PEDIATRICS

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Pediatrics 2004;113;1297-1305
DOI: 10.1542/peds.113.5.1297

Cognitive and Motor Development Among Small-for-Gestational-Age Infants: Impact of Zinc Supplementation, Birth Weight, and Caregiving Practices

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ABSTRACT. ***Objective.*** **Infants who are born small for gestational age (SGA) are at risk for developmental delays, which may be related to deficiencies in zinc, an essential trace metal, or to deficiencies in their ability to elicit caregiver responsiveness (functional isolation hypothesis). The objective of this study was to evaluate at 6 and 10 months of age the impact of a 9-month supplementation trial of 5 mg of zinc on the development and behavior of infants who were born SGA and to evaluate infants' ability to elicit responsive caregiver behavior.**

Methods. **A randomized, controlled trial of zinc supplementation was conducted among 200 infants in a low-income, urban community in Delhi, India. Infants were recruited when they were full term (>36 weeks) and SGA (birth weight <10th percentile weight-for-gestational age). Infants were randomized to receive daily supplements of a micronutrient mix (folate, iron, calcium, phosphorus, and riboflavin) with or without 5 mg of zinc sulfate. The supplement was administered by field workers daily from 30 days to 9 months of age. At 6 and 10 months, infant development and behavior were measured in a clinical setting using the Bayley Scales of Infant Development II. Caregiver responsiveness, observed on an Indian version of the Home Observation for Measurement of the Environment scale, was measured during a home visit at 10 months. During both the clinic and home visits, caregivers reported on their infant's temperament.**

Results. **There were no direct effects of zinc supplementation on the infants' development or behavior at either 6 or 10 months. In a subgroup analysis among the zinc-supplemented infants, lower birth weight infants were perceived to be more temperamentally difficult than higher weight infants; in the control group, birth weight was not associated with temperament. Heavier birth weight infants had better scores on all measures of development and behavior at 6 months and on changes in mental and motor development from 6 to 10 months, compared with lighter birth weight infants. Boys had better weight gain and higher scores on mental development and emotional regulation than girls. Infants who were from families of higher socioeconomic status (indexed by parental education, house size, and home ownership) had higher scores on mental development and orientation/engagement (exploratory behavior) than infants who were from families of lower socioeconomic status. In keeping with the functional isolation hypothesis, caregiver responsiveness was associated with infant irritability, controlling for socioeconomic status, gender, birth weight, and weight gain. Responsive mothers were more likely to perceive their infants to be temperamentally easy than less responsive mothers.**

Conclusion. **Possible explanations for the lack of effects of zinc supplementation on infant development and behavior include 1) subtle effects of zinc supplementation that may not have been detected by the Bayley Scales, 2) interference with other nutritional deficiencies, or 3) no impact of zinc deficiency on infants' development and behavior. The link between birth weight and irritability among infants in the zinc supplementation group suggests that the response to zinc supplementation may differ by birth weight, with irritability occurring among the most vulnerable infants. Longer term follow-up studies among zinc-supplemented infants are needed to examine whether early supplementation leads to developmental or behavioral changes that have an impact on school-age performance. The relationship between infant irritability and low maternal responsiveness lends support to the functional isolation hypothesis and the importance of asking caregivers about infant temperament.** ***Pediatrics*** **2004;113:1297–1305;** ***zinc deficiency, cognitive development, mental development, motor development, behavior, temperament, maternal responsiveness.***

ABBREVIATIONS. SGA, small for gestational age; BSID II, Bayley Scales of Infant Development II; HOME, Home Observation for Measurement of the Environment.

Cognitive and motor development during infancy form the basis for children's subsequent development and are influenced by both biological and environmental factors.[1] Infants who experience nutritional deficiencies in utero and are born small for gestational age (SGA) are at risk for cognitive deficits that can undermine their academic performance during school age,[2–4] adolescence,[5,6] and adulthood.[7,8] There has been little attention to mechanisms that may affect early cognitive and motor development among SGA children. Infants who are born SGA may be more vulnerable to nutritional deficits than infants who are born with birth weight

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Received for publication Feb 12, 2003; accepted Oct 20, 2003.

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appropriate for gestational age and may have specific micronutrient deficiencies that interfere with their development.[9–11] With a small liver and thus very limited hepatic stores of zinc[12] and increased requirements for catch-up growth, they are at risk for zinc deficiency.

