Published in final edited form as:
J Nutr. 2003 November ; 133(11 Suppl 2): 3927S–3931S.

Micronutrient Deficiencies and Cognitive Functioning1,,2

Maureen M. Black[3]
Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD 21201

Abstract

The relationship between four micronutrient deficiencies (iodine, iron, zinc and vitamin B-12) and children's cognitive functioning is reviewed. Iodine deficiency during pregnancy has negative and irreversible effects on the developing fetus. Although there is some evidence that postnatal iodine deficiency is associated with cognitive deficits, the findings are controversial. Iron deficiency is widespread and has been associated to cognitive deficits, but the results of prevention trials are inconsistent. Zinc deficiency has been linked with low activity and depressed motor development among the most vulnerable children. Associations with cognitive development are less clear and may be limited to specific neuropsychological processes. Vitamin B-12 deficiency has been associated with cognitive problems among the elderly, but little is known about its effect on children's cognitive functioning. Rates of vitamin B-12 deficiency are likely to be high because animal products are the only source of vitamin B-12. Although micronutrient deficiencies often co-occur in the context of poverty, little is known about the impact of multiple micronutrient deficiencies on cognitive development. J. Nutr. 133: 3927S–3931S, 2003.

Keywords

micronutrients; iron; iodine; zinc; vitamin B-12; cognitive development

Recent evidence suggests that micronutrient deficiencies may play a role in children's development. Micronutrient deficiencies are a critical concern among children throughout the world. Approximately 30% of the world's population live in iodine-deficient areas and 25% of the world's children under age 3 y have iron-deficiency anemia, with higher rates in developing countries (1). When iron deficiency without anemia is considered, rates are even higher (2). Less is known about the prevalence of zinc and vitamin B-12 deficiency. Based on the dietary intakes of children from developing countries, there is a high rate of zinc deficiency among infants and toddlers (3), and recent data suggest that inadequate zinc intakes may be common among middle-class infants and toddlers in America (4). Because animal products are the only source of vitamin B-12, rates of vitamin B-12 deficiency are likely to be high among children who consume little or no meat or milk.

[1]Presented at the conference "Animal Source Foods and Nutrition in Developing Countries" held in Washington, D.C. June 24–26, 2002. The conference was organized by the International Nutrition Program, UC Davis and was sponsored by Global Livestock-CRSP, UC Davis through USAID grant number PCE-G-00-98-00036-00. The supplement publication was supported by Food and Agriculture Organization, Land O'Lakes Inc., Heifer International, Pond Dynamics and Aquaculture-CRSP. The proceedings of this conference are published as a supplement to The Journal of Nutrition. Guest editors for this supplement publication were Montague Demment and Lindsay Allen.

[2]This work is funded by grants from the National Institute of Child Health and Human Development (R01 HD374430) and The Gerber Foundation.

[3]To whom correspondence should be addressed. mblack@umaryland.edu.

The relationship between micronutrient deficiency and early cognitive development has captured recent attention because micronutrients are related to specific physiological processes (5). Therefore, programs designed to prevent or treat micronutrient deficiencies can be targeted toward specific recommendations. At least four micronutrients have been linked to cognitive processes in infants and young children and are the focus of this review: iodine, iron, zinc and vitamin B-12.

The research examining the effects of micronutrient deficiencies on children's cognitive and motor development suffers from many of the same methodological problems that have hindered research examining the effect of protein-energy malnutrition. Micronutrient deficiencies often occur in the context of poverty and among families who are beset by multiple stressors that may interfere with the healthy development of their children. In addition, micronutrient deficiencies often co-occur, particularly if the micronutrients are derived from the same source. For example, meat, fish and poultry are important sources of iron, zinc and vitamin B-12. If children are deficient in multiple micronutrients, it can be difficult to interpret the effects of single micronutrient supplementation trials.

Observational studies have compared children with and without micronutrient deficiencies. Although these studies can yield useful information about micronutrients and differences in development, they lack the rigor of randomized trials because there are often factors that differ between separating the groups that may influence children's development, such as care-giving practices (6). Randomized trials can often clarify differences related to the effects of micronutrients, but they are expensive and must also control for confounding factors that may influence children's development, such as the quality of the care-giving environment. In addition, as the evidence demonstrating the detrimental effects of specific micronutrient deficiencies on children's development is clarified (e.g., the effect of iodine deficiency), it becomes unethical to identify micronutrient-deficient children and then not to offer treatment.

