Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions1–3

Usha Ramakrishnan, Phuong Nguyen, and Reynaldo Martorell

ABSTRACT

Background: Micronutrient interventions have received much attention as a cost-effective and promising strategy to improve child health, but their roles in improving child growth remain unclear.

Objective: Meta-analyses of randomized controlled trials were conducted to evaluate the effect of micronutrient interventions on the growth of children aged <5 y old.

Design: Eligible studies were identified by PubMed database searches and other methods. Weighted mean effect sizes and 95% CIs were calculated for changes in height, weight, and weight-for-height z scores (WHZ) by using random-effect models. Tests for publication bias were done by using funnel plots, heterogeneity, and stratified analyses by predefined characteristics.

Results: Interventions including iron (n = 27) or vitamin A (n = 17) only had no significant effects on growth. Interventions including zinc only (n = 43) had a small positive effect (effect size = 0.06; 95% CI: 0.006, 0.10) on change in WHZ but no significant effect on height or weight gain. Multiple micronutrient interventions (n = 20) improved linear growth (0.09; 95% CI: 0.008, 0.17).

Conclusions: Our findings confirm earlier results of no benefits for interventions including iron and vitamin A only but differ from the earlier meta-analysis that found improvements in linear growth for zