

Effect of zinc supplementation of pregnant women on the mental and psychomotor development of their children at 5 y of age¹⁻³

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ABSTRACT

Background: A negative effect of prenatal zinc deficiency on brain function has been well established in experimental animals, but this association in humans is controversial.

Objective: We evaluated the effect of prenatal zinc supplementation on the mental and psychomotor development of 355 children whose mothers participated in a double-blind trial of zinc supplementation that resulted in increased head circumference and birth weight.

Design: The children took 6 tests—the Differential Ability Scales, Visual Sequential Memory, Auditory Sequential Memory, Knox Cube, Gross Motor Scale, and Grooved Pegboard tests—at a mean age of 5.3 y. The scores were compared between the children of women who received a daily oral dose of 25 mg Zn during the second half of pregnancy and the children of women who received placebo.

Results: There were no differences in the test scores of neurologic development between the 2 groups. We analyzed the scores in 4 subgroups on the basis of maternal body mass index, because the increases in birth weight and head circumference due to the supplementation occurred only in the children of women with a body mass index (in kg/m²) < 26.0 in the original trial. No differences in the scores were found between these subgroups.

Conclusions: Zinc supplementation of women in the latter half of pregnancy had no effect on the neurologic development of their children at age 5 y. It is not known whether our findings of no positive effect in the population with apparently inadequate zinc nutriture can be readily extrapolated to other populations. *Am J Clin Nutr* 2003;77:1512-6.

KEY WORDS Mental and psychomotor development, prenatal zinc supplementation, fetal zinc nutriture, head circumference, birth weight

INTRODUCTION

Zinc is known to be essential for the normal growth and development of the fetus. A deficiency of this nutrient in pregnant animals has been shown to result in malformations and abnormal development and functioning of the central nervous system of the offspring (1-4). Many investigators have evaluated the association between fetal zinc nutriture and brain development in early life and established a negative effect of prenatal zinc deficiency on the brain function of experimental animals. Adverse consequences include reduced activity and responsiveness; impaired learning ability, attention, and memory; and increased aggressiveness.

Several possible mechanisms for this association have been proposed (5, 6). During the past decade, many trials were performed to evaluate the effect of postnatal zinc supplementation on mental and psychomotor development during infancy and childhood; however, these investigations provided conflicting results (7-15). Studies on the relation between prenatal zinc nutriture and brain development in fetuses, infants, or children are extremely scarce (16-18).

We showed, in a double-blind clinical trial, that daily oral supplementation with 25 mg Zn during the second half of pregnancy resulted in a significantly increased birth weight in the infants of a population of African American women of low socioeconomic status (SES) who had low plasma zinc concentrations (19). We also observed a significantly greater head circumference in neonates born to women who received zinc supplementation than in neonates born to those who did not, and we thought that this finding could be reflective of increased brain size. On the basis of that finding, we hypothesized that the larger head size and possibly enhanced brain growth associated with prenatal zinc supplementation would lead to better mental and psychomotor development of children at a later age. We tested this hypothesis by evaluating the effect of prenatal zinc supplementation on the mental and psychomotor development of children at age 5 y. Furthermore, in the original study, the selection of women who had low plasma zinc concentrations at the first prenatal visit resulted in a high mean prepregnancy body mass index (BMI; in kg/m²) of 28.0. We evaluated the effect of zinc supplementation by dividing our population into 2 subgroups according to maternal BMI. The supplementation resulted in a significant increase in birth weight (248 g) and head circumference (0.7 cm) in newborns of women with a BMI < 26.0, whereas the effect was not significant in newborns of women with a BMI ≥ 26.0 (19). Therefore, we analyzed the effect of zinc supplementation on developmental test scores in these 4 subgroups.

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TABLE 1

Selected characteristics of mothers and children in the zinc and placebo groups

	Zinc group (n = 173)	Placebo group (n = 182)
Mothers		
Age at follow-up (y)	29.1 ± 5.7 ¹	28.3 ± 5.8
Multiparous (%)	57.0	56.6
BMI (kg/m ²)	28.7 ± 7.8	27.8 ± 6.8
Smokers (%)	6.4	5.5
Alcohol or drug users (%)	12.7	13.7
No. of prenatal care visits	11.3 ± 2.6	10.8 ± 2.6
Wide Range Achievement Test score	43.9 ± 7.0	43.6 ± 8.3
Peabody Picture Vocabulary Test score	73.2 ± 12.1	73.1 ± 11.7
Home Screening Questionnaire score	36.9 ± 7.0	37.8 ± 6.7
Children at birth		
Gestational age (wk)	39.1 ± 2.3	38.4 ± 2.9 ²
Birth weight (g)	3267 ± 592	3117 ± 666 ³
Head circumference (cm)	34.2 ± 1.9	33.7 ± 2.2
Children at follow-up		
Age (y)	5.3 ± 0.3	5.3 ± 0.3
Weight (kg)	21.8 ± 11.7	21.8 ± 8.8
Height (cm)	112 ± 7	112 ± 6
Head circumference (cm)	51.1 ± 4.0	51.2 ± 3.1

