

PAEDIATRIC EPIDEMIOLOGY

Effect of zinc supplementation on growth in West African children: a randomized double-blind placebo-controlled trial in rural Burkina Faso

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Objective	To analyse the effects of zinc supplementation on growth parameters in a representative sample of young children in rural Burkina Faso.
Design	Randomized, double-blind, placebo-controlled efficacy trial.
Setting	Eighteen villages in rural northwestern Burkina Faso.
Subjects	In all, 709 children aged 6–31 months were enrolled; 685 completed the trial.
Intervention	Supplementation with zinc (12.5 mg zinc sulphate) or placebo daily for 6 days a week for 6 months.
Outcomes	Weight, length/height, mid-arm circumference, and serum zinc.
Results	In a representative subsample of study children, 72% were zinc-deficient at baseline. After supplementation, serum zinc increased in zinc-supplemented but not in control children of the subsample. No significant differences between groups were observed during follow-up regarding length/height, weight, mid-arm circumference, and z scores for height-for-age, weight-for-age, and weight-for-height.
Conclusions	We conclude that zinc supplementation does not have an effect of public health importance on growth in West African populations of young children with a high prevalence of malnutrition. Multinutrient interventions are likely to be more effective.
Keywords	Zinc, growth, malnutrition, children, Africa, Burkina Faso

Malnutrition and micronutrient deficiencies are highly prevalent in developing countries, and it has been estimated that malnutrition is the underlying cause for up to 50% of all deaths among children in these populations.^{1–5} Zinc is important for a number of biological functions, and zinc deficiency has been associated with complications in pregnancy and childbirth, lower birthweight and poor growth in childhood, reduced

immuno-competence, and increased infectious disease morbidity.^{6–8} As there are no reliable biochemical indices of marginal zinc status, controlled supplementation trials are the best method to study the relation between zinc deficiency and health parameters in human populations.⁹ A number of such trials have consistently demonstrated an association between zinc supplementation and major reductions of morbidity due to respiratory infections and diarrhoea in young children of developing countries.¹⁰ More recently, a controlled trial on zinc supplementation during pregnancy has been able to demonstrate a reduced frequency of diarrhoea, dysentery, and impetigo in low birthweight infants born to mothers in the zinc-supplemented group.¹¹

The impact of zinc supplementation on growth parameters has also been studied in countries of Asia, Latin America, and Africa. Trials in different populations of young children from

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these countries have provided conflicting results on the effects of zinc supplementation on growth. While some have found no effect, others provided evidence for zinc supplementation increasing growth velocity.^{12–20} In a meta analysis of 25 studies, there were small but highly significant effect sizes for changes in height and weight of +0.22 SD and 0.26 SD respectively with zinc supplementation.¹²

We undertook a randomized placebo-controlled zinc supplementation trial in young children of rural Burkina Faso. Results on morbidity outcome have been published elsewhere.²¹ Here we report our findings on anthropometric measurements associated with zinc supplementation during this trial.

Subjects and Methods

Study area

The study area was in the Nouna Health District in north-western Burkina Faso. The trial took place June–December 1999. The Nouna area is a dry orchard savanna, populated almost exclusively by subsistence farmers of different ethnic groups. The rainy season usually lasts from June until October, and the average annual rainfall is 700 mm. The main staple food in the study area is millet, with young children usually receiving a diet that contains very little protein. Traditional rearing of animals is practised mainly for income generation. During the rainy season, when villager's workload as well as disease incidence are high, food intake is particularly low.²²

Study design

The study design has been described in detail.²¹ In brief, children aged 6–31 months at enrolment were recruited by lottery from 18 villages of the study area of the *Centre de Recherche en Santé de Nouna* (CRSN).²³ Children found to have serious underlying illness were excluded from enrolment. Children were individually allocated supplementation with zinc or placebo in blocks of 30 (15 zinc, 15 placebo) by computer-generated randomly permuted codes (prepared by WHO/Geneva). Study children were supplemented with 12.5 mg (half of a 25-mg tablet) of zinc sulphate or placebo every morning (except Sundays) during a 6-month period. Zinc and placebo tablets were identical in appearance and taste (Biolectra Zinc, Hermes Arzneimittel GMBH, München, Germany). Supplementation was done through village-based fieldworkers supervised through specific field supervisors and a Nouna-based study physician (AB). Compliance with the supplementation was systematically investigated in all study children in October 1999. On a semi-quantitative measurement scale (very good, good, acceptable, difficult, bad) and based on specific standard guidelines, compliance was judged as acceptable or better in 80% of study children by the responsible field staff.

