Effect of zinc supplementation on development and growth of Chilean infants

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Objective: To evaluate the effect of zinc supplementation on growth and development during infancy.

Design: We randomized 150 term neonates of low socioeconomic status to receive supplemental zinc 5 mg/d (SG) or a lactose placebo (PG); 112 completed a 1-year follow-up. All were breast-fed and given cow milk formula after weaning; solid foods and iron were added at 5 months. Anthropometry measured monthly, psychomotor development (PDI), mental development (MDI), and behavior including motor quality factor were assessed by Bayley Scales at 6 and 12 months. The groups were comparable in maternal characteristics, birth weight, home environment, and mother-infant interaction.

Results: No effects of zinc on weight, length, and weight for length at 12 months were found controlling for sex and breast-feeding. The mean PDI (SG: 84.5 ± 11.5 vs PG: 87.6 ± 9.9) and MDI (90.9 ± 10.5 vs 88.9 ± 9.1) were similar; however, 46 of 52 infants in the PG scored <100 in MDI vs 42 of 57 in the SG ($P < .05$). A smaller proportion of the SG, 2 of 57, scored low in motor quality factor at 6 months compared with the PG, 8 of 52 ($P = .02$). The mean at 12 months for the SG was 31.9 ± 2.8 and for the PG 30.8 ± 2.9 ($P < .05$); zinc supplementation entered the multiple regression at 12 months ($P = .037$).

Conclusions: Zinc supplementation may have a beneficial effect on mental development and motor quality behavior of healthy term infants. (J Pediatr 2001;138:229-35)

Malnutrition has declined in Chile during the last 20 years. However, deficiencies of the micronutrients, iron and zinc, still persist.[1,2] These are prevalent in low-income groups and are associated with cow milk-based diets and low intake of flesh foods.

Clinical effects of zinc deficiency in children have been studied around the world; a negative impact on growth and immunity has been noted.[1,3-6] Studies in animals demonstrate effects on psychomotor development, spontaneous locomotor activity, exploration, and working memory.[7,8] Preliminary studies in children suggest effects on motor development and on neuropsychologic performance.[9,10] No controlled studies of zinc supplementation on the neurodevelopment of healthy term infants have been conducted. The aims of this study were to assess the effect of zinc supplementation on neurodevelopment (psychomotor, mental, and behavioral) and growth in infants of low socioeconomic status. We hypothesized that zinc supplementation improves development and growth of infants at risk of zinc deficiency.

ANOVA	Analysis of variance
BRS	Behavior rating scale
MDI	Mental development index
PDI	Psychomotor development index
PG	Placebo group
SG	Supplemented group

SUBJECTS AND METHODS

Infants (n = 150) were selected from those entering well baby care at a national health service clinic in an urban slum in Santiago, Chile. Inclusion criteria were term (≥37 weeks) singleton; birth weight >2300 g (appropriate for gestational age), no evidence of toxoplasmosis, rubella, herpes, cytomegalovirus, or Chagas disease, fetal alcohol syndrome, or congenital malformations that affect growth. Mothers

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had to be literate and without a history of drug abuse. The age range was 18 to 40 years. Infants were randomly assigned to a supplemented group receiving 5 mg zinc per day as sulfate in a single dose or to a placebo group receiving an equivalent dose of lactose in a double-blind fashion before 20 days of age. Codes were kept secret, and solutions were given monthly at the time of the visit. Subjects were monitored monthly until 6 months and then every 2 months until 12 months of age.

All infants received iron (sulfate) drops, 1 to 2 mg/kg/d, after 5 months of age to prevent the confounding effect of iron deficiency based on the link between development and iron deficiency anemia.[2] The iron/zinc ratio of total intake was approximately 1:1 in the SG and 2:1 in the PG. Infants were monitored for anemia at 6 months, and those with hemoglobin <10.5 g/dL were excluded. Reasons for dropping out from the study were recorded.