¹ $\bar{x} \pm SD$.^{2,3}Significantly different from the zinc group: ² $P > 0.01$, ³ $P > 0.03$.

SUBJECTS AND METHODS

Subjects

The mothers of the children evaluated in this study were selected from 580 participants in a double-blind trial carried out between 1990 and 1993 to evaluate the effect of prenatal zinc supplementation on fetal growth in the Birmingham area (19). These women were originally selected because their plasma zinc concentrations at the first prenatal visit were below the established median for gestational age in a population from which >3700 pregnant women were screened (20). After a computer-generated random number assignment, 294 pregnant women received a daily oral dose of 25 mg Zn as zinc sulfate (zinc group) and the remaining 286 received placebo (placebo group) starting at ≈ 19 wk of gestation. Zinc supplementation resulted in a significantly greater birth weight (126 g increase) and head circumference (0.4 cm increase) among the infants of the women in the zinc group than were seen among the infants of the women in the placebo group (19). All mothers were African Americans who received their prenatal care through the local public health system and were eligible for the Women, Infants, and Children supplemental program. Of this population, <5% breastfed their infants. All mother-child pairs in which the mothers agreed to their participation in the present study were included in the evaluation. However, because of an inability to locate some families and constraints on resources, a total of 355 children (178 girls) participated in the evaluation of mental and psychomotor development at a mean age of 5.3 y. We aimed at detecting 5-point differences in various tests with a power of 80% ($P < 0.05$). The study was reviewed and approved annually by the Institutional Review Board of the University of Alabama at Birmingham.

Mental and psychomotor tests

Mother-child pairs took the tests at a mean time of 5.3 y after delivery. Mothers completed the Home Screening Questionnaire,

the Wide Range Achievement Test, and the Peabody Picture Vocabulary Test for evaluations of their cognitive functions (21–23). At the same time, children were given tests including the Differential Ability Scales [nonverbal, verbal, and general conceptual ability (intelligence quotient, IQ)], Visual Sequential Memory, Auditory Sequential Memory, Knox Cube, Gross Motor Scale, and Grooved Pegboard (dominant and nondominant hands) tests (24–28). Comprehensive reviews of these tests have been published (29–31). In short, the Differential Ability Scales is a standardized test of intelligence to assess cognitive abilities. The tests of visual or auditory sequential memory are designed to assess visual or auditory memory span. The Knox Cube test is an index of attention span and short-term memory. The Gross Motor Scale evaluates the development of gross motor function, and the Grooved Pegboard test assesses manipulative dexterity. In selecting these tests for the present investigation, we considered the following issues: 1) tests were standardized for the age group of our subjects and had adequate reliability; 2) validity for assessing the construct of interest was a requirement; 3) instruments were used that included a representative number of lower-SES, African American children or statistical weighting of norms to be equivalent to a representative US population; 4) the attention and time limitations were considered appropriate for 5-y-old children and their mothers or caretakers; 5) the tests had the ability to detect subtle deficits in learning, behavior, or coordination in addition to major disabilities; and 6) the tests provided multiple approaches to testing. Evaluators with extensive training in the methodology administered these tests, and they did not have knowledge of the zinc supplementation of the mothers or of the neonatal conditions, including birth weight, of the children.

Statistical analysis

Data are presented as means \pm SDs when appropriate. The differences in the test scores between the zinc and placebo groups and among the 4 subgroups based on maternal BMI with a cutoff of 26.0 (19) were evaluated with the use of Student's *t* test with Bonferroni's correction where appropriate. Furthermore, the test scores were compared after adjustment for factors that could influence test results using linear regression analyses, which included the child's birth weight, gestational age at birth, and sex and the mother's age, BMI, smoking status, alcohol and illicit drugs use, and scores on the Peabody Picture Vocabulary Test and the Home Screening Questionnaire. The interactions between zinc supplementation and maternal BMI were analyzed with the use of two-factor analysis of variance.