Zinc supplementation trials among nutritionally deficient infants have demonstrated beneficial effects on mortality[13] and on health indicators, including growth,[14] diarrhea,[15] and pneumonia morbidity.[16] Zinc deficiency may be particularly relevant to early development because it is an essential trace element that plays fundamental roles in cell division and maturation and in the growth and function of many organ systems, including the neurologic system.[17,18]

Investigations of zinc supplementation on infants' development and behavior have yielded inconsistent findings.[19] In trials among nutritionally deprived infants and toddlers, zinc supplementation has been associated with vigorous play activity among Indian infants,[20] functional activity among Guatemalan toddlers,[21] motor development among Canadian infants born at <1500 g,[22] motor quality among Chilean infants,[23] and cooperative behavior during testing among Brazilian infants.[24] Zinc supplementation during pregnancy has been associated with increased fetal activity.[25] In contrast, other trials have found no differences or negative findings related to zinc supplementation during infancy or pregnancy on measures of motor[23,24,26,27] or cognitive performance during infancy[22–24,26,27] or at age 5.[28]

The functional isolation hypothesis provides an alternative explanation for developmental delays among nutritionally deprived infants.[29,30] Nutritionally deficient infants, who are smaller and less active than better nourished infants, may be less able to elicit age-appropriate expectations from their caregivers.[31–34] Caregivers who perceive their nutritionally deficient infants to be temperamentally difficult may limit their responsiveness and opportunities for enrichment.

This investigation was designed to test whether zinc deficiency and functional isolation are explanatory factors in the association between birth weight and early cognitive and motor development. To increase the likelihood of zinc deficiency, we recruited infants who were born SGA in a very-low-income community in India where rates of fetal malnutrition are high and most community members are vegetarian and consume few sources of bioavailable zinc.[35] We examined whether the effects of zinc supplementation were greater among the most vulnerable infants—those born with birth weight <2500 g or ponderal index (weight in g/length in cm^3) <2.5. We also examined whether caregiver responsiveness varied by maternal perceptions of infant temperament. We reasoned that mothers would be more responsive to infants who were perceived as easy, rather than infants who were perceived as irritable. We examined whether zinc supplementation modified this relationship by altering maternal perceptions of temperament.

METHODS

This study was conducted in Sangam Vihar, a very-low-income, resettlement community in New Delhi, India.[13] The community had no paved streets, electricity, household water or sewerage, and few health services. The infant mortality was 83 per 1000. Approximately 14% of the deliveries were preterm, and 42% of birth weights were <2500 g.[13] More than two thirds of the women were illiterate. Most infants were born at home (72%) and were breastfed exclusively for the first several months of life.

Detailed methods have been published previously[13] and are summarized. Pregnant women were identified as part of a household survey. After delivery, a team composed of a physician, a nutritionist, and a field assistant visited the home and recorded the infant's weight, length, and head circumference and conducted an examination to determine gestational age. Weight was measured to 10 g using an electronic scale (SECA Corporation, Columbia, MD), and the Capurro method was used to determine gestational age.[36] Infants were eligible for enrollment when their gestational age was >36 weeks; their birth weight was below the 10th percentile for gestational age[37]; and they had no congenital problems, disabilities, or severe illnesses.

The eligible neonates were permanent residents of the community. They were randomly allocated to 1 of 4 supplement groups: 1) a micronutrient mix including riboflavin (0.5 mg/day), calcium (180 mg/day), phosphorus (90 mg/day), folate (60 μmol/day), and iron (10 mg/day) with 5 mg of zinc sulfate; 2) the same micronutrient mix without zinc; 3) riboflavin; and 4) riboflavin with 5 mg of zinc sulfate. The supplements were provided by Research Laboratories (Gurgaon, India). The micronutrient preparations were identical in taste, consistency, appearance, and acceptability. Field workers visited the homes daily (6 days a week) and administered the supplement directly to the infants. On holidays (Sundays) and when infants were not available, the supplement was given to the mother with instructions to give it to the infant. The supplement was given from 30 days through 9 months of age. There were no adverse effects associated with the supplement. The randomization procedure was designed to ensure that no members of the field or evaluation teams were aware of group assignment.

The randomization charts were designed to select 200 infants (100 each from groups 1 and 2) for the developmental substudy. Allowing for attrition, a sample size of at least 64 children per group and power of 0.80 would enable us to detect a difference of 0.5 standard deviations (a moderate effect size) between groups. The 200 infants in the developmental substudy did not differ from the overall sample in birth weight, gestational age, or socioeconomic status. The study was approved by the Institutional Review Boards of the University of Maryland School of Medicine, Johns Hopkins University Bloomberg School of Public Health, Annamalai University, and the Society for Essential Health Action and Training (a nongovernmental organization in Delhi, India).

