCG interagency meeting on zinc status indicators. Food and Nutrition Bulletin, 28, Suppl 3, 480S-484S (5). Retrieved from

<http://www.ingentaconnect.com/content/nsinf/fnb/2007/00000028/A00303s3/art00006>

Lexi-comp™. (2011). Zinc Sulfate. Retrieved from: <http://online.lexi.com/crlsql/servlet/crlonline>

National Academy of Sciences. (2001). Dietary reference intakes for Vitamin A, Vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. [Consensus Report] pages 442-501. Retrieved from:

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

http://books.nap.edu/openbook.php?record_id=10026&page=442

Updated 2/2011; 3/2011, 5/2011;6/2011; 8/2011;9/2011 11/2011 (nha)

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Abdulhamid 2008

Methods	Prospective double blind placebo controlled study,
Participants	26 children ages 7 to 18 years old with CF exhibiting mild to moderate lung disease
Interventions	Treatment: daily dose of 30 mg of elemental Zn as Zn gluconate (15 mg/capsule) to group A for 12 consecutive months. Placebo: "placebo preparation" The treatment and placebo groups were further stratified into zinc sufficient (zinc level > 90 mcg/dl and zinc deficient (≤ 89 mcg/dl) groups. Participants in each group were followed every 3 months.
Outcomes	<u>Zinc Adequate</u> No. of episodes requiring IV Antibiotics No. of episodes requiring oral Antibiotics % Compliance Plasma Zinc Level
Notes	Exclusion criteria for the study included presence of acute severe infection at the time of enrollment, renal disease, severe hepatic disease, gall bladder disease, sickle cell disease (SCD), use of oral immunosuppressive drugs (steroids and non-steroid anti-inflammatory drugs), diuretics and Zn supplements.

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	stated random, but did not elucidate
Allocation concealment (selection bias)	Unclear risk	
Blinding (performance bias and detection bias)	Low risk	supplements were made by outside lab
Incomplete outcome data (attrition bias)	Low risk	One participant dropped out of the zinc supplemented group.
Selective reporting (reporting bias)	High risk	Although all the groups had a normal zinc level based on the laboratory used for the study, the investigators chose ≤ 89 as deficient and ≥ 90 as sufficient. No mention of how those between 89 and 90 were handled.
Other bias	Low risk	

Al-Gurairi 2002

Methods	RCT
Participants	N=80 subjects with viral warts were recruited. Inclusion criteria: > 15 warts, warts were recalcitrant after conventional treatment, and otherwise healthy. N= 40 in treatment group; 4-50 years of age N= 40 in control group; 7-37 years of age Iran Teaching Hospital during May 1999 to April 2000.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Interventions Zinc treated N=23 (4-50 years of age)
 First group (treatment group) received oral Zn sulphate (10mg) in a dose of 10 mg/kg daily in three divided doses up to 600 mg/day.
 The second group (control group) was given a placebo oral treatment in the form of glucose.

All subjects were instructed not to take any treatment other than prescribed in this trial. It is not clear if elemental zinc or zinc sulfate was dosed.

Outcomes Serum zinc pre and one month post treatment.
 The primary outcome measures were complete disappearance of the lesions without residual scarring.

Notes The treatment continued for 2 months while the follow-up period lasted up to 6 months.
 During treatment period the subjects were evaluated and examined every 2 weeks for evidence of partial or complete regression of their lesions, to record any adverse effects and to ensure that the patients were not using other treatments.

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	High risk	Sequence was generated by odd numbered days treatment, even numbered days placebo.
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias)	High risk	Subjects were blinded to the type of treatment; observer was not.
Incomplete outcome data (attrition bias)	High risk	Only 23 subjects of the group and 20 subjects of the second group completed the study and they only report on the completers.(57% and 50% completers respectively)
		In all subjects the serum level of Zn was low at the outset of the study.
Selective reporting (reporting bias)	High risk	
Other bias	Low risk	

Bin 2008

Methods RCT

Participants 36 adults (18-47 years) homozygous SCD.

Interventions Zinc group: 25 mg of zinc as the acetate salt orally 3 times per day for 3 months.

Outcomes Blood: plasma zinc concentration, nitrite and nitrate (NOx), antioxidant power, DNA oxidation products, lipid peroxidation products, soluble vascular cell adhesion molecule-1 (VCAM-1), soluble intercellular

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

adhesion molecule-1 (ICAM-1), and soluble E-selectin, as well as ex vivo study of nuclear factor-kappa B (NF- κ B) DNA binding, TNF-, IL-1, IL-2, and IL-2 receptor-alpha (IL-2R) mRNAs in isolated mononuclear cells (MNCs)

- Infections
- Acute vaso-occlusive pain crises

Notes Excluded subjects who were non ambulatory, received > 6 transfusion/year or taking hydroxyurea, history of substance abuse, neurological or psychiatric deficits, + HIV, and + Hep B. Those taking zinc supplements

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	technician blindly chose one of two identical bottles labeled as "study drug". One bottle contained zinc the other did not.
Allocation concealment (selection bias)	Low risk	all persons were blinded including ID physicians who evaluate infections and hemologist who evaluated pain crises.
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Unclear risk	They do not report on each subject for each lab analysis. They do not acknowledge missing subjects.
Selective reporting (reporting bias)	High risk	For all laboratory analysis, they compare the supplemented group to themselves, not the placebo group. In other charts and text they compare SCD to healthy adults.
Other bias	Low risk	

Berger 2005

Methods	Prospective, RCT
Participants	Singleton breast-fed infants, age 4-7 months, from 24 communities of Que Vo, a rural & poor district NW of Hanoi in the Red River Delta in Vietnam. Approx 140 subjects per group.
Interventions	Treatment group: 10 mg zinc sulphate daily. Control group: placebo Supplements were placed in 2mL sweet-tasting syrup, in a similar coded bottle, given to mouth of infant via small plastic syringe. Supplements were given 7 days/wk during 6 months by trained field workers, one in each village. Supplementation was given between 0700-0900. No food/beverage given to infant after 2 hrs after treatment.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Outcomes Measurements include weight & height monthly from baseline to end of study.
 Non-fasting blood samples collected in am at baseline & after 26 weeks to assess Hgb, serum ferritin & zinc.

Notes Exclusion criteria: infants with chronic or acute illness, severe malnutrition or congenital abnormality, infants with Hgb <70g/l.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Unclear risk	Infants were randomly assigned, following a computer-generated block randomized group allocation.
Allocation concealment (selection bias)	Low risk	Computer generated.
Blinding (performance bias and detection bias)	Low risk	Supplements were presented in similar coded bottles avoiding participants and health workers to differentiate between treatments. Supplements were coded with a letter at production & the code-allocation kept secret until the end of the statistical analysis.
Incomplete outcome data (attrition bias)	Low risk	Discussed exclusion/drop-outs: Total of 915 included in study & 784 infants completed 6 mo supplementation period. Dropout rate of 14.3% in each group. Drop-out reasons as follows: difficulty parents to bring infant daily to treatment place (93), refusal of 2nd blood sampling (38). Zinc group: N=247. refusal of blood sampling=18, hemoglobin<70 grams/L=8, dropped out=20, absent at final evaluation=6 Placebo group: N=247. refusal of blood sampling=19, Hgb < 70 grams/L=2, dropped out=15, absent at final evaluation=13 Per protocol analysis used. Treatment group (zinc) = 81% follow-up. Placebo group = 80% follow-up.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Castillo-Duran 1995

Methods RCT

Participants 80 infants born 38-41 week PMA (< 10 percentile on the Lubchenco charts)

Interventions Treatment group: 3 mg of zinc/day as the acetate salt (1mg Zn/ml).
 Placebo: solution without zinc

Outcomes Anthropometrics: weight , length, and OFC
 Compliance
 Laboratory: 30, 60, 140 and 180 days blood samples, hair samples, milk (formula or breast milk? not clear in methods.)

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Notes Excluded infants with congenital malformations, asphyxia, congenital infection, or if mother had preeclampsia or intrahepatic cholestasis. Infants with less than 50% compliance were excluded (12 infants, not certain to which group they were assigned.)

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Random assignment within blocks of 20
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	Per protocol analysis.
Selective reporting (reporting bias)	Unclear risk	They said they analyzed milk-
Other bias	Unclear risk	

Cole 2010

Methods cross-sectional study

Participants 292 children in Atlanta were recruited, 280 qualified for analysis. Mean age was 2.5 +/- 1.2 years.

Interventions

Outcomes 3 day food diary, hemoglobin, serum ferritin, zinc, copper and C-reactive protein. Growth by direct measure- length < 2 standing height > 2 years

Notes Children with elevated C-reactive protein were excluded, as were children with sickle cell anemia, acute diarrhea or respiratory illness.
non fasting blood draws
Zinc deficiency was defined pre hoc as a serum zinc concentration < 10.7 micromole/L

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Unclear risk	convenience sampling, age 12-60 months
Allocation concealment (selection bias)	High risk	cross-sectional study
Blinding (performance bias and detection bias)	High risk	cross-sectional study
Incomplete outcome data (attrition bias)	High risk	cross-sectional study
Selective reporting (reporting bias)	Low risk	cross-sectional study
Other bias	Low risk	

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

deOliveria 2009

Methods	RCT single blinded
Participants	Football players (N=47), on a junior soccer team in Rio de Janeiro 12-week, single-blinded, intervention trial with two randomly selected groups mean age 13 ± 0.4 years adolescent football (soccer) players,
Interventions	Zinc Supplement (N=21) group one capsule daily 22 mg of zinc as zinc gluconate Placebo group (N=26) took one capsule daily of similar appearance containing maltodextrin. Blood and urine samples were obtained before (baseline) and after the 12-week of treatment.
Outcomes	Lab results The objective of this study was to evaluate the effect of zinc supplementation on the antioxidant status, and on zinc, iron, and copper status in physically active male adolescents.

Notes

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Unclear risk	Authors state randomized, but do not give specifics
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Unclear risk	Subjects only were blinded
Incomplete outcome data (attrition bias)	Low risk	All completed the study
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Dijkhuizen 2008

Methods	4 sites RCT
Participants	Infant between 4-6 months of age. Sites (number) included Thailand (4), Vietnam, and Indonesia (2). Two other Indonesia dropped out, and data from these sites are not included in the analysis. (One had different study design and one decided not to participate.) There were four supplementation groups Zinc only, iron only, zinc+iron and placebo. This analysis includes zinc vs. placebo only. 3 sites administered a high Vitamin A dose (one site 150 micrograms (50,000 international units), and 2 sites 300 micrograms (100,000 international units).
Interventions	Treatment 10 mg of zinc as the sulfate salt Placebo: syrup with Vitamin C

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

supplementation was 5-7 days per week depending on site

Outcomes Anthropometrics; health, diet, lactation history; and possible adverse effects. Blood samples were taken at 6 months, venipuncture from 3 sites and heel-stick at one site.

Notes They used the NCHS growth charts and WHO charts, reporting on the NCHS charts so comparison can be made with other studies.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Not described in this article, but could find parent article
Allocation concealment (selection bias)	Low risk	labels to supplement placed at product manufacturing site
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	Not all sights obtained blood work, not all measured zinc concentrations.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	sponsored by UNICEF

Fischer Walker 2009

Methods Prospective, RCT

Participants Breast fed infants, age 5-6 months, permanent residents of selected villages in Bangladesh. Treatment group N=141, Control group N=140.

Interventions Treatment group: 20 mg elemental zinc & 1 mg riboflavin or control group: 1 mg riboflavin. Weekly supplementation given by trained community health worker (CHW) @ home visit. Measurements taken @ enrollment & q2 mo thereafter (6, 8, 10 & 12 mo age).

Outcomes Measurements included length, weight, and mid-upper arm circumference (MUAC)

Notes Exclusion criteria: low weight-for-age, severely anemic, or showed any signs of neurological disorder, physical handicap, or chronic illness affecting feeding, activity or cognitive development.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Block randomization, stratified by length for age Z score using -2Z as cutoff.
Allocation concealment (selection bias)	Unclear risk	Was not described in this article. The article stated that study design, population, trial profile & methods were published previously.
Blinding (performance bias and detection bias)	Low risk	Blinding was not described in detail for this study. There was no mention of CHW blinding. Measurements were taken by anthropometrist that was blinded to the supplementation allocation.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Incomplete outcome data (attrition bias)	High risk	All calculations assumed a 10% loss to follow-up. Per protocol analysis used. Treatment group (zinc) = 86% follow-up. Control group = 89% follow-up.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Hamadani 2001

Methods	RCT
Participants	Infants 1-6 months of age. N=213 (272 in the original group, 59 dropped out, do not know how many from each group.
Interventions	Treatment- 5 mg of elemental zinc as zinc acetate N= 104 Control- cellulose substance given as an identical syrup N=109
Outcomes	Bayley Scale MDI and PDI, Behavior rating, Home stimulation, socioeconomic status, and anthropometric measures

Notes

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	randomized, double-blind, controlled trial
Allocation concealment (selection bias)	Unclear risk	Did not state
Blinding (performance bias and detection bias)	Low risk	Double blind - families and the personnel who administered the Bayley were unaware of the group assignment.
Incomplete outcome data (attrition bias)	Low risk	Per protocol analysis, however, statistics were done to see if the loss may have biased the findings.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Heinig 2006

Methods	RCT
Participants	Healthy term breast fed infants of mothers who planned to fully breast feed and not feed complementary foods before 4 months 4-10 months of age 85 enrolled, 70 completed the study Power analysis performed need 70 total or 35 per group to see a difference in weight gain. Need > 1000 in each group to discern differences in performance on motor development tool used.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Interventions Treatment: 5 mg/d of zinc as zinc sulfate
Placebo

Outcomes Growth, morbidity, motor development, plasma zinc, iron and copper, plasma ferritin, Hemoglobin and hematocrit
Record of complementary foods
5 major morbidity codes respiratory, diarrhea, otitis media, fever and other (all defined)
Motor development used the AIMS or the Alberta Infant Motor Scale.

