# Comparison of the effects of zinc delivered in a fortified food or a liquid supplement on the growth, morbidity, and plasma zinc concentrations of young Peruvian children[1–3]

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**ABSTRACT**

**Background:** Zinc supplementation decreases morbidity from infections and increases growth of stunted children, but there is little information on functional responses to zinc delivered in fortified foods.

**Objective:** The aim was to examine the effects of zinc fortification on the growth, morbidity from infections, and plasma zinc concentrations of young children.

**Design:** We compared the physical growth, morbidity, and micronutrient status of 6–8-mo-old Peruvian children with initial length-for-age *z* score (LAZ) $< -0.50$ who were randomly assigned to receive one of the following treatments daily for 6 mo: *1*) 30 g dry weight of an iron-fortified cereal porridge and a separate dose of an aqueous multivitamin (MV) supplement between meals (control group), *2*) the same porridge and MV with 3 mg Zn added to the supplement dose (ZnSuppl group), or *3*) the porridge with added zinc (150 mg/kg dry weight) and MV without zinc (ZnFort group).

**Results:** The children consumed a mean of 22–26 g dry porridge/d and 96% of the possible MV doses. After adjustment for small baseline differences in socioeconomic status and morbidity, no significant differences in weight or length increments were observed between the groups, even among the subset with an initial LAZ $< -1.5$, and no significant differences in the rates of common illnesses were observed. Mean plasma zinc concentrations decreased in the control group ($-3.9$ $\mu$g/dL), increased in the ZnSuppl group (4.3 $\mu$g/dL), and did not change significantly in the ZnFort group ($-1.5$ $\mu$g/dL; $P < 0.001$ for group-wise comparison).

**Conclusions:** Provision of additional zinc, either in an aqueous supplement or a fortified porridge, did not significantly affect the children's physical growth or morbidity from infections, possibly because they were not sufficiently growth-restricted or zinc-deficient initially or because the level of zinc intake or absorption was inadequate. Additional studies of the functional effect of zinc-fortified foods are needed in populations that are known to respond to zinc supplements. *Am J Clin Nutr* 2007;85:538–47.

**KEY WORDS** Zinc, fortification, supplementation, growth, diarrhea, infants

## INTRODUCTION

Adequate zinc nutrition is essential for normal growth and immune function in children (1). Multiple community-based intervention trials in resource-poor countries have found that zinc supplementation of young children in these settings decreases their rates of morbidity from common infections, such as diarrhea and pneumonia (2). Moreover, several groups of investigators have reported reduced mortality rates among children who received supplemental zinc (3–6). In addition to these morbidity-related outcomes, a meta-analysis of placebo-controlled intervention trials concluded that zinc supplementation enhances the growth of stunted or underweight children when the population's mean height-for-age or weight-for-age *z* score is $< -1.5$, although there is no apparent growth effect of zinc in populations experiencing less growth restriction (7).

The International Zinc Nutrition Consultative Group (IZiNCG) currently recommends several possible intervention strategies for improving the zinc nutrition of populations at risk of deficiency (1). The most promising of these strategies for relatively rapid implementation are zinc supplementation and fortification. Fortification is particularly attractive because of its relatively low cost and long term sustainability, but there is limited information on the efficacy of zinc fortification programs. Previous stable isotope tracer studies conducted in Peru (8) and elsewhere (9, 10) have documented that children's total absorbed zinc is greater when they consume zinc-fortified foods in addition to their usual diet, but few studies have examined the functional effect of these fortified foods. The present study was therefore designed to examine the effects of zinc fortification compared with those of either zinc supplementation or no additional zinc on the growth, morbidity from infections, and plasma zinc concentrations of young Peruvian children at risk of stunting. We hypothesized that the children's linear growth and plasma zinc concentrations would increase by consuming additional zinc, regardless of the mode of delivery, and their morbidity from common infections would be decreased compared with those who received no additional zinc.

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## SUBJECTS AND METHODS

### Study design and study site

The study was designed as a randomized, double-masked, community-based intervention trial implemented among young Peruvian children with a presumed high risk of zinc deficiency. The study was carried out from October 2003 to November 2004 in several low-income, periurban communities of Trujillo, a city of ≈600 000 inhabitants located on the northern coast of Peru.

### Study subjects

Initially, we completed a door-to-door census to identify families with young infants who were then invited to attend screening examinations at local community health clinics. During the screening examinations, we measured the weight, length, and hemoglobin concentrations of 927 infants aged 5–7 mo to select a subset of 408 of them who satisfied the following eligibility criteria: length-for-age *z* score (LAZ) < −0.5 (to identify those at risk of stunting), weight-for-length *z* score > −3 (to exclude those with acute malnutrition, who were referred for treatment), hemoglobin >8.0 g/dL, no congenital abnormalities or chronic diseases affecting growth, and no use of infant formula providing >1 mg Zn/d ≥5 times/wk. Infants with a twin enrolled in the study and families that were not planning to remain in the study community for the next 7 mo were also excluded. The rationale for the length-for-age criterion was to select infants believed to be at risk of nutritional stunting, based on earlier observations in a similar community in Lima, Peru. In that study, infants whose LAZ was < −0.5 at 6 mo of age had a mean LAZ < −1.5 at 12 mo of age (11). In a separate meta-analysis of zinc supplementation and growth, we found that children had an increased growth response to zinc supplementation only when their initial mean height-for-age *z* score was < −1.5 (7).

A field supervisor visited the home of the 408 eligible children within 2 d of the screening examination to explain the procedures of the intervention trial, discuss the consent form, and obtain written, informed consent from families interested in participating in the project. The research protocol was approved by the Institutional Review Boards of the University of California, Davis and the Instituto de Investigación Nutricional, Lima, Peru.

### Baseline examinations

The parents of 360 of the 408 eligible infants agreed to participate in baseline, preintervention home visits by a surveillance worker 2–3 times/wk during one month and to provide information on illness symptoms, as described below. The purposes of the baseline assessments were to permit retrospective comparisons of the infants' morbidity rates before the onset of the intervention by treatment group and to permit any necessary adjustments in their postintervention morbidity rates.

### Interventions

After the baseline observation period, the parents of 58 infants decided to withdraw from the study. The remaining 302 infants were stratified by sex, initial LAZ (−0.5 to −1.0, or < −1.0), and whether or not they were assigned to participate in studies of body composition (*see* below) and then were randomly assigned to 1 of 3 treatment groups by using a block randomization scheme, with a varied block length of 3 or 6 (12). The supplementation regimens for the 3 treatment groups were the following: *1*) daily provision of a wheat-based, iron-fortified porridge without added zinc and a liquid multivitamin supplement without zinc (referred to as the control group), *2*) the same porridge provided daily and the same liquid multivitamin supplement to which zinc was added (referred to as the zinc supplementation group, ZnSuppl), or *3*) the same daily porridge to which zinc was added and the liquid multivitamin supplement without zinc (referred to as the zinc fortification group, ZnFort). The porridge that was provided to children in all groups was prepared from partially refined wheat flour (651 g/kg), whole-milk powder (123 g/kg), palm lard (77 g/kg), sugar (66 g/kg), soy protein isolate (64 g/kg), and vanilla flavoring (19 g/kg) and was fortified with ferrous sulfate to contain 30 mg Fe/kg dry-weight porridge. The porridge supplied to children in the ZnFort group was also fortified with zinc sulfate to yield a final concentration of 150 mg Zn/kg dry weight. This zinc fortification level was calculated to supply an additional 3 mg Zn/d, assuming an average porridge consumption of 20 g/d dry weight, as was observed in a previous study in Peru (13). On the basis of information derived from the US Department of Agriculture food-composition tables (14) and confirmed by laboratory analysis, the food components of the porridge contained a total of ≈0.39 mg Zn/20 g dry weight (≈0.26 mg from wheat flour, ≈0.08 mg from powdered milk, and ≈0.05 from soy protein isolate), with a phytate:zinc molar ratio of ≈20 in the unfortified porridge and ≈2.3 in the zinc-fortified porridge.

The liquid multivitamin supplement was made from a commercially available, fruit-flavored children's supplement (Supradyn; Productos Roche, Sao Paulo, Brazil) that was diluted with distilled water. The liquid supplement with added zinc provided a 3 mg daily dose of zinc as zinc sulfate. The daily supplement dose (with or without added zinc) contained the following amounts of vitamins in each 0.5 mL dose: vitamin A, 225 μg retinol equivalents; vitamin B-1, 0.5 mg; vitamin B-2, 0.38 mg; pantothenic acid, 2.5 mg; vitamin B-6, 0.5 mg; vitamin C, 20 mg; vitamin D, 225 IU; vitamin E, 3.8 mg; biotin, 50 μg; and niacin, 3.8 mg.

Fieldworkers delivered the dry porridge to the subjects' homes once per week in a coded, sealed plastic bag containing 260 g dry weight of the porridge. The caregivers were encouraged to prepare the porridge 2–3 times/d (10–15 g dry porridge/serving) with preboiled water. Compliance was assessed by *1*) weighing the full bag before delivery to the household and the amount left over when the bag was retrieved from the home and *2*) a combination of observation by a fieldworker 2–3 times/wk and the caregiver's recall of number of spoonfuls prepared and served (and an estimated weight of 12.5 g dry weight/spoonful) during the days the fieldworker did not visit the home. As described previously (15), these methods were also validated by whole-day direct observations of the children's food intakes.

During the first 2 mo that each infant participated in the study, community assistants hired by the project administered the liquid supplement each day in the early morning, ≈2 h before consumption of any non-breastmilk foods. During the following month, the assistants visited the homes on alternate days to administer the supplement, and the caregiver was instructed to give the supplement on days when the assistant did not visit. During the rest of the study, the caregivers administered the supplement each day, with periodic supervision by the fieldworkers who were monitoring porridge intake. The supplement bottles were also weighed 2–3 times/wk by the fieldworkers for the

duration of the intervention to measure the disappearance of the supplement.

### Data collection

The major outcomes of the study were physical growth, morbidity from infections, and change in biochemical indicators of zinc and iron status. Descriptive information was also collected on the household (socioeconomic status; SES) to control for potential confounding. Information on the infants' dietary intakes will be reported separately, as will data on their body composition and plasma concentrations of hormones related to appetite control, which were studied in a subset of the subjects.

The infants' weights and lengths were measured at the time of randomization to treatment group and 3 and 6 mo later. Weight was measured by using a frequently standardized infant balance with 15 g precision (Seca Model 345; Seca, Hamburg, Germany), and recumbent length was measured to 0.01 cm on a digital infantometer (447 Infantronic Digital Infantometer, Quickmedical, Snoqualmie, WA). All measurements were performed in duplicate by the same person.

Data on infant morbidity and appetite were collected 2 or 3 d/wk, both during the month before the start of the intervention and during the 6 mo of the intervention period. Fieldworkers visited the infants' homes to inquire systematically about symptoms of illness, including stool number and the frequency and the presence of cough, nasal discharge, fever, and other nonspecific symptoms of illness during each day since the previous visit. On the days when cough was reported (and once monthly when cough was not reported), the fieldworker counted the respiratory rate of the infant twice for 1 min each time.

Diarrhea was defined as excretion of ≥3 loose or liquid stools/d, and a new episode had to be separated from a previous one by ≥2 d during which the stool pattern no longer satisfied these criteria. Diarrhea was also defined by using a more demanding cutoff of ≥4 loose or liquid bowel movements/d to explore whether this affected the conclusions. An episode of diarrhea was designated as severe if any one of the following occurred on any day of the episode: >6 loose or liquid stools, dehydration, fever, vomiting, or fecal blood or mucous; and an episode was defined as persistent if it lasted ≥14 d. Upper respiratory infection (URI) was defined as the presence of cough and nasal discharge; whereas lower respiratory infection (LRI) was defined as the presence of cough and elevated respiratory rate >50/min for infants <12 mo of age and >40/min for children ≥12 mo of age, as per World Health Organization recommendations (16). The prevalence of diminished appetite was defined as the number of days with reported appetite either "somewhat diminished" or "very diminished." In general, prevalence rates are presented for diarrhea, URI, fever, and diminished appetite. In contrast, incidence rates are reported for severe diarrhea (because an episode was classified as severe if the associated severity indicators occurred during any day of the illness) and LRI (because fieldworkers were not able to count respiratory rates on all days of the illness).

Venous blood samples were obtained initially at the time of randomization (or at the time of the screening examination in the case of hemoglobin) and again at the end of the period of supplementation for measurement of hemoglobin, plasma ferritin, C-reactive protein (CRP), zinc, and copper concentrations. When the children were acutely ill with diarrhea or fever on the day of a scheduled blood drawing, the sample collection was slated to be postponed until the symptoms resolved, and, in the case of the final blood sample, supplementation was continued until the day before the sample was obtained. The samples were drawn in the morning at the study center by using 1 of 2 protocols. Among those infants who participated in the body composition studies, the blood samples were collected exactly 90 min after breastfeeding. For the other infants, the sample collections were not standardized in relation to breastfeeding or meals, but the times of the sample and of the most recent food or milk intake were recorded. Analyses of the relations between plasma zinc concentration and the times of the blood sampling and the previous meal will be reported separately.

Hemoglobin was analyzed in the field by using a HemoCue photometer (Hemocue, Inc, Lake Forest, CA). Plasma was separated from the remainder of the blood sample and stored frozen at −20 °C in the field office. The samples were transported to UC Davis on dry ice for laboratory analyses. Plasma ferritin was determined by enzyme immunoradiometric assay (Coat-A-Count Ferritin IRMA; Diagnostic Products Corporation, Los Angeles, CA), and CRP was measured by radial immune assay (The Binding Site; San Diego, CA). Plasma zinc and copper concentrations were measured by inductively coupled plasma atomic emission spectrophotometry (ICP-AES, Vista; Varian Inc, Walnut Creek, CA) at the Children's Hospital of Oakland Research Institute.

Household SES was assessed by a structured interview designed to elicit information on the household demographic structure, parental education and employment, and material possessions and by inspection of housing quality. SES data were reduced by using principal components analyses, and the final models included factors that represented housing quality, possessions, household size, and maternal age, marital status, and employment status.

### Sample size and statistical analyses

The major outcome variables were physical growth and change in plasma zinc and serum ferritin concentrations. To detect treatment-related differences having an effect size of 0.5 SD, with the use of 3-way group-wise comparisons and two-sided statistical tests, a sample size of 79 subjects per treatment group was necessary ($P < 0.05$, power 80%). We therefore planned to enroll 100 infants per group to allow for ≈20% attrition. We were also interested in illness morbidity rates as secondary outcomes, and, based on the observed variability in prevalence rates during the trial, the available sample size permitted us to detect with 80% power group-wise differences of 4 percentage points in diarrhea prevalence (relative percent difference of 38%), 2 percentage points in fever prevalence (relative percent difference of 29%), and 6 percentage points in the prevalence of diminished appetite (relative percent difference of 32%).

All data were edited before linking to treatment group, and initial group-wise comparisons were completed without revealing the identity of the individual treatments. All variables were examined initially by using descriptive statistics and were transformed if appropriate to conform to a normal distribution with homogeneity of variance. Group means for baseline descriptive information, initial (preintervention) morbidity variables, and compliance variables were compared by using analysis of variance, weighted by the number of days of observation in the case of the morbidity and compliance measures. Group means

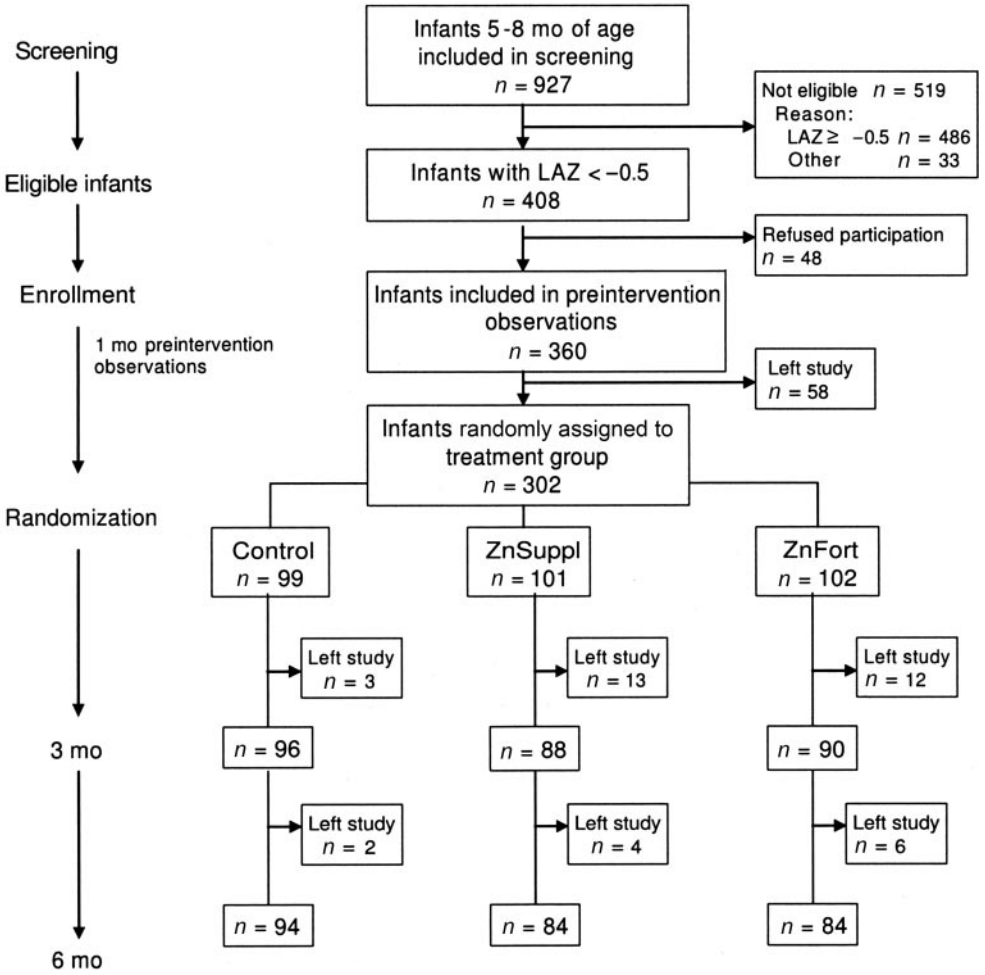


**FIGURE 1.** Flow diagram of the progress of the study. LAZ, length-for-age *z* score; ZnSuppl, zinc supplemented group; ZnFort, zinc fortified group.

for postintervention morbidity rates and changes in anthropometric and biochemical variables were compared by using analysis of covariance, with the respective baseline value serving as the primary covariate. After these preliminary analyses of covariance, key outcome variables were reexamined with the following additional covariates included in the model, as appropriate: maternal factors (maternal age, marital status, employment, height, and body mass index), household SES (housing quality, size, and possessions), infant anthropometric measures (initial LAZ and weight-for-length *z* score), infant preintervention morbidity (prevalence of diarrhea, URI, fever, and poor appetite), infant zinc and iron status indicators (initial plasma zinc and ferritin concentrations and hemoglobin concentration), and other infant characteristics (infant sex and initial breastfeeding status). In addition, all interactions of the foregoing variables with treatment group were tested for statistical significance. Nonsignificant variables were removed in stepwise fashion until all remaining variables in the model had a $P$ value $< 0.05$. Tukey's test was used for post hoc comparisons of groups. Categorical variables were compared by chi-square analyses or logistic regression, after control for baseline variables and other covariates. All analyses were completed by using SAS for WINDOWS release 9 (SAS Institute, Cary, NC).