Iodine deficiency

The link between prenatal iodine deficiency and cognitive development is direct, but can be prevented through public health methods, making iodine deficiency the most preventable cause of mental retardation in the world (7). Iodine deficiency is a major problem that affects children in areas where iodine is depleted from the soil, primarily mountainous regions, such as the Himalayas and the Andes, and in flood plains (8). A 1993 World Health Organization report estimates that 1.6 billion people or 30% of the world's population live in iodine-deficient areas and are therefore at risk for iodine deficiency (1). Public health methods, such as iodized salt, injections of iodinated oil or oral iodine, have been effective in preventing congenital hypothyroidism and the associated mental retardation (7).

Iodine is an essential component of at least two thyroid hormones that are necessary for skeletal growth and neurological development (8). When iodine is deficient, hypothyroidism occurs, resulting in increased production of thyroid stimulating hormones and goiter (8).

When iodine deficiency occurs in utero, it leads to fetal hypothyroidism and irreversible neurological and cognitive deficits manifested as cretinism. Neurological cretinism includes mental retardation, primitive reflexes, visual problems, facial deformities, stunted growth and diplegia (9). In addition to cognitive delays, primitive reflexes and pyramidal signs, myxodematous cretinism includes severe growth retardation, dry skin and electrocardiogram abnormalities. Randomized iodine supplementation trials from iodine-deficient areas of Asia, Africa and South America have shown that children whose mothers were supplemented before conception or early in pregnancy have better developmental outcomes than those whose mothers are not supplemented (10).

When iodine deficiency occurs postnatally, the child may experience thyroid failure that can lead to hypothyroidism. Observational studies that have compared children with and without goiter have had mixed results; some have reported cognitive deficits among children with goiters and others have not. One explanation for the lack of clarity may be that differing levels of hypothyroidism can lead to a goiter (9). In a metaanalysis of 18 observational studies that compared children based on whether they lived in an iodine-deficient area or not, children who lived in iodine-deficient areas had deficits in cognitive functioning (11). In a well-controlled observational study in Bangladesh, investigators found that children with mild hypothyroidism had deficits in spelling and reading compared to healthy controls (12). Although evidence from these studies is compelling, families who live in iodine-deficient areas are often more impoverished than families in areas where iodine status is adequate.

Several randomized trials have been conducted to examine the impact of iodine supplementation on the cognitive performance of children in iodine-deficient areas. However, results have not been consistent. In a recent longitudinal follow-up of school-age children, all of whom received iodine, those who received iodine in utero before the third trimester had better scores on a measure of psychomotor performance than children who received iodine later in pregnancy or at age 2 y (13). There was a similar trend when measures of cognitive performance were considered; however, the differences did not reach statistical significance. Thus, the effects of postnatal iodine deficiency on children's cognitive performance are less clear than the effects of prenatal iodine deficiency. In addition, many of the studies have had methodological problems that interfere with interpretation.

Universal salt iodization is a public health priority for women of childbearing age to protect their unborn children from the severe consequences of hypothyroidism. In cases where iodine deficiency is common, but iodized salt is either not consumed or unavailable, iodized oil can be used. Although iodine supplementation will reduce the incidence of goiter in children, the impact on their cognitive development requires further investigation.

Iron deficiency

Iron deficiency is the most common nutritional deficiency in the world. WHO estimates that worldwide there are 2 billion individuals with anemia and up to 5 billion who are iron deficient (2). The highest risk of iron deficiency occurs during times of rapid growth and nutritional demand, especially age 6–24 mo, adolescence and pregnancy. Iron is necessary for hemoglobin synthesis. Iron deficiency leads to reduced oxygen carrying capacity and can impact immunity, growth and development. Only 50% of anemia is caused by iron deficiency. The remainder is caused by vitamin A deficiency, deficiencies of vitamin B-12 and folate, malaria, HIV, other infectious diseases, sickle cell disease, or other inherited anemias (14).