Growth

The infants' growth was measured at 6 and 9 months of age, when supplementation ended. Infants were weighed and measured using systematic procedures and were examined by a physician. Children were weighed unclothed to the nearest 100 g. Recumbent length was measured to the nearest 0.1 cm by placing the child in a supine position on a length board with shoes removed. Measurements were compared with age- and gender-specific standards from the National Center for Health Statistics and converted into *z* scores for comparison.[38]

Infant Development

A developmental clinic was established in the study community and staffed by 3 child development specialists, who had either a doctorate degree in psychology or a master's degree in child development. The examiners were not aware of the infants' supplementation status, anthropometry, or home environment. Children were transported to the clinic for evaluations.

At 6 and 10 months, mental, motor, and behavioral development were assessed by the Bayley Scales of Infant Development II (BSID II).[39] The BSID II was chosen because it provides an assessment of complex, integrated functioning that is empirically derived, is based on recent findings from infant development, and can be compared across ages or cultures.[40] Reliability was established when all examiners achieved >90% agreement on the mental, psychomotor, and behavior scales from videotaped recordings of the administration of the BSID II. Two examiners were present for each administration of the BSID II—1 to administer and the other to score the test. At the completion of each administration, scores for the mental, motor, and behavior scales were tabulated and discrepancies were resolved.

Using standard procedures, raw scores for the mental and motor scales were converted to the age-normed Mental Development Index and Psychomotor Development Index. These index scores have a population mean of 100 and a standard deviation of 15. For the 3 behavioral scales (orientation/engagement, emotional regulation, and motor quality), raw scores were converted to age-normed percentile scores. Analyses were conducted with both raw scores and standard scores. Findings did not differ. Standard scores based on US norms are reported to facilitate comparability across studies.

Caregiver Perception of Infant Temperament

Caregiver perception of infant temperament was measured by a modified version of the fussy-difficult factor of the Infant Characteristics Questionnaire.[41] The 4-item questionnaire used a 4-point Likert scale to ask caregivers how much their infant cried and how easy or difficult it was to calm their infant, to put their infant to sleep, and to provide daily care (1 = very easy, 4 = very difficult). Identical versions of the scale were administered to caregivers in the developmental clinic and in the home. Because the scales were correlated across the 2 administrations ($r = 0.68$, $P < .001$), with adequate internal consistencies within each site (Cronbach's coefficient $\alpha = .73$ and .79, respectively), the results were averaged to form a single temperament scale with high scores representing high levels of irritability.

Maternal Responsiveness

The quality of the home and maternal responsiveness to the infant were measured using the Home Observation for Measurement of the Environment (HOME) Scale.[42] The HOME is an observation scale that has been used widely in international child development research and has shown a strong relationship between the quality of the home environment and subsequent intellectual development and achievement performance.[43] The scale has been adapted for use in India.[44] Items from 4 subscales (Parental Responsivity, Acceptance of Child, Parental Involvement, and Organization of the Environment), totaling 28 items, were selected to describe the quality of the relationship between the mother and the child. The internal consistency of the scale, defined by Cronbach's coefficient α, was .74. Training and interrater reliability were conducted to ensure agreement on the items. Home observations were conducted when the infants were 10 months of age by trained observers who were unaware of the infants' zinc status, anthropometry, or performance on the developmental assessments.

Socioeconomic Status

Data were gathered using multiple indicators of socioeconomic status. To characterize the socioeconomic level of the families, we constructed a variable that included 1 point for each parent who had attended school, for owning a home, and for having a house with >1 room (range: 0–3).

Analysis Plan

We examined baseline demographic differences between the zinc and no-zinc groups using analysis of variance for continuous variables and χ^2 analysis for categorical variables, and we examined the relationship among predictor and outcome variables using correlations. We adjusted for socioeconomic status and gender, and to account for both prenatal and postnatal growth patterns, we adjusted for birth weight and weight gained since birth. We examined the impact of zinc supplementation on infants' development and behavior, using multiple regression analyses.

We examined whether the impact of zinc supplementation was moderated by birth weight or ponderal index by introducing the interaction term of birth weight (or ponderal index) and zinc status into the regression analyses. Significant interaction terms were plotted to compare differences in the relation between zinc status and the dependent variable by dividing the groups by supplementation status.[45]

To examine whether maternal responsiveness varied by maternal perceptions of infant temperament, we conducted regression analysis using maternal responsiveness as the dependent variable, controlling for birth weight and ponderal index. To examine whether relationships were altered by zinc supplementation, we introduced zinc and 2 interactions (zinc by birth weight and zinc by ponderal index) into the models.