Notes

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Used a formal randomization tool the Moses-Oakford algorithm
Allocation concealment (selection bias)	Low risk	Lab assistant assigned labels and color coded. 4 colors assigned to reduce revealing accidentally
Blinding (performance bias and detection bias)	Low risk	Investigators and mothers only knew color assigned
Incomplete outcome data (attrition bias)	Unclear risk	Intention to treat analysis. however the statement is made: Because exclusion of infants who were excluded did not affect any results they were included in the analysis. Funny.
Selective reporting (reporting bias)	High risk	Did not report on plasma levels. Mothers would not allow blood draws. AIMS score tool would require > 1000 in each group to discern difference
Other bias	Unclear risk	

Henderson 1995

Methods two way cross over, four phase design. Washout of 7 days between treatments.

Participants 10 healthy adult volunteers, 5 female. 20-23 years of age. 120% ideal body weight.

Interventions Phase one: zinc acetate administered to subjects pre treated with famotidine (Pepcid) 40 mg oral suspension. Intra-gastric pH ≥ 5 (acetate high pH= AH)

Phase two: zinc oxide administered to subjects pretreated with a single oral does of famotidine 40 mg oral suspension. Intra-gastric pH ≥ 5 / (oxide high pH= OH)

Phase 3: zinc acetate administered to subjects with an intra-gastric pH ≤ 3 (acetate low pH= AL)

Phase 4: zinc oxide administered to subjects with an intra-gastric pH ≤ 3 (acetate low pH= OL)

All zinc doses were equivalent of 50 mg of elemental zinc. Subjects were fed a zinc controlled diet (18 mg zinc/d) on treatment day and the subsequent day for each treatment.

Outcomes 24 hour urine collection, intragastric pH monitoring for 4 hours after Zn administration, blood collection 1 hour after zinc

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

administration. *In vitro* dissolution tests of each salt at various pHs. Data collected: plasma zinc, urinary zinc.

Notes

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	cross over design, served as own control
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	Unclear risk	Unclear, not certain of subjects could discern the treatments.
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Hershkovitz 1999

Methods	RCT with matching to 10 healthy controls
Participants	Infants aged 3-9 months with non organic failure to thrive,
Interventions	Recommended to discontinue breast feeding
	Group A: 2 mg/kg/d elemental zinc as zinc acetate.
	Group B: placebo- the solution used to dissolve the zinc as in group A
Outcomes	Lab values: Serum IGF-1, Serum IGFBP-3, and anthropometrics
Notes	Israel

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Randomization is not described
Allocation concealment (selection bias)	Low risk	Bottles were color coded.
Blinding (performance bias and detection bias)	High risk	7 infants were excluded per protocol analysis
Incomplete outcome data (attrition bias)	High risk	22% did not complete the protocol, not certain which group to which they were assigned.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Hettiarachichi 2008

Methods	RCT
Participants	821 adolescents age 12-16 years. All were treated for parasite infection prior to the study. Hemoglobin > 80 g/L. Zinc and iron deficiency are prevalent in the region of Sri Lanka where the study was completed.
Interventions	Each group received 2 capsules per school day of: 1:Iron- 50 mg/d as ferrous fumarate 2:Zinc-14 mg/d as zinc sulphate 3:Combined iron and zinc as above 4:Placebo Intervention was for 24 weeks.
Outcomes	Hbg concentration, serum zinc- skewed distribution, therefore log transformed. Serum ferritin Serum zinc Growth using CDC/WHO weight for age and height for age z scores, BMI
Notes	Of 821 enrolled, 774 (91%) completed the study. Baseline outcomes were not different when completers were compared with non completers.

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Subjects were blinded by classroom in a double blind fashion
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	Low risk	Teachers gave the children the capsules, they were not aware of the group assignment
Incomplete outcome data (attrition bias)	Unclear risk	Per protocol analysis. Teachers kept records of capsules taken and records were checked every 2 weeks for compliance to taking capsules. 58% of subjects took all doses (120), 32% received 110-119 doses and only 2% received < 100 doses. Reasons for non completing- withdrawal and blood draw refusal, absent on day of blood draw.
		Sample size was calculated at 180 per group; enrollment was inflated to 200 per group to account for drop outs. Completers met power requirements.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Holtz 2005

Methods RCT

Participants Non-anemic but low iron stores (normal Hbg, but low ferritin) women 19-44 years of age.

Study was powered to detect a group difference of 8% zinc absorption by having 15 subjects per group (2 tailed test, SD 10.5, $\alpha= 0.05$. 80% power) However the SD from the first subjects completing the study were lower than above, the number of subjects was decreased. All were in the follicular stage of the menstrual cycle.

Interventions Addition of the test zinc salt to equal 40 mg zinc/ kg flour.

- Group one: Zinc oxide
- Group two: Zinc oxide + Na₂EDTA
- Group Three: Na₂ZnEDTA
- Group Four: ZnSo₄

Outcomes

- urine zinc,
- fractional absorption of zinc (calculated using the tracer to tracee method)
- serum zinc
- hemoglobin
- C-reactive protein

Notes They did not meet power for any group, but justified it by saying the SD of the first groups was lower than the population they based the power analysis upon. They state a smaller number of subjects is justified for this reason.

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	Unclear risk	Blinding not described at all. Not certain if lab personnel knew which groups the specimens they handled were from.
Incomplete outcome data (attrition bias)	High risk	It appears they did a power analysis, and then did not pay attention to it. They explained their way around it.
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	2 samples were lost due to electrical failure in the laboratory, both from the zinc oxide group.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Kennedy 2010

Methods	prospective observational study receiving a habitual maize-based high-phytate diet; these children served as their own controls
Participants	10 Malawian children, ages 2-5 years, at risk for zinc deficiency and receiving a habitual maize-based high-phytate diet. Power analysis was done.
Interventions	each child received 170 micrograms IV labeled zinc followed by marking and collecting stool and keeping weighed food records Subjects were given phytate-reduced maize for 40 days- enzymatic techniques (phytase) to reduce phytate were used. Food samples were analyzed. Phytate was reduced in the flour by 96%. Dietary phytate was reduced by 65%
Outcomes	Fecal zinc, clean void urine, pre and post 40 days of phytate reduction
Notes	The primary limitation of the study is that concomitant dietary zinc absorption data are not available in these children, which would allow for interpretation of EFZ with respect to net zinc retention. Because they did not measure dietary zinc absorption, they cannot be certain whether EFZ was inappropriately high.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	not randomized
Allocation concealment (selection bias)	High risk	all received the low phytate flour
Blinding (performance bias and detection bias)	High risk	no intention to blind
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk.	not a robust design,

Kennedy 2010

Methods	prospective observational study receiving a habitual maize-based high-phytate diet; these children served as their own controls
Participants	10 Malawian children, ages 2-5 years, at risk for zinc deficiency and receiving a habitual maize-based high-phytate diet. Power analysis was done.
Interventions	each child received 170 micrograms IV labeled zinc followed by marking and collecting stool and keeping weighed food records Subjects were given phytate-reduced maize for 40 days- enzymatic techniques (phytase) to reduce phytate were used. Food samples were analyzed. Phytate was reduced in the flour by 96%. Dietary phytate was reduced by 65%
Outcomes	Fecal zinc, clean void urine, pre and post 40 days of phytate reduction

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Notes The primary limitation of the study is that concomitant dietary zinc absorption data are not available in these children, which would allow for interpretation of EFZ with respect to net zinc retention. Because they did not measure dietary zinc absorption, they cannot be certain whether EFZ was inappropriately high.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	not randomized
Allocation concealment (selection bias)	High risk	all received the low phytate flour
Blinding (performance bias and detection bias)	High risk	no intention to blind
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk.	not a robust design,

Mazariegos 2006

Methods cross sectional- cohort

Participants 60 Guatemalan schoolchildren between ages 7.5 - 12 years

Interventions children were fed low-phytate maize, or 1 of 2 control maizes for 10 weeks
 Treatment 1- low phytate maize- 60% less phytate
 Treatment 2- wild-type isohybrid of maize fed in treatment 1
 Treatment 4- locally grown maize

Outcomes Zinc intake, phytate:zinc ratio; plasma zinc; fractional absorption of zinc; total absorbed zinc

Notes Study conducted in Guatamala, but analysis was done in Colorado

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Unclear risk	Not clear "families were approached for participation in the basis of the age of their apparently healthy children (6-11 years), their willingness to allow their children to participate in the study, and the willingness of the entire family to consume the study maize.
Allocation concealment (selection bias)	Low risk	participants "probably distinguished the local control maize;" A power analysis was performed. Need 20 subjects per intervention group.
Blinding (performance bias and detection bias)	Low risk	investigators in Colorado were blinded to the treatment group assignments
Incomplete outcome data (attrition bias)	Low risk	one dropout, intention to treat analysis
Selective reporting (reporting bias)	High risk	The data they collected did not show what they expected. They did a post hoc analysis to report a significant finding.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Other bias

Low risk

Mazariegos 2010

Methods	Blinded RCT
Participants	Infants 6-12 months of age N=420 Did power analysis based on linear growth velocity (6% increase in linear growth rate). The study was also powered to detect an interaction between the zinc supplement and low phytate maize to determine whether the effect of the zinc supplement differed between the 2 maize treatment groups. They recruited 412 infants between 2004-2006 and 384 subjects completed the study.
Interventions	Treatment one: Low phytate ~ 80% reduced Treatment two: High phytate ~ 710 mg/100 g [Zn]=2.6 mg/100 g of both types of maize (this is 50% higher than most maize) Each maize treatment group was further randomized to zinc treatment groups Treatment one: Zinc 5 mg/d Treatment two: Placebo (mother had to score and break the tablet and administer 0.5 tablet per day. She also had to assure the tablet was dissolved and swallowed)
Outcomes	Primary outcome linear growth velocity Secondary outcomes: other growth measures, neurodevelopment and prevalence and incidence of infectious disease morbidity. Plasma zinc
Notes	The study was done in Guatemala, and analyzed in Colorado Hypothesis one: low phytate maize would increase infant linear growth velocity between 6 and 12 months independent of the receipt of a zinc supplement. Hypothesis two: a small zinc supplement (5 mg/d) would increase infant linear growth velocity independent of the type of maize eaten.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	permuted blocks of 6 for both flour and zinc.
Allocation concealment (selection bias)	Low risk	Each sack of flour was color coded. Families were assigned a color. Only flour with that colored label was distributed.
Blinding (performance bias and detection bias)	Low risk	Only one author who over saw grain quality was not blinded. He did not see families.
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	
Other bias	Low risk	

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Pongcharoen 2011

Methods	Follow-up study 1998-1999 original- the original was a randomized 2X2 factorial, double blind placebo controlled trial. Follow-up cross sectional study conducted from August 2007 to January 2008
Participants	560 children aged 9 y or 92% of those who had participated in a RCT involving 4 groups who received daily iron, zinc, iron plus zinc or a placebo 2 ml dose for 6 months. Group 1- 5 grams/L iron as iron sulfate Group 2- 5 grams /L zinc as zinc sulfate Group 3- 5g/L iron as iron sulfate and 5 grams /L zinc as zinc sulfate Group 4- Placebo Administered by parents using a oral medication syringe, given between meals. Compliance monitored by village health volunteers. Monthly measurement of syrup administered
Interventions	Wechsler intelligence Scale for Children-Third Edition (Thai Version), the Ravens Colored Progressive Matrices, and school performance tests. General linear mixed models were used to assess long-term effects
Outcomes	Full IQ scale, serum zinc, weight z-score, length z-score
Notes	Went to original study, to get enrollment information see: Wasantwisut 2006

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Randomized 2X2 factorial process. Power calculation was done to detect a difference in length for age z-score of 0.15. Stratified by age and sex.
Allocation concealment (selection bias)	Low risk	Random numbers generated by statistician not involved in the study. Syrups were made and labeled by a pharmacy not other wise involved. allocation codes were kept at the UNICEF office until the end of data analysis
Blinding (performance bias and detection bias)	Low risk	clinical psychologists were unaware of the child's intervention group
Incomplete outcome data (attrition bias)	Low risk	This is a 9 year follow up study. Located 562 of the original 609 children for follow-up testing (92%)
Selective reporting (reporting bias)	Low risk	both WISC-III and Ravens CPM tests were adm by clinical psychologists using standard protocol
Other bias	Low risk	

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Taneja 2009

Methods	RCT
Participants	2052 hospital born term (> 37 weeks) infants with BW ≤ 2500 g
Interventions	Treatment: zinc 5 mg/d- 2 weeks of age to 6 months and 10 mg/d > 6 months Placebo: tablets with out zinc Parents were given zinc sulfate tablets or placebo tablets. Instructed to dissolve in 5 ml of breast milk for young infants or breast milk or water for older infants. Sample size was estimated on the reduction of all cause hospitalizations in this age group. Sample size required 2000 infants.
Outcomes	Monthly visits for compliance, every three months for measures blood work at conclusion only 15 percent of infants at start and stop of study all cause hospitalizations prevalence of diarrhea acute lower respiratory tract infections visits to health care providers weights and lengths at 3, 6, 9 and 12 months.