A number of observational studies have found that children who experienced anemia early in life continued to demonstrate lower academic performance during their school-age years, even after the anemia had been treated. For example, Hurtado and colleagues examined the records of children who enrolled in the Special Supplemental Nutrition Program for Women, Infants and Children before age 5 y (15). Those who were anemic were more likely to experience academic problems at 10 y of age, compared to children who were not anemic on enrollment. Concurrent iron status is also related to academic performance, as demonstrated in a recent investigation using data from 5398 children aged 6–16 y from the NHANES III survey in the United States (16). When standardized mathematics test scores were examined controlling for background variables, children with iron deficiency, with and without

anemia, had lower scores than children with normal iron status. These findings suggest that iron deficiency, even without anemia, may place children at risk for cognitive delays.

Treatment for anemic children

A Cochrane Review in 2001 focused on randomized placebo-controlled trials that had been conducted to examine the impact of iron therapy on development among children under age 3 y with iron deficiency anemia (17). Among the five trials of short-term treatment, involving 180 children, iron therapy resulted in no differences in the children's mental or motor performance. There were two trials of longer-term therapy (over 30 d), involving 160 children. One study tested children 2 mo after iron treatment, using a screening test (the Denver Test), and found no difference in performance (18). The other study, conducted in Indonesia, found that 4 mo of iron treatment produced 18-point improvements in both mental and motor scores on a standardized assessment (Bayley Scales of Infant Development) (19). Although the evidence from the Indonesia trial regarding long-term treatment is very encouraging, more randomized trials are needed. There have been other randomized trials of iron treatment that showed no treatment effect on cognitive performance; however, most investigators have relied on nonanemic control groups to avoid the ethical dilemma of denying iron therapy to anemic children.

Prevention trials

There are at least seven published randomized control prevention trials that have been conducted among children under 3 y of age. Three found no effect of iron supplementation on cognitive performance (20–22), but four found beneficial effects of iron supplementation on varying aspects of children's behavior and development (23–26). In a trial conducted in Papua, New Guinea, findings may have been blunted due to confounding with malaria (20). Four of the investigators used the Bayley Scales to measure mental and motor development (21–24). Only one found effects—iron supplemented infants had better motor development at 9- and 12- mo of age, but not at 15 mo (23). In a trial that used the Griffiths Scale to measure development, children who received iron experienced less decline in developmental skills over the first year of life (25). In a recent trial from Zanzibar that used maternal report of developmental skills, children who received iron for 1 y had better language scores (26). Children who had low hemoglobin initially also had better motor scores after iron therapy (26). Lozoff et al. found beneficial effects of iron on visual perceptual skills (24). Infants with iron-deficient anemia have been described as wary and irritable (27,28). Iron-supplemented children have been described as less wary and hesitant than those who were not supplemented (28); behavioral differences continued into childhood even after the children's iron status had been corrected. Taken together, these findings illustrate the complexity of using general cognitive assessments and suggest that iron deficiency may be related to specific processes, especially when it occurs early in life. Additional iron supplementation trials are needed, especially in younger children.

Iron has multiple roles in neurotransmitter systems and may affect behavior through its effects on dopamine metabolism. Dopamine clearance has strong effects on attention, perception, memory, motivation and motor control (29).

Zinc deficiency

Low zinc intake appears to be a major public health problem (30). However, biological measures of zinc status, such as plasma and hair zinc, are imperfect indicators of functional impairment due to zinc deficiency, and response to randomized trials of zinc supplementation conducted in zinc-deficient populations has been an important means to examine the consequences of zinc deficiency (31). Supplementation trials among

nutritionally deficient infants have demonstrated beneficial effects of zinc on growth (32), diarrhea and pneumonia morbidity (33) and on mortality (34).

An early observational study from Egypt demonstrated a link between maternal micronutrient intake and infants' developmental skills (35). Several supplementation trials among pregnant women, infants and toddlers have shown increased activity and motor development among zinc-supplemented groups (36–40). However, a recent trial among women who received zinc supplementation during pregnancy found no differences in their children's mental and motor performance at age 5 y (41).

Trials that have examined changes in cognitive functioning have found either no differences related to zinc supplementation (36,40,42) or, as in two recent studies from Bangladesh, found lower scores among zinc-supplemented infants (43,44). In one trial, zinc supplementation was delivered to infants (43) and, in the other, it was delivered to their mothers during pregnancy (44). Both trials reported that at 12 mo, zinc-supplemented infants achieved lower scores on a measure of cognitive development than control infants.