RESULTS

The comparison between the zinc and placebo groups for selected characteristics of mothers and children (at birth and at follow-up 5.3 \pm 0.3 y later) is shown in **Table 1**. There were no significant differences in various characteristics of mothers and children between the groups except that gestational age at birth, birth weight, and head circumference were significantly higher in the children in the zinc group than in those in the placebo group. This observation was consistent with the findings in the original population, and it indicates that the mother-child pairs selected for the present investigation reasonably represented the original 580 pairs (19). Other anthropometric measurements of

TABLE 2
Child developmental test scores in the zinc and placebo groups¹

	Zinc group (n = 173)	Placebo group (n = 182)
Differential Ability Scales score		
Nonverbal ability	86.2 ± 16.5	88.6 ± 15.1
Verbal ability	80.0 ± 11.0	80.3 ± 10.7
General conceptual ability, IQ	81.5 ± 13.8	82.6 ± 11.4
Visual Sequential Memory score	33.7 ± 7.0	34.5 ± 6.8
Auditory Sequential Memory score	36.8 ± 6.2	36.2 ± 5.8
Knox Cube score	5.0 ± 1.5	4.9 ± 1.3
Gross Motor Scale score	331 ± 16	333 ± 10
Grooved Pegboard score		
Dominant hand	98.0 ± 14.8	95.5 ± 21.0
Nondominant hand	94.8 ± 16.8	93.6 ± 20.7

¹ $\bar{x} \pm SD$. IQ, intelligence quotient. There were no significant differences between groups.

children at follow-up did not differ significantly between the groups (data not shown). For the 2 groups combined, the mean maternal age was 28.7 ± 5.8 y, and mothers delivered singleton infants at a gestational age of 38.7 ± 2.7 wk with a mean birth weight of 3190 ± 635 g. The mean scores on the Home Screening Questionnaire (37.4 ± 6.9), Wide Range Achievement Test (43.8 ± 7.7), and Peabody Picture Vocabulary Test (73.1 ± 11.9) were similar to those of inner-city populations with low SES (32).

Comparison of the scores on various tests of mental and psychomotor development between the children of the zinc and placebo groups at follow-up is shown in **Table 2**. There were no significant differences between the 2 groups, and there was no trend suggestive of any effect of zinc supplementation.

In the original trial, the increases in birth weight and head circumference associated with zinc supplementation were significant only in newborns of mothers with a BMI < 26.0 (19). Therefore, each group was divided into 2 subgroups according to maternal BMI for evaluation of whether the effects of zinc supplementation on the mental and psychomotor development of children differed with maternal BMI. The characteristics of mothers and children in these 4 subgroups are shown in **Table 3**. There were no significant differences in the characteristics of mothers in both BMI categories and their children (at birth and follow-up) between the zinc and

placebo groups. When the characteristics were compared between the 2 BMI categories (zinc and placebo groups combined), mothers with higher BMI were significantly ($P < 0.0001$) older (29.8 ± 5.9 y compared with 27.3 ± 5.3 y) and were significantly ($P < 0.005$) more likely to be multiparous (63% compared with 48%) than were mothers with a lower BMI. The mean height at follow-up of the children whose mothers had a higher BMI was significantly ($P = 0.002$) greater than that of the children whose mothers had a lower BMI (112.7 ± 5.7 compared with 110.6 ± 6.8 cm).

As is shown in **Table 4**, in both maternal BMI groups, test scores did not differ significantly among children whose mothers received zinc or placebo. Furthermore, after adjustment for other factors known to affect cognitive scores, including the infant's sex, birth weight, and gestational age at birth, the mother's score on the Peabody Picture Vocabulary Test, and the presence of child care, a linear regression analysis indicated that none of the differences persisted between the zinc and placebo groups regardless of maternal BMI. These findings indicate that there was essentially no effect of daily oral zinc supplementation during pregnancy on the mental and psychomotor development of children evaluated at follow-up. All of the variables in Tables 3 and 4 were analyzed with the use of the two-factor analysis of variance with interaction, and we found that the variables of interest including general conceptual ability (IQ) and the Knox Cube test score had significant interaction terms between zinc supplementation and BMI ($P = 0.029$ and 0.044, respectively).