For surveillance of morbidity, mortality, and periods of absence, children were seen daily except Sundays by their respective fieldworker. In addition, three cross-sectional surveys were undertaken at baseline (June), mid study (September), and end of study (December). Children were seen and examined by the same physician (OM) during all survey visits. Anthropometric measurements were made on all children, while serum zinc level was measured in a random subsample of 100 children.

Laboratory procedures

Venous blood taken during the surveys was kept in a cold box until centrifugation, which was done on the same day in Nouna. Serum samples were stored at -20°C until zinc determination took place at the Heidelberg University laboratory by flame atomic absorption spectrometry (Perkin-Elmer 1100 B, Germany).

Anthropometry

Weight and mid-upper-arm circumference (MUAC) were measured during each of the three surveys, while height/length was measured only at baseline (before supplementation) and the end-of-study survey. Weight was measured with one Salter hanging spring scale with 100-g gradations which was calibrated and controlled daily before and after use. Children were allowed to wear a minimum of light clothes. Recumbent length and standing height were measured with a locally produced length board with an upright wooden base and a moveable headpiece and a simple anthropometer respectively. MUAC was taken with a flexible non-stretch measuring tape.²⁴ Measures included weight to the nearest 0.1 kg, height/length to the nearest 1.0 cm, and MUAC to the nearest 0.5 cm. Anthropometric measurements were usually performed by the same fieldworker following standard techniques.²⁵ The SD scores for height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) were calculated in comparison to the National Center for Health Statistics (NCHS) standard population, using Epi Info, version 6.0.²⁶ Age calculations were based on the precise information available through the existing demographic surveillance system in the study area.²⁴ Stunting, underweight, and wasting were defined as HAZ ≤ -2 , WAZ ≤ -2 , and WHZ ≤ -2 respectively.²⁷

Statistical analysis and data management

Field data forms were checked manually by supervisors for completeness before independent computer entry (Microsoft ACCESS, version 97) at the *Centre de Recherche en Santé de Nouna*. All data were checked for range and consistency, and survey data were double-entered. Any differences were resolved by checking against the original case record forms. The randomization code was broken after the database was closed.

All analyses were done with SAS (version 8.1). Differences among zinc supplementation and placebo group with respect to the anthropometric measures were analysed as follows. For each child we calculated the individual 6-month difference. The effect of zinc supplementation as well as possible confounding factors (age, sex, height and weight at baseline, ethnic group) on these differences were investigated using a linear regression model (SAS PROC REG). Changes in anthropometric measures were also analysed separately for children who were stunted at baseline (HAZ < -2).

Ethical aspects

Approval was granted by the Ethical Committee of the Heidelberg University Medical School and the Ministry of Health in Burkina Faso. The trial was explained in detail to local authorities, to study village populations and to the respective head of each participating compound. Oral consent was sought from the parents and caretakers of study children before enrolment.

Results

The trial profile is given in Figure 1. Of 713 children eligible for the study (one small village only had 23 children of the required age group), 709 children were enrolled and randomized to supplementation with zinc ($n = 356$) or placebo ($n = 353$). Children were not supplemented on 4349 days in total due to absence: average 6.3 days missing for each child (2163 zinc, 2186 placebo). During cross-sectional surveys, 661/685 (96%) of study children were examined at baseline, mid study, and end of study respectively.

Baseline data

In June 1999, the overall age distribution of study children was as follows: 26% were 6–12 months, 27% were 13–18 months, 26% were 19–24 months, and 21% were 25–31 months old. Of zinc supplemented children, 165/332 (50%) and 160/329 (49%) of placebo children were male. Overall, 304/661 (46%), 129/661 (20%), 130/661 (20%), and 77/661 (12%) of study children belonged to the ethnic group of Marka, Mossi, Bwaba, and Peulh respectively. Zinc and placebo groups were similar at baseline regarding all demographic parameters, except that zinc children were slightly older compared with placebo children (18.7 versus 17.6 months).

The prevalence of malnutrition was high at baseline, with 36.3% of children below -2 z score for height for age (stunting) and 24.6% below the -2 z score for weight for height (wasting). The children in our study were not significantly different from the normally poor nutritional status in the Sahel region.²⁸ Baseline characteristics of study children by treatment group are shown in Table 1.

