

# Effect of zinc supplementation on growth and body composition of Ugandan preschool children: a randomized, controlled, intervention trial<sup>1-3</sup>

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## ABSTRACT

**Background:** Despite ample food supplies, the incidence of childhood underweight and stunting remains high in Uganda. Many factors contribute to this situation, but the role of low zinc intakes has not been adequately explored.

**Objective:** Our objective was to study the effect of zinc supplementation on growth and body composition of preschool children by using the outcome measures of weight, height, and midupper arm circumference (MUAC).

**Design:** The study was randomized, double-blind, placebo-controlled, parallel, and 8 mo long, and incorporated 6 mo of zinc supplementation. Children ( $n = 153$ ) aged  $55.8 \pm 11.2$  mo from 3 randomly selected nursery schools of medium, low, and very low socioeconomic status in a suburb of Kampala took part. The intervention comprised 10 mg Zn (as ZnSO<sub>4</sub>) or placebo daily in freshly prepared fruit juice, Monday to Friday inclusive.

**Results:** Zinc supplementation increased MUAC by the end of the study ( $P = 0.029$ ) and led to greater weight gain in children from the school of medium socioeconomic status at 3 and 8 mo ( $P = 0.019$  and  $P = 0.038$ , respectively). There was no effect on weight gain of the children from the other schools. Zinc supplementation had no influence on height. Infection rates (of which 82% were recorded as malaria) were lower in the zinc-supplemented group than in control subjects ( $P = 0.063$ ).

**Conclusions:** Zinc supplementation may counter the age-related decrease in MUAC often observed in preschool children in developing countries. The study provides evidence that zinc may not be the most limiting nutrient for weight gain in children of poor nutritional status, but may become so as nutritional status improves. *Am J Clin Nutr* 1998;68:1261-6.

**KEY WORDS** Zinc, Uganda, developing country, supplementation, growth, infection, preschool-age children, midupper arm circumference

## INTRODUCTION

Zinc is required for the normal growth and development of all animal species, including humans, and its deficiency results in reduced growth of the young (1, 2). Zinc is also essential for the integrity of the immune system; deficiency results in reduced immunocompetence and decreased resistance to infections (1-4). A growth-limiting, mild zinc-deficiency syndrome has

been identified in children from medium- to low-income families in developed countries (5-9). The problem of marginal zinc status is likely to be worse in children in developing countries because of more general poverty, which results in inadequate zinc intakes as a consequence of the predominance of vegetarian diets high in fiber and phytates (10, 11). A recent study on the nutritional adequacy of traditional children's foods in Uganda showed that the zinc content of the foods was below recommended amounts (12). The problem of marginal zinc status is exacerbated by increased zinc losses through blood parasites, particularly those causing malaria, and through the high prevalence of diarrheal diseases (10, 11). Despite suggestions that the growth retardation commonly seen in children in developing countries is related to a nutritional deficiency of zinc (2, 10, 11, 13), few well-designed studies of this problem have been reported (10, 13).

It is now well established that malnourished children, including those with diarrheal diseases, are in negative zinc balance and would therefore benefit from zinc supplementation (14-19). However, zinc supplementation studies on growth-retarded but relatively healthy children in developing countries have not been conclusive. Work in Gambia (10) and Guatemala (13) found positive changes in body composition favoring the zinc-supplemented children but there was no overall effect of zinc supplementation on the growth of the children. The present study was therefore undertaken to investigate further the role of zinc in the nutrition of growth-retarded but relatively healthy children in a developing country.

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## SUBJECTS AND METHODS

The subjects were preschool children from 3 randomly selected nursery schools in a low-income suburb of Kampala, Uganda. Although the schools were all in the low-income category, each had its own ethos and form of administration. The schools will hereafter be referred to as schools 1, 2, and 3 in descending order of their socioeconomic status. School 1 was of a slightly higher socioeconomic status than the other 2 schools because most of the children's parents had formal education and had moderately well-paid employment. The school charged higher fees than the other schools and the children were given supplementary food daily during break time, which included tea with milk or cereal porridges, both accompanied by bread. The parents of most of the children in school 2 were low-paid workers (eg, cleaners and drivers) at Makerere University. School 3 had the lowest socioeconomic status of the 3 schools because the parents of most of the children were low-income petty traders and manual workers.

