

Neurocognitive Function and Trace Elements

The Evidence Linking Zinc Deficiency with Children's Cognitive and Motor Functioning^{1,2}

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ABSTRACT The role of zinc in children's cognitive and motor functioning is usually assessed by the response to supplementation in populations thought to be zinc deficient. A review of published zinc-supplementation trials that examined behavior and development identified one trial in fetuses, six trials in infants and toddlers and three trials in school-age children. The three studies that examined activity reported that zinc supplementation was associated with more activity. Of the five studies that examined motor development in infants and toddlers, one found improvements among very low-birth-weight infants, one found improvements in the quality of motor development and three found no impact. Of the four studies that examined mental development in infants and toddlers, three found no impact of zinc supplementation and one found that zinc-supplemented children had lower scores than control children. Among school-age children, one study found no impact of zinc supplementation on cognitive performance and two found a beneficial impact of neuropsychological processes, specifically reasoning. The evidence linking zinc deficiency to children's cognitive and motor functioning suggests a relationship among the most vulnerable children but lacks a clear consensus, highlighting the need for additional research into the timing of zinc deficiency and the co-occurrence with other micronutrient deficiencies. *J. Nutr.* 133: 1473S–1476S, 2003.

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Zinc is a trace mineral that is involved with RNA and DNA synthesis and is critical to cellular growth, differentiation and metabolism (1–3). Zinc deficiency can interfere with multiple organ systems particularly when it occurs during a time of rapid growth and development, such as infancy, when nutritional demands are high (1).

Investigators often use indirect measures of zinc status because only a small percentage of the body's zinc is in plasma (4). Most of the body's zinc is located in muscle, bone and liver, where it turns over slowly. Biological measures of zinc status,

such as plasma and hair zinc, are useful at a population level but are imperfect indicators of individual functional impairment related to zinc deficiency (5). Dietary restrictions are used to assess the consequences of zinc deficiency in animals. In humans the consequences of zinc deficiency on behavior and development are frequently assessed by the response to randomized trials of zinc supplementation conducted in populations thought to be zinc deficient.

The small rapidly exchangeable pool of zinc, which is important in cell division and metabolism, is dependent on a steady source of zinc from the diet. The optimal source of zinc is from animal sources, such as beef, lamb and oysters (6). Healthy infants are usually able to get an adequate amount of zinc from breastfeeding during the first six months of life, as long as the mother's milk supply is adequate and breast milk is not displaced by complementary foods (7,8). However, infants who are small for their gestational age and premature infants may benefit from zinc supplementation in addition to the zinc they receive from breastfeeding (7). During the second six months of life when complementary foods are introduced, the risk for zinc deficiency increases because most traditional complementary foods are low in bioavailable zinc (9). The prevalence of zinc deficiency throughout childhood is estimated to be high, primarily related to the low consumption of foods high in bioavailable zinc (6,10).

Zinc deficiency is regarded as a major public health problem with multiple health consequences (10). Zinc supplementation trials among zinc-deficient infants have demonstrated beneficial effects of zinc on growth (11), diarrhea and pneumonia morbidity (12,13) and mortality (14). In addition, zinc

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deficiency may compromise behaviors necessary for cognitive functioning including activity and attention (1,15,16).

Zinc deficiency and behavior in animals

Zinc deficiency has been studied in animals by restricting zinc intake during pregnancy or specific developmental periods. Rats have been used to examine zinc deficiency during the prenatal and infancy periods. Animals who experienced severe zinc deficiency early in their fetal development were at increased risk for abortion and fetal abnormalities (17). Animals who experienced zinc deficiency, after the period of organogenesis but during early development, and were reared and tested as adults had difficulty in maze-learning tasks, particularly when shock was used in the learning procedure (18,19). They responded with increased emotionality that was evidenced by their aggression, poor memory and difficulty avoiding the shock. Thus, zinc deficiency early in life appeared to have long-lasting effects on the animals' responses to stress, which interfered with performance in learning situations.

Rhesus monkeys have been used to study zinc deficiency during infancy and childhood. Golub has simulated zinc deficiency during childhood by feeding well-nourished juvenile monkeys a zinc-deficient diet (20–23). Short-term (15-wk) moderate zinc deprivation in prepubertal monkeys resulted in reduced motor activity and less accurate performance on measures of attention and short-term memory (21).

Primates who experienced long-term moderate zinc deficiency initiated during the prepubertal period and extending through puberty (18–33 mo of age) were less active than primates fed a zinc-sufficient diet when tested during the premenarchial period. Differences in activity preceded differences in growth and plasma zinc levels (23). Specifically, zinc deficiency was associated with decreased activity and accuracy related to inhibitory control (measured by accuracy on a continuous performance task), but only during the premenarchial period (23). During the postmenarchial period there were no differences in activity or inhibitory control related to zinc deprivation. In contrast, monkeys in the zinc-deprivation group did not experience reduced growth rates or lower levels of plasma zinc until they entered their growth spurt (27–33 mo of life). Thereafter, zinc-deficient monkeys demonstrated lower rates of growth and plasma zinc levels than adequately nourished monkeys. The finding that diminished activity and inhibitory control occurred before changes in growth and plasma zinc levels suggests that the animals may have conserved energy or control in response to zinc deprivation. There was no impact of zinc deprivation on a measure of attention, but the testing periods were relatively brief and may not have adequately assessed sustained attention.

Studies of severe zinc deprivation in monkeys before weaning showed that zinc-deficient animals were emotionally less mature; this was demonstrated by their difficulty with separation and the increased protective behavior by their mothers (24). There were also cognitive deficits associated with severe zinc deprivation among juvenile monkeys (those who had been weaned), indicated by their difficulty in retaining previously learned visual-discrimination problems and in learning new problems.

Zinc supplementation and infant development

Observational studies have been used to examine children with and without zinc-deficient diets. Although observational studies can yield useful information about zinc deficiency, findings may be confounded by poverty and other nutritional

deficiencies because they often co-occur with zinc deficiency and are associated with children's development (25). Randomized trials are necessary to examine the specificity of zinc deficiency on children's behavior and development. Several reviews have examined the relationship between zinc nutrition and children's behavior and development (1,15,16).

Although zinc supplementation during pregnancy has been associated with several indicators of reproductive success including fetal growth, birth weight, lack of congenital malformations and term delivery, results have been difficult to replicate, which has produced inconsistent findings (26–29). One trial of zinc supplementation during pregnancy examined fetal heart rate and activity. Pregnant women who received 15 mg of daily zinc, along with iron and folate supplementation, had fetuses with an increased fetal heart rate and more vigorous fetal activity compared to fetuses of nonsupplemented women (30). Both measures are indices of fetal well-being that may be related to subsequent development (31).

Observational studies in Egypt reported an association between mothers' diets and their infants' early behavior and development (32,33). Mothers who consumed diets high in animal products had infants who were more attentive shortly after birth, as measured on the Brazelton Neonatal Behavioral Assessment Scale, than infants of mothers who consumed diets low in animal products. At 6 mo, infants whose mothers consumed diets that were primarily plant based, and therefore low in bioavailable zinc, had lower motor scores on the Bayley Scales of Infant Development than infants whose mothers consumed animal-based diets. Motor development was also related to infant diarrhea and psychosocial factors such as household socioeconomic status. These findings demonstrate the multiple impacts of maternal dietary choices and psychosocial risk on children's early motor functioning.

There are at least six zinc-supplementation trials that have examined the effects of zinc supplementation on activity or development among infants. In India, low-income toddlers who received 10 mg of elemental zinc daily for 6 mo had more vigorous activity during play, compared with control toddlers (34). In Guatemala, stunted toddlers who received 10 mg of oral zinc daily for 7 mo had more functional activity during play, compared with control toddlers (35). However, the toddlers did not differ on an observational assessment of motor development. A supplementation trial among very low-birth-weight infants (< 1500 g) from Canada (36) showed that infants who received formula with a higher concentration of zinc (11 vs 6.7 mg/L) for the first 5 mo of life had better scores in motor development, measured on the Griffiths' Developmental Assessment, but not in other areas of development. In Brazil, low-birth-weight infants who received 5 mg of zinc for 8 wk were more cooperative during developmental testing but there were no differences in their mental or motor development when measured on the Griffiths' Assessment (37). In Chile, low-income infants who received 5 mg of elemental zinc daily for 1 y had higher scores in motor quality (gross and fine-motor movement and control), but there were no differences in the children's mental or motor scores on the Bayley Scales (38). In Bangladesh, low-income infants received 5 mg of elemental zinc daily from 4 wk to 6 mo of life (39). When the evaluations were conducted by administering the Bayley Scales at 7 and 12 mo, there were no differences in motor development at either evaluation time; but at the 12-mo assessment the zinc-supplemented infants had slightly lower cognitive scores compared with control infants (103.1 vs 106.4). Thus, the evidence linking zinc supplementation to early cognitive and motor development is inconclusive. There are suggestions that zinc supplementation may promote activity and perhaps motor