## RESULTS

### Study profile

Of the 927 infants originally screened, 408 (44.0%) were eligible to participate in the trial. The major reason for disqualification was because of an initial length LAZ $> -0.5$. The families of 360 (88.2%) of the eligible infants agreed to participate in the baseline observations, and 302 of them (74.0% of those originally eligible) decided to continue in the intervention trial. As shown in the profile of study subjects (**Figure 1**), 274 (90.7%) of the infants assigned to 1 of the 3 treatment groups completed ≥3 mo of observation, and 262 (86.8%) completed the full 6 mo of study. Infants assigned to the 2 zinc groups (ZnSuppl and ZnFort) were significantly more likely to exit the study early than were those in the control group (82.8% compared with 94.9%, respectively; $P = 0.013$). For the purpose of comparing baseline characteristics of those who departed from the study early and those who completed the full set of observations (as presented in the following section), we defined dropouts as those 40 children who were assigned to treatment group but failed to provide information on both anthropometric and biochemical outcomes at the end of the 6-mo intervention period.

**TABLE 1**
Initial characteristics of study subjects and their households[1]

| Variable | Treatment group | | | $P^2$ |
|---|---|---|---|---|
| | Control ($n = 99$) | ZnSuppl ($n = 101$) | ZnFort ($n = 102$) | |
| Male (%) | 48.5 | 48.5 | 44.1 | 0.77 |
| Infant age at enrollment (mo) | 7.4 ± 0.9[3] | 7.6 ± 0.9 | 7.5 ± 0.9 | 0.11 |
| Percentage breastfeeding infants (%) | 97.0 | 92.1 | 96.1 | 0.24 |
| Body weight (kg) | 7.6 ± 0.9 | 7.6 ± 0.8 | 7.6 ± 0.9 | 0.80 |
| Length (cm) | 65.2 ± 2.0 | 65.6 ± 1.9 | 65.2 ± 2.1 | 0.39 |
| Weight-for-age *z* score | −0.66 ± 0.86 | −0.84 ± 0.95 | −0.63 ± 0.84 | 0.20 |
| Length-for-age *z* score | −1.18 ± 0.49 | −1.20 ± 0.54 | −1.20 ± 0.52 | 0.94 |
| Weight-for-length *z* score | 0.56 ± 0.99 | 0.36 ± 1.00 | 0.63 ± 0.89 | 0.11 |
| Maternal age (y) | 25.8 ± 7.0 | 27.7 ± 6.4 | 26.3 ± 6.2 | 0.11 |
| Paternal age (y)[4] | 29.6 ± 7.3 | 30.7 ± 6.6 | 30.7 ± 9.1 | 0.53 |
| Maternal height (cm) | 148.4 ± 5.0 | 147.5 ± 5.2 | 148.6 ± 5.4 | 0.27 |
| Maternal BMI (kg/m$^2$) | 25.6 ± 4.1 | 26.0 ± 3.9 | 25.7 ± 3.5 | 0.71 |
| Maternal education (% completing secondary school) | 32.3[a,b] | 25.0[a] | 41.2[b] | 0.05 |
| Paternal education (% completing secondary school)[5] | 38.3 | 37.1 | 47.9 | 0.25 |
| Mother employed (%) | 37.3 | 38.0 | 31.4 | 0.55 |
| Father employed (%)[5] | 58.2 | 52.3 | 52.1 | 0.64 |
| Piped water in house (%) | 61.0 | 54.7 | 50.6 | 0.35 |
| Indoor toilet (%) | 45.5 | 48.0 | 45.1 | 0.90 |
| Cement floor (%) | 38.4 | 34.0 | 34.3 | 0.77 |
| Gas or electric cook stove (%) | 53.5[a] | 36.0[b] | 47.1[a] | 0.043 |
| Infant preintervention morbidity rates | | | | |
| Prevalence of diarrhea (% of d with ≥3 loose stools)[6] | 10.3 ± 13.0 | 13.7 ± 15.9 | 11.1 ± 13.8 | 0.30 |
| Prevalence of diarrhea (% of d with ≥4 loose stools)[7] | 5.6 ± 10.1 | 8.2 ± 12.1 | 5.4 ± 8.9 | 0.15 |
| Prevalence of upper respiratory infection (% of d)[6] | 31.2 ± 28.2 | 37.6 ± 27.6 | 31.9 ± 27.2 | 0.095 |
| Prevalence of fever (% of d)[6] | 9.4 ± 9.5 | 11.6 ± 9.5 | 8.9 ± 8.6 | 0.075 |
| Prevalence of diminished appetite (% of d)[6] | 21.8 ± 22.1 | 23.8 ± 23.6 | 17.6 ± 17.8 | 0.20 |
| Infant biochemical assessments | | | | |
| Plasma zinc concentration (μg/dL) | 78.6 ± 15.1 | 76.6 ± 14.8 | 77.7 ± 14.9 | 0.67 |
| Low plasma zinc concentration, <64 μg/dL (%) | 14.3 | 17.6 | 18.5 | 0.73 |
| Hemoglobin (g/dL) | 10.5 ± 1.0 | 10.5 ± 1.1 | 10.6 ± 0.9 | 0.70 |
| Anemia, hemoglobin <11 g/dL (%) | 66.7 | 67.3 | 59.8 | 0.46 |
| Plasma ferritin (μg/L)[7] | 24.4 ± 31.1[a] | 32.8 ± 32.0[b] | 29.3 ± 31.6[a,b] | 0.038 |
| Low plasma ferritin, <12 μg/L (%) | 44.4[a] | 26.7[b] | 36.3[a,b] | 0.045 |
| Elevated C-reactive protein, >10 mg/L (%) | 15.6 | 29.3 | 25.3 | 0.079 |
| Iron deficiency anemia, hemoglobin <11 g/dL and plasma ferritin <12 μg/L (%) | 35.6 | 23.3 | 28.6 | 0.19 |
| Plasma copper (μg/dL) | 155.1 ± 29.4 | 164.1 ± 34.5 | 155.5 ± 35.0 | 0.12 |

[1] ZnSuppl,zinc-supplemented group; ZnFort, zinc-fortified group. Values with different superscript letters are significantly different, $P < 0.05$ (Tukey's or Bonferroni test).
[2] Significance of group-wise comparison by ANOVA or chi-square analysis.
[3] $\bar{x}$ ± SD (all such values).
[4] $n = 286$.
[5] $n = 275$.
[6] Variables transformed and analyzed by using square root transformation.
[7] Variables transformed and analyzed by using logarithmic transformation.