Notes

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	permuted blocks of fixed length of 20
Allocation concealment (selection bias)	Low risk	statistician not involved with the study created randomization list and labeled the supplements
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Unclear risk	Per protocol analysis, only 15% of infants had blood work drawn at the beginning and end of the study.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Tran 2004

Methods	Cross over design
Participants	8 healthy adults (3 men and 5 women) Age 33.8 ± 9.8 years
Interventions	Aqueous zinc sulfate was administered (one pair per phase). Three week washout between phases Phase 1: 2 and 5 mg

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Phase 2: 10 and 15 mg
 Phase 3: 20 and 30 mg
 Each solution was administered over a 15 week period and

Outcomes

Fractional absorption of zinc and absorbed zinc

Notes

Goal was to find dose-response data for the absorption of zinc from a range of oral doses to assist in establishing dosage guidelines for short term relatively high dose zinc supplementation.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	"Phase' of zinc supplementation was randomized
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Unclear risk	Power analysis performed- 8 subjects
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Walravens 1983

Methods

pair matched cohort

Participants

28 pairs, Hispanic American children aged 2-6 years

Interventions

Treatment : 5 mg of zinc as zinc sulphate 2 times per day for one year

Placebo: cherry flavored syrup for one year

Outcomes

Anthropometrics, Dietary evaluation, Pre and Post plasma zinc levels, Plasma copper, s. albumin, total protein, cholesterol, alkaline phosphatase, and vitamin A.

Notes

Handling of drop outs "When a member of a pair defaulted, the other was re-matched with the first suitable candidate (either a compatible participant already waiting to be paired or a new entrant."

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Unclear risk	"The first member of the pair was assigned randomly to either the zinc supplement or placebo" Comment- do not state how random occurred.
Allocation concealment (selection bias)	Unclear risk	No stated- plus if a member of a pair dropped out, the remaining subject was

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

assigned to a compatible participant- assigned need to know which group the drop out was in

Blinding (performance bias and detection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	High risk	Per protocol analysis, dropouts were not included
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Wasantwisut 2006

Methods	RCT
Participants	560 4-6 month old children from rural Thai villages. Healthy
Interventions	2 ml/d dose for 6 months. Group 1- 5 grams/L iron as iron sulfate Group 2- 5 grams /L zinc as zinc sulfate Group 3- 5g/L iron as iron sulfate and 5 grams /L zinc as zinc sulfate Group 4- Placebo Administered by parents using a oral medication syringe, given between meals. Compliance monitored by village health volunteers. Monthly measurement of syrup administered
Outcomes	Anthropometrics- length for age z-score, weight for age z-score and weight for length z-score.
Notes	

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Randomized 2X2 factorial process. Power calculation was done to detect a difference in length for age z-score of 0.15. Stratified by age and sex.
Allocation concealment (selection bias)	Low risk	Random numbers generated by statistician not involved in the study. Syrups were made and labeled by a pharmacy not otherwise involved. allocation codes were kept at the UNICEF office until the end of data analysis
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	blood only obtained from mother's who consented to blood draws
Other bias	Low risk	

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Weuhler 2008

Methods	Double blind RCT. Participants were stratified by age (12–20 or 21–30 mo old) and sex. Children in each of the study groups consumed 1 of 5 daily supplements containing 3, 7, or 10 mg Zn as zinc sulfate, 10 mg Zn 0.5 mg Cu as copper sulfate, or placebo per 5 mL of flavored syrup. The randomization lists for each of these strata were generated independently by using a fixed block randomization procedure.
Participants	631 Ecuadorian (non-anemic) children aged 12–20 mo old LAZ < -1.3 21–29 mo old LAZ < -1.5 as compared to the 1978 WHO data and NCHS international data. Hemoglobin > 10.5/dl Growth response to zinc occurs among populations with LAZ < -1.5
Interventions	Treatment 1: 3 mg of zinc as zinc sulfate daily Treatment 2: 7 mg of zinc as zinc sulfate daily Treatment 3: 10 mg Zn as zinc sulfate, daily Treatment 4: 10 mg Zn as zinc sulfate and 0.5 mg Cu as copper sulfate daily Treatment 5: placebo as flavored syrup.
Outcomes	Measure the effects of different doses of supplemental zinc on the plasma zinc concentration, morbidity, and growth of young children; to detect any adverse effects of 10 mg supplemental Zn on markers of copper or iron status; and to determine whether any adverse effects are alleviated by providing copper with zinc.

Notes

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Fixed block randomization schedules, configured independently for each strata.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias)	Low risk	Supplements compounded and labeled at central pharmacy
Incomplete outcome data (attrition bias)	High risk	Used subsets of groups for obtaining blood levels of Zn and Cu. The sets from which final blood samples were obtained were randomly determined. Per protocol analysis.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Yip 1985

Methods Survey

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

- Participants** 467 infants seen for 1 year well visit between 7/1980 and 9/1983. Healthy, term infants seen at an US Air Force base medical center.
- Interventions** First Study:
- Diet history taken by physician or nurse
 - 10 ml of non fasting venous blood for hemoglobin, MCV, serum ferritin, erythrocyte protoporphyrin as serum iron/iron binding capacity (Fe/TIBC) serum zinc and serum copper.
- Second study:
- Treatment: 291 subjects were randomized to receive iron or placebo using an odd/even day schedule.
 - Medication was labeled by code 30 mg/kg/d elemental iron for 3 months.
 - Blood work was repeated in compliant children at 15 mo visit.
- Outcomes** Relationship between dietary factors and results of laboratory tests at 12 months of age.
Compliance to iron/placebo administration.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	odd/ even day is not an appropriate way to randomize
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Zemel 2002

- Methods** RCT
- Participants** 42 children (20 girls and 22 boys) pre-pubertal children aged 4-10 with sickle cell disease.
- Interventions** Treatment : 10 mg/d of zinc in cherry syrup (5 ml/d) N=20
Placebo: cherry syrup without zinc (5 ml/d) N=22.
Evaluations occurred at 3,6 and 12 months after supplementation began.
- Outcomes** Anthropometrics- height and sitting height, weight, upper arm circumference skin folds at biceps, triceps, sub scapular, and supra iliac sites in triplicate- compared to NCHS charts
Sexual maturation
Body Composition
Dietary Intake
Fasting blood samples for: plasma zinc

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Compliance: calendars, return syrup containers every three months, interview. $\geq 75\%$ of the time, $< 75\%$ of time or uncertain were cutoffs.

Notes Stature at beginning of study < 2 SD below the mean, they did not report standard deviation on plasma zinc scores, so cannot use this data.

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Unclear risk	They used a random number table to establish an unbiased order of contacting and recruiting subjects. They were randomized again after study enrollment.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias)	Low risk	Research pharmacy prepared the syrups.
Incomplete outcome data (attrition bias)	High risk	
Selective reporting (reporting bias)	High risk	Younger taller girls and shorter boys were over represented. 38 of 42 subjects completed the study. A per protocol analysis was done. The four children who did not complete the study had significantly lower height for age z-scores.
Other bias	Unclear risk	Some children were taking zinc supplements and were asked to refrain for 1 month prior to study enrollment- not sure which children they were maybe the taller girls?

Characteristics of excluded studies

Silva 2006

Reason for exclusion 40 percent dropout rate. No description of reason for drop outs or from which group they were from.

López de Romaña 2003

Reason for exclusion Use geometric means for analysis. No numbers were reported, only graphs.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Author(s) Nancy H Allen, Sally J Shubat, Kelly J Hodges, Daniela S Pirvu, Ross E Newman, Elizabeth M Carlson, Jarrod Dusin, Barb Gordon, Christina Gutierrez, and Jackie Bartlett

Date: 2011-05-27							Summary of findings					Importance
Quality assessment							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc supplement v. Placebo	control	Relative (95% CI)	Absolute		
Plasma or Serum Zinc by Age Group (follow-up 2-12 months; measured with: Serum of Plasma zinc (mcg/dl) ; range of scores: 30-200; Better indicated by higher values)												
7	randomized trials ¹	no serious limitations ²	serious ³	no serious indirectness	no serious imprecision	none	539	565	-	SMD 0.57 higher (0.12 lower to 1.26 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Plasma or Serum Zinc by Age Group - Infants (follow-up 6-12 months; range of scores: 30-200; Better indicated by higher values)												
4	randomized trials	serious ²	very serious ^{3,4,5}	no serious indirectness	no serious imprecision	none	439	461	-	SMD 1.13 higher (0.22 to 2.05 higher)	⊕○○○ VERY LOW	CRITICAL
Plasma or Serum Zinc by Age Group - > 12 months and < 6 years (follow-up 1 years; range of scores: 30-200; Better indicated by higher values)												
1	randomized trials	serious ⁶	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	32	-	SMD 0.22 lower (0.71 lower to 0.27 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Plasma or Serum Zinc by Age Group - > 6 years (follow-up 3-12 months; measured with: change from baseline; Better indicated by higher values)												
2	randomized trials	serious ^{7,8}	very serious ⁸	no serious indirectness	no serious imprecision	none	33	39	-	SMD 0 higher (0.46 lower to 0.46 higher)	⊕○○○ VERY LOW	CRITICAL
Plasma or Serum Zinc by Age Group - Small for Gestational Age (follow-up 180 days; measured with: change from baseline; Better indicated by higher values)												
1	randomized trials	serious ⁹	no serious inconsistency	no serious indirectness	no serious imprecision	none	35	33	-	SMD 0.16 higher (0.32 lower to 0.63 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Change in Weight for Height z score (follow-up 6-13 months; measured with: NCHS growth chart; Better indicated by higher values)												
5	randomized trials	no serious limitations ⁶	no serious inconsistency	no serious indirectness	no serious imprecision	none	1073	1094	-	MD 0.1 higher (0.04 to 0.16 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

¹ Most studies are in the infant group.

² Incomplete outcome data is the most frequent bias in studies.

³ For the series of all studies that reported changes in plasma or serum zinc the I² = 96%.

⁴ Various zinc doses (5-10 mg/d) and various times of follow-up.

⁵ Some report serum or plasma zinc levels, other report change in serum or plasma zinc level.

⁶ number of drop outs not stated, nor was the group assignment of drop outs stated. It was a per protocol analysis, drop outs were not included in the analysis.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

⁷ zinc dose varied from 15 mg/d- 22 mg/d.

⁸ deOliveria was teenager (~13 years) football (soccer) players in Brazil, the Abdulhamid study was 7-18 year olds with mild to moderate cystic fibrosis.

⁹ Per protocol design

Author(s): Nancy H Allen, Sally J Shubat, Kelly J Hodges, Daniela S Pirvu, Ross E Newman, Elizabeth M Carlson, Jarrod Dusin, Barb Gordon, Christina.Gutierrez, Jackie Bartlett

Date: 2011-02-22

Question: Should Zinc supplement be used in Pediatrics?

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc supplement	control	Relative (95% CI)	Absolute		
Wart remained at 2 months (follow-up 2 months; physical exam)												
1 ¹	randomized trials	serious ^{2,3}	no serious inconsistency	no serious indirectness	serious ⁴	none	3/23 (13%)	20/20 (100%)	OR 0 (0 to 0.09)	-	⊕⊕⊕ LOW	IMPORTANT
Change in Height for age (follow-up 4-12 months; measured with: change in length or height in centimeters; range of scores: 0-10; Better indicated by higher values)												
6 ⁵	randomized trials	serious ⁶	very serious ⁷	no serious indirectness ⁸	serious ⁹	none	453	467	-	MD 0.43 higher (0 to 0.87 higher)	⊕⊕⊕ VERY LOW	CRITICAL
Change in Weight for age (follow-up 4-12 months; Better indicated by higher values)												
5 ¹⁰	randomized trials	serious ⁶	very serious ^{7,11}	no serious indirectness	serious ⁸	none	425	439	-	MD 0.12 higher (0.02 lower to 0.25 higher)	⊕⊕⊕ VERY LOW	CRITICAL
Mid Upper Arm Circumference (follow-up 4-12 months; Better indicated by higher values)												
3	randomized trials	serious ¹¹	no serious inconsistency	no serious indirectness ¹²	no serious imprecision	none	223	222	-	MD 0.16 higher (0.36 lower to 0.67 higher)	⊕⊕⊕ MODERATE	IMPORTANT
Number underweight at 12 months												
1	randomized trials	serious ^{11,13}	no serious inconsistency	no serious indirectness	no serious imprecision	none	506/976 (51.8%)	484/947 (51.1%)	OR 1.03 (0.86 to 1.23)	7 more per 1000 (from 38 fewer to 51 more)	⊕⊕⊕ MODERATE	

¹ Algurairi 2002, Iran

² sequence generation by odd and even days

³ Investigator not blinded to treatment group allocation

⁴ Small study

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

⁵ Berger 2005 Vietnam, FischerWalker 2009 Bangladesh, Heinig 2006 USA, Mozaffair-Khosravi 2008 Iran, Silva 2006 Brazil, & Walravens 1983 USA.