When behavior changes related to zinc supplementation were considered, in Brazil zinc-supplemented infants were more responsive than control group infants (42). Although the evidence from the supplementation trials among vulnerable infants and toddlers suggests that zinc deficiency may compromise children's early motor development, the evidence linking zinc deficiency to cognitive development is not conclusive (45).

There have been at least three randomized trials of zinc supplementation measuring cognitive development among school-age children. A trial in Canada found no differences when children were tested with subscales from the Detroit Test of Learning Abilities (46). However trials in China and Mexican-American children from Texas have found that zinc-supplemented children demonstrated superior neuropsychological performance, particularly reasoning, when compared with controls (47–49). The evidence for improved neuropsychological performance among zinc-supplemented children is increasing, but more work is needed to replicate existing studies and clarify the effect on academic performance.

Vitamin B-12 deficiency

Because animal products are the only source of vitamin B-12, infants breastfed by mothers with low intakes of these products, and children who do not consume them, are at risk for vitamin B-12 deficiency. Research from rural Kenya presented by Siekmann et al. in this supplement indicates that over two thirds of the school-age children are experiencing vitamin B-12 deficiency (50). The worldwide prevalence of vitamin B-12 deficiency may be very high.

Vitamin B-12 deficiency is a recognized problem among geriatric populations even in wealthier countries, often related to their diminished ability to absorb the vitamin. Consequently, most of the research linking vitamin B-12 deficiency to cognitive functioning has been conducted in the elderly, where it has been associated with dementia and neurobehavioral deficits (51).

Most of the research on the relationship between vitamin B-12 deficiency and cognitive functioning in children is limited to case studies of infants of mothers with pernicious anemia (who are unable to absorb vitamin B-12) or vegan mothers (52). These infants are at risk for delayed developmental milestones.

There have been at least two observational studies among children with B-12 deficiency. In the first study, infants of macrobiotic mothers in The Netherlands had delayed motor and

language development compared to infants of omnivores (53). At age 12 y, the children had higher methylmalonic acid levels and scored lower than the omnivores on standardized assessments, including the Raven's progressive matrices, Digit Span and Block Design, even though their current diet contained almost their recommended daily intake of vitamin B-12 (54). The second study was conducted among Guatemalan school-age children. Children with vitamin B-12 deficiency had slower reaction time on neuropsychological tests of perception, memory and reasoning, along with academic problems including lower academic performance, lower teacher ratings, more attentional problems and more delinquent behavior (55,56). These observational studies provide evidence that vitamin B-12 deficiency is associated with poorer cognitive performance, but intervention trials are needed for confirmation.

Most of the research examining the impact of micronutrient deficiencies on children's development has hypothesized a direct effect, possibly through changes in neuroanatomy or neurotransmission (57). However, it is also possible that behavior changes associated with micronutrient deficiencies alter the caregiving that the child receives, thereby compromising the child's development even further. For instance, if an iron deficient child is wary and unable to elicit or to benefit from nurturant interactions from a caregiver, that child may be denied the enrichment that is known to promote early development. The result could be a child who experiences both the neurological changes that have been associated with iron deficiency together with limited environmental enrichment. This process, whereby nutritional deficiencies are partially mediated through caregiving behavior, is known as functional isolation (58). Future research should consider how the caregiving system is related to child development and whether it mediates the effects of micronutrient deficiencies.

The findings linking micronutrient deficiencies to child development point to the importance of effective prevention programs that begin prenatally or early in life and extend through the periods of vulnerability, which may include adolescence. There are many unanswered questions regarding micronutrient deficiencies and child development that require further research, including the initial severity and timing of the deficiency, the long-term consequences on academic achievement, the specific processes involved and the impact of multiple micronutrient deficiencies.