RESULTS

There were no differences between the 2 supplementation groups in birth weight, length, head circumference, ponderal index, gestational age, or socioeconomic measures at baseline (Table 1). Most fathers (72%) had some schooling, but only 27% of the mothers had been to school. Most families (66%) owned their own home, but only 29% lived in a house that included >1 room. Family size ranged from 2 to 10, with a mean of 5, and 37% of the children were first born.

Of the 200 children enrolled, 186 (93%) infants were available at 6 months, 162 (81%) infants were available at 10 months, and 150 (75%) infants were available across 6 and 10 months. Infants who were retained in the sample did not differ from those who were lost to follow-up on birth weight, ponderal index, gestational age, maternal education, or paternal education.

At both 6 and 10 months, all measures of infant development and behavior were correlated with birth weight, and none was correlated with ponderal index (Table 2). At 10 months, several measures of infant behavior and development were positively correlated with socioeconomic status and maternal responsiveness and negatively correlated with maternal perceptions of infant irritability. Infant irritability was negatively correlated with maternal responsiveness ($r = -0.23$, $P = .007$), indicating that mothers of irritable infants were relatively low in responsiveness. At 10 months, boys had higher scores on mental development and emotional regulation than girls.

Weight gain was correlated with birth weight and with socioeconomic status at both measurement points (Table 2). Boys gained more weight than girls at 6 and 9 months, although there were no gender differences in birth weight.

At the 6-month evaluation, there were no differences between the 2 supplementation groups on any of the measures of development or behavior (Table 1). Multiple regression equations were calculated to examine the predictors of development and behavior at 6 months. There were no direct effects of zinc supplementation in any of the models (Table 3). All models were significant as a result of the contribution of birth weight. The interaction between zinc supplementation and either birth weight or ponderal index was not significant in any of the models.

At the 9-month evaluation, there were no differences between the 2 supplementation groups on anthropometry. Stunting (length for age <-2 z scores) occurred in 43.8% of the infants, and wasting (weight for length <-2 z scores) occurred in 14.2% of the infants.

TABLE 1. Demographic, Anthropometric, Developmental, and Behavioral Scores at 6 and 10 Months by Supplementation Group

	Supplementation Group	
	Zinc	No Zinc
Family and infant characteristics at birth		
N	100	100
Maternal education, % school	26	29
Paternal education, % school	75	69
Own house, %	63	69
House >1 room, %	26	31
Sociodemographic index	1.8 ± 1.1	2.0 ± 1.1
Gestational age, wk	39.4 ± 1.2	39.6 ± 1.1
Gender, % male	42	49
Birth weight, g	2390 ± 285	2451 ± 293
Birth length, cm	47.4 ± 2.2	47.5 ± 2.3
Ponderal index	2.3 ± 0.3	2.3 ± 0.3
Infant characteristics at 6 mo		
N	79	71
Age, mo	6.1 ± 0.2	6.1 ± 0.2
Weight gain since birth, kg	3.2 ± 0.8	3.2 ± 0.9
Length gain since birth, cm	14.4 ± 3.0	14.2 ± 2.9
MDI	82.7 ± 8.6	82.0 ± 9.1
PDI	89.6 ± 11.2	87.8 ± 12.3
Orientation/engagement percentile	56.3 ± 23.7	55.8 ± 25.8
Emotional regulation percentile	88.4 ± 16.6	84.4 ± 26.0
Motor quality percentile	87.9 ± 26.9	83.4 ± 32.4
Anthropometry at 9 mo		
Age, mo	8.9 ± 0.7	9.0 ± 0.3
Weight gain since birth, kg	4.1 ± 0.8	4.2 ± 0.9
Length gain since birth, cm	18.7 ± 3.2	18.6 ± 2.6
Length for age, *z* score	−1.8 ± 1.1	−2.0 ± 1.1
Weight for length, *z* score	−1.1 ± 0.9	−0.9 ± 0.9
Infant characteristics at 10 mo		
N	85	77
Age, mo	10.1 ± 0.1	10.1 ± 0.1
MDI	86.2 ± 4.9	86.4 ± 5.1
PDI	91.7 ± 9.8	91.5 ± 14.2
Orientation/engagement percentile	55.4 ± 23.9	55.1 ± 23.1
Emotional regulation percentile	86.2 ± 20.8	87.9 ± 15.9
Motor quality percentile	93.0 ± 17.2	92.0 ± 18.2
Temperament*	0.1 ± 0.7	−0.1 ± 0.6
Maternal responsiveness	22.7 ± 2.3	23.1 ± 2.2

MDI indicates Mental Development Index; PDI, Psychomotor Development Index.
* Low scores optimal.