⁶ For the Heinig study, mothers of infants refused blood draws.

⁷ Wide heterogeneity

⁸ Three studies are breast feed infants and 3 are children.No application to older children.

⁹ The effect was only seen in one small study Mozaffari-Khosravi 2008, otherwise, little or no difference seen.

¹⁰ Berger 2005 Vietnam, FischerWalker 2009 Bangladesh, Heinig 2006 USA, Mozarari-Khosravi 2008 Iran and Walravens 1983 USA

¹¹ Most used per protocol analysis

¹² One infant and two child studies

¹³ Only 15% of subjects had serum levels of zinc determined.

Author(s): Nancy H Allen, Sally J Shubat, Kelly J Hodges, Daniela S Pirvu, Ross E Newman, Elizabeth M Carlson, Jarrod Dusin, Barb Gordon, Christina Gutierrez and Jackie Bartlett

Date: 2011-02-22

Question: Low Phytate v High Phytate for zinc absorption.

Quality assessment							Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Low Phytate v High Phytate	control	Relative (95% CI)	Absolute		
Fecal zinc microgram/kg/d (Better indicated by lower values)												
1	randomized trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	10	10	-	MD 0.4 higher (16.32 lower to 17.12 higher)	⊕⊕○○ LOW	
Plasma zinc μmol/L (Better indicated by lower values)												
1	randomized trials	serious ¹	no serious inconsistency	no serious indirectness	serious ¹	none	10	10	-	MD 0.5 higher (1.76 lower to 2.76 higher)	⊕⊕○○ LOW	IMPORTANT

¹ Cross over design of only 10 patients

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Risk of bias summary	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdulhamid 2008	+	?	+	+	-	+
Al-Gurairi 2002	-	-	-	-	-	+
Bao 2008	+	+	+	?	-	+
Berger 2005	?	+	+	+	+	+
Castillo-Duran 1995	+	+	+	-	?	?
Cole 2010	?	-	-	-	+	+
deOliveria 2009	?	?	?	+	+	+
Dijkhuizen 2008	+	+	+	+	+	+
Fischer Walker 2009	+	?	+	-	+	+
Hamadani 2001	+	?	+	+	+	+
Heinig 2006	+	+	+	?	-	?
Henderson 1995	+	+	?	+	+	+
Hershkovitz 1999	?	+	-	-	+	+
Hettiarachchi 2008	+	+	+	?	+	?
Holtz 2005	+	+	?	-	+	?
Kennedy 2010	-	-	-	+	+	?
Mazariegos 2006	?	+	+	+	-	?
Mazariegos 2010	+	+	+	?	?	?
Pongcharoen 2011	+	+	+	+	+	+
Prasad 1999	?	?	?	?	?	?
Taneja 2009	+	+	+	?	+	+
Tran 2004	+	+	+	?	?	?

please contact bnewell@cmh.edu

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Forest Plots

Figure 1 . Zinc supplement vs. placebo: Plasma or serum zinc by age group

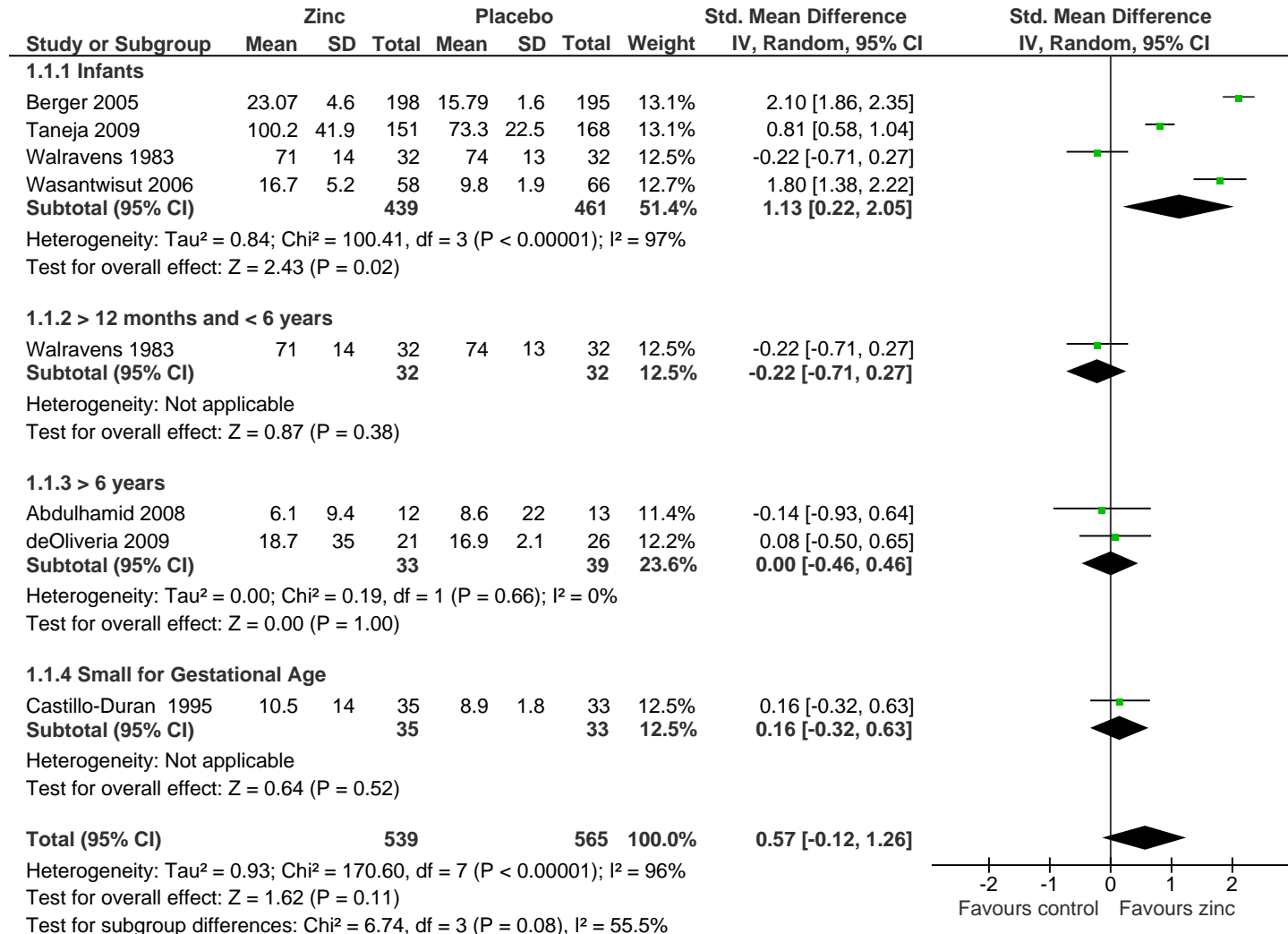
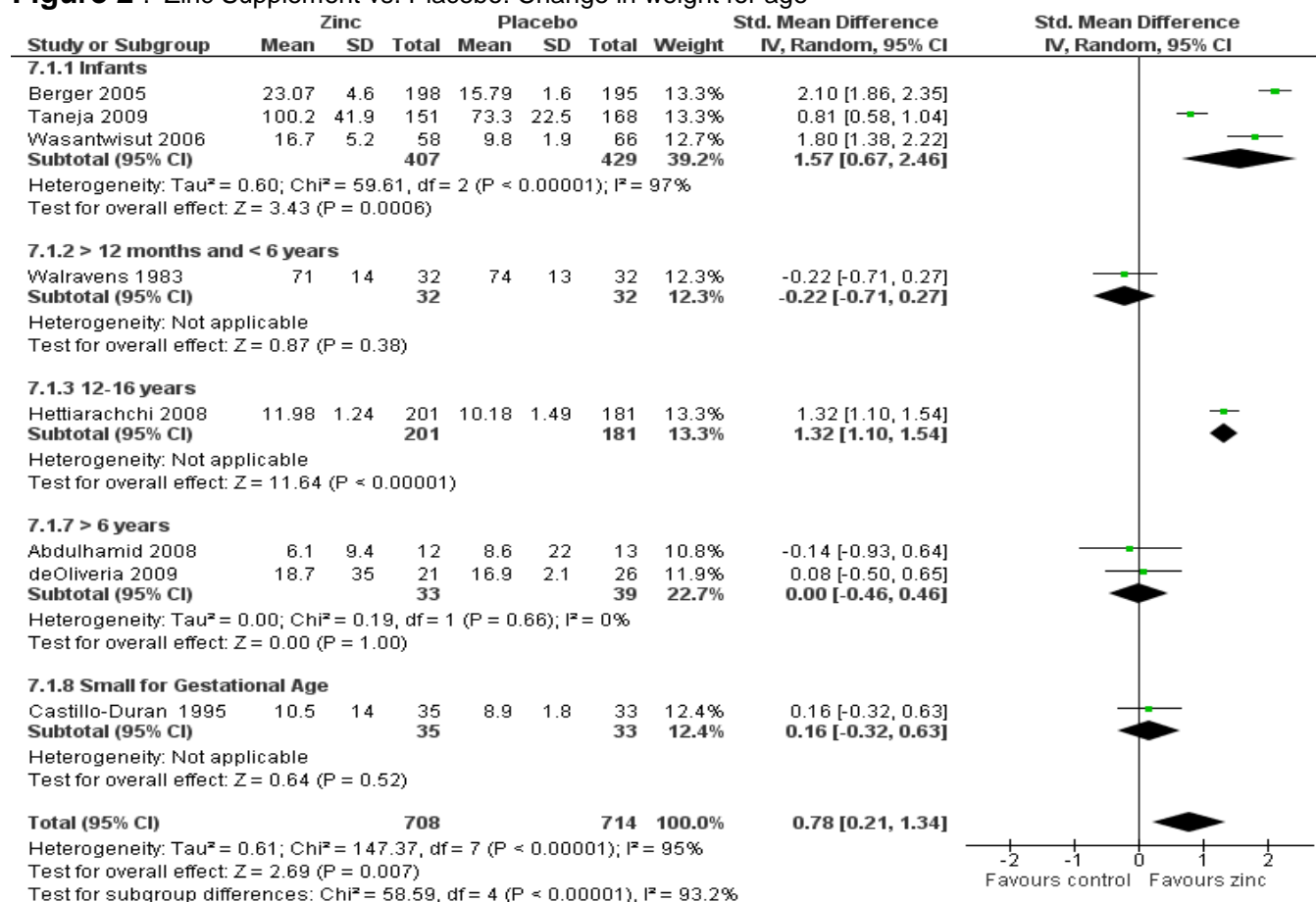
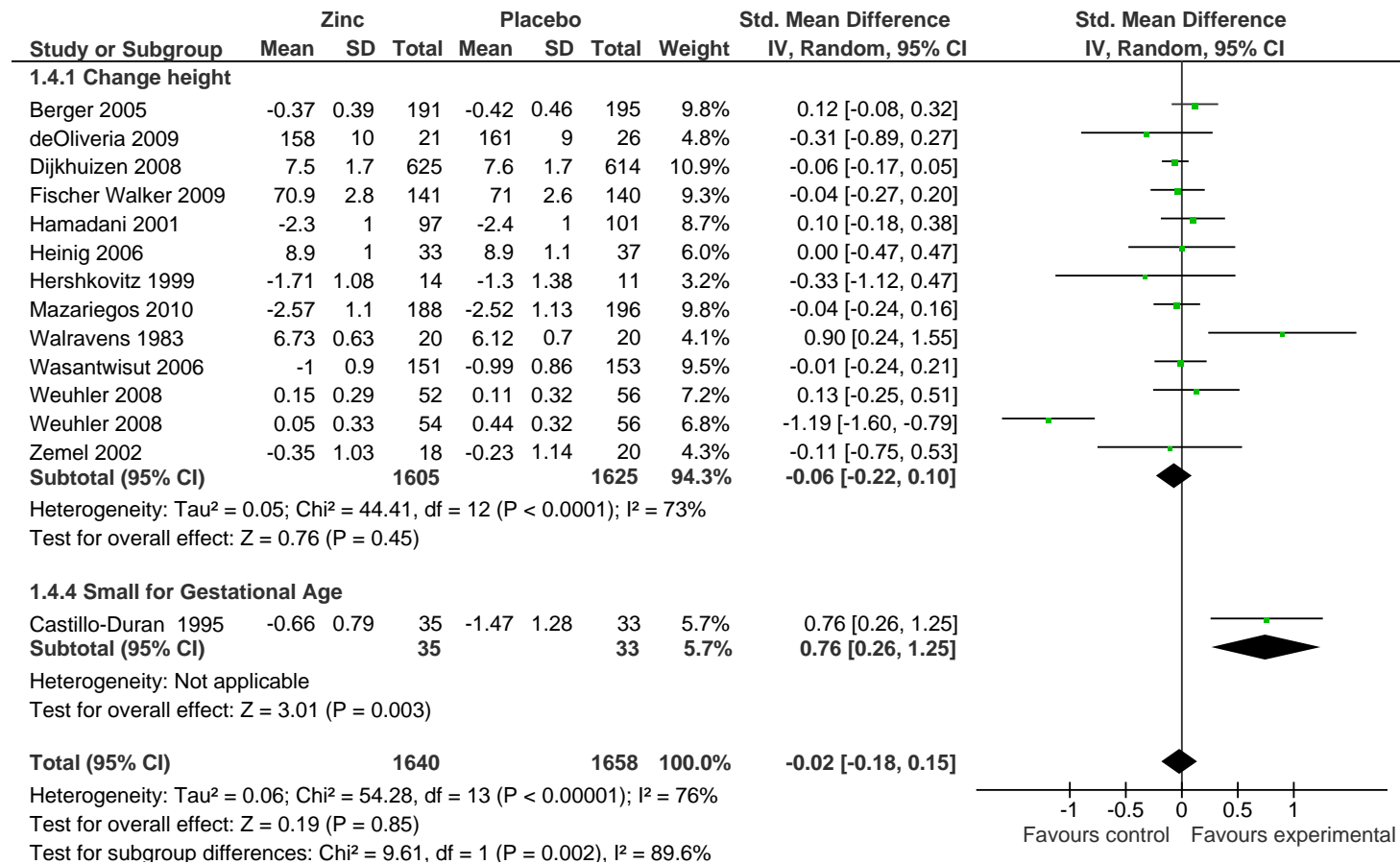