LITERATURE CITED

1. World Health Organization. MDIS Working Paper No. 1. World Health Organization; Geneva, Switzerland: 1993. Global prevalence of iodine deficiency disorders.
2. World Health Organization. Maternal Health and Safe Motherhood Programme. WHO/MCH/MSM/92.2. 2. World Health Organization; Geneva, Switzerland: 1992. The Prevalence of Anemia in Women: A Tabulation of Available Information.
3. Briefel RR, Bialostosky K, Kennedy-Stephenson J, McDowell MA, Ervin RBR, Wright JD. Zinc intake of the U.S. population: findings from the third National Health and Nutrition Examination Survey, 1988–1994. J Nutr. 2000; 130:1367S–1373S. [PubMed: 10801945]
4. Skinner JD, Carruth BR, Houck K, Coletta R, Cotter R, Ott D, McLeod M. Longitudinal study of nutrient and food intakes of infants aged 2 to 24 months. J Am Diet Assoc. 1997; 97:496–504. [PubMed: 9145087]
5. Grantham-McGregor S, Ani C. The role of micronutrients in psychomotor and cognitive development. Br Med Bull. 1999; 55:511–527. [PubMed: 10746342]
6. Engle PL, Pelto G, Bentley P. The role of care in nutrition programmes: current research and a research agenda. Proc Nutr Soc. 2000; 59:25–35. [PubMed: 10828171]
7. Stanbury, JB. The Damaged Brain of Iodine Deficiency. Cognizant Communication; Elmsford, NY: 1994.

8. Dunn JT. Iodine deficiency—the next target for elimination. N Engl J Med. 1992; 326:267–268. [PubMed: 1309392]
9. Halpern, J. The neuromotor deficit in endemic cretinism and its implications for the pathogenesis of the disorder. In: Stanbury, JB., editor. The Damaged Brain of Iodine Deficiency. Cognizant Communication; Elmsford, NY: 1994. p. 15-24.
10. Ferald, L. Iodine deficiency and mental development. In: Grantham-McGregor, SM., editor. Nutrition, Health, and Child Development Recent Advances and Policy Recommendations. Pan American Health Organization; Washington, D.C: 1998. p. 234-255.
11. Bleichrodt, N.; Resing, W. Measuring intelligence and learning potential in iodine-deficient and noniodine deficient populations. In: Stanbury, JB., editor. The Damaged Brain of Iodine Deficiency. Cognizant Communication; Elmsford, NY: 1994. p. 27-36.
12. Huda SN, Grantham-McGregor SM, Rahman KM, Tomkins A. Biochemical hypothyroidism secondary to iodine deficiency is associated with poor school achievement and cognition in Bangladeshi children. J Nutr. 1999; 129:980–987. [PubMed: 10222389]
13. O'Donnell KJ, Rakeman MA, Zhi-Hong D, Xue-Yi C, Mei ZY, DeLong N, Brenner G, Tai M, Dong W, DeLong GR. Effects of iodine supplementation during pregnancy on child growth and development at school age. Dev Med Child Neurol. 2002; 44:76–81. [PubMed: 11848114]
14. Yip R. Iron deficiency: contemporary scientific issues and international programmatic approaches. J Nutr. 1994; 124:1479S–1490S. [PubMed: 8064407]
15. Hurtado EK, Claussen AH, Scott KG. Early childhood anemia and mild and moderate mental retardation. Am J Clin Nutr. 1999; 69:115–119. [PubMed: 9925132]
16. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics. 2001; 107:1381–1386. [PubMed: 11389261]
17. Martins, S.; Logan, S.; Gilbert, R. The Cochrane Library. Update Software; Oxford, UK: 2001. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia (Cochrane Review).
18. Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. Arch Dis Child. 1986; 61:849–857. [PubMed: 2429622]
19. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. Lancet. 1993; 341:1–4. [PubMed: 7678046]
20. Heywood A, Oppenheimer S, Heywood P, Jolley D. Behavioral effects of iron supplementation in infants in Madang, Papua New Guinea. Am J Clin Nutr. 1989; 50:630–640. [PubMed: 2773841]
21. Walter T, de Andraca I, Chadud P, Perales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. Pediatrics. 1989; 84:7–17. [PubMed: 2472596]
22. Morley R, Abbott R, Fairweather-Tait S, MacFadyen U, Stephenson T, Lucas A. Iron fortified follow on formula from 9 to 18 months improves iron status but not development or growth: a randomized trial. Arch Dis Child. 1999; 81:247–252. [PubMed: 10451399]
23. Moffatt MEK, Longstaffe S, Sesant J, Dureski C. Prevention of iron deficiency and psychomotor decline in high risk infant through iron fortified infant formula: a randomized clinical trial. J Pediatr. 1994; 125:527–534. [PubMed: 7523647]
24. Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E, Jimenez R, Mora LA, Gomez I, Krauskoph D. Iron deficiency anemia and iron therapy effects on infant developmental test performance. Pediatrics. 1987; 79:981–995. [PubMed: 2438638]
25. Williams J, Wolff A, Daly A, MacDonald A, Aukett A, Booth IW. Iron supplemented formula milk related to reduction in psychomotor decline in infants from inner city areas: randomized study. BMJ. 1999; 318:693–697. [PubMed: 10074011]
26. Stoltzfus RJ, Kvalsvig JD, Chwaya HM, Montresor A, Albonico M, Tielsch JM, Savioli L, Pollitt E. Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: double blind, placebo controlled study. BMJ. 2001; 323:1389–1393. [PubMed: 11744561]
27. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med. 1991; 325:687–694. [PubMed: 1870641]