Compliance with zinc supplement/placebo intake and iron drops was evaluated at weekly home visits by field workers who recorded solution remaining in the bottle, and morbidity was also registered. Infants whose monthly zinc intake was <50% of the prescribed volume were excluded. Anthropometry was recorded monthly; weight was measured with 10 g error in a Seca scale (Seca Corp, Columbia, MD). Length and cranial circumference expressed in centimeters to 1 decimal place were measured with a Harpenden stadiometer (Harpenden, Crymych, UK) and metal tape, respectively. If weight gain was unsatisfactory according to National Center for Health Statistics-World Health Organization growth charts, or if the mother could not breast-feed during the first 5 months, a powder formula based on whole cow milk diluted to 7.5% with 5% sucrose and 1.5% vegetable oil (before 3 months) or 5% sucrose and 3% cereals (after 4 months) (70 kcal/dL) was provided following the Chilean Infant Health Program. Solids including potatoes, vegetables, vegetable oil, and meat or poultry were recommended after 5 months of age. Socioeconomic level was assessed by a modified Graffar scale adapted to Chile.[11] It includes data on family income, housing, marital status, parental schooling, number of beds, sewage and plumbing, access to health and social security status (retirement benefits), and home appliances.

Development was evaluated by a trained psychologist at 6 and 12 months with the Bayley II Scale for infants (second edition, 1993).[12] The scales for mental development index and psychomotor development index are standardized to a mean of 100 ± 15. In addition, this test analyzes qualitative aspects of behavior through the behavior rating scale, which includes the study of attention/arousal factor (only for infants <6 months of age), orientation/engagement, motor quality factor, and emotional regulation factor. The motor quality factor evaluates gross and fine motor movement, control of movement, hypotonicity and hypertonicity, tremulousness, slow and delayed movement, frenetic movement, and hyperactivity through a qualitative score. The emotional regulation factor characterizes the child's activity, adaptability, affect, cooperation, persistence, and tolerance to frustration. Each factor can fall into 1 of 3 descriptive categories: within normal limits (score ranking ≤26th percentile for age), questionable (scores from the 11th to 25th percentiles for age), or nonoptimal (scores ≤10th percentile for age). The psychologist who applied the test was trained until she attained a reliability coefficient >0.85 compared with a certified Chilean psychologist.

At 11 months the mother-infant relationship was analyzed at home, because it may have been a potential confounder or an outcome of the study. It was studied through a videotape of their playing time in the afternoon in 2 settings: a natural and a structured condition. Each one was observed for 6 minutes.[13] An observational guide proposed by Hans and Bernstein[14] was applied that evaluates maternal factors through 20 items (responding to child's needs and wants, sensitivity to child's interest, affection shown to child, and helping child to learn) and child aspects through 16 items (expression of needs and wants, using parent's help, involvement with parent, affection shown to parent, language). Each video was independently analyzed by 2 trained psychologists; differences in scores were discussed until an agreement was reached. Results were categorized as normal, questionable, and at risk. To categorize the mother-infant relationship as at risk, at least half the items had to be altered.

The quality of home stimulation was evaluated by means of the Home Observation for the Measurement of the Environment[15] during a visit by a trained psychologist in the morning. This evaluation was performed when the infant was 10 months old. The mean of the scale is 30.[15]

Hemoglobin was assessed through the cyanmethemoglobin method. A hair sample was obtained from the occipital scalp; hair zinc levels were analyzed by atomic absorption spectrophotometry (Perkin-Elmer-2280, Norwalk, CT).[16]

The study was approved by the Ethics Committee at the Institute of Nutrition and Food Technology. Written informed consent was requested from the mothers of subjects.

Sample size was calculated based on the results of previous studies of iron nutrition and psychomotor development conducted by Walter et al.[2] Considering that a difference of 5 points between the means on the Bayley test are clinically meaningful, assuming a 0.05 level of significance and a power of 0.8, a total of 60 infants per group was needed. Given an expected dropout rate of 20%, a total of 75 infants per group was estimated as a desirable sample size. Data were analyzed with the SAS program (SAS Institute, Cary, NC). Statistical analysis included 1-way analysis of variance, ANOVA for repeated measurements, χ^2 analysis, and *t* test. To evaluate the effect of zinc supplementation on MDI, PDI, and motor quality factor, multiple regression analyses were performed at 6 and 12 months, separately. Changes in MDI, PDI, and behavior items were analyzed with multiple regression, where the dependent variable was the difference between 6 and 12 months. Pearson correlation was calculated on the test-retest for MDI, PDI, and motor quality factor. Weight and length were analyzed as *z* scores of the National Center for Health Statistics standards, with adjustment for real age (in days) when the measurement was performed. Cranial circumference was analyzed by comparing the absolute measurements with the National Center for Health Statistics standards. Frequency distributions of Bayley scores were studied with discriminating cutoff points.