Figure 2 . Zinc Supplement vs. Placebo: Change in weight for age



Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Figure 3 Zinc Supplement vs. Placebo: Change in height (length) for age



Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Figure 4 Zinc Supplement vs. Placebo: Change in weight for height (length) z-score

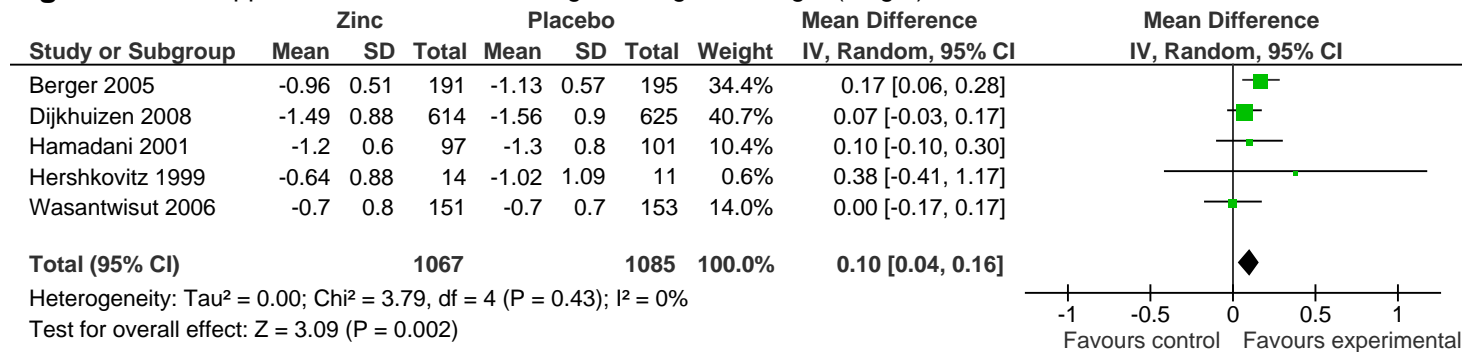


Figure 5 . Zinc Supplementation v. Placebo: IQ score at 9 years of age

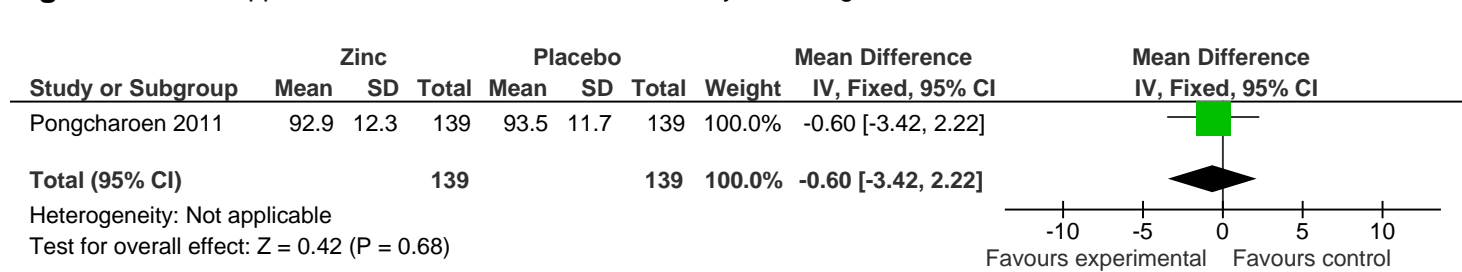


Figure 6 Low Phytate vs. High Phytate Diet: Fecal zinc (mcg/kg/d)

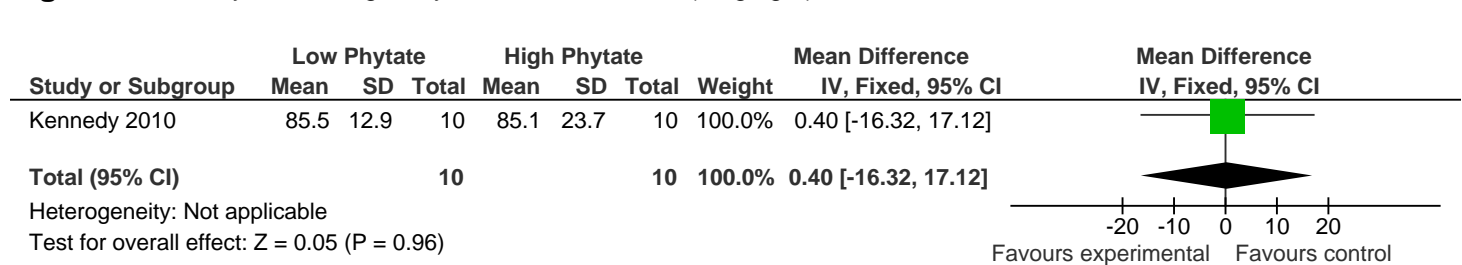


Figure 7 Low Phytate vs. High Phytate Diet: Plasma zinc micromole/L

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

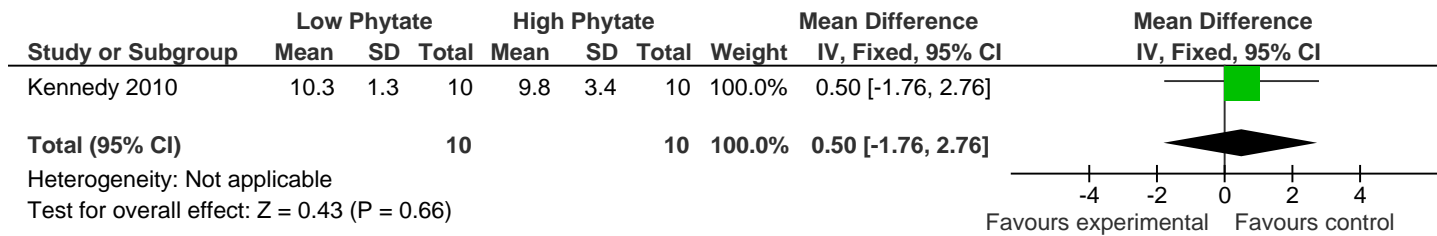


Figure 8 . Zinc supplement v. Placebo: Wart remained at 2 months

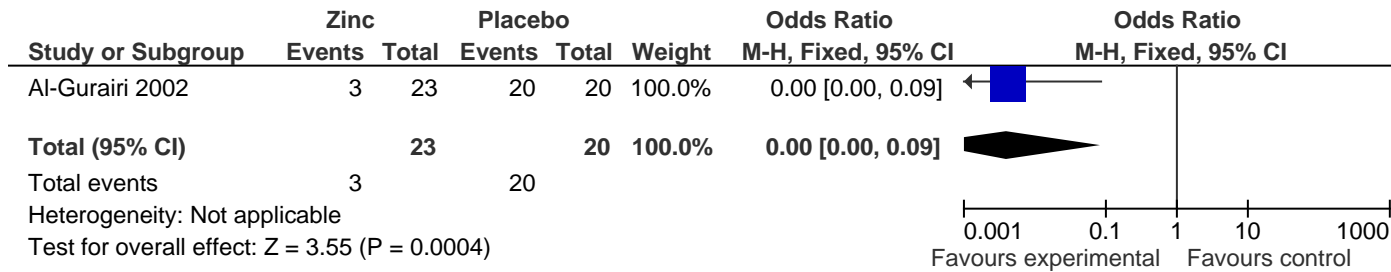


Figure 9 Absorption of Zn from various salts in tortilla, outcome: 6.1 Serum Zinc.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

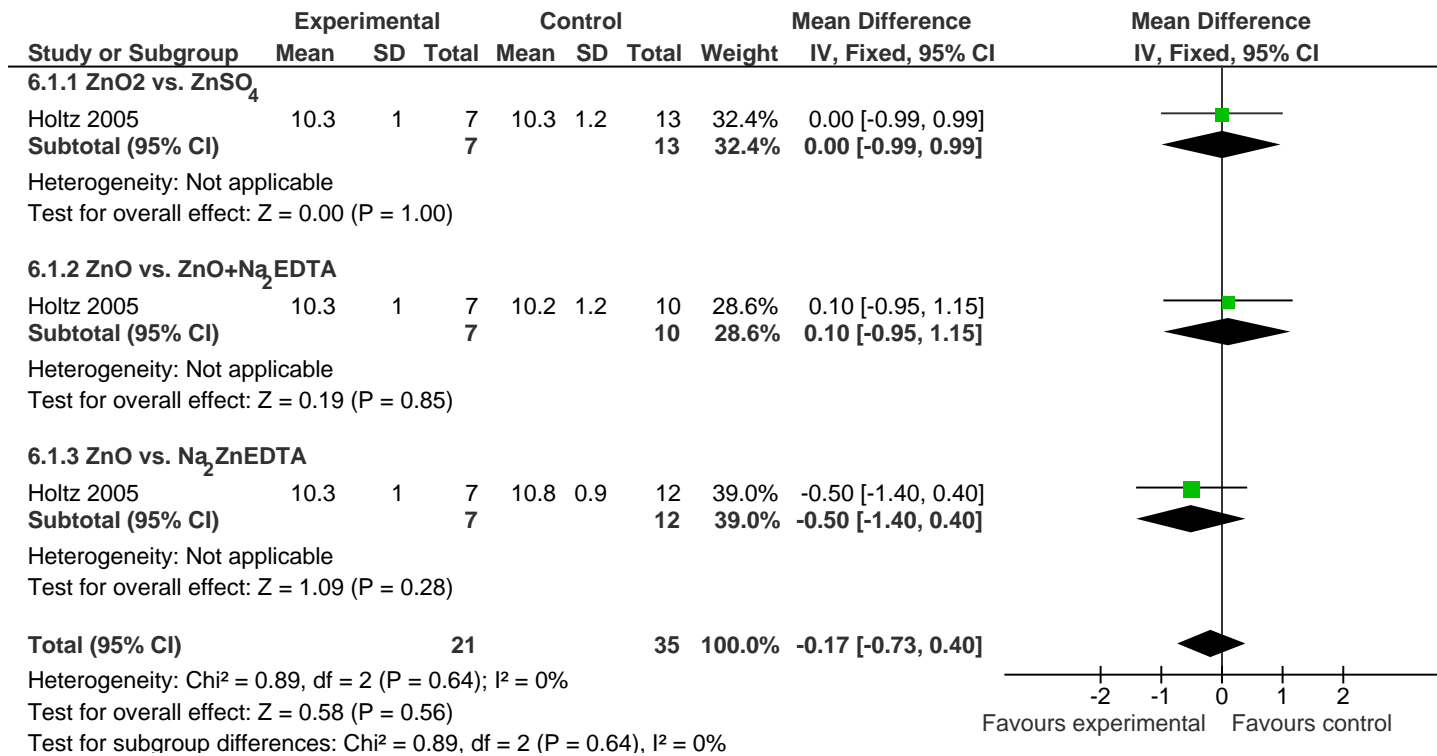
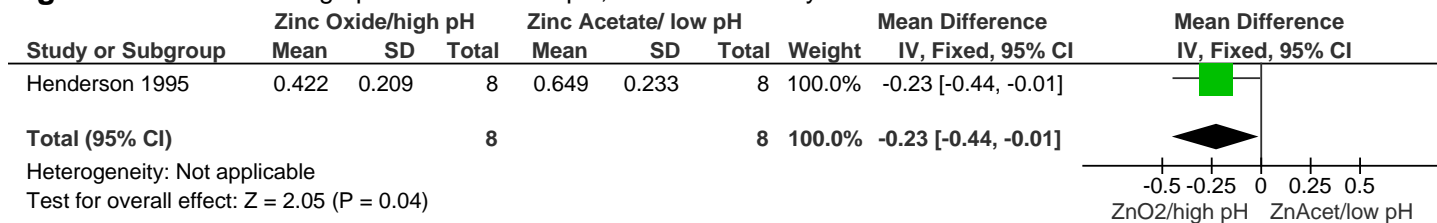


Figure 10 Zinc Oxide High pH v ZnAcet Low pH, outcome: Urinary zinc.



Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Figure 11 . Zinc Oxide High pH v ZnAcet Low pH, outcome: Plasma zinc.

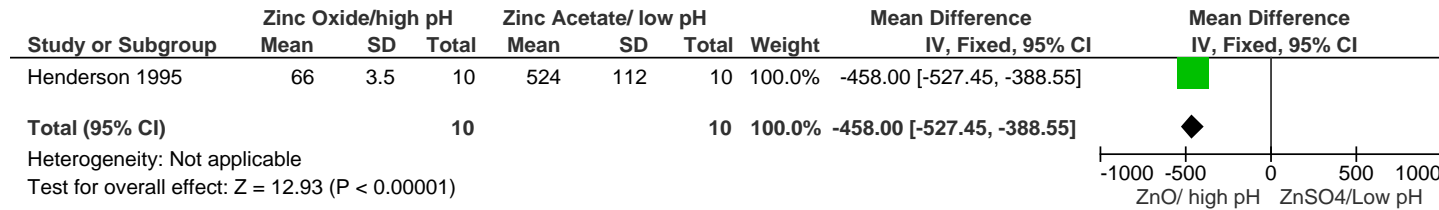
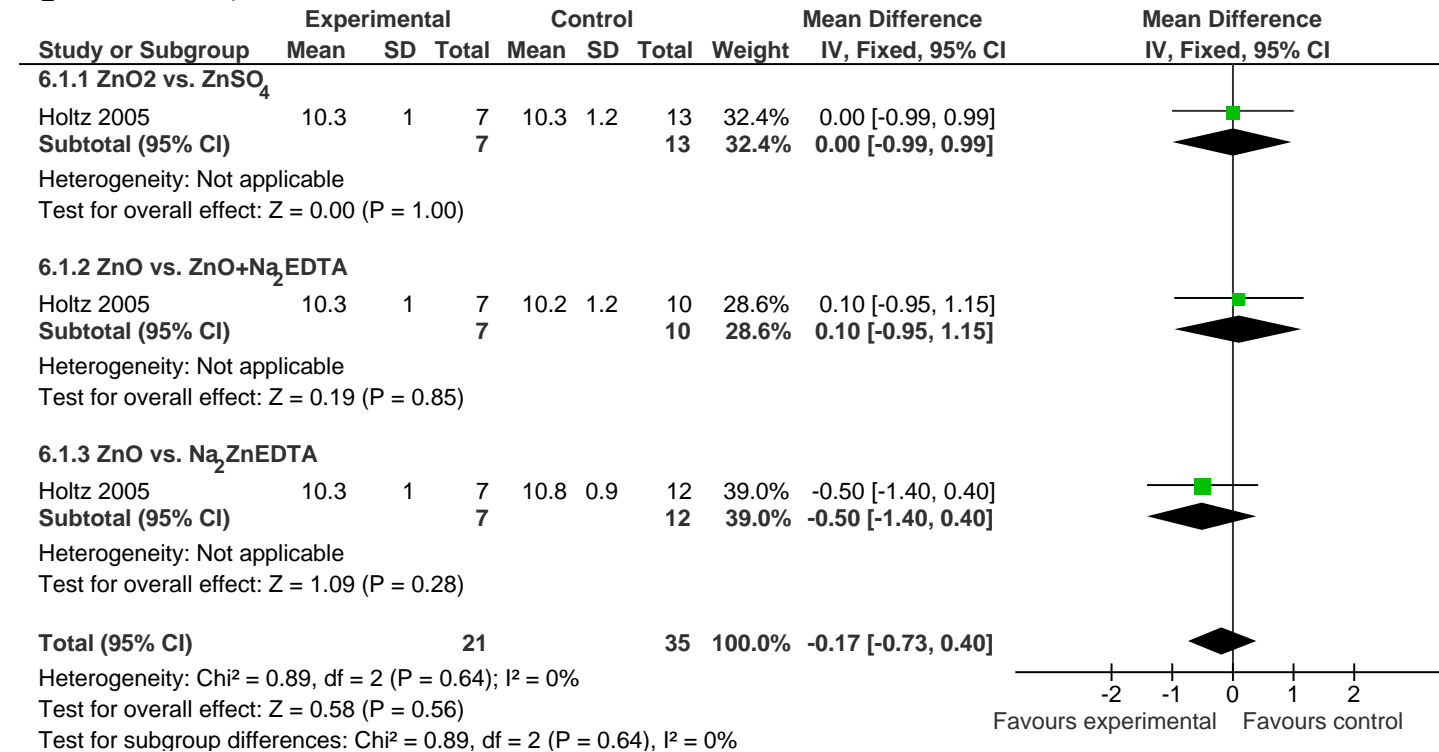


Figure 12 Absorption of Zn from various salts in tortilla, outcome: Serum Zinc



Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Figure 13 . Zinc v Placebo, outcome: Wart remained at 1 month

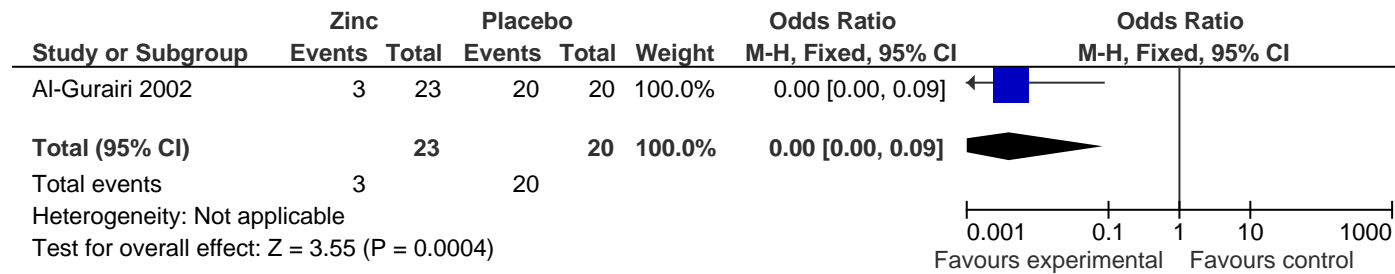
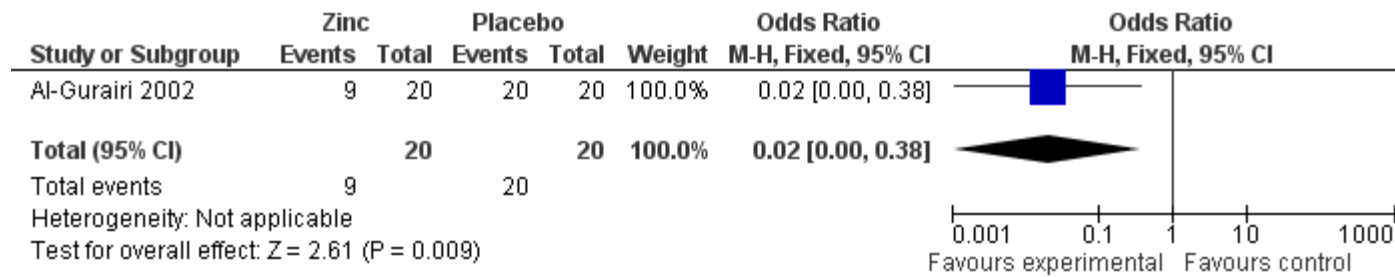


Figure 14 . Zinc v Placebo, outcome: Pain episodes in SCD

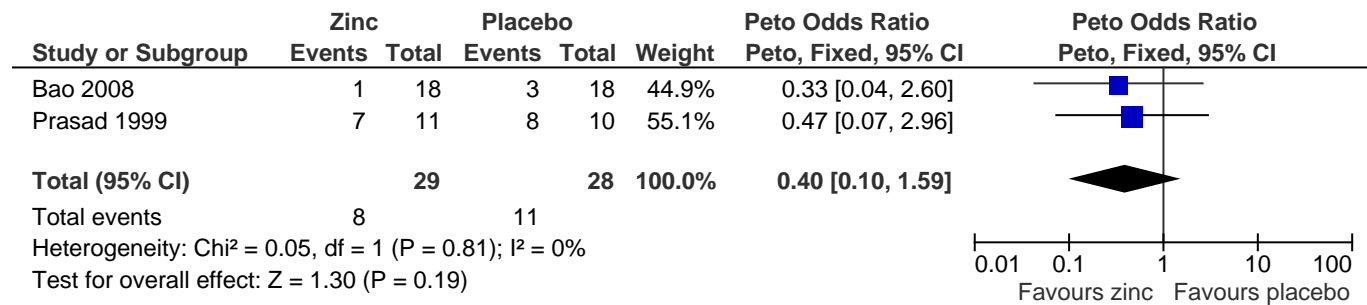
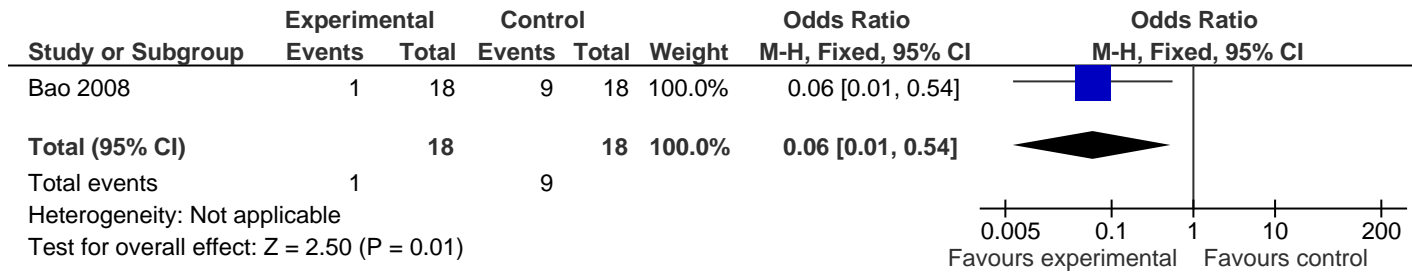


Figure 15 . Zinc v Placebo, outcome: Number of infections in SCD

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc



Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

Zinc Absorption Critically Appraised Topic (CAT)

This synthesis includes 19 papers and other resources that are not amenable to be analyzed with RevMan or GradePro.

Synthesis of relevant studies:

Author, date, country, and industry of funding	Patient Group	Research Design	Treatments & Outcomes	Significant results	Notes & Limitations
International and U. S. Government Documents					
De Benoist, B., Darnton-Hill, I, Davidsson, L., Fonatin, O., & Hotz, C. (2007), Conclusions of the Joint WHO/UNICEF/IZI NCG interagency meeting on zinc status indicators. <i>Food and Nutrition Bulletin</i> , 28, 3(supplement) S480-S487.	Children and adults	Narrative summary of a meeting.	N/S	<p>Three categories of population indicators considered were biochemical, dietary and functional</p> <p><u>Biochemical</u>: serum or plasma zinc best for population risk of zinc deficiency. Inadequate for individuals because blood levels are affected by recent meals, time of day, age, sex, presence of systemic infection or inflammation.</p> <p>They recommend cutoffs based on age, sex, time of day</p> <p><u>Dietary</u>: useful for assessing risk for zinc deficiency in a population. Useful and should be used in conjunction with biochemical measures. The Estimated Average Requirement (EAR) should be used for determining dietary adequacy. "Risk of zinc deficiency is considered to be elevated and a public health concern when prevalence or probability of inadequate intake is > 25% of the population.</p> <p><u>Functional</u>: Height of length for age- although not specific for Zn deficiency and can only be used in children. Need to know the exact age of the child. For population assessment children under 5 years who are > -2SD below the age specific median of the reference population.</p>	
MetaAnalyses that cannot be entered into GradePro					
Dekker, L. H., & Villamor, E. (2010).	21 RCTs including	Meta-analysis	<u>Treatment</u> : Doses ranged 10-	Hemoglobin concentration: 2 studies were determined to be outliers, since their	Well done MA, did not report all data necessary to enter

If you have questions regarding this Specific Care Question – please contact bnewell@cmh.edu