DISCUSSION

In a double-blind clinical trial to evaluate the effect on fetal growth of zinc supplementation during the second half of pregnancy, we found that supplementation resulted in a significant increase in head circumference and birth weight in the newborns (19). The positive response to the supplementation by the women, who were all African Americans with low SES living in the Birmingham area, led us to believe that in general they had suboptimal zinc nutriture (19, 20). We postulated that the increased head circumference of their newborns reflected better prenatal brain growth and would result in better mental and psychomotor development of their children later in childhood. To test this hypothesis, we evaluated the mental and psychomotor development of the children when they were ≈5 y old. Contrary to our expectation,

TABLE 3
Selected characteristics of mothers and children in the zinc and placebo groups subdivided by maternal BMI¹

	BMI ≥ 26.0		BMI < 26	
	Zinc group (n = 95)	Placebo group (n = 94)	Zinc group (n = 75)	Placebo group (n = 83)
Mothers				
Age at follow-up (y)	29.7 ± 5.7 ²	29.9 ± 6.1	28.4 ± 5.7	26.3 ± 4.8
Multiparous (%)	61.1	64.9	51.4	44.6
BMI (kg/m ²)	33.7 ± 7.1	32.7 ± 5.6	22.5 ± 1.9	22.3 ± 2.5
Children at birth				
Gestational age (wk)	39.0 ± 2.8	38.5 ± 3.0	39.2 ± 1.5	38.4 ± 2.5
Birth weight (g)	3250 ± 676	3173 ± 699	3290 ± 480	3075 ± 607
Head circumference (cm)	34.2 ± 2.2	34.0 ± 2.3	34.2 ± 1.5	33.4 ± 2.1
Children at follow-up				
Age (y)	5.3 ± 0.3	5.3 ± 0.4	5.3 ± 0.3	5.3 ± 0.2
Height (cm)	112.9 ± 6.4	112.6 ± 5.0	110.7 ± 6.5	110.5 ± 7.1
Weight (kg)	21.8 ± 4.7	22.1 ± 5.7	21.8 ± 16.9	21.6 ± 11.6
Head circumference (cm)	51.2 ± 3.7	51.4 ± 3.5	50.9 ± 4.5	51.0 ± 2.6

¹There were no significant main effects or interactions.

² $\bar{x} \pm SD$.

TABLE 4

Mental and psychomotor test scores of mothers and children in the zinc and placebo groups subdivided by maternal BMI¹

	BMI ≥ 26.0		BMI < 26	
	Zinc group (n = 95)	Placebo group (n = 94)	Zinc group (n = 75)	Placebo group (n = 83)
Mothers				
Wide Range Achievement Test score	43.4 ± 7.4	43.1 ± 8.5	44.6 ± 6.3	44.0 ± 8.3
Peabody Picture Vocabulary Test score	74.6 ± 13.4	73.2 ± 12.6	71.7 ± 10.5	72.8 ± 10.9
Home Screening Questionnaire score	36.5 ± 7.6	38.0 ± 7.1	37.3 ± 6.3	37.6 ± 6.3
Children				
Differential Ability Scales score				
Nonverbal ability	82.8 ± 15.9	87.5 ± 14.9	90.2 ± 16.6	89.9 ± 15.7
Verbal ability	78.4 ± 10.8	80.8 ± 11.2	81.8 ± 10.9	79.7 ± 10.4
General conceptual ability, IQ ²	78.2 ± 13.3	82.1 ± 11.8	85.4 ± 13.6	83.3 ± 11.3
Visual Sequential Memory score	32.8 ± 7.0	34.7 ± 7.1	35.0 ± 6.8	34.6 ± 6.4
Auditory Sequential Memory score	36.0 ± 6.9	36.1 ± 5.2	37.7 ± 5.1	36.3 ± 6.5
Knox Cube score ²	4.8 ± 1.5	5.0 ± 1.3	5.3 ± 1.4	4.9 ± 1.2
Gross Motor Scale score	331 ± 14	332 ± 12	332 ± 18	335 ± 5
Grooved Pegboard score				
Dominant hand	97.9 ± 14.8	94.3 ± 23.9	98.1 ± 15.0	96.5 ± 17.8
Nondominant hand	93.6 ± 17.8	92.1 ± 23.6	96.2 ± 16.0	95.5 ± 17.4

¹ $\bar{x} \pm SD$. There were no significant main effects of zinc supplementation or BMI for any test.²Significant interactions between zinc supplementation and BMI for general conceptual ability (IQ, intelligence quotient) and Knox cube ($P = 0.029$ and 0.044 , respectively).


however, prenatal zinc supplementation did not have a positive effect on the mental and psychomotor development of these children (Table 2), whose overall cognitive performance was, on average, 1 SD below national norms. Thus, the null hypothesis was not rejected.