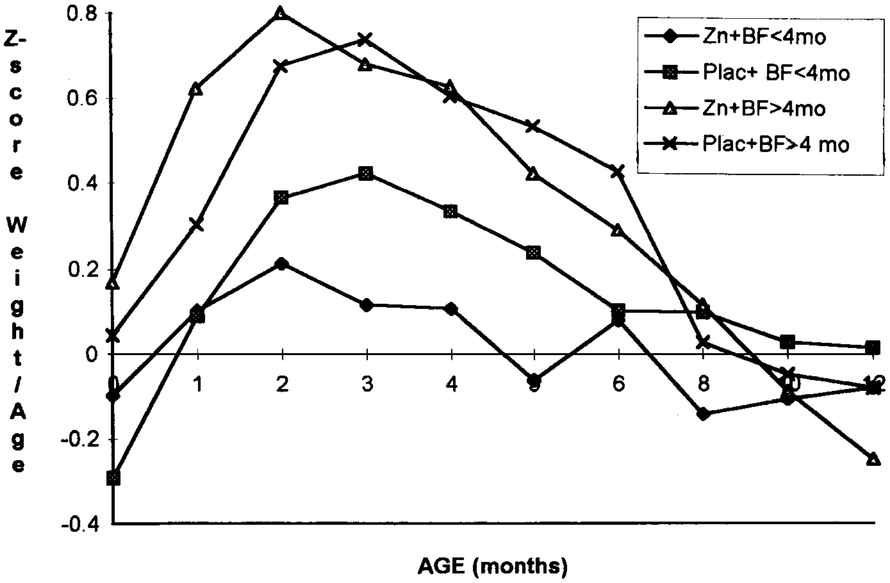

Fig 1. Weight/age *z* score of zinc-supplemented (n = 57) and placebo (n = 55) groups during 12 months of follow-up according to duration of breast-feeding (*BF,* < or >4 months of age). Each point represents mean.

Table I. Characteristics of infants on admission to the study[*]

Characteristic	Zinc-supplemented	Placebo
Sex (M/F)	27/30	30/25
Socioeconomic level (modified Graffar)	34.8 ± 5.8[†]	34.8 ± 4.6
(range)	(24-48)	(25-45)
Maternal schooling (y)	10.2 ± 2.1	9.9 ± 2.1
(range)	(4-12)	(4-12)
Maternal age (y)	26.7 ± 6.1	26.7 ± 5.8
Parity	2.08 ± 0.9	1.80 ± 0.9
Paternal age (y)	28.8 ± 6.3	29.1 ± 7.4
Birth weight (g)	3400 ± 328	3353 ± 365
(range)	(2560-3940)	(2370-4000)
Length at birth (cm)	50.3 ± 1.6	50.3 ± 1.6
(range)	(47.0-54.5)	(45.5-54.0)
Cranial circumference (cm)	34.4 ± 1.2	34.5 ± 1.2
(range)	(30.0-37.0)	(31.5-37.5)

[*] No significant differences were seen between the 2 groups of infants.
[†] Mean ± SD.

RESULTS

After randomization was performed, 18 infants from the SG and 20 from the PG were excluded: 24 because of lack of compliance with the administration of the solution, 5 moved away, 3 were diagnosed with a congenital malformations after admission to the study, 4 were excluded because of anemia at 6 months of age (3 from the PG and 1 from the SG), and 2 were fed fortified formulas. Three infants had incomplete psychomotor evaluation information.

Biodemographic characteristics of infants were similar (Table I). All infants were initially breast-fed, but the duration of exclusive breast-feeding was longer in the SG than in the PG (5.9 ± 3.3 vs 4.3 ± 2.8 months, *t* test *P* = .007). The zinc content in 10 samples of cow milk formula was 2.2 ± 0.2 mg zinc per liter. Solid foods prepared at home were not analyzed for zinc content. None of the infants required hospitalization during the study. The number of upper respiratory infections was comparable in both groups (SG: 4.5 episodes per child, range 1 to 8; PG: 4.1 episodes per child, range 1 to 10). Four pneumonias were observed in each group; diarrheal episodes were observed in 3 infants in the SG and in 5 infants in the PG.