TABLE 2. Correlations Between Birth Weight, Ponderal Index, Gender, Socioeconomic Status, Caregiver Perceptions of Infant Irritability, and Maternal Responsiveness With Change in Weight and Scores on Measures of Development and Behavior

	Birth Weight	Ponderal Index	Gender*	Socioeconomic Status	Infant Irritability†	Maternal Responsiveness
6 mo						
Weight change	0.19‡	−0.03	−0.27‖	0.20§		
MDI	0.40‖	0.02	−0.07	0.02		
PDI	0.43‖	0.03	−0.05	−0.01		
Orientation/engagement	0.40‖	−0.07	−0.06	−0.03		
Emotional regulation	0.31‖	−0.08	0.02	−0.04		
Motor quality	0.29‖	−0.05	−0.02	0.04		
10 mo						
Weight change	0.20§	−0.04	−0.25‖	0.20‡	−0.03	0.05
MDI	0.27§	0.07	−0.18‡	0.27§	−0.16‡	0.18‡
PDI	0.45‖	−0.03	−0.11	0.14	−0.19‡	0.15‡
Orientation/engagement	0.24§	0.04	−0.14	0.17†	−0.08	0.13
Emotional regulation	0.21§	0.06	−0.18‡	0.10	−0.12	0.11
Motor quality	0.29‖		−0.04	0.12	−0.14	0.12

MDI indicates Mental Development Index; PDI, Psychomotor Development Index.
* Male = 1, female = 2.
† Low scores optimal.
‡ $P < .05$.
§ $P < .01$.
‖ $P < .001$.

At 10 months, there were no supplementation group differences on any of the measures of development or behavior, maternal responsiveness, or infant temperament (Table 1). Multiple regression models were fitted to examine the change on BSID II scales from 6 to 10 months and on temperament at 10

TABLE 3. Unstandardized* Regression Coefficients, Confidence Intervals, Adjusted R^2, and Model Summaries Examining the Effect of Zinc Supplementation on Infant Development and Behavior at 6 Months

	Motor Development				Mental Development				Orientation/ Engagement				Emotional Regulation				Motor Quality			
	B	CI	R^2	*P*	B	CI	R^2	*P*	B	CI	R^2	*P*	B	CI	R^2	*P*	B	CI	R^2	*P*
Zinc	2.94	−0.68 to 6.26			1.11	−1.12 to 4.16			0.18	03.87 to 6.10			4.53	−1.62 to 11.79			6.17	−3.08 to 15.51		
Model summary			.23	.001			.15	.007			.13	.001			.09	.004			.06	.02

CI indicates confidence interval.
* Adjusted for birth weigh, weight gained since birth, gender, and socioeconomic status.

months (Table 4). There were no direct effects of zinc supplementation on any of the measures of development or behavior. Birth weight was a significant predictor of the change in mental and motor development and of temperament at 10 months. Male gender was a significant predictor of mental development and emotional regulation, and socioeconomic status was a significant predictor of orientation/engagement and mental development.

The interaction between birth weight and zinc supplementation was a significant predictor of motor development ($P < .05$) and approached significance in the prediction of temperament ($P = .056$). Four infants had a Psychomotor Development Index <70, indicating significantly delayed performance (3 in the control group and 1 in the zinc group). When children with significantly delayed performance were removed from the analysis, the interaction was no longer significant. Plots and partial correlations were conducted to examine the interaction between birth weight and zinc supplementation in the prediction of infant temperament, controlling for gender, weight gain, and socioeconomic status. In the zinc supplementation group, birth weight was negatively associated with maternal perceptions of infant irritability ($r = -0.46$, $P = .001$); lower birth weight infants were perceived to be more temperamentally difficult than higher birth weight infants. In the control group, there was no association between birth weight and maternal perceptions of infant irritability ($r = -0.13$, $P = .30$).

A multiple regression model was used to evaluate determinants of caregiver responsiveness, observed at 10 months (Table 5). The relationship between infant temperament and caregiver responsiveness was significant, with caregivers demonstrating low levels of responsiveness to infants who were perceived to be temperamentally difficult or irritable. Caregiver responsiveness was positively related to socioeconomic status, indexed by parental education, house size, and home ownership but not to birth weight, weight gain, gender, zinc supplementation, or the interaction between zinc supplementation and birth weight (Table 5).