28. Lozoff B, Klein NK, Nelson EC, McClish DK, Manual M, Chacon ME. Behavior of infants with iron-deficiency anemia. Child Dev. 1998; 69:24–36. [PubMed: 9499554]
29. Beard JL. Iron deficiency alters brain development and functioning. J Nutr. 2003; 133:1468S–1472S. [PubMed: 12730445]
30. Sandstead HH. Zinc deficiency: a public health problem? Am J Dis Child. 1996; 145:853–859. [PubMed: 1858720]
31. Hambidge M, Krebs NF. Zinc metabolism and requirements. Food Nutr Bull. 2001; 22:126–132.
32. Brown KH, Peerson JM, Rivera J, Allen L. Effects of supplemental zinc in growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2002; 75:1062–1075. [PubMed: 12036814]
33. Bhutta ZA, Black RE, Brown KH, Gardner JM, Gore S, Hidayat A, Khatun F, Martorell R, Ninh NX, Penny ME, Rosado JL, Roy SK, Ruel M, Sazawal S, Shankar A. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized clinical trials. J Pediatr. 1999; 135:689–697. [PubMed: 10586170]
34. Sazawal S, Black RE, Menon VP, Dingra P, Caulfield LE, Dingra U, Bagati A. Zinc supplementation in infants born small for gestational age reduces mortality: a prospective, randomized, controlled trial. Pediatrics. 2001; 108:1280–1286. [PubMed: 11731649]
35. Kirksey A, Wachs TD, Yunis F, Srinath U, Rahmanifar A, Mc Cabe GP, Galal OM, Garrison GG, Jerome NW. Relation of maternal zinc nutriture to pregnancy outcome and infant development in an Egyptian village. Am J Clin Nutr. 1994; 60:782–792. [PubMed: 7942587]
36. Friel JK, Andrews WL, Matthew JD, Long DR, Cornel AM, Cox M, McKim E, Zerbem GO. Zinc supplementation in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr. 1993; 17:97–104. [PubMed: 8350219]
37. Meraldi M, Caulfield LE, Zavaleta N, Figueroa A, DiPetro JA. Adding zinc to prenatal iron and folate tablets improves fetal neurobehavioral development. Am J Obstet Gynecol. 1999; 180:483–490. [PubMed: 9988823]
38. Sazawal S, Bentley M, Black RE, Dhingra P, George S, Bhan MK. Effect of zinc supplementation on observed activity in preschool children in an urban slum population. Pediatrics. 1996; 98:1132–1137. [PubMed: 8951265]
39. Bentley ME, Caulfield LE, Ram M, Santizo MC, Hurtado E, Rivera JA, Ruel MT, Brown KH. Zinc supplementation affects the activity patterns of rural Guatemalan infants. J Nutr. 1997; 127:1333–1338. [PubMed: 9202087]
40. Castillo-Duran C, Perales CG, Hertrampf ED, Marin VB, Rivera FA, Icaza G. Effect of zinc supplementation on development and growth of Chilean infants. J Pediatr. 2001; 138:229–235. [PubMed: 11174621]
41. Tamura T, Goldenberg RL, Ramey SL, Nelson KG, Chapman VR. Effect of zinc supplementation of pregnant women on the mental and psychomotor development of their children at 5 y of age. Am J Clin Nutr. 2003; 77:1512–1516. [PubMed: 12791632]
42. Ashworth A, Morris SS, Lira PI, Grantham-McGregor SM. Zinc supplementation, mental development, and behaviour in low birth weight infants in northeast Brazil. Eur J Clin Nutr. 1998; 52:223–227. [PubMed: 9537309]
43. Hamadani JD, Fuchs GJ, Osendarp SJM, Khatun F, Huda SN, Grantham-McGregor SM. Randomized controlled trial of the effect of zinc supplementation on the mental development of Bangladeshi infants. Am J Clin Nutr. 2001; 74:381–386. [PubMed: 11522564]
44. Hamadani JD, Fuchs GJ, Osendarp SJM, Huda SN, Grantham-McGregor SM. Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. Lancet. 2002; 360:290–294. [PubMed: 12147372]
45. Black MM. Zinc deficiency and child development. Am J Clin Nutr. 1998; 68:464S–469S. [PubMed: 9701161]
46. Gibson RS, Vanderkooy PDS, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc-deficiency syndrome in some Southern Ontario boys with low height percentiles. Am J Clin Nutr. 1989; 49:1266–1273. [PubMed: 2729165]