## Baseline characteristics

Selected initial characteristics of the study subjects and their families are displayed by treatment group in **Table 1**. No significant differences in infant sex ratios, age at enrollment, initial breastfeeding status, or anthropometric indicators of nutritional status by treatment group were observed. As dictated by the study protocol, all of the infants had a negative LAZ; and the overall mean LAZ was approximately −1.20 at baseline. Household SES did not differ significantly by treatment group, except that mothers of infants in the ZnFort group were more likely to have completed secondary school than mothers of those in the ZnSuppl group, and the latter mothers were slightly less likely to cook with gas or electricity than were the former women. No significant group-wise differences in the infants' preintervention prevalence rates of diarrhea, URI, fever, or diminished appetite were observed. The rates of LRI were not obtainable during the baseline period because respiratory rates were not ascertained, and the incidence of severe diarrhea was too low to provide a useful point estimate during the 1-mo baseline period; therefore, this information is not included in the table.

**TABLE 2**
Biochemical indicators of micronutrient status at baseline, by concentration of C-reactive protein (CRP)

| Variable | Plasma CRP concentration: Normal, <10 mg/L ($n$ = 208) | Plasma CRP concentration: Elevated, ≥10 mg/L ($n$ = 64) | $P^1$ |
|---|---|---|---|
| | $\mu$g/dL | | |
| Plasma zinc | 78.9 ± 14.6[2] | 73.7 ± 15.6 | 0.015 |
| Plasma ferritin | 25.8 ± 27.8 | 37.6 ± 40.2 | < 0.001 |
| Plasma copper | 154.3 ± 30.6 | 171.6 ± 38.4 | 0.007 |

[1] Means were compared by $t$ test; logarithmic transformation of ferritin was used.
[2] $\bar{x}$ ± SD (all such values).

The infants' mean plasma zinc concentrations ranged from 77 to 79 $\mu$g/dL in the 3 treatment groups, and ≈17% of the infants had plasma zinc concentrations that were less than the cutoff of 65 $\mu$g/dL suggested by IZiNCG (1). Nearly two-thirds of the infants had mild anemia (hemoglobin <11 g/dL), 36% had low plasma ferritin concentrations (<12 $\mu$g/L), and 29% had iron deficiency anemia (hemoglobin <11 g/dL and plasma ferritin <12 $\mu$g/L). Overall, fewer than 2% of the infants had low plasma copper concentrations (<80 $\mu$g/dL).

As indicated in Table 1, 23% of the infants had elevated plasma CRP concentrations (>10 mg/L) initially. Infants with elevated CRP values at the time of their baseline blood sampling had significantly lower mean plasma zinc concentrations and significantly greater mean plasma ferritin and copper concentrations (**Table 2**). Although the percentage of infants with low initial plasma ferritin concentrations was significantly greater in the control group than in the ZnSuppl group (Table 1), this difference was no longer statistically significant after adjustment for the presence of elevated CRP values.

The baseline characteristics of the 40 children who left the study early, as described above, were compared with those of the children who completed the full set of observations. The children who departed from the study early were less likely to be breast-feeding at enrollment (85.0% compared with 96.6%, $P = 0.008$), and they had lower initial mean weight-for-age $z$ scores (−0.98 compared with −0.67, $P = 0.036$) and LAZs (−1.35 compared with −1.17, $P = 0.031$) and a higher mean prevalence of diarrhea during the baseline period (15.6% compared with 11.1% days of observation, $P = 0.02$). The children who withdrew prematurely did not differ significantly with the children in the study with regard to any of their biochemical indicators of nutritional status or SES variables, except that they had slightly smaller mean household sizes (4.9 compared with 5.9 persons per household, $P = 0.01$).

## Compliance with treatment

As indicated above, porridge consumption was estimated both by disappearance of the amount delivered to the households each week and by the combination of fieldworker direct observations and caregiver reports of the amounts prepared and served each day. The former method probably overestimates actual consumption, because it includes any losses, plate wastes, and amounts consumed by other members of the household. The children reportedly were served at least some of the porridge on ≈86% of possible study days (**Table 3**). Notably, the children who were assigned to the ZnFort group received the porridge on a slightly lower percentage of days than those who were assigned to the non-zinc-fortified porridge. As expected, the estimated average amounts of porridge consumed were slightly greater when estimated from disappearance rates than from observations or reports of consumption. Regardless of the estimation technique, children who were assigned to the zinc-fortified product consumed slightly less of the porridge. Nevertheless, according to the observed and reported intake data, children in the ZnFort group consumed a mean (±SD) of 21.9 ± 8.4 g dry weight of porridge/d, which would have provided them with an additional 3.3 ± 1.3 mg Zn/d.

The liquid supplement was reportedly offered to the children on ≈96% of possible study days, and this did not differ significantly by treatment group (Table 3). According to the fortnightly disappearance rates of the liquid supplements, the children received a mean intake of ≈0.39 mL/d overall, and there were no significant differences by treatment group. The mean amount of the liquid supplement consumed by those in the ZnSuppl group (0.38 mL/d) would have provided an additional 2.3 ± 0.4 mg Zn/d.

## Growth

The mean changes in infant body weight, length, and anthropometric indexes are listed by treatment group in **Table 4**. Data

**TABLE 3**
Reported frequency and daily amounts of consumption of porridge and liquid supplements by treatment group[1]

| Variable | Treatment group: Control ($n$ = 99) | Treatment group: ZnSuppl ($n$ = 101) | Treatment group: ZnFort ($n$ = 102) | $P^2$ |
|---|---|---|---|---|
| Reported frequency of any porridge consumption (% of d) | 87.8 ± 8.3[a] | 87.1 ± 9.1[a] | 83.6 ± 11.8[b] | 0.006 |
| Amount of porridge consumption, weekly disappearance of amount delivered (g/d) | 28.8 ± 5.2[a] | 28.5 ± 5.7[a] | 26.4 ± 6.5[b] | 0.007 |
| Amount of porridge consumption, observed and reported amounts served (g/d) | 24.4 ± 7.1[a] | 25.4 ± 7.5[a] | 21.9 ± 8.4[b] | 0.005 |
| Reported frequency of liquid supplement consumption (% of d) | 96.3 ± 3.9 | 95.9 ± 4.2 | 95.3 ± 6.7 | 0.17 |
| Amount of supplement consumption, based on fortnightly disappearance of amount delivered (mL/d) | 0.40 ± 0.08 | 0.38 ± 0.07 | 0.39 ± 0.08 | 0.14 |

[1] All values are $\bar{x}$ ± SD. ZnSuppl, zinc-supplemented group; ZnFort, zinc-fortified group. Groups with different superscripts are significantly different, $P < 0.05$ (Tukey's test).
[2] Treatment group means were compared by ANOVA, weighted by the number of days of observation.