DISCUSSION

This investigation yielded important information about early development and behavior among infants who were born SGA. There were no direct effects of zinc supplementation on infant development or behavior at either 6 or 10 months. These findings are generally consistent with previous studies reporting no effects of zinc supplementation on cognitive or motor functioning among zinc-deficient infants and toddlers.[22–24,26–28] Although zinc supplementation has been shown to enhance growth,[14] there were no effects of zinc on growth in this sample. Zinc has also been shown to improve infant cooperation[24] and activity,[20,21] but in this sample, there were no effects of zinc on observations of infant behavior during testing.

There are several possible explanations for the lack of direct effects between zinc supplementation and early development and behavior. One possibility is

TABLE 4. Unstandardized Regression Coefficients, CIs, Adjusted R^2, and Model Summary, Examining Predictors of Change in Development and Behavior From 6 to 10 Months and Temperament at 10 Months

Predictor	Mental Development (Regression Coefficient [CI])	Motor Development (Regression Coefficient [CI])	Orientation/Engagement (Regression Coefficient [CI])
Birth weight	1.12 (−1.68 to 4.01)*	9.96 (3.37 to 16.55)*	7.53 (−5.73 to 21.00)
Weight gain	−0.57 (−1.52 to 0.39)	2.00 (−0.27 to 4.27)	1.72 (−2.86 to 6.26)
6-mo score	0.19 (0.03 to 0.21)	0.39 (0.24 to 0.56)*	0.11 (−0.13 to 0.35)
Gender	−2.05 (−3.59 to −0.50)†	−1.60 (−5.22 to 2.07)	−7.08 (−15.01 to 0.70)
Socioeconomic status	1.43 (0.72 to 2.14)*	0.77 (−0.82 to 2.49)	5.16 (1.66 to 8.65)*
Temperament	−0.75 (−2.00 to 0.49)	−1.34 (−4.59 to 1.13)	2.42 (−3.62 to 8.38)
Maternal responsivity	0.60 (−0.28 to 0.39)	0.38 (−0.50 to 1.27)	−0.34 (−2.23 to 1.56)
Zinc	0.18 (−1.32 to 1.69)	1.21 (−2.30 to 4.72)	0.71 (−6.60 to 8.03)
Zinc × birth weight	1.16 (−3.84 to 6.16)	−11.32 (−22.76 to 0.12)*	0.003 (0.02 to 0.03)
Model summary	R^2 = .25, P = .0001	R^2 = .41, P = .0001	R^2 = .15, P = .03
Predictor	**Emotional Regulation (Regression Coefficient [CI])**	**Motor Quality (Regression Coefficient [CI])**	**Temperament (Regression Coefficient [CI])**
Birth weight	2.55 (−3.72 to 8.99)	0.97 (−1.15 to 3.31)	−0.66 (−1.07 to −0.31)*
Weight gain	0.35 (−1.93 to 2.60)	0.44 (−0.35 to 1.23)	0.02 (−0.12 to 0.16)
6-month score	0.11 (0.02 to 0.19)†	0.04 (0.23 to 0.65)†	NA
Gender	−4.69 (−8.49 to −0.99)†	−0.31 (−1.62 to 0.99)	−0.11 (−0.34 to 0.12)
Socioeconomic status	0.91 (−0.79 to 2.61)	0.34 (−0.25 to 0.94)	−0.02 (−0.13 to 0.09)
Temperament	−0.85 (−3.76 to 2.06)	−0.40 (−1.41 to 0.61)	NA
Maternal responsivity	0.19 (−0.72 to 1.11)	−0.10 (−0.43 to 0.22)	−0.08 (−0.13 to −0.03)*
Zinc	0.44 (−3.10 to 3.99)	0.47 (−0.77 to 1.71)	0.15 (−0.07 to 0.37)
Zinc × birth weight	−0.001 (−0.01 to 0.02)	−0.001 (−0.005 to 0.003)	−0.73 (−1.47 to 0.01)‡
Model summary	R^2 = .14, P = .03	R^2 = .20, P = .001	R^2 = .19, P = .001

* $P < .01$.
† $P < .05$.
‡ $P = .056$.