47. Penland JG, Sandstead HH, Alcock NW, Dayal HH, Chen XC, Li JJ, Zhao F, Yang JJ. A preliminary report: effects of zinc and micronutrient repletion on growth and neuropsychological function of urban Chinese children. J Am Coll Nutr. 1997; 16:268–272. [PubMed: 9176834]
48. Penland J, Sanstead H, Egger N, Dayal H, Alcock N, Plotkin R, Rocco C, Zavaleta A. Zinc, iron and micronutrient supplementation effects on cognitive and psychomotor function of Mexican-American school children. FASEB J. 1999; 13:A921.
49. Sanstead HH, Penland JG, Alcock NW, Dayal HH, Chen XC, Li JS, Zhao F, Yang JJ. Effects of repletion with zinc and other micronutrients on neuropsychologic performance and growth of Chinese children. Am J Clin Nutr. 1998; 68:470S–475S. [PubMed: 9701162]
50. Siekmann JH, Allen LH, Bwibo NO, Demment MW, Murphy SP, Neumann CG. Micronutrient status of Kenyan school children: response to meat, milk, or energy supplementation. J Nutr. 2003; 133:3972S–3980S. [PubMed: 14672298]
51. Rosenberg IH, Miller JW. Nutritional factors in physical and cognitive functions of elderly people. Am J Clin Nutr. 1992; 55:1237S–1243S. [PubMed: 1590263]
52. Lampkin BC, Saunders EF. Nutritional vitamin B12 deficiency in an infant. J Pediatr. 1969; 75:1053–1055. [PubMed: 5352832]
53. Schneede J, Dagnelie PC, Van Staveren WA, Vollset SE, Refsum H, Ueland PM. Methylmalonic acid and homocysteine in plasma as indicators of functional cobalamin deficiency in infants on macrobiotic diets. Pediatr Res. 1994; 36:194–201. [PubMed: 7970934]
54. Louwman MW, Van Dusseldorp M, Van de Vijver FJ, Thomas CM, Schneede J, Ueland PM, Refsum H, Van Staveren WA. Signs of impaired cognitive function in adolescents with marginal cobalamin status. Am J Clin Nutr. 2000; 72:762–769. [PubMed: 10966896]
55. Allen LH, Penland JG, Boy E, DeBaessa Y, Rogers LM. Cognitive and neuromotor performance of Guatemalan schoolers with deficient, marginal and normal plasma B-12. FASEB J. 1999; 13:A544.
56. Penland J, Allen LH, Boy E, DeBaessa Y, Rogers LM. Adaptive functioning, behavior problems and school performance of Guatemalan children with deficient, marginal and normal plasma vitamin B-12. FASEB J. 2000; 14:A561.
57. Rao, R.; Georgieff, MK. Early nutrition and brain development. In: Nelson, CA., editor. The Effects of Early Adversity on Neurobehavioral Development. The Minnesota Symposium on Child Psychology. Lawrence Erlbaum Associates Publishers; Mahwah, NJ: 2000. p. 1-30.
58. Levitsky DA, Barnes RH. Nutritional and environmental interactions in the behavioral development of the rat: long term effects. Science. 1972; 176:68–73. [PubMed: 5062235]