No significant differences were found in hair zinc concentrations between the groups on admission (SG: 83.2 ± 15.8, PG: 83.2 ± 7.3 μg/g), at 6 months (SG: 101.8 ± 32.4, PG: 101.2 ± 31.9 μg/g), or at 12 months (SG: 103.1 ± 32.7, PG: 90.0 ± 32.9 μg/g). At 6 months 11 of 57 infants in the SG and 6 of 55 infants in the PG had hair zinc below the cutoff point in our laboratory (90 μg/g) (not significant). At 12 months 15 of 57 infants of the SG and

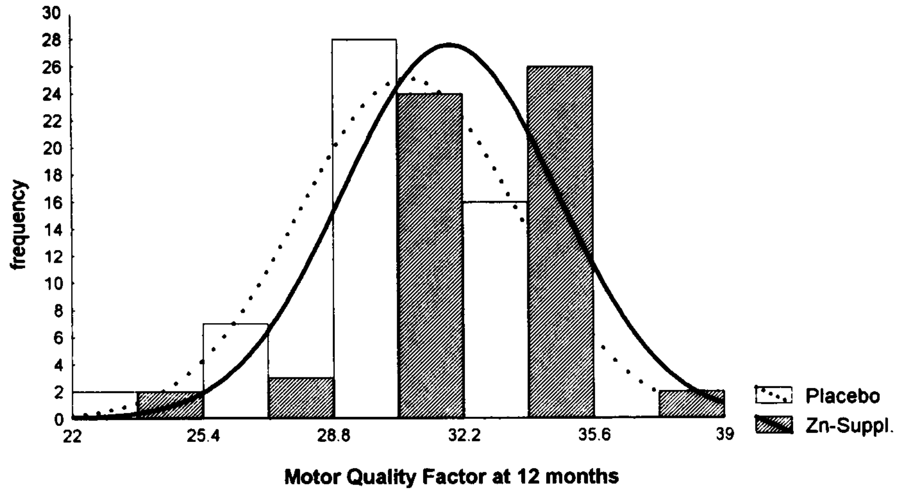

Fig 2. Histogram and estimated normal curves for motor quality factor (item of behavior), evaluated by Bayley test at 12 months of age, based on quintiles distribution for zinc-supplemented (n = 57) and placebo groups (n = 52). More infants in PG than in SG scored under 50th percentile (*P* = .04).

Table II. Psychologic outcomes (mean ± SD and ranges) of infants from zinc-supplemented (n = 57) and placebo groups (n = 52) at 6 months and 12 months of age*

	6 Months		12 Months	
	Zinc-supplemented	Placebo	Zinc-supplemented	Placebo
Mental Development Index	90.1 ± 5.6 (60-100)	90.8 ± 7.8 (64-102)	90.9 ± 10.5 (70-109)	88.9 ± 9.1 (72-111)
Psychomotor Development Index	87.4 ± 8.5 (61-111)	87.7 ± 8.9 (67-108)	84.5 ± 11.5 (61-105)	87.6 ± 9.9 (57-105)
Behavior Rating Scale				
Orientation/ engagement	40.9 ± 4.0 (27-49)	41.2 ± 4.3 (32-49)	40.1 ± 5.8 (25-52)	39.1 ± 5.6 (23-53)
Emotional regulation	36.4 ± 2.9 (27-40)	36.9 ± 2.9 (27-40)	34.2 ± 2.9 (27-40)	33.8 ± 2.7 (27-39)
Motor quality factor	31.2 ± 3.1 (24-35)	31.9 ± 2.2 (24-35)	31.9 ± 2.8* (22-35)	30.8 ± 2.9* (23-39)

*Significant differences between groups were found in motor quality factor at 12 months, *P* = .047.

16 of 55 of the PG had hair zinc concentrations below the zinc cutoff point (not significant).

Mean ± SD growth parameters were similar for both groups. At 6 months *z* scores were weight-for-age, SG: 0.24 ± 0.83, PG: 0.23 ± 0.86; length-for-age, SG: –0.06 ± 0.74, PG: –0.06 ± 0.75; and weight-for-length, SG: 0.30 ± 0.87, PG: 0.26 ± 0.94. At 12 months they were weight-for-age, SG: –0.23 ± 1.04, PG: 0.22 ± 0.86; length-for-age, SG: –0.44 ± 0.94, PG: –0.07 ± 0.75; and weight-for-length, SG: 0.18 ± 0.88, PG: 0.26 ± 0.95. We analyzed growth according to duration of breast-feeding, because we have demonstrated that small for gestational age infants who are weaned earlier than 4 months grow less than those breast-fed longer, unless they are zinc-supplemented.[5] As shown in Fig 1, no significant effect of breast-feeding on weight-for-age *z* scores was found independent of zinc supplementation. The repeated measure ANOVA found no effect of breast-feeding duration on growth measurements controlling for sex and birth weight. The mother-infant relationship was similar across groups; the proportion of infants in the at risk category was 21.5% for SG and 14.5% for PG. The home stimulation quality index was also similar; the SG had 30.8 ± 6.1, whereas the PG had 30.7 ± 6.9.