development in the most vulnerable infants. Although motor development is thought to promote cognitive development by enabling children to be more independent and to explore their surroundings (40), the only evidence linking zinc supplementation to cognitive development is counter intuitive.

Zinc supplementation among school-age children

In observational studies among elementary school-age children, hair zinc was related to reading ability, suggesting that zinc deficiency interfered with academic performance (41,42). 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 (43). Trials in Chinese children and Mexican-American children from Texas have found that zinc-supplemented children demonstrated superior neuropsychological performance, particularly in reasoning, when compared with controls (44–46). These trials suggest that the beneficial impact of zinc supplementation may have an impact on specific neuropsychological processes that are evident in time-dependent challenging tasks, namely attention and reasoning, rather than in general performance tasks (46). More research is needed to replicate existing studies and to clarify the timing and duration of the relationship between zinc status, neuropsychological functioning and academic performance.

Zinc deficiency and depression

There has been some suggestion that zinc deficiency may be related to anxiety and depression. In a small observational study, patients with primary affective disorders had lower plasma zinc levels than comparison patients on admission (47). By the time they were ready for discharge, the patients' plasma zinc levels had increased significantly. In a randomized trial of zinc supplementation (50 mg/d of elemental) among adolescents with anorexia nervosa, those who received the supplement had lower levels of depression and anxiety on standardized measures, compared with the control group of adolescents (48). Both groups of adolescents with anorexia nervosa had low zinc intake before supplementation, based on dietary data, which suggests that they were zinc deficient. The association between zinc deficiency and an increased risk of anxiety and depression may be related to the stress reaction observed in zinc-deprived animals (18).

Methodological considerations

Most of the research linking zinc to child development has not addressed the possibility of interactions with other micronutrient deficiencies (25,49). Animal products, a primary source of zinc, are also important sources of iron and vitamin B-12, which suggests that children who are zinc deficient are also likely to be deficient in iron and vitamin B-12. All three micronutrients have been associated with deficits in cognitive functioning (25), which highlights the need for studies that address comorbidity and the interrelationships among micronutrients.

Mechanisms

It is not clear exactly how zinc may influence cognitive and motor functioning. In the central nervous system, zinc is concentrated in the synaptic vesicles of specific glutaminergic neurons, which are found primarily in the forebrain and

connect with other cerebral cortices and limbic structures (50). During synaptic events, zinc is released and passes into post-synaptic neurons, serving as a neurotransmitter. Because zinc binds with proteins and is considered to be essential for nucleic acid and protein synthesis (50), zinc deficiency may interfere with these processes and compromise subsequent development.

Zinc deficiency may be particularly relevant to early development because it plays fundamental roles in cell division and maturation, and in the growth and function of many organ systems, including the neurological system (1,2,50). In addition, there is suggestive evidence from animal models (18) and psychiatric patients (47,48) that zinc deficiency may affect emotionality and response to stress, factors that may influence infant development.

Zinc deficiency may also influence children's development by altering a child's ability to elicit or use nurturant interactions from caregivers. For example, a zinc-deficient child who may be inactive or overly responsive to stress may not be able to use the environmental enrichment that promotes early development. The process in which the impact of nutritional deficiencies on development is mediated through the caregiving system is known as functional isolation and was described initially in animals (51). Functional isolation may operate together with neural processing changes related to zinc deficiency to interfere with optimal development. Although initial findings provide some convincing evidence linking zinc deficiency to compromises in activity and motor development, additional research is needed to examine the impact of the timing and severity of zinc deficiency, its reversibility and its long-term consequences, along with the mediating role of the caregiving system.

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