**TABLE 4**
Mean change in weight, length, and anthropometric indexes during the 6-mo intervention period and percentage of infants stunted at the end of the study, by treatment group[1]

| | Treatment group | | | |
|---|---|---|---|---|
| Variable | Control ($n$ = 92) | ZnSuppl ($n$ = 83) | ZnFort ($n$ = 84) | $P^2$ |
| Change in weight (kg) | 1.33 ± 0.46 | 1.37 ± 0.53 | 1.28 ± 0.54 | 0.64 |
| Change in length (cm) | 7.0 ± 1.1 | 7.0 ± 1.0 | 6.9 ± 1.1 | 0.75 |
| Change in weight-for-age $z$ score | −0.69 ± 0.51 | −0.59 ± 0.65 | −0.74 ± 0.63 | 0.51 |
| Change in length-for-age $z$ score | −0.16 ± 0.37 | −0.15 ± 0.33 | −0.18 ± 0.38 | 0.81 |
| Change in weight-for-length $z$ score | −0.56 ± 0.65 | −0.47 ± 0.77 | −0.60 ± 0.74 | 0.90 |

[1] All values are $\bar{x}$ ± SD. ZnSuppl, zinc-supplemented group; ZnFort, zinc-fortified group.
[2] Treatment group means for the change from initial to final value for each variable were compared by ANCOVA, with control for the initial value of the respective variable and other relevant covariates and potential modifying effects, as described in Methods.

are presented in the table only for those subjects who completed 6 mo of observation, although separate analyses were completed for all children who remained in the study for ≥3 mo, and the conclusions of the latter analyses were consistent with those from the 6-mo observations. Overall, the children gained an average of ≈1.32 kg in body weight and ≈7 cm in length during the 6-mo period of observation. Their LAZs declined by an average of −0.17, and the final overall mean LAZ was −1.33. No significant differences in growth increments or change in anthropometric indexes were observed by treatment group, even after control for potential confounders, and there were no significant interactions between treatment group and baseline anthropometric status or other potential modifying effects of response to treatment.

## Morbidity

The prevalence or incidence rates for diarrhea, respiratory infections, fever, and diminished appetite are presented in **Table 5**. No significant differences in diarrhea rates were observed by treatment group, regardless of the definition applied or the presence of selected indicators of illness severity, and there were no significant interactions between any of the infants' baseline characteristics and treatment group. Factors associated with greater diarrhea prevalence were child sex (boys had slightly higher rates than did girls), SES (specifically, poorer housing quality and less maternal education), and a greater initial prevalence of diarrhea during the preintervention period.

No significant treatment-related differences in the prevalence of URI or interactions between baseline characteristics and treatment group were observed. The only factor related to URI prevalence during the intervention period was the initial prevalence of URI during the baseline (preintervention) period.

The diagnosis of LRI was based on the presence of cough and elevated respiratory rate. Fieldworker observations of respiratory frequency were available on 29% of days when mothers reported that the children were breathing rapidly and 11% of days when the mothers reported that their children were breathing normally. The fieldworker was able to confirm an age-specific elevated respiratory rate only 22% of the time the mothers reported rapid breathing, although a non-elevated respiratory rate could be verified 98% of the time that the children's breathing was reportedly normal. Because of the low sensitivity of the mothers' diagnosis of elevated respiratory rate, we considered LRI to be present only when a fieldworker or study physician could confirm an elevated respiratory rate. No significant group-related differences in the incidence of LRI were observed, and there were no interactions between the infants' baseline status (including baseline prevalence of URI, which was associated with subsequent LRI incidence) and treatment group.

**TABLE 5**
Mean prevalence or incidence of selected illnesses or illness symptoms during the intervention period, by treatment group[1]

| | Treatment group | | | |
|---|---|---|---|---|
| Variable | Control ($n$ = 99) | ZnSuppl ($n$ = 101) | ZnFort ($n$ = 102) | $P^2$ |
| Prevalence of diarrhea, >3 loose stools/d (%) | 9.4 ± 6.9 | 12.0 ± 10.3 | 11.1 ± 8.7 | 0.67 |
| Prevalence of diarrhea, >4 loose stools/d (%) | 5.2 ± 4.1 | 7.3 ± 7.5 | 6.0 ± 5.7 | 0.61 |
| Incidence of severe diarrhea (episodes/100 d of observation) | 1.76 ± 1.27 | 2.29 ± 2.12 | 2.07 ± 1.87 | 0.65 |
| Prevalence of URI (%) | 33.0 ± 19.3 | 36.6 ± 21.0 | 32.7 ± 18.4 | 0.84 |
| Incidence of LRI (episodes/100 d at risk) | 0.20 ± 0.41 | 0.24 ± 0.57 | 0.22 ± 0.59 | 0.61[3] |
| Prevalence of fever (%) | 6.9 ± 4.0 | 7.7 ± 4.5 | 6.3 ± 4.3 | 0.083 |
| Prevalence of diminished appetite (%) | 17.5 ± 12.1 | 19.8 ± 13.2 | 19.8 ± 13.6 | 0.26 |

[1] All values are $\bar{x}$ ± SD; means are weighted by number of days of observation. ZnSuppl, zinc-supplemented group; Zn:Fort, zinc-fortified group; URI, upper respiratory infection; LRI, lower respiratory infection.
[2] Treatment group means were compared by ANCOVA, with control for the initial value of the respective variable and other relevant covariates and potential modifying effects, as described in the Methods.
[3] Compared by Kruskal-Wallis test.

**TABLE 6**
Mean changes in biochemical indicators of nutritional status during the 6-mo intervention period, by treatment group[1]

| Variable | Treatment group | | | $P^2$ |
|---|---|---|---|---|
| | Control ($n$ = 77–91) | ZnSuppl ($n$ = 67–81) | Zn Fort ($n$ = 70–83) | |
| Change in plasma zinc ($\mu$g/dL) | −3.9 ± 15.2[3,a] | 4.3 ± 15.3[b] | −1.5 ± 13.7[a] | < 0.001 |
| Change in hemoglobin (g/dL) | −0.26 ± 1.05 | −0.01 ± 1.26 | −0.12 ± 1.08 | 0.17 |
| Change in percentage anemia, hemoglobin <11 g/dL (%) | 6.6 (−0.9, 14.1)[4] | −2.5 (−16.0, 11.1) | 3.6 (−9.8, 17.0) | 0.31 |
| Change in serum ferritin ($\mu$g/L) | −14.3 ± 27.4 | −20.9 ± 28.7 | −15.3 ± 43.4 | 0.51 |
| Change in percentage low serum ferritin, <12 $\mu$g/L (%) | 28.6 (15.9, 41.3) | 29.9 (15.8, 43.9) | 31.4 (17.6, 45.2) | 0.13 |
| Change in percentage iron deficiency anemia, hemoglobin <11 g/dL and serum ferritin <12 $\mu$g/L (%) | 19.7 (8.5, 30.9) | 18.2 (3.9, 32.4) | 18.8 (5.6, 32.0) | 0.38 |
| Change in plasma copper ($\mu$g/dL) | 9.6 ± 33.7 | 4.1 ± 39.4 | −5.1 ± 37.2 | 0.38 |

[1] ZnSuppl, zinc-supplemented group; Zn Fort, zinc-fortified group. The number of observations vary for each outcome within ranges indicated. Values with different superscript letters are significantly different, $P < 0.05$ (Tukey's test).
[2] Groups were compared by ANCOVA, with control for the initial value of the respective variable and other relevant covariates and potential modifying effects, as described in the Methods.
[3] $\bar{x}$ ± SD (all such values).
[4] $\bar{x}$; 95% CI in parentheses (all such values).