Mental development scores demonstrated significantly fewer infants scoring <100 in the SG than in the PG at 12 months (SG: 42 of 57 vs PG: 46 of 52; χ^2 3.82, *P* < .05) (Table II). No significant differences in means at 6 months were found. The PDI was not significantly different when the SG and PG were compared at 6 months and at 12 months, nor was the change in index scores significantly different between 6 and 12 months (ANOVA for repeated measurements, not significant) (Table II).

Analysis of the effect of zinc supplementation on behavior shows that no significant differences were found in the orientation/engagement and emotional regulation factors (Table II). At 6 months mean scores for motor quality factor were not significantly different between both groups (31.2 ± 3.1 vs 31.9 ± 2.2), but the proportion with nonoptimal scores was lower in the SG. When infants below the 11th percentile (proposed by the Bayley scale as the cutoff point to discriminate a probable motor dysfunction) are considered, 2 of 57 in the SG and 8 of 52 in the PG demonstrated motor dysfunction (*P* = .04). The most affected items were gross and fine motor movement and control of movement. Tremulousness, slow and delayed movement, and hyperactivity were less affected. At 12 months distribution of the motor quality factor of the SG was shifted to the right in relation to that of the PG (Fig 2). The mean scores for motor quality factor were higher in the SG, 31.9 ± 2.8, than in the PG, 30.8 ± 2.9 (*P* = .047). Two of 57 infants in the SG and 6 of 52 in the PG scored <11th percentile (*P* = .08).

Table III. Multiple regression coefficient estimates of variables influencing motor quality factor of infants at 6 months or 12 months of age

	Intercept	Birth weight (kg)	Breast-feeding (mo)	Sex (female)	Weight at 5 months – Birth weight (kg)	Zinc supplement
6 Months						
Estimate	22.5620	2.5277	0.0101	0.4773	0.1311	–0.5371
F statistic		11.44	0.01	0.78	0.09	1.04
P value		.0010	.9082	.3783	.7588	.3103
12 Months						
Estimate	32.1072	–0.2817	–0.0288	–0.3943	0.3205	–1.2571
F statistic		0.12	0.09	0.44	0.47	4.74
P value		.7317	.7647	.5064	.4937	.0317

Because Friel et al[9] found an effect of zinc supplementation on growth rate and development in low birth weight infants, we analyzed the infants in our study according to birth weight over and under 3000 g. As indicated in the Methods section, all infants were appropriate for gestational age. We found 7 infants in the SG and 9 in the PG with a birth weight <3000 g, with no differences between groups on growth or development measurements. The interpretation of this result is limited by insufficient power and the post-hoc nature of the analysis.

Multiple regression analysis for variables influencing MDI and PDI did not show any effect. The motor quality factor revealed that at 6 months of age, birth weight was the main variable that explained the motor quality factor score (P = .0009); at the 12-month measurements, zinc supplementation appeared as the only variable influencing it (P = .037) (Table III).

We studied associations among MDI, PDI, and motor quality factor scores, with variables of growth analyzed as continuous or categorized variables, according to z scores above and below the mean (weight/age, weight/length, length/age) at 6 or 12 months, or analyzed as change between 0 to 6 and 0 to 12 months. No association was found in these analyses, nor was an association found for any other variables of behavior except for motor quality factor, with birth weight, length, or cranial circumference at birth.

DISCUSSION

The association of low motor quality score at 6 months with birth weight raises the possibility that the effect of zinc supplementation is manifested only in term infants born with low birth weight.[5] Previous data demonstrated an interaction between iron deficiency and low birth weight, with psychomotor development.[17] A suboptimal motor quality score (<11th percentile) based on published work has been demonstrated to be associated with neuromotor dysfunction later in childhood and was a better predictor than the PDI for such alterations.[18] These disturbances may persist as a handicap later in life.[19,20]

The Bayley scale has not been validated in Latin America, and sociocultural factors may explain the lower mean values observed in both study groups relative to the reference population. There are no follow-up studies using the new edition of the Bayley Scale, and the application of this test during the first year of life is still being discussed. However, this is the most commonly used instrument to test psychomotor development.