TABLE 5. Unstandardized Regression Coefficients, CIs, Adjusted R^2, and Model Summary, Examining Maternal and Infant Predictors of Maternal Responsiveness

Predictor	Regression Coefficient	CI
Maternal		
Socioeconomic status	0.47	0.11 to 0.82*
Infant		
Birth weight	−1.01	−0.01 to 0.00
Weight gain	0.11	−0.38 to 0.61
Gender	0.14	−0.67 to 0.94
Temperament	−1.00	−1.62 to −0.37†
Zinc	−0.33	−1.10 to 0.44
Model summary	R^2 = .14, P = .003	

* $P < .05$.
† $P < .01$.

that the infants were not zinc deficient. However, zinc deficiency seems likely because we recruited a very vulnerable sample of infants (weight for age <10th percentile based on National Center for Health Statistics norms), and birth weight has been shown to correlate with zinc concentration in India.[46,47] In another investigation involving many of the same infants, zinc supplementation was associated with a reduction in mortality.[13] Another possibility is that the dose did not sufficiently alter the infants' zinc status. We administered 1 recommended dietary allowance of zinc for infants in a micronutrient mixture, along with folate, iron, calcium, phosphorus, and riboflavin. Although controversial, there is some evidence that supplementation with iron and zinc together may interfere with absorption of both minerals.[48] In the absence of reliable methods of measuring zinc status, we cannot be sure that the dose was sufficient. A third possibility is that the BSID II may not have captured the specific processing skills influenced by zinc. Evidence from animal models suggests that zinc deficiency may affect emotionality and response to stress[18,49]—factors that play critical roles in shaping infant responsiveness and development[50] but are not directly assessed by the BSID II. Investigations among school-aged children have demonstrated the beneficial impact of zinc supplementation on 2 neuropsychological processes (attention and reasoning) when time-dependent, challenging tasks were administered.[51,52] The mental scale of the BSID II requires integration of multiple systems, including attention, motivation, and cognitive processing. Most items are not timed, and the infants may use compensatory skills. Although we included the Behavior Rating Scales, subtle changes in attention and reasoning related to zinc supplementation may not have been detected. In the future, it may be useful for investigators to include both specific information-processing tests and general developmental measures to gain a more comprehensive understanding of the possible mechanisms linking micronutrients with infant development and behavior. A fourth possibility is that the infants may have experienced other nutritional deficiencies that interfered with zinc absorption or with early development. The high rate of stunting at 9 months indicates the chronic malnutrition experienced by the infants. Finally, the evidence from this and other trials suggests that zinc deficiency may not be related to early development and behavior.

We also examined whether observations of maternal responsiveness or maternal perceptions of infant temperament varied by zinc supplementation. There were no differences in maternal responsiveness across groups, but contrary to expectations, zinc supplementation was associated with more caregiver-reported irritability among the infants with the lowest birth weights. The association between zinc supplementation and irritability has not been reported previously, and to our knowledge, this is the first zinc supplementation study that included a caregiver questionnaire regarding infant behavior.

Our initial interpretation of this counterintuitive finding was that because rates of SGA are high in this community, mothers may have become accustomed to the lethargic behavior associated with SGA infants[31] and may have interpreted the development skills of their zinc-supplemented infants as indicators of temperamental difficulty. If this interpretation were accurate, then the "temperamentally difficult" infants would have relatively high scores on measures of development and behavior. However, we found the opposite. Infants who were reported to be temperamentally difficult had lower scores on mental and motor development than infants who were reported to be temperamentally easy. In addition, infants who were perceived to be irritable experienced less responsive interactions with their caregivers, regardless of their zinc status. Thus, the mothers' rating of their zinc-supplemented infants as temperamentally difficult or irritable did not seem to be a misinterpretation of the infants' developmental skills.

There is not a clear explanation for why zinc supplementation would alter caregiver perceptions of infant temperament. Many of the infants in this investigation were chronically undernourished and may have experienced other nutritional deficiencies. Infants with iron-deficient anemia have been described as wary and irritable,[32] but little is known about the relation between other micronutrient deficiencies and infant behavior.

Our finding that infant irritability was associated with low developmental performance and mothers' relative lack of responsivity is consistent with theoretical predictions and findings from other investigators.[29,53] Mothers of temperamentally difficult infants were less responsive during the home visit, even after adjusting for socioeconomic status, gender, and weight, thereby lending support to the functional isolation hypothesis. Mothers often react to infant irritability either by withdrawing or by limiting their interactions to caregiving behaviors that are designed to soothe the infant (eg, holding, feeding).[53] Thus, irritable infants may not receive the enriching stimulation that they need to enhance their development. This pattern illustrates the transactional process between infant and maternal behavior that underlies the functional isolation hypothesis.[29,30] Future investigations of early infant development should include measures of infant temperament and irritability and examine their relationship with maternal responsiveness and with infant development and behavior.