The study protocol was approved by The University of Reading Research and Ethics Committee in the United Kingdom and the National Council of Science and Technology Ethical Committee in Uganda. Informed consent was obtained from the parents of the children before the start of the trial. All the children in the youngest classes of the selected nursery schools were targeted for inclusion in the study. The children were examined by the pediatrician in the investigating group and those with major medical or physical problems were excluded from the study but followed up and treated by the pediatrician. One hundred fifty-five children, 84 boys and 71 girls, within an age range of 33–89 mo ( $55.8 \pm 11.2$  mo;  $\bar{x} \pm SD$ ), qualified to participate in the trial.

The children were randomly assigned to 1 of 2 supplementation regimens: zinc ( $n = 79$ ) or placebo ( $n = 76$ ). The randomization procedure was stratified according to sex to ensure a relatively equal number of boys and girls in each treatment group. Forty-five boys and 34 girls fell into the zinc group and 39 boys and 37 girls into the placebo group. The zinc and placebo tablets, which were indistinguishable in both color and taste, were dissolved in freshly prepared fruit juice and administered to the children every day, except weekends, for 6 mo. The children in the zinc group received 10 mg Zn (as  $ZnSO_4$ )/d. This level of supplementation is  $\approx 1.5$  times the reference nutrient intake for children aged 1–6 y (20). The zinc and placebo tablets were supplied by Lamberts HealthCare Ltd, Tunbridge Wells, United Kingdom. Because of the nature of school terms in Uganda, the treatment period was 2-phased, each phase lasting 3 mo with a 2-mo period in between with no supplements when the children were on vacation.

Anthropometric measurements [weight, height, and midupper arm circumference (MUAC)] of the children were taken at the beginning of the trial (baseline) and 2, 3, 6, 7, and 8 mo after the start of the trial. The measurements were taken according to international guidelines (21) by the same person throughout the trial. Weight measurements were taken to the nearest 0.1 kg by using a standardized 25-kg spring scale (Salter Weight-Tronix Ltd, West Bromwich, United Kingdom). The standing height of the children was recorded to the nearest 0.1 cm by using Short's height measuring board (Short Productions, Woonsocket, RI). The MUAC of each child's left arm was measured by using a nonstretch insertion tape supplied by Teaching Aids at Low Cost (St Albans, United Kingdom). The age of the children, to the nearest month, was calculated from the children's birth records. The height- and

weight-for-age percentiles of the children at baseline and their height- and weight-for-age  $z$  scores were calculated from the US National Center for Health Statistics reference data (22).

Incidences of sickness in the children were monitored throughout the trial and used as a proxy for resistance to infection. All illnesses that required a visit to the clinic or treatment at home were recorded. Each child who became ill was assigned one sickness point for that week for illnesses presenting as malaria; diarrhea; typhoid; ear, eye, or skin infections; chicken pox; toothache; or measles. Minor illnesses, including cough, influenza, and headaches, were not recorded. If the child fell sick more than once in a week, he or she received only one point, but if the sickness continued to the following week the child was given a new point for the new week. The sickness rates were therefore calculated as sickness score per group per week. Owing to the fact that only children who were seriously ill were taken to the clinic to see a doctor, it was not possible to find a more objective index for determining infection rates, nor was it possible to determine the severity of the illnesses.

The children's diets were assessed by means of an administered diet history and food-frequency questionnaire. A random sample of  $\approx 15$  children per school was selected, their homes were visited, and the parents or guardians were assisted in filling out the questionnaire. Some questions about the children's background and socioeconomic home environment were also included in the questionnaire.

The primary outcome used in designing the study was weight gain (kg). A sample size of 150 children was chosen for the study, allowing for 25% dropout. This figure was based on an SD of  $\pm 2$  kg for mean weight change over an 8-mo period obtained in other studies of children in developing countries, and was calculated to detect a difference in weight of 1.0 kg between the zinc group and the control group with a power of 80% at the 5% significance level. The data were analyzed by using SAS (SAS Institute, Inc, Cary, NC). Mean changes in weight, weight-for-age  $z$  scores, height, height-for-age  $z$  scores, MUAC, and sickness scores were compared for the zinc- and placebo-treated groups by using planned analysis of variance (ANOVA) for repeated measures to examine time trends and interactions with time. No attempt was made to disaggregate the illnesses during statistical analysis because classification was based on clinical presentation of infection and was not confirmed by laboratory analysis. Planned ANOVAs of changes in the various measures were also done at 3 mo to test short-term effects of supplementation and at the end of the study to test long-term effects. School, sex, and age were included as covariates in the ANOVA so that treatments were compared with adjustment for these effects and so that interactions with treatment could be investigated.