Follow-up data

Paired serum zinc values for June and September (baseline and mid-study survey) were available for 81 (41 zinc, 40 placebo) of study children. Mean zinc levels at baseline were $11.7 \mu\text{mol/l}$ with no differences between zinc and placebo group, and 72% of study children were zinc deficient according to the reference laboratory defined threshold value of $13.0 \mu\text{mol/l}$. In September (mid-study survey), after 3 months of supplementation, children in the zinc group had significantly higher values compared with

Table 1 Baseline characteristics of study children in intervention and control group

	Zinc ($n = 332$)	Placebo ($n = 329$)
Age (months)	18.7 ± 7.0	17.6 ± 6.5
Height (cm)	76.0 ± 6.7	75.3 ± 6.5
Weight (kg)	8.8 ± 1.8	8.6 ± 1.9
MUAC ^a (cm)	13.6 ± 1.3	13.6 ± 1.5
HAZ ^b	-1.6 ± 1.3	-1.5 ± 1.6
WAZ ^c	-2.0 ± 1.1	-2.0 ± 1.3
WHZ ^d	-1.2 ± 1.0	-1.3 ± 1.0

Data are mean \pm SD.

^a Mid-upper-arm circumference.

^b Height-for-age Z score.

^c Weight-for-age Z score.

^d Weight-for-height Z score.

A few study children were missing individual measurements for length ($n = 37$), weight ($n = 32$), MUAC ($n = 31$), HAZ ($n = 37$), WAZ ($n = 32$), and WHZ ($n = 40$).

placebo children (15.3 versus $12.4 \mu\text{mol/l}$, $P = 0.005$) and the proportion of zinc-deficient children has significantly declined in the zinc but not the placebo group (11/41 versus 28/40, $P = 0.0001$).

Changes in length/height, weight, MUAC, and scores for WAZ/HAZ/WHZ after 6 months of intervention are shown in Table 2. Linear growth averaged 5 cm over the 6-month period, which can be considered as normal. However, weight gains were rather low (about 1 kg) so that gains in weight for age, weight for height, and arm circumference tended to be negative. There were however no significant differences between treatment and placebo groups, even after controlling for sex, ethnic group, age, weight, and height at baseline. When considering changes in anthropometric indicators for stunted children only (HAZ < -2), there was again no significant effect of zinc on growth parameters.

Discussion

It has been estimated that 42% of children less than 5 years old who are living in low-income countries are stunted (HAZ < -2), a situation which has changed little over recent decades.³ High incidence rates of infectious diseases in combination with poor nutritional quality of traditional diets contributing to insufficient food intake are considered the main causes of malnutrition in such populations.^{1,29}

We also found a high prevalence of stunting in this rural West African study area, a situation furthermore complicated by a high prevalence of wasting. The nutritional indicators were particularly bad in children aged 12–24 months (data not shown), which is typical for young children in rural Africa where bulky weaning diets of low energy density prevail.

Given the low intake of animal products in the study area, the existence of a high prevalence of zinc deficiency in young children is very likely. This is supported by the finding of low serum zinc levels in the study population, and by the significant increase of serum zinc levels in children supplemented with zinc compared to control children.

In this study, we have not found any significant effect of zinc supplementation on nutritional indicators at a level verifiable with standard anthropometric equipment in developing

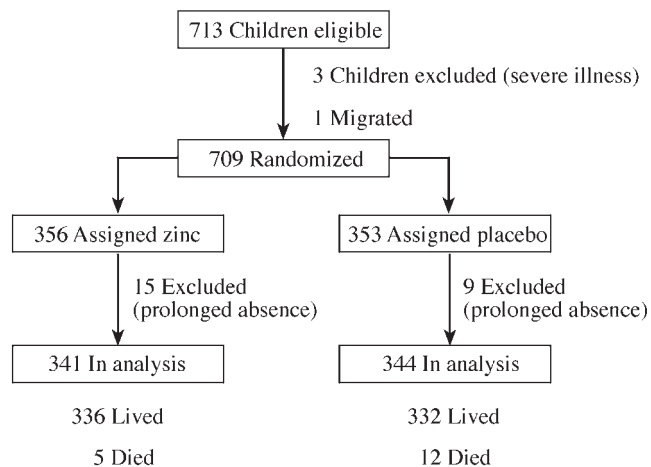


Figure 1 Trial profile

Table 2 Effect of zinc supplementation on growth velocity of study children in intervention and control group