There was no relationship between maternal responsiveness and either birth weight or weight gained. Although mothers may be expected to be more responsive to infants who are larger and perhaps could be perceived as more mature or competent, the young age and developmental immaturity of the infants in this sample may have interfered with this relationship. It is likely that as the infants mature, begin to walk, and become more mobile, maternal responsiveness will be more closely tied to infant behavior.

Many of the relationships with infant development and behavior were consistent with general expectations. For example, birth weight had a strong and enduring association with weight gain, with all measures of infant development and behavior at 6 months, and with changes in mental and motor development from 6 to 10 months of age. Heavier birth weight infants gained more weight and were more competent, in comparison with lighter birth weight infants, emphasizing the importance of promoting prenatal growth. Consistent with a long tradition of male preference in India,[54] sons had more weight gain and higher scores on several measures of development and behavior than daughters.

Within this low-income community in India, where most mothers were illiterate, socioeconomic status was an important component of infant growth and development. Infants whose parents were better educated and had more resources had greater weight gain, better mental development, and higher scores on orientation/engagement (indicating more exploratory behavior) than infants from lower socioeconomic group families, perhaps because their mothers were more attentive and responsive. These findings illustrate the importance of promoting parental literacy and access to resources as a means of enhancing early infant development.

Methodologic Limitations

There are several methodologic considerations related to the sample and to the assessment procedures that may influence interpretation of the findings. One concern is that we cannot be sure of the infants' zinc status at 10 months, ~1 month after cessation of the supplementation. The consistency of findings between 6 and 10 months argues against the possibility of any systematic change in zinc status between 2 groups. A previous zinc supplementation trial in a similar community found large increases in plasma zinc among the supplemented group.[55]

An additional concern is that the findings may generalize only to infants who have low birth weight and live in impoverished conditions and not to samples of better nourished infants. Unfortunately, low birth weight is all too common, with rates of 7% in the United States, 22% in low-income countries, and 33% in South Asia.[56] Thus, the findings may be informative to large populations of vulnerable infants who live in poverty throughout the world.

A final concern is the use of assessments that were not developed for the population on which they were used. We used several strategies to handle this concern. We worked with an anthropologist from India to adapt the HOME and temperament scales so that they would be culturally appropriate. The measures were translated into Hindi for training and administration. The temperament scale was administered twice, with correlated results, and the internal consistencies of the maternal responsive scale of the HOME and temperament scales were adequate. In addition, the relationships among other contextual measures, infant development and behavior, and the maternal responsiveness and temperament scales were generally consistent with theoretical expectations. The BSID II was selected because it was designed to measure development and behavior in infants, has been used previously in international research, and was recently revised.[39] In addition, we included local toys in a warm-up play period to help the infants and parents feel at ease with the testing environment.

Clinical Implications

The findings from other investigations linking zinc supplementation to beneficial effects in growth,[14] morbidity,[15,16] and early activity and motor development[21–24] among zinc-deficient infants illustrate the importance of preventing zinc deficiency among infants. Longer term follow-up of early supplementation trials is warranted to examine whether zinc supplementation affects subtle cognitive processes, such as attention and reasoning, that may not be apparent until school age.

The association of zinc supplementation with increased caregiver perceived irritability needs to be investigated further to determine associations with infant development and infants' ability to seek stimulation from caregivers. Infants who are born SGA may benefit from developmentally oriented intervention programs that promote responsive caregiver interactions.

ACKNOWLEDGMENTS

Support was provided by the National Institute of Child Health and Human Development (R01 HD374430), The Gerber Foundation, The Thrasher Foundation, Child Health at Johns Hopkins University, and the Lanata-Piazzon Partnership.

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FATAL CONFLICT OF INTEREST

"A leading medical journal said yesterday it should not have published a controversial 1998 study that claimed a link between childhood vaccinations and autism.

The editor of the *Lancet*, Dr Richard Horton, said Dr Andrew Wakefield and a team of British scientists who conducted the study on the triple measles-mumps-rubella (MMR) vaccine didn't reveal that they were being paid by a legal aid service looking into whether families could sue over the immunizations.

Horton called it a 'fatal conflict of interest.'

Wakefield's study suggested that the MMR vaccine could put children at risk of autism—a developmental disorder often arising in the first few years of life—and inflammatory bowel disease.

The paper has since been discredited on scientific grounds, but some parents have clung to the findings and health officials say that vaccinations have fallen dangerously low since its publication."

IJ News Service. Journal says it was wrong in printing vaccine study. February 22, 2004

Submitted by Student