We observed that the increases in birth weight and head circumference secondary to zinc supplementation were more pronounced in newborns of mothers with a BMI < 26.0 in the original trial (19). Therefore, we further analyzed the test scores on the basis of maternal BMI to evaluate whether the effects of the supplementation on the mental and psychomotor development of children were limited to children born to mothers with a BMI < 26.0 (Table 4). The overall findings were, however, similar to those found in the 2 subgroups combined, regardless of maternal BMI (Table 2). Therefore, it is likely that the increase in head circumference, 0.3 mm in the present population (Table 1), seen in the infants born to mothers who received zinc did not result in an advantage in mental and psychomotor development in later life.

It has been well established in experimental animals that prenatal and postnatal zinc deficiency leads to malformation and abnormal development and functioning of the brain (1–3, 5, 6). However, human studies to evaluate the effect of postnatal zinc supplementation on the mental and psychomotor development during infancy and childhood provided conflicting results among populations presumably having inadequate zinc nutrition (4, 7–15). Furthermore, to our knowledge, only 2 studies of the association between zinc nutrition during pregnancy and cognitive and motor development appear in the literature (16, 17). In 1994, Kirksey et al (16) reported the positive relation of the intake of estimated available dietary zinc during pregnancy to neonatal behavior and the motor development at 6 mo of age in ≈30 Egyptian mother-infant pairs. In 1998, Merialdi et al (17) evaluated the effect of 15 mg of zinc supplementation during pregnancy on the neurobehavioral development of the fetuses of 55 Peruvian women. They electronically monitored fetal heart rate and movement patterns at ≈36 wk of gestation and found that zinc supplementation led to fewer episodes of

minimal fetal heart rate variability and to increases in fetal movement (17). The findings of these studies suggest a positive association between prenatal zinc nutrition and early brain development. However, it may be problematic to compare our findings and those of these earlier reports involving physiologic and early motor development (16, 17), because our findings in a population with inadequate zinc nutrition were focused on more global indicators of children's competence in later life. In contrast to these earlier 2 studies, Hamadani et al (18) recently reported as part of a large-scale Bangladeshi study that maternal zinc supplementation (30 mg/d) during pregnancy had no positive effect on the mental and psychomotor development of 13-mo-old Bangladeshi infants. Their original study was performed to evaluate growth and morbidity in infants born to mothers with generally poor nutritional status. The findings by Hamadani et al (18) are consistent with ours; however, we evaluated the children at age 5 y and they did so at age 13 mo, and it is known that evaluation at 5 y correlates better with longer-term mental development of children than does that at 13 mo. It is not clear, however, whether there is a longer-term effect of inadequate prenatal zinc nutrition on mental and behavioral outcome of these subjects in adult life, and that question is worth investigating.

Low SES is known to influence the mental and cognitive development of children. In the present study, however, our comparison of developmental status scores between the zinc and placebo groups is not confounded by SES, because all participants had low SES. Furthermore, the overall assessment of the developmental outcomes did not change after regression analyses adjusting for maternal SES. One possible explanation for the failure of prenatal zinc supplementation to improve the test scores at age 5 y is that our population of children was so educationally neglected that any positive prenatal effect was overwhelmed. The overall mean IQ of 82 in these children may support this possibility, as do the low scores related to the Home Screening Questionnaire. Therefore, our findings may be limited and may preclude generalization to populations with higher SES.

In summary, we found no effect of prenatal zinc supplementation during the second half of pregnancy on the mental and psychomotor development of children aged ≈ 5 y. Our findings are not consistent with the well-established negative effects of prenatal zinc deficiency on the biochemistry and function of the brain of experimental animals (5, 6). It was disappointing for us not to identify a positive effect in our population of children whose mothers had apparently inadequate zinc nutrition, despite the earlier reported benefit of an increase in head circumference and birth weight in response to zinc supplementation (18). It may be that the long-term positive effect of prenatal zinc supplementation on neurologic development, if any, was obscured by extremely poor environmental influences on this group of children. Therefore, we are not certain whether our findings can be readily extrapolated to other populations. 

TT designed the study and wrote the manuscript; RLG (principal investigator) designed the study and interpreted the data; SLR (principal investigator) and KGN were responsible for conducting the mental and psychomotor tests; and VRC was responsible for statistical analyses. None of the authors had any financial interest or conflict of interest with the study.

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