	All children			HAZa ≤-2 baseline		
	Zinc (n = 332)	Placebo (n = 329)	P-value ^b (95% CI)	Zinc (n = 119)	Placebo (n = 112)	P-value ^b (95% CI)
Gain in height (cm/6 months)	5.0 ± 2.2	4.9 ± 2.1	0.45 (-0.21, 0.48)	5.1 ± 2.5	4.8 ± 2.4	0.52 (-0.44, 0.88)
Gain in weight (kg/6 months)	1.0 ± 0.7	0.9 ± 0.7	0.16 (-0.03, 0.18)	1.1 ± 0.7	0.9 ± 0.7	0.11 (-0.034, 0.35)
Change in MUAC ^c (cm/6 months)	-0.3 ± 1.0	-0.4 ± 1.1	0.13 (-0.04, 0.29)	-0.1 ± 1.0	-0.3 ± 1.1	0.22 (-0.11, 0.45)
Change in HAZ	0.06 ± 0.8	-0.02 ± 0.8	0.24 (-0.05, 0.20)	0.3 ± 0.8	0.3 ± 0.8	0.46 (-0.13-0.29)
Change in WAZ ^d	-0.002 ± 0.6	-0.08 ± 0.6	0.13 (-0.02, 0.18)	0.2 ± 0.6	0.07 ± 0.6	0.12 (-0.032, 0.30)
Change in WHZ ^e	-0.09 ± 0.8	-0.1 ± 0.7	0.72 (-0.10, 0.15)	-0.01 ± 0.9	-0.1 ± 0.8	0.38 (-0.13, 0.34)

Data are mean ±SD.

^a Height-for-age Z score.

^b Effect of zinc on anthropometric variables by t-test.

^c Mid-upper-arm circumference.

^d Weight-for-age Z score.

^e Weight-for-height Z score.

countries. However, these results have to be interpreted with caution, as the study was not primarily designed to measure the nutritional effects of zinc.²¹ Moreover, the pattern of observed growth velocity is not usual in this age range, and is due primarily to the heavy presence of malaria during the rainy season.

The differences between zinc and placebo groups were indeed remarkably small, so that if there is any nutritional impact of zinc supplementation it is likely to be of small magnitude. However, it should be noted that differences tended to be in the expected direction, that is slightly higher weight and height gains and smaller losses in MUAC in zinc-supplemented compared with not zinc-supplemented children, especially in the subgroup of stunted children. It remains therefore possible that a larger trial might have detected minor differences between groups in favour of zinc supplementation.

Small but real effects of zinc on nutritional improvement have been considered likely in a recent meta-analysis of published studies.¹² Moreover, there is evidence for such effects primarily being attributed to the effects of zinc on increasing appetite and decreasing infectious disease morbidity.²⁰ Growth velocity changes, that might be associated with the reduced diarrhoea morbidity observed in our study population, appear to have been small and were not detected by our anthropometric procedures followed here.²¹

There is now increasing evidence for a number of micronutrients being implicated in linear growth, not just zinc.³⁰ Consequently, it has been shown in a Chinese population that supplementation with zinc plus other micronutrients was superior compared with zinc alone in increasing growth velocity.¹⁶ It has furthermore been shown that zinc was an effective micronutrient in children with relatively better nutritional status, whereas those with poorer nutritional status were deficient in other nutrients that limited the response to zinc supplementation.¹⁵ As the nutritional status of our study children was rather poor, this might further explain our non-significant results. Such an interpretation is furthermore supported by the lack of an effect on growth velocity in children

of all three zinc supplementation trials from Africa which were included in the meta-analysis,¹² as well as by newer studies on children with a poor nutritional status from Mexico and Jamaica.^{14,31} The obvious policy implications would be to avoid single-nutrient interventions in favour of multinutrient programmes in populations of young children with a high prevalence of malnutrition.

It is noteworthy to comment on our results in the light of the meta-analysis by Brown *et al.*¹² In our study the estimated effect of zinc supplementation on change in weight is +0.08 kg with 95% CI (-0.03, 0.18) which corresponds to 0.11 SD. Given the study size of our trial, an observed difference of about 0.14 SD of weight gain would appear significant with $P = 0.05$. In the meta-analysis an effect size of 0.26 SD was calculated (95% CI: 0.17, 0.36). Although our results are in line with several of the studies included, overall our study therefore does not support the general conclusion of the meta-analysis. For height we have a similar result. Since our study appears larger than each single study, inclusion would have a considerable impact towards a lower overall effect.

In conclusion, zinc supplementation had no measurable effect on growth velocity in young children in rural Burkina Faso. If a small but real effect of zinc on nutritional development exists, such an effect will not be of major public health importance.

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