

Benefits of zinc supplementation for child growth^{1,2}

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Brown et al (1) have updated a meta-analysis of the effects of zinc supplements on the growth of children in developing countries. The new analysis, which was based on 33 randomized controlled trials, shows a highly significant aggregate effect size of 0.350 (95% CI: 0.189, 0.511) for height, 0.309 (95% CI: 0.178, 0.439) for weight, and ≈ 0 for weight-for-height increments. The previous effort found smaller but significant effects, for example, an effect size of 0.22 for height increments (2).

Several factors may explain the differences in effect sizes between the 2 analyses. The inclusion criteria were modified in the most recent analysis and trials lasting <8 wk and that included premature or severely malnourished infants, a total of 9 studies, were omitted. These changes in inclusion criteria are justified and make the findings relevant to nonhospitalized children. Fourteen studies were additions to the second analysis (although 5 were published before 1996, the upper bound of the first analysis), and only 20 were common to both analyses. Both analyses included prepubertal children but the age range was narrower in the second (from 0 to 10 y rather than to 13 y).

A major criticism of meta-analyses is known as the “file drawer problem” (3, 4). This is the fear that the literature includes a preponderance of papers that show significant results while the file drawers of researchers back at the office are filled with papers that were rejected or never submitted for publication because they lacked significant results. Brown et al assessed the extent of publication bias in 2 ways. First, if studies with nonsignificant results and with small sample sizes are more likely to be excluded, one should find a negative correlation between sample size and effect size across studies. Brown et al reported a correlation of -0.28 for height increments, the key outcome. The negative sign is in the direction of the predicted bias but is nonsignificant ($P > 0.05$, two-tailed test) for a sample size of 33 studies. Second, the authors estimated the number of studies with a zero effect size that would be required to “invalidate the reported findings,” that is, to make the significance test for the aggregate effect size become nonsignificant. They report that >500 such studies would be required, a number that unquestionably exceeds the likely number of unpublished studies. But what number would trigger concern? This is likely to vary by subject. Rosenthal (3) offers a rule of thumb of $5k + 10$, where k is the number of studies included in the meta-analysis. For the zinc meta-analysis, the tolerance level is 175 studies, also an unlikely number of unpublished studies.

It is not unusual to report that a huge number of zero-effect studies are needed to make the aggregate test in a meta-analysis insignificant. However, these conclusions are misleading because they ignore effect size (4). Aggregate study results could still be

significant after adding a large number of zero-effect studies (for example, the 175 found by the Rosenthal formula), even though the resulting mean effect size would be tiny. It is more useful to estimate the number of studies required to bring the effect size down to a specific level beyond which we do not care (4). The number of required studies (x) is estimated as $x = k [(\bar{d}_k/\bar{d}_c) - 1]$, where k is the number of studies included in the meta-analysis, \bar{d}_k is the aggregate effect size found, and \bar{d}_c is the threshold effect size stipulated. For example, if we set \bar{d}_c at 0.1 for height increments, a very small effect size, the number of studies required to bring the effect size to this level is 83. The zinc research community is small and the authors, very active within this group, uncovered several unpublished studies, one of which was included in the analysis. Because it is doubtful that their network missed 83 studies, we should view the results as robust.

Brown et al also included an analysis of effects on serum zinc concentrations and concluded that the population mean is a useful indicator of successful delivery and efficacy of supplementation (or indeed of any intervention aimed at improving zinc status). The effect size found for serum zinc concentrations was large, 0.820 (95% CI: 0.50, 1.14). This is an important demonstration because of the known unreliability of a single serum zinc determination in an individual.

Poorer growth at baseline was associated with an enhanced response in growth across studies but serum zinc concentration was not. Effect sizes for height increments were about twice as large when the initial z score for height or weight was below -2 SDs compared with when they were not. Surprisingly, the mean age of the children at baseline was not a predictor of response, although a trend toward larger effect sizes was observed for studies of younger children.

What are the implications for targeting programs? Undoubtedly, where considerable stunting exists and diets are judged to be deficient in available zinc, zinc deficiency is likely to exist. These populations should be given priority for interventions, but within a given population, it would be inappropriate to target by level of stunting. Some benefit would be lost to nonstunted children and, more importantly, young children on the road to stunting would be missed. Should zinc interventions be aimed at all

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prepubertal children regardless of age? To answer this question properly, we need to also consider effects on other outcomes. A pooled analysis of studies of children aged <5 y, an approach that differs from meta-analysis in the use of individual-level data rather than just study means, showed that zinc supplementation was associated with an 18% reduction in diarrhea incidence and a 41% reduction in pneumonia, the leading causes of morbidity, stunting, and death in young children in developing countries (5). Recently, zinc supplementation was found to reduce mortality by 68% among infants born full term and small for gestational age (6). These findings underscore that young children should be the priority of zinc improvement programs, even if the effect of zinc supplementation on growth is independent of age.

There remains no doubt that dietary quality matters and that nutritional needs, especially in young children, are unlikely to be met in poor countries, even when enough food is consumed to meet energy needs. Now that evidence has accumulated to view zinc deficiency as an additional, important micronutrient problem in many developing countries, the pressing questions are about what to do. Daily supplementation with zinc, even in combination with other nutrients, is too complicated and expensive for poor countries. Improving complementary feeding through nutrition education has potential but is not easy to do. The foods richest in zinc are from animal sources, but these are not often included in toddlers' diets because of entrenched custom, religion, or cost (7). The use of fortified complementary foods appears promising and several experiences in Latin America with industrially prepared foods are being evaluated for cost-effectiveness (8). Home-level fortification of complementary foods by mothers is a cheaper approach that was shown to be efficacious for treating anemia (9) and that needs to be tested for zinc and other deficiencies. ❁

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