## RESULTS

Two children from school 3, one from the zinc and the other from the control group, dropped out of the trial before the end of phase 1 because of insufficient funds for tuition. Their results were dropped from the analysis, leaving a sample size of 153 children ( $n = 78$  for the zinc group and  $n = 75$  for the placebo group) who completed phase 1. Forty children (26.1%) did not return for phase 2 of the trial, mainly because of a change of schools or insufficient funds. The mean baseline weights of the children who dropped out after phase 1 ( $n = 40$ ) and those who completed phase 2 ( $n = 113$ ) were not significantly different.

**TABLE 1**Baseline mean age, weight, height, and midupper arm circumference (MUAC) of the children according to treatment<sup>1</sup>

Variable	Zinc group (n = 78)	Placebo group (n = 75)
Age (mo)	55.5 ± 11.8 (33.0–89.0)	56.1 ± 10.5 (33.0–87.0)
Weight (kg)	16.7 ± 1.9 (12.7–20.6)	16.6 ± 2.1 (12.8–22.1)
Height (cm)	103.5 ± 5.7 (91.5–115.5)	103.2 ± 5.6 (90.8–121.9)
MUAC (mm)	163.9 ± 11.6 (142.0–198.0)	165.9 ± 11.1 (136.0–198.1)

<sup>1</sup> $\bar{x} \pm SD$ ; range in parentheses. Total n = 153 (excluding the 2 children who dropped out in phase 1). There were no significant differences between groups.

Compliance was good but it was inextricably linked to school attendance because the supplemented juice could only be administered when the children were at school. Those children in the treated group who dropped out after phase 1 consumed  $38.6 \pm 4.4$  tablets of 10 mg Zn, whereas those who continued to the end of the study consumed an average of  $82.5 \pm 9.4$  zinc tablets.

The mean baseline age, weight, height, and MUAC of the children was well distributed with no significant differences between the zinc and placebo groups for any baseline variable (Table 1). Shown in Table 2 are the mean weight, weight-for-age z score, height, height-for-age z score, and MUAC for the zinc- and placebo-supplemented children for all 5 measurement periods, ie, 2, 3, 6, 7, and 8 mo after the start of the trial. The mean weight and height of the children increased with time in both the zinc and placebo groups. There was a slight improvement in the weight- and height-for-age z scores of both groups toward the end of the trial. The mean MUAC values of the children were variable, being less than baseline at some stages in the trial, particularly for the placebo-supplemented children. After 2 and 3 mo there was no significant difference in weight gain between children who dropped out at the end of phase 1 and those who continued to the end of phase 2, either overall or when analyzed according to treatment group.

The least-squares mean changes in weight, weight-for-age z score, height, height-for-age z score, and MUAC for the children (from the ANOVA by treatment group after adjustment for the effects of sex and school) are presented in Table 3. Mean weight increases tended to be greater in the zinc-supplemented children

at each successive stage of measurement throughout the trial than in the control children. The effect, though progressive, was not significant. There were no treatment effects on the heights of the children nor on the weight- and height-for-age z scores. However, zinc supplementation had a significant effect on the MUAC of the children. In the early stages of supplementation, MUAC decreased in both groups of children, but at the end of the trial the zinc-supplemented group had positive changes in the measurement, whereas those for the control group were negative (Table 3). ANOVA of MUAC at the end of the trial showed these differences to be significant ( $P = 0.029$ ), even though the results of ANOVA for repeated measures of MUAC throughout the trial showed that the treatment effects for the between-subject variation were not significant ( $P = 0.07$ ).

The school  $\times$  treatment interactions were significant for weight changes at 3 and 8 mo. This was due to an increase in weight in the zinc-supplemented children in school 1, the school with the highest socioeconomic status and a feeding program, at 3 and 8 mo ( $P = 0.019$  and  $P = 0.038$ , respectively; Table 4). The weights of the children from the 2 other schools were not significantly affected by zinc supplementation.