Similar to the foregoing disease entities, there were no significant differences in the rates of reported symptoms of fever or diminished appetite by treatment group, and there were no significant interactions between the children's baseline characteristics and treatment group. The only factors associated with the prevalence of these symptoms during the intervention period were their prevalence rates during the baseline observation period.

### Biochemical indicators of nutritional status

As shown in **Table 6**, there were significant differences ($P <$ 0.001) in the mean changes in plasma zinc concentration by study group. The mean plasma zinc concentration declined significantly ($P = 0.009$) in the control group and slightly, but not significantly ($P = 0.18$), in the ZnFort group, whereas the mean plasma zinc concentration increased significantly ($P = 0.004$) in the ZnSuppl group. The results for the control group and the ZnFort group were not significantly different, and when the data for the 2 groups were aggregated, the combined mean value differed significantly from zero ($P = 0.005$). No significant interaction between treatment group and the baseline plasma zinc concentrations was observed.

No significant differences in final plasma ferritin or copper concentrations were observed by treatment group after adjustment for appropriate covariates, and no interactions between the treatment group variable and covariates in the model (eg height-for-age and baseline plasma zinc concentration) were observed. Likewise, there were no significant group-wise differences in the changes in the percent of children with anemia, iron deficiency, or iron deficiency anemia.

Because of the significant association between elevated plasma CRP concentrations and indicators of zinc, iron, and copper status at baseline, we also developed more complex statistical models to account for CRP status when assessing the effect of the interventions on final biochemical indicators of nutritional status. In particular, we adjusted the initial plasma zinc, ferritin, and copper concentrations for CRP status and then compared the final concentrations of the nutritional status indicators by treatment group using analysis of covariance and with control for the initial adjusted concentration of the respective indicator and the final CRP status and their interactions with treatment group. In all cases, the significant associations between CRP status and the plasma concentrations of the nutritional status indicators that were seen at baseline were also present at the end of the trial.

A significant interaction between CRP status and treatment group was observed for the change in plasma zinc concentration ($P = 0.028$). Specifically, among children with normal final CRP status, those in the ZnSupp group had a significantly greater ($P =$ 0.009) mean change from baseline plasma zinc concentration compared with those in the control group and a nonsignificant greater change ($P = 0.099$) than those in the ZnFort group. In contrast, among children with elevated final CRP values, there was a significantly greater decline ($P < 0.025$) in mean plasma zinc concentrations among those in the control group compared with those children in the 2 groups that received zinc. No significant interactions between CRP status and treatment group were observed for plasma ferritin or copper concentrations.

## DISCUSSION

The results indicate that providing additional zinc to young children in this study population, either as a supplement or as a zinc-fortified food, did not affect their growth performance or rates of morbidity from common childhood infections. The final mean plasma zinc concentration increased significantly among children who received zinc in the form of an aqueous supplement but not among those who received a slightly greater amount of zinc in a fortified food. The overall lack of functional response to additional zinc was unexpected, because the study subjects were selected based on their presumed elevated risk of zinc deficiency. In particular, we enrolled infants 5–7 mo of age whose initial LAZs were < –0.5, because previous longitudinal observations in other low-income Peruvian communities found that such infants had mean LAZ scores < –1.5 at 12 mo (11). However, the children in the present study had final mean LAZs > –1.5, which is the level of growth restriction at which previous intervention trials found a positive growth response to zinc supplementation (7). Thus, the children in the present study may not have been sufficiently growth-restricted to respond to additional zinc with

increased rates of growth. Moreover, low initial plasma concentrations were present among slightly fewer than 20% of the study population, which is the prevalence of low plasma zinc concentrations considered to be indicative of population zinc deficiency (1). Thus, the children in the present study may not have been sufficiently zinc-deficient to respond to the intervention, despite the selection criteria applied.

Other possible explanations for the negative results are that the amount of additional zinc provided was insufficient to normalize the children's zinc status or the additional nutrients provided by the porridge and vitamin supplements contributed independently to the children's growth performance and therefore blunted our ability to detect a zinc-specific effect. With regard to the dose of zinc that was provided, previous zinc supplementation trials that yielded a positive effect on children's growth used doses ranging from 5–20 mg Zn/d (1). However, none of these former studies compared multiple doses in the same trial, so the minimum effective supplement dose is still uncertain, and this will likely vary depending on the population's usual dietary zinc intake. In any case, the IZiNCG recommends that the dietary zinc intake for children 6–11 mo be 4–5 mg/d (depending on the zinc bioavailability from the diet), suggesting that the dose of supplement used in the present study, when provided in addition to the children's usual dietary intake of ≈1.5 mg/d, should have been adequate to meet their physiologic zinc requirements. Because all of the study groups in the current trial received both the iron-fortified porridge and the liquid vitamin supplement, it is not possible to determine whether these had any independent effects on the children's growth or morbidity.

One of the original objectives of the present study was to measure the functional effect of providing additional zinc in a fortified food. However, because of the lack of functional response in the ZnSuppl group, we cannot assess the effect of the zinc-fortified food in the present study. Nevertheless, the lack of a positive response in plasma zinc concentrations in the ZnFort group provides cause for concern. Almost all previous zinc supplementation trials in young children reported increased plasma zinc concentrations, which was also the case in the present study. Thus, the lack of response to a zinc-fortified food containing a similar, indeed slightly greater, total amount of zinc suggests that the zinc may have been less well absorbed from the fortified product. On the other hand, previous tracer studies, albeit carried out in slightly older children, found that total absorbed zinc did increase when children received zinc-fortified foods (8–10). Thus, further studies will be needed in populations that are more zinc-deficient than the present study population to determine whether the amount of zinc absorbed from a fortified food is sufficient to produce the desired functional responses.