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<p>Zinc supplementation in children is not associated with decreases in hemoglobin concentrations. <i>Journal of Nutrition, 140, 5, 1035-1041.</i></p>	<p>3869 subjects 0-15 years old. Duration of treatment 4-15 months.</p>		<p>20 mg/d of zinc <u>Outcome:</u> Hemoglobin conc</p>	<p>effect sizes were 3-5 times as large as the next largest effect size. With the excluded studies effect size was 0.8 g/L (95%CI: -0.6,202: p=0.27) Without the excluded studies the effect size was -0.2 g/L (95% CI: -0.9, 0.5 p-0.59).</p>	<p>into GradePro “Confirm there is no consistent evidence for an adverse effect of zinc supplementation on hemoglobin among apparently healthy children.”</p>
<p>Ramakrishnan, U., Nguyen, P., & Martorell, R. (2009). Effects of micronutrients on growth of children under 5 y of age: Meta-analysis of single and multiple nutrient interventions. <i>American Journal of Clinical Nutrition, 89, 191-203.</i></p>	<p>56 RCTs on children < 5 years old. Median duration of studies was 8-64 weeks, Number of subjects included was 11,547.</p>	<p>Meta analysis</p>	<p><u>Treatment:</u> Zinc supplementation doses ranged from 20 mg/week to 20 mg/d. <u>Outcomes:</u> Length (height) for age Weight gain Weight for length z score. Using the WHO growth standards.</p>	<p>Length for age- thirty studies had a positive effect, and 11 were statistically significant. However the weighted mean effect was small and not significant. (0.07; 95% CI: -0.03, 0.17). Weight gain: 33 studies had a positive effect, and 10 were statistically significant. The overall weighted mean effect was 0.09 (95% CI: -0.11,0.25) Weight for length z score- 22 studies (33 data sets) weighted mean effect size was 0.06 (95% CI; 0.006, 0.11).</p>	<p>Well done MA, did not report all data necessary to enter into GradePro. Different from the results by Brown et al. Authors postulate The inclusion of more recent studies not included in Brown may be a factor Prevalence of stunting in the recent studies may be lower Decrease in publication bias, more studies with negative results may be published.</p>
<p>Treatment of Disease</p>					
<p>Bose, A., Coles, C. I., Gunavathi, H.J., Prabhakar, M., Raghupathy, P., Kirubakaran, C., Black, R. E., Brooks, W. A., Santosham, M. (2006). Efficacy of zinc in the treatment of severe pneumonia in hospitalized children < 2 years old. <i>American Journal of Clinical Nutrition, 83, 1089-1096.</i></p>	<p>299 children aged 2-23 months in South India.</p>	<p>RCT</p>	<p><u>Treatments:</u> Treatment group: 10 mg zinc sulfate tablets twice daily Control: 10 mg placebo tablet twice daily. Both group received standard treatment for severe pneumonia <u>Outcomes:</u> Time to resolution of these three symptoms:</p>	<p>Time to resolution 1) Outcome one- not significantly different Zinc- 82.2 (68.1, 87.3) Control- 75.9 (71.2, 88.0) RR 0.93 (0.74,1.17) p=0.722 2) Outcome two- not significantly different Zinc- 87.2 (70.7,95.2) Control- 76.2 (72.3,88.1) RR 0.93 (0.72,1.21) p=0.589 3) Outcome three- not significantly different Zinc- 111.3 (88.5, 138.0) Control- 96.7 (78.2, 112.9) RR 0.86 (0.62,1.18) p=0.353 Duration of hospitalization (hours) Zinc- 71.1 (68.1, 87.3)</p>	<p><u>Notes:</u> Each subject received 2 tablets twice on day 1, and one table, twice daily thereafter. Tablets were dissolved in 1 tsp distilled water for young infants. <u>Limitations:</u> Analyzed by intention to treat analysis. 3 subjects withdrew, one in the treatment group and two in the control group. State ITT, but one subject in the zinc group was excluded from the analysis.</p>

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<p>India</p> <p>Pneumonia</p>			<p>1.) RR > 50 bpm and SaO₂ < 93%</p> <p>2.) Outcome one AND inability to drink</p> <p>3.) Outcome one AND chest in-drawing</p> <p>Duration of hospitalization</p> <p>Plasma zinc level at discharge.</p>	<p>Control- 72.3 (67.7,79.6)</p> <p>RR- 0.93 (0.74-1.17)</p> <p>p=0.550</p> <p>Discharge serum zinc</p> <p>Zinc- 13.0±2.5 mM/L</p> <p>Control-12.0±4.1 mM/L</p> <p>P=0.013</p>										
<p>Mehdizadeh, M., Zamani, G., & Tabatabaee, S. (2008). Zinc status in patients with major β-thalassemia. <i>Pediatric Hematology and Oncology</i>, 25, 49-54.</p> <p>β-thalassemia</p>	<p>64 patients with β-thalassemia on regular blood transfusion . compared with 64 healthy matched controls.</p>	<p>Case control</p>	<p>Serum zinc levels</p> <p>Ferritin levels</p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 30%;"></th> <th style="width: 30%;">Zinc (mcg/dl)</th> <th style="width: 40%;">Ferritin</th> </tr> </thead> <tbody> <tr> <td>β-thalassemia</td> <td>108.17 ±17.72</td> <td>DNR</td> </tr> <tr> <td>Control</td> <td>93.48 ±13.62</td> <td>DNR</td> </tr> </tbody> </table>		Zinc (mcg/dl)	Ferritin	β-thalassemia	108.17 ±17.72	DNR	Control	93.48 ±13.62	DNR	<p>Excluded if on hydroxyl urea or zinc dietary supplement in the last year.</p> <p>Collected Demographic and anthropometric data, time of diagnosis, initiating time of blood transfusion, as well as chelation therapy, daily dose of desferrioxamine as iron), patient's compliance toward desferrioxamine, time interval between blood transfusions, history of splenectomy, and patient medications</p> <p>They did not report ferritin levels</p>
	Zinc (mcg/dl)	Ferritin												
β-thalassemia	108.17 ±17.72	DNR												
Control	93.48 ±13.62	DNR												
<p>Absorption</p>														
<p>Henderson, L. M., Brewer, G. J., Dressman, J. B., Swidan, S. Z., DuRoss, D. J., Adair, C. H., Barnett, J. L., & Berardi, R. R. (1995). Effect of intragastric pH on the absorption of oral zinc acetate</p>	<p>10 healthy subjects (5 males)</p>	<p>2 way 4 phase crossover study</p>	<p><u>Treatments:</u></p> <p>High pH (≥ 5)</p> <p>Low pH (≤3)</p> <p>Zinc acetate</p> <p>Zinc oxide</p> <p>Single oral zinc equivalent to 50 mg of elemental zinc.</p> <p><u>Outcomes:</u></p>	<p>Plasma zinc</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 20%;"></th> <th style="width: 20%;">ZnAcet</th> <th style="width: 20%;">ZnOxide</th> </tr> </thead> <tbody> <tr> <td>Low pH</td> <td>524±112</td> <td>364 ±152</td> </tr> <tr> <td>High pH</td> <td>378 ± 126</td> <td>66 ± 35</td> </tr> </tbody> </table>		ZnAcet	ZnOxide	Low pH	524±112	364 ±152	High pH	378 ± 126	66 ± 35	<p>Authors suggest taking zinc away from taking pH altering medicines.</p>
	ZnAcet	ZnOxide												
Low pH	524±112	364 ±152												
High pH	378 ± 126	66 ± 35												

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

and zinc oxide in young healthy volunteers. <i>Journal of Parenteral and Enteral Nutrition</i> , 19, 393-397.			Plasma zinc- area under the curve.		
Hunt, J. R., Beiseigel, J. M., and Johnson, L. K. (2008). Adaptation in human zinc absorption as influenced by dietary zinc and bioavailability. <i>American Journal of Clinical Nutrition</i> , 87, 1336-1345. North Dakota	821 children aged 12-16 years. HGB > 80 g/L. Zinc and iron deficiency is prevalent in this region this study was carried out.	RCT- four groups Power calculation based on the prevalence of anemia was calculated to be 180 subjects per group. Sample size inflated to 200 per group to account for drop outs. Stratified by classroom using a double blind approach.	Each group was pretreated for parasites, and then received 2 capsules per day of: 1:Iron- 50 mg/d as ferrous fumarate 2:Zinc-14 mg/d as zinc sulphate 3:Combined iron and zinc as above 4:Placebo For 24 weeks on school days <u>Outcomes:</u> Hbg concentration, serum zinc-skewed distribution, therefore log transformed. Serum ferritin Serum zinc Growth using CDC/WHO weight for age and height for age z scores, BMI	Stunting and underweight was similar across groups. Iron deficiency was more prevalent in the group that received iron only, and zinc deficiency was higher in the groups that received zinc (zinc only and zinc + iron). 774 completed the study (91%). Baseline outcomes were not different when the completers were compared to the non completers.	
Jalla, S., Krebs, N. F., Rodden, D., & Hambidge, K. M. (2004). Zinc homeostasis in premature infants	Healthy adults N= 109 (21-51 years) 4 week dietary	Cross over design. Goal was to use data generated to create	<u>Treatments</u> 4 week equilibration to experimental diet a. High zinc	Lower zinc intake resulted in higher fractional zinc absorption. Higher zinc increased the amount of zinc absorbed	It is a predictive model, not a comparative study.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<p>does not differ between those fed preterm formula or fortified human milk. <i>Pediatric Research</i>, 56, 4, 615-620.</p> <p>Colorado</p>	<p>zinc equilibration 8 week dietary zinc equilibration Subjects consumed 4-29 mg Zn/d with five molar ratios of phytate to zinc from 2 to 7 AND 5 molar ratios from 15 to 23</p>	<p>predictive models of zinc absorption with varying zinc and phytate concentrations 1.</p>	<p>diet b. Low zinc diet 8 week equilibration to experimental diet (women) a. All zinc level diets</p> <p><u>Outcomes</u> Zinc absorption Biochemical indexes of zinc status</p>	<p>The bioavailability of zinc appears to be more important than the amount of zinc in the diet. Fraction absorption is more dependent on phytate concentration than zinc concentration.</p> <p>They conclude, base on the predictive model, if the phytate:zinc > ~ 12, the DRI does not provide an amount of absorbed zinc to meet physiologic requirements.</p> <p>They concur with the Food and Nutrition Board that plasma zinc is not a useful status indicator</p>	
<p>Keyzer, J.J., Oosting, E., Wolthers, B. G., & Muskiet, F. A. J. (1983). Zinc absorption after oral administration of zinc sulfate. <i>Pharmaceutisch Weekblan Scientific Edition</i>, 5, 252- 253.</p>	<p>6 normal males from 27-44 years of age with possible zinc deficiency.</p>	<p>Cohort</p>	<p><u>Treatment:</u> First test: 200 mg of zinc sulfate was administered in a fasting state. Second test: 200 mg of zinc sulfate was administered with a light meal (4 slices whole grain bread with butter and cheese, 1 glass of milk) <u>Outcomes:</u> Serum zinc at 0.5, 1, 2 4 and 6 hours.</p>	<p>In the fasting group, serum zinc levels rose after ingestion of supplemental zinc. At 2 hours post ingestion, s. zinc was 159 % higher than fasting zinc level</p> <p>In the group that ingested a light meal along with supplemental zinc, s. zinc levels remained lower than fasting levels for 6 hours after ingestion of the supplement. Notably, s. zinc was 13% below fasting level at 1 hour and 8% below fasting at 2 hours.</p>	<p>Tests were performed on the same subjects 5 days apart.</p> <p>200 mg of zinc sulfate = 45 mg elemental zinc.</p> <p>When zinc was taken in the fasting state, subjects complained of light nausea in the first hour post supplement ingestion.</p>
<p>Mazariegos, M., Hambidge, K.M., Krebs, N.F., Westcott, J.E., Lei, S., Grunwald, G.K.,</p>	<p>14 infants (8 male) Mean gestational age of 31</p>	<p>Cohort</p>	<p><u>Treatment:</u> Treatment 1 Mother's own milk fortified with human milk</p>	<p>They state" There was no significant difference of any variable between the preterm formula and fortified human milk; outcomes included are dietary zinc, fraction absorption of zinc, total absorbed</p>	<p>Nestle Nutrition sponsored a researcher, no role of Nestle employees stated in the paper. Low risk for bias. In reporting the outcomes, the</p>

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<p>Campos, R., Barahona, B., Raboy V., Solomons, N. (2006). Zinc absorption in Guatemalan schoolchildren fed normal or low-phytate maize. <i>American Journal of Clinical Nutrition</i>, 83, 59-64.</p> <p>Guatemala</p>	<p>weeks. Appropriate for gestational age.</p> <p>Long recruitment period 1991-1998.</p> <p>Recruitment halted due to change in HMF formulation</p>		<p>fortifier. N=5 Treatment 2 Preterm formula N= 9</p> <p><u>Outcomes:</u> Dietary zinc Fractional absorption Total absorbed Zn Endogenous fecal Zn Net absorbed Zn Net retention of Zn</p>	<p>zinc, net absorbed zinc and net retention of zinc... All infants achieved a positive net absorption and net retention. The size of the exchangeable zinc pool did not differ between groups.”</p>	<p>data table does not line up. Data reported in the paper does not match data in the abstract. Difficult to make sense of what the outcomes really are. High risk for bias</p>
<p>McKenna, A. A., Ilich, J. Z., Andon, M. B., Wang, C., & Matkovic, V. (1997). Zinc balance in adolescent females consuming a low-or high-calcium diet. <i>American Journal of Clinical Nutrition</i>, 65, 1460-1464.</p>	<p>26 adolescent females during a 14 day period.</p>	<p>Crossover study. Consumed a metabolic diet containing 722 mg Ca and 6.3 mg Zn.</p>	<p><u>Treatment:</u> Group 1- 1000 mg supplemental Ca/d as citrate malate salt. Group 2: placebo.</p>	<p>There was no difference in the components of zinc metabolism when 1000 mg of Ca in the form of calcium-citrate-malate was supplemented. Components of zinc metabolism include zinc intake, fecal excretion of zinc, urinary excretion of zinc, zinc balance, net absorption of zinc and zinc absorption (% of intake).</p>	
<p>Nève, J., Hanocq, M., Peretz, A., Khalil, F. A., & Pelen, F. (1991). Absorption and metabolism of oral zinc gluconate in humans in fasting state, during and after a meal. <i>Biological Trace Element Research</i>, 32, 201-201.</p> <p>Belgium</p>	<p>10 subjects.</p>	<p>Crossover</p>	<p><u>Treatment:</u> 45 mg of zinc as zinc gluconate (Rubozinc®) administered under 3 conditions Condition 1: after an overnight fast Condition 2: during a standardized breakfast and Condition 3: 2 hours after this meal.</p> <p><u>Outcome:</u></p>	<p>Taking zinc with a meal increases the time for the appearance of the ingested zinc to be detectable in the serum. Taking zinc with a meal also reduced the maximum serum zinc level obtainable and the total zinc absorbed. Zinc absorption rate, maximum concentration and area under curve (AUC) was not different when zinc taken fasting was compared to zinc taken 2 hours after a meal.</p>	