Interactions between the sex of the children and treatment were also analyzed because some workers have found sex-influenced responses to zinc supplementation (5, 6). However, there were no significant sex  $\times$  treatment interactions in the weight, height, and MUAC changes of the children in the present study. Because the children had a wide range of ages (33–89 mo), the age effect was investigated to find out if it had any significant

**TABLE 2**Mean weight, weight-for-age z score (WAZ), height, height-for-age z score (HAZ), and midupper arm circumference (MUAC) of the children at different stages of zinc treatment<sup>1</sup>

Treatment	Weight	WAZ	Height	HAZ	MUAC
	kg		cm		mm
Zinc					
Baseline	16.67 ± 1.9	-0.39 ± 0.96	103.46 ± 5.8	-0.62 ± 1.44	164.0 ± 11.7
2 mo <sup>2</sup>	16.89 ± 2.0	-0.43 ± 0.95	104.09 ± 5.7	-0.73 ± 1.11	162.9 ± 11.1
3 mo	17.05 ± 2.0	-0.42 ± 0.94	104.66 ± 5.6	-0.72 ± 1.10	163.2 ± 10.4
6 mo	17.75 ± 2.1	-0.29 ± 0.88	106.68 ± 5.5	-0.55 ± 0.95	164.5 ± 13.4
7 mo	17.90 ± 2.1	-0.27 ± 0.88	107.58 ± 5.5	-0.50 ± 0.94	164.2 ± 12.9
8 mo	18.06 ± 2.1	-0.27 ± 0.88	108.10 ± 5.5	-0.50 ± 0.92	165.1 ± 12.6
Placebo					
Baseline	16.65 ± 2.1	-0.44 ± 0.78	103.18 ± 5.9	-0.78 ± 1.09	165.9 ± 11.1
2 mo	16.83 ± 2.1	-0.54 ± 0.86	103.74 ± 5.8	-0.90 ± 1.06	164.7 ± 11.2
3 mo	16.97 ± 2.1	-0.32 ± 0.83	104.30 ± 5.8	-0.89 ± 1.06	164.7 ± 11.3
6 mo	17.62 ± 2.0	-0.33 ± 0.71	106.89 ± 5.4	-0.56 ± 1.00	166.0 ± 11.5
7 mo	17.79 ± 2.0	-0.30 ± 0.75	107.62 ± 5.4	-0.44 ± 0.96	164.7 ± 12.0
8 mo	17.95 ± 2.1	-0.27 ± 0.70	107.95 ± 5.4	-0.48 ± 0.95	165.6 ± 11.2

<sup>1</sup> $\bar{x} \pm SD$ ; n = 153 children (78 zinc and 75 placebo) for phase 1 (0–3 mo) and n = 113 children (59 zinc and 54 placebo) for phase 2 (6–8 mo). 10 mg Zn/d given to zinc group.<sup>2</sup>The supplementation period was 6 mo with a 2-mo break (months 4 and 5), making a total trial period of 8 mo.

**TABLE 3**

Least-squares mean (LSM) changes in weight, weight-for-age *z* score (WAZ), height, height-for-age *z* score (HAZ), and midupper arm circumference (MUAC) of the children at 3 and 8 mo of the study<sup>1</sup>

Variable	Zinc	Placebo
Weight (kg)		
0–3 mo	0.39 ± 0.04	0.31 ± 0.04
0–8 mo	1.33 ± 0.07	1.21 ± 0.07
WAZ		
0–3 mo	−0.035 ± 0.02	−0.079 ± 0.02
0–8 mo	0.069 ± 0.04	0.050 ± 0.05
Height (cm)		
0–3 mo	1.20 ± 0.06	1.13 ± 0.06
0–8 mo	4.38 ± 0.10	4.25 ± 0.10
HAZ		
0–3 mo	−0.097 ± 0.01	−0.109 ± 0.01
0–8 mo	0.042 ± 0.03	−0.005 ± 0.03
MUAC (mm)		
0–3 mo	−0.88 ± 0.42	−1.25 ± 0.42
0–8 mo	0.86 ± 0.57	−0.82 ± 0.60 <sup>2</sup>

<sup>1</sup>LSM ± SE. 10 mg Zn/d given to zinc group. The supplementation period was 6 mo with a 2-mo break (months 4 and 5), making a total trial period of 8 mo.