Although it is conceivable that greater doses of zinc may be necessary to boost plasma zinc concentrations and functional responses, the level of fortification used in the current study (150 mg Zn/kg dry product) was already considerably greater than that recommended by IZiNCG (1) for universal flour fortification programs (≈30–70 mg/kg flour). Thus, higher levels of fortification may be suitable only for products specifically targeted to young children, and the sensory acceptability of these higher levels of fortification would need to be confirmed. Earlier studies by our group found that adults began to detect less desirable sensory attributes of zinc-fortified pasta when the level of fortification reached 100 mg/kg (17). Moreover, the slightly lower level of consumption of the zinc-fortified porridge in the present study suggests that the children may have sensed some undesirable attributes of the zinc-fortified product. Thus, it may not be possible to increase the level of fortification further unless taste-masking compounds or encapsulated forms of zinc are added, which of course would raise the cost of the final products.

Most previous zinc intervention trials among young children found decreased rates of morbidity from diarrhea, respiratory infections, or both (2). Thus, the lack of a similar benefit of zinc in the current study was somewhat surprising. However, the sample sizes were adequate to detect only relatively large decreases in morbidity of ≈30–40%, whereas the overall reduction in diarrhea rates observed in earlier trials was ≈15–20%; the number of episodes of LRI in the present study was also very low. Thus, there may not have been adequate power to detect any effect of providing additional zinc. Alternatively, the children may not have been sufficiently zinc-deficient to benefit from zinc or the doses provided may have been too low, as discussed above.

Importantly, there were no significant treatment group-related differences in the postintervention indicators of iron or copper status or presence of anemia. Thus, there were no detectable adverse effects of zinc on these other conditions. Iron status declined appreciably during the course of the study (as frequently occurs among children of this age range), despite the fact that the porridge provided to the children was iron-fortified. Presumably, the level of iron fortification, which was consistent with the existing national policy, was not sufficient to allow the children to recover fully from preexisting iron deficiency.

One possible limitation of our study was the disproportionate number of dropouts from the 2 groups that received additional zinc and the fact that those who left the study early differed slightly with regard to their initial rates of breastfeeding, anthropometric indicators of nutritional status, and prevalence of diarrhea. Nevertheless, the baseline characteristics of children who completed the study were included in all the final statistical models, so any possible biases introduced by the differential dropout rate would have been adjusted statistically. In fact, the overall attrition rate was relatively small, as were the differences between the children who left the study early and those who completed the study, so these should not have exerted any major effect on the results.

In conclusion, provision of additional zinc, either in the form of an aqueous zinc-containing, multinutrient supplement or a zinc-fortified cereal porridge did not affect the physical growth or morbidity from common childhood infections among the children in this study population, possibly because they were not sufficiently growth restricted or zinc deficient initially or because the level of zinc intake or absorption was inadequate. Whereas the mean plasma zinc concentration increased significantly among those who received zinc in the form of an aqueous supplement, there was no plasma zinc response to the zinc-fortified product. Nevertheless, it is conceivable that children could benefit functionally from a zinc-fortified food even if there is no effect on their plasma zinc concentration. Thus, additional studies of the functional effect of zinc-fortified foods are still needed in populations that are known to respond to zinc supplements. No adverse effects of either form of additional zinc on indicators of the children's iron or copper status were observed. Thus, there is no reason to refrain from adding zinc to the premix of mineral-fortified foods in populations at risk of zinc deficiency, even though the efficacy of zinc fortification for young children remains uncertain.

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KHB was responsible for the study design, overall supervision of the research team, interpretation of results, and preparation of the manuscript. DLdR and JEA supervised the day-to-day implementation of the project in the field and assisted with the interpretation of results and preparation of the manuscript. MEP assisted with the study design, training of field staff, interpretation of results, and preparation of the manuscript. JMP completed the statistical analyses and assisted with the interpretation of results and preparation of the manuscript. None of the authors has any conflict of interest.

## REFERENCES

1. International Zinc Nutrition Consultative Group. Assessment of the risk of zinc deficiency in populations and options for its control. Hotz C, Brown KH (eds). Food Nutr Bull 2004;25:S94–S203.
2. Bhutta ZA, Black RE, Brown KH, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. J Pediatr 1999;135:689–97.
3. Sazawal S, Black R, Menon V, et al. Zinc supplementation in infants born small for gestational age reduces mortality: A prospective, randomized, controlled trial. Pediatrics 2001;108:1280–6.
4. Müller O, Becher H, van Zweeden AB, et al. Effect of zinc supplementation on malaria and other causes of morbidity in West African children: randomised double blind placebo controlled trial. BMJ 2001;322:1567–72.
5. Baqui AH, Black RE, El Arifeen S, et al. Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. BMJ 2002;325:1059–64.
6. Brooks WA, Santosham M, Naheed A, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. Lancet 2005;366:999–1004.
7. Brown KH, Peerson JM, Rivera J, Allen LH. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2002;75:1062–71.
8. Lopez de Romaña D, Salazar M, Hambidge KM, et al. Longitudinal measurements of zinc absorption in Peruvian children consuming wheat products fortified with iron only or iron and 1 of 2 amounts of zinc. Am J Clin Nutr 2005;81:637–47.
9. Herman S, Griffin IJ, Suwarti S, et al. Cofortification of iron-fortified flour with zinc sulfate, but not zinc oxide, decreases iron absorption in Indonesian children. Am J Clin Nutr 2002;76:813–7.
10. Hettiarachchi M, Hilmers DC, Liyanage C, Abrams SA. Na2EDTA enhances the absorption of iron and zinc from fortified rice flour in Sri Lankan children. J Nutr 2004;134:3031–6.
11. Lopez de Romaña G, Brown KH, Black RE, Kanashiro HC. Longitudinal studies of infectious diseases and physical growth of infants in Huascar, an underprivileged peri-urban community in Lima, Peru. Am J Epidemiol 1989;129:769–84.
12. Moses LE, Oakford RY. Tables of random permutations. Stanford, CA: Stanford University Press, 1963.
13. Duggan C, Penny ME, Hibberd P, et al. Oligofructose-supplemented infant cereal: 2 randomized, blinded, community-based trials in Peruvian infants. Am J Clin Nutr 2003;77:937–42.
14. US Department of Agriculture. USDA National Nutrient Database for Standard Reference, Release 15. Internet: http://www.nal.usda.gov/fnic/foodcomp/Data/SR15/asc/sr15fg.html (accessed 31 August 2006).
15. Hess SY, Peerson JM, Huapaya A, et al. Comparison of techniques to assess young children's consumption of processed complementary foods in community-based studies. FASEB J 2006;20:A1048 (abstr).
16. World Health Organization. Management of a child with a serious infection or severe malnutrition: Guidelines for care at the first-referral level in developing countries. Geneva, Switzerland: World Health Organization, 2000.
17. Lopez de Romaña D, Brown KH, Guinard J-X. Sensory trial to assess the acceptability of zinc fortificants added to iron-fortified wheat products. J Food Sci 2002;67:461–5.