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

			Serum zinc at - 0.50, -0.25 0.00(ingestion of zinc supplement), 0.25, 0.50, 0.75, 1.00,1.25, 1.50, 1.75, 2.00, and then ever 0.5 hour until 8 hours after zinc ingestion.		
Oksel, F., Köksyo, H., Taneli, B. (1996). Zinc tolerance test patterns in normal children and in moderate and severe zinc deficiency states. <i>Indian Journal of Pediatrics</i> , 63, 655-658. Turkey	60 Guatemala n school children Age 7.5-12 years	Cross-sectional cohort study	<u>Treatment</u> Children were fed low-phytate maize, or 1 of 2 control maizes for 10 weeks Treatment 1- low phytate maize- 60% less phytate Treatment 2- wild-type iso-hybrid of maize fed in treatment 1 Treatment 4- locally grown maize <u>Outcomes:</u> Zinc intake, phytate:zinc ratio; plasma zinc; fractional absorption of zinc; total absorbed zinc	Did not find significant difference in growth velocity with the reduction of dietary phytate, addition of zinc supplement (5 mg/d) nor with the combination of reducing phytate and adding zinc.	The authors opine that since maize makes up a small proportion of complimentary foods in this group difference was not seen.
Spencer, H., Rubio, N., Kramer, L., Norris, C., & Osis, D. (1987). Effect of zinc supplements on the intestinal absorption of calcium. <i>Journal of</i>	15 adult males in a metabolic research ward 2 subjects had renal failure, one mild	Cohort, crossover design	16 Calcium absorption studies were carried out. Nine studies on a low calcium diet (230 mg Ca/d) Seven studies were on a	High zinc intake decreased Ca absorption at low Ca intake, but not at normal Ca intake. When zinc supplement was added, Ca ⁴⁷ (calcium marker) decreased and fecal Ca increased. Same effect was seen with zinc sulfate and with zinc gluconate.	What they call a study is really one patient completing that section of the crossover design investigation. When using high doses of supplemental zinc, should assure patient is on at least DRI for calcium.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

<p><i>the American College of Nutrition</i>, 6, 1. 47-51.</p>	<p>(BUN= 48 & Creat =4.0 mg%),)and one chronic stable (BUN = 26 & Creat = 26 mg%) No other medications</p>		<p>normal calcium diet (800 mg/d)</p> <p>Also re-did the same study in two subject but used zinc gluconate.</p>																							
<p>Tran, C. D., Katsikeros, R., Manton, N., Krebs, N. F., Hambidge, K. M., Butler, R. N., & Davidson, G.P. (2011). Zinc homeostasis and gut function in children with celiac disease. <i>Am. Journal of Clinical Nutrition</i>. [DOI: 10.3945/ajcn.111.018093]</p> <p>Australia</p>	<p>Children with celiac disease (CD) (Marsh score ≥ 3 use as diagnostic criteria) n=16 were compared to children without CD n= 22. Age of children recruited was 2-18 years.</p>	<p>Quasi-experimental the CD cohort was compared to the not CD cohort.</p>	<p>Zinc absorption</p> <p>Exchangeable zinc pool</p>	<p>No significant difference in fractional zinc absorption between children with CD than those without CD.</p> <p>There was a significant difference in the exchangeable zinc pool between children with CD and those without CD. Children with CD had an exchangeable zinc pool that was 32% smaller.</p> <table border="1" data-bbox="1031 805 1493 1060"> <thead> <tr> <th>Zinc dose</th> <th>FAZ</th> <th>AZ (mg)</th> </tr> </thead> <tbody> <tr> <td>2 mg</td> <td>0.73 \pm 0.18</td> <td>1.6 \pm 0.4</td> </tr> <tr> <td>5 mg</td> <td>0.68 \pm 0.25</td> <td>3.5 \pm 1.3</td> </tr> <tr> <td>10 mg</td> <td>0.71 \pm 0.11</td> <td>7.4 \pm 1.0</td> </tr> <tr> <td>15 mg</td> <td>0.62 \pm 0.14</td> <td>9.5 \pm 2.2</td> </tr> <tr> <td>20 mg</td> <td>0.54 \pm 0.2</td> <td>11.0 \pm 2.2</td> </tr> <tr> <td>30 mg</td> <td>0.37 \pm 0.07</td> <td>11.2 \pm 2.1</td> </tr> </tbody> </table>	Zinc dose	FAZ	AZ (mg)	2 mg	0.73 \pm 0.18	1.6 \pm 0.4	5 mg	0.68 \pm 0.25	3.5 \pm 1.3	10 mg	0.71 \pm 0.11	7.4 \pm 1.0	15 mg	0.62 \pm 0.14	9.5 \pm 2.2	20 mg	0.54 \pm 0.2	11.0 \pm 2.2	30 mg	0.37 \pm 0.07	11.2 \pm 2.1	<p>Comparison of cohorts, not experimental</p>
Zinc dose	FAZ	AZ (mg)																								
2 mg	0.73 \pm 0.18	1.6 \pm 0.4																								
5 mg	0.68 \pm 0.25	3.5 \pm 1.3																								
10 mg	0.71 \pm 0.11	7.4 \pm 1.0																								
15 mg	0.62 \pm 0.14	9.5 \pm 2.2																								
20 mg	0.54 \pm 0.2	11.0 \pm 2.2																								
30 mg	0.37 \pm 0.07	11.2 \pm 2.1																								
<p>Tran, C. D., Miller, L. V., Krebs, N. F., Lei, S., & Hambidge, K. M. (2004). Zinc absorption as a function of the dose of zinc sulfate in aqueous solution. <i>American Journal of Clinical Nutrition</i>, 80:1570-</p>	<p>8 healthy adults (3 men and 5 women) Age 33.8 \pm 9.8 years</p>	<p>Crossover study Zinc administered as 6 different concentrations in three phases. There was a three week washout period</p>	<p>Treatment: Phase 1: 2 and 5 mg of aqueous Zn Phase 2: 10 and 15 mg of aqueous Zn Phase 3: 20 and 30 mg of aqueous Zn</p> <p>Outcomes: Fractional</p>	<p>FAZ= fractional absorption of zinc AZ = absorbed zinc</p> <p>Using regression analysis, 13 mg of zinc as aqueous zinc sulfate is an estimate of the maximum amount of zinc that will be absorbed, regardless of the amount of zinc ingested. Increments in absorbed zinc were progressively smaller as the size of the dose increased.</p>	<p>Population of this study is healthy adults Zinc absorption from aqueous solution is different than zinc from foods. No data for tablets or capsules.</p>																					

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

1573. Australia		between phases.	absorbed zinc Absorbed zinc		
Growth					
Nakamura, T., Nishiyama, S., Futagoishi-Suginohara, Y, Matsuda, I., & Higashi, A. (1993). Mild to moderate zinc deficiency in short children: Effect of zinc supplementation on growth velocity. <i>Journal of Pediatrics</i> , 123, 65-69.	21 children prepubertal, (11 male) short, without endocrine abnormality Mild to moderate zinc deficiency by zinc kinetics studies		Group 1: n= 10, (5 boys) 5 mg/kg zinc sulfate orally for 6 months Group 2:n= 11 (6 boys) control Outcomes Weight Height Zinc clearance Serum zinc	Report linear growth velocity, calorie intake serum levels of zinc, calcium, phosphorus, and alkaline phosphatase, the percentage of tubular re-absorption of phosphorus TmP/GER ration and serum level of osteocalcin and plasma level of IGF-1 were all improved at least P< 0.05	220 screened, 11 selected Height for age < 2 SD <ul style="list-style-type: none"> • Apparently good health • S. growth hormone > 10 ng/ml insulin • Zinc clearance > 20 ml/kg per hour • Pre-pubertal status throughout the study (Tanner staging) •
Japan					
Epidermolysis Bullosa					
Allman, S., Haynes, L, MacKinnon, P., & Atherton, D. J. (1992). Nutrition in dystrophic epidermolysis bullosa. <i>Pediatric Dermatology</i> , 9, 3, 231-238.	Children with dystrophic EB	Cohort	<u>Treatment</u> All were treated with diet instruction, All were supplemented with fortified cow milk supplement, Sustained release zinc sulfate for those with low plasma zinc or dietary intakes < 10 mg/d (22 mg	Initial plasma zinc was low in 5 of 13 subjects and serum albumin was low in 5 of 14 subjects. Many were already on supplemental zinc and total zinc intake was not correlated to zinc level. Parents described sporadic administration of zinc d/t difficulties giving the supplement Recommend alternating iron and zinc due to competition, however, other studies have shown otherwise. (See Dekker, 2010)	Difficult to assess if outcomes were truly assessed. Many biases, poor design.

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

			<p>elemental zinc) Sodium iron edetate elixir for those with had increase TIBC, low serum iron or dietary intake <10mg/d. Vitamins when dietary intake was poor. <u>Outcomes</u> Anthropometrics Dietary intake</p>		
<p>Fine, J. D., Tamura, T., Johnson, L. (1989). Blood vitamin and trace metal levels in epidermolysis bullosa. <i>Archives of Dermatology</i>, 125, 374-379.</p>	<p>73 subjects with EB.</p> <p>Types: Simplex- 48 Junctional-10 Recessive dystrophic-9 Dominant dystrophic- 6</p>	<p>Cross sectional laboratory survey</p>	<p><u>Treatment</u> None <u>Outcomes</u> Blood levels of the following nutrients Vitamins A, C, B12, B6 and thiamine, riboflavin and folate Minerals zinc, copper and iron.</p>	<p>EB simplex (2/43), junctional (1/10) and dominant dystrophic (1/6) were zinc deficient.(erythrocyte zinc)</p>	<p>Imprecise. Low number of cases with low zinc levels.</p>
Eczema					
<p>Hinks, L. J. Young, S., & Clayton. (1987), Trace element status in eczema and psoriasis. <i>Clinical and Experimental Dermatology</i>, 12, 93-97.</p>	<p>23 with psoriasis</p> <p>24 with eczema</p> <p>Adults 18-82 years.</p>	<p>Cross sectional laboratory survey Compared with 2 healthy controls</p>	<p><u>Treatment</u> None <u>Outcomes</u> Plasma and leukocyte conc. of zinc copper and selenium.</p>	<p>There was no difference in plasma or leukocyte zinc between subjects with eczema and controls</p>	
Contamination					
<p>Krone, C. A., Wyse, E. J. & Ely, J. T. A. (2001). <i>International Journal of Food Sciences and Nutrition</i>, 52, 379-</p>	<p>No subjects</p>	<p>Bench study 7 zinc supplements were analyzed for zinc (Zn) and</p>		<p>See Table 1. (Below) Krone postulated Cd exposure in childhood via Zn supplementation may be a factor in early occurrence of renal dysfunction in the future. “efforts should be made to identify the sources and more strictly control the</p>	<p>The FDA Total Diet Study suggests that the mean lifetime exposure to total Cd from all food (excluding shellfish) is 10 µg/person/day.</p>

Synopsis: Office of Evidence Based Practice – Specific Care Question Zinc

382.		cadmium (Cd).		levels of Cd in Zn-containing supplements”.	
------	--	---------------	--	---	--

Table 1. Zinc and Cadmium content of various zinc supplements.

	Salt form (single or multi supplement)	Stated Zn/Tablet (mg)	Measured Zn/Tablet (mg)	Measured Cadmium/Tablet µg
1	Zinc gluconate(single)	50	50.3	0.18
2	Zinc gluconate (single)	60	62.2	0.19
3	Zinc citrate, chelate, picolinate (multi)	50	50.8	0.19
4	Zinc chelate (multi)	50	31.0	2.0
5*	Zinc –not stated	50	71.0	3.6
6	Zinc sulfate (multi)	7.5	9.79	0.95
7	Zinc gluconate (single)	50	54.3	1.14

*experimental formulation, not available to the public.

Cadmium facts:

- Tolerable Daily Intake (TDI) = 55µg/day
- Absorbed Cd is eliminated slowly, Biological half life is ~ 38 years
- Deposited in the kidneys
- Long term exposure with an accumulation of Cd levels 180-220 µg/g tissue kidney dysfunction can occur

-