<sup>2</sup>Significantly different from zinc,  $P = 0.029$ .

influence on the treatment variables. For this analysis, the children were divided into 2 age groups: those <5 y (≤59 mo) and those >5 y (>59 mo) of age. There were no significant age-influenced treatment effects on changes in weight, height, or MUAC of the children at 3 and 8 mo of the trial.

The infection rate was high in this cohort of children. Of 242 recorded illnesses, 198 were malaria, 10 were diarrhea, 1 was typhoid, 3 were ear infections, 9 were skin infections, 11 were eye infections, 4 were toothaches, and 6 were measles. The most prevalent infection was malaria, which accounted for >80% of the illnesses (82%). There were also high incidences of cough and influenza during the rainy season but these were not recorded. Diarrhea was of minor importance in the children, although there was one case of typhoid in school 3 in the placebo group, which was treated. Overall, the zinc-supplemented children had fewer infections than the control subjects (106 compared with 136, respectively). Expressed per week, the mean (±SE) number of infections of the zinc-supplemented children was  $1.36 \pm 0.17$  compared with  $1.82 \pm 0.17$  for the control subjects ( $P = 0.063$ ). School 3 had a significantly ( $P = 0.048$ ) higher score than the other 2 schools:  $1.95 \pm 0.21$  compared with  $1.60 \pm 0.21$  and  $1.22 \pm 0.20$  for schools 1 and 2, respectively.

Attendance of the children was recorded daily, Monday to Friday inclusive. If a child was absent, the reason for the absence, when available, was recorded when the child returned to school. Days of treatment were inextricably linked to attendance because the children took the supplement only when they came to school. Attendance was low mainly because nursery school children are not reprimanded for missing a day from school; hence, children missed school for minor reasons. The most common causes of absenteeism were sickness, insufficient funds for school fees, and rain in the mornings. Although the zinc-supplemented children had slightly better attendance records than the control children ( $71.99 \pm 2.37$  compared with  $70.45 \pm 2.40$  d:  $\bar{x} \pm SE$ ), the difference was not significant.

Our study of the children's diets and socioeconomic backgrounds showed that foods consumed included sweet potatoes,

**TABLE 4**

Least-squares mean (LSM) changes in weight according to school and treatment at 3 and 8 mo of the study<sup>1</sup>

School and treatment	Baseline weight <sup>2</sup> ( <i>n</i> = 153)	Change in weight <sup>3</sup>	
		0–3 mo ( <i>n</i> = 153)	0–8 mo ( <i>n</i> = 113)
	kg	kg	
School 1			
Zinc	16.6 ± 2.3	0.59 ± 0.07	1.51 ± 0.12
Placebo	16.0 ± 1.7	0.36 ± 0.07 <sup>4</sup>	1.14 ± 0.12 <sup>5</sup>
School 2			
Zinc	16.9 ± 2.0	0.34 ± 0.06	1.41 ± 0.11
Placebo	16.6 ± 2.1	0.30 ± 0.06	1.46 ± 0.13
School 3			
Zinc	16.5 ± 1.4	0.24 ± 0.06	1.07 ± 0.11
Placebo	17.4 ± 2.1	0.27 ± 0.07	1.03 ± 0.11

<sup>1</sup>The supplementation period was 6 mo with a 2-mo break (months 4 and 5), making a total trial period of 8 mo. Preschools in Kampala, Uganda, were rated according to socioeconomic criteria; school 3 was the poorest.

<sup>2</sup> $\bar{x} \pm SD$ .

<sup>3</sup>LSM ± SE.

<sup>4,5</sup>Significantly different from zinc: <sup>4</sup> $P = 0.019$ , <sup>5</sup>0.038.

rice, plantains, cassava, maize meal, beans, peanuts, meat, fruit, and vegetables. Details of the diets are reported elsewhere (23). The results also revealed that there were no significant differences in the diets of the children in the 2 treatment groups. The supplementary feeding program in school 1 provided the children with cow milk, cereal porridges (maize and millet), sugar, and bread. Most of the children in school 1 came from homes of better socioeconomic status than the children in schools 2 and 3, where most of the children came from homes of low and very low socioeconomic status, respectively. Children from homes with a higher socioeconomic environment consumed a more varied diet than children from homes with a lower socioeconomic environment.