The results on effects of zinc supplementation on motor quality factor agree with those obtained with experimental animals. Golub et al[21] found lower postural muscle tone in newborn Rhesus monkeys born to mothers with marginal zinc deficiency during pregnancy. Earlier studies by Golub et al[8] in Rhesus monkeys with marginal zinc deprivation during the first year of life found decreased spontaneous locomotor activity only in males at 1 month. At 10 months the zinc-deficient monkeys failed to reach discrimination reversal criterion. No effects on behavioral development or in emotional adaptability were observed. Further studies by Golub et al[22] of behavioral performance in prepubertal monkeys reported lower spontaneous activity performance in a visual-attention task and decreased short-term memory task during zinc deficiency. In moderately zinc-deprived adolescent monkeys, the same authors found a decrease in daytime activity levels and in attention performance.[23] Other studies in experimental animals have analyzed the effect of zinc deficiency on behavior during critical periods of brain growth, finding impaired working memory[7] and reduced activity and exploration.[8]

Very few studies have analyzed the effect of zinc deficiency on behavior in humans. Cavan et al[24] in Guatemala failed to find any effects of zinc supplementation on cognition in schoolchildren. Friel et al,[9] who provided zinc supplements to very low birth weight infants, found an effect on growth and motor development assessed with the Griffiths Mental Development Scales. Ashworth et al[25] developed a double-blind, partly randomized efficacy trial of zinc supplementation for 8 weeks starting at birth in infants born to families of low income. They found at 12 months of age no differences in mental or psychomotor development index of Bayley scale but a significantly better rating with zinc supplementation in the responsiveness item of behavior.

No effects of zinc supplementation were observed on weight, length, and cranial circumference growth during the study. Mean z scores for growth variables in all groups were close to the median World Health Organization-National Center for Health Statistics. No significant effects of zinc supplementation were observed even in the specific subgroup analysis of undergrown infants. These infants were all breast-fed for a mean of 4 to 5 months; thus breast-feeding protected them from zinc deficiency at least during the first semester of life.[26] We cannot exclude the possibility that cow milk formula and solid complementary foods given to the control group may have induced marginal zinc deficiency, affecting growth after our 12-month follow-up. Estimated zinc intake after weaning was 2.4 to 2.6 mg, considering a mean content of 1.6 mg zinc in 750 mL of cow milk formula and 0.8 to 1.0 mg in 2 daily servings of solid foods prepared at home. Home-prepared foods in low-income groups in Chile are currently based on vegetables and unfortified cereals and low in flesh foods. Thus zinc intake for our infants was low relative to the 5 mg zinc recommended United States/National Research Council Recommended Daily Allowance. These results may be generalized to infants in other countries who are fed in similar ways. This feeding pattern is observed in most low-income groups in developing countries. Privileged groups around the world use micronutrient-supplemented commercial formulas to feed their infants if they are not breast-fed. These results suggest that psychomotor development appears to be more sensitive to zinc deficiency than growth. This finding is in accordance with observations of Golub et al,[8] who found that zinc-deprived monkeys who demonstrated behavioral deficits continued to grow rapidly. Potential mechanisms have been proposed to explain the effects of zinc deprivation on behavior including zinc effects on central nervous system development, changes in zinc fingers affecting gene expression, zinc-dependent enzyme activity affecting neurotransmitters, and neuroendocrine and growth factor zinc-mediated effects.[27]

No association between hair zinc levels with indexes of mental development or growth was found. This result suggests that hair zinc has a low sensitivity to detect marginal zinc deficiency. The effect of the zinc supplementation could have been more evident if it was possible to separate zinc-deficient from normal infants in a clear manner.

Acute studies in the literature demonstrate that a supplement with an iron/zinc ratio >2:1 in adults limits zinc absorption, yet this effect was not present when supplements were given with a meal.[28] Thus anemia or iron inhibition of zinc absorption most likely does not explain our results. Other confounders that should be considered in evaluating the effect of mild zinc deficiency on psychomotor development include low birth weight, breast-feeding, protein energy malnutrition, infectious morbidity, poverty, and social deprivation.[29] In our study we controlled these factors, but isolating the effect of zinc in other developing communities may be more difficult, because these variables are intrinsically linked.

New studies will be required to analyze the long-term effects on psychomotor development of zinc deficiency. It remains to be seen whether they are similar to the effects of iron deficiency anemia during the first year of life, which can still be observed at 6 years of age after a recovery from the deficiency.[30]

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