## DISCUSSION

Currently, there is no single sensitive and foolproof index of mild zinc deficiency in humans (7, 10, 13, 24). A combination of biochemical and functional indexes are usually used, but these do not always reflect the true picture at the tissue level (6, 9, 10). The current method for the assessment of zinc status in children is an indirect one, ie, through a response to supplementation in well-randomized and controlled trials (7, 13). These supplementation trials, however, have often had conflicting outcomes.

Mild zinc deficiency has been proposed as one of the dietary risk factors for the poor growth of children in Uganda. Although our group of study children was classified as being relatively healthy, almost one-half (46.3%) of the children were below the 20th height-for-age percentile and more than one-quarter (29.3%) were below the 20th weight-for-age percentile at baseline. There is no documented record of research on zinc nutrition of either adults or children in Uganda. Diets in Uganda, like those in many developing countries, are predominantly vegetarian with low energy and zinc contents (12). Poor zinc status may be exacerbated by increased zinc losses through malaria and gastrointestinal diseases, both of which are endemic in Uganda (23).


Several supplementation trials have found a significant effect of zinc supplementation on weight or height gains both in relatively healthy (5–9) and in malnourished children (15–19). The

present study, however, found no significant overall effect of zinc supplementation on the weight and height gains of the children studied. These results agree with reports by other workers who also found no overall effect of zinc supplementation on the growth of children (11, 13, 25). The short supplementation period could have accounted in part for the lack of a significant effect in the linear growth of the children.

Despite the lack of effect of zinc supplementation on growth when data from all children were analyzed, a differential effect emerged when the socioeconomic status of the schools was considered. The children from the school with the highest socioeconomic status, and therefore a better nutritional background, responded significantly in weight gain to zinc supplementation whereas the children from the poorer schools did not. The higher socioeconomic status coupled with the school feeding program suggests that the children in school 1 were better fed than the children in the other 2 schools, even though this is not clearly shown by their anthropometric indexes. Zinc supplementation had a short-term effect (ie, within 3 mo:  $P = 0.019$ ) on the weight gains of children in school 1. This indicated that zinc was the limiting nutrient in the nutrition of the children with relatively better nutritional status, whereas those with poorer nutritional status were deficient in other nutrients that limited the response to zinc supplementation. A study done in Gambia (10) also concluded that zinc may not be limiting if there is an inadequate supply of other nutrients. This might partly explain the lack of response to zinc supplementation in studies of children in developing countries (10), whereas studies in developed countries (5–9), where the children had better nutritional status, showed positive responses. Further research is needed to explain this finding. This is especially so in light of the fact that in a Guatemalan study (13), in which all participating children received a multivitamin and mineral (excluding zinc) supplement during the study period, there was still no overall effect of zinc supplementation on growth variables. To add to the complexity, a recent study of the zinc nutriture of relatively healthy, free-living Zimbabwean schoolchildren (26) found a positive effect of zinc supplementation on the growth of the children only when their food intake was low because of drought; the effect disappeared when the children were put on a feeding program.

Zinc supplementation increased the MUAC of the children in this trial. At the end of the trial, the zinc-supplemented children had gained 1.1 mm from baseline values whereas the placebo-supplemented children had lost 0.3 mm (Table 2). These were small differences and although they were significant at the 5% level, they could have arisen by chance. A positive response in MUAC to zinc supplementation was reported in Gambian (10) and Guatemalan (13) children. The mechanism through which zinc supplementation affects the MUAC of children is not clear. It could be a result of a zinc-facilitated increase in lean tissue accretion (27) or increased intake and efficient utilization of energy-yielding nutrients (13, 28). Zinc supplementation also tended to reduce the sickness scores of the children. However, because the method of determining bouts of illness was quite subjective in this trial, our data on morbidity need to be substantiated by further research with a more objective morbidity assessment index.

In summary, the results of the present trial showed a mild but significant effect of zinc supplementation on the MUAC of Ugandan children. Response in weight to zinc supplementation was found to be dependent on improvement of the general nutri-

tional status of the children. Bouts of sickness, indicating poorer resistance to infection, tended to decrease with zinc supplementation. However, further research using a wider cross section of the children, a longer supplementation period, and a stricter morbidity protocol, is needed to ascertain the role of zinc in the health and nutrition of children in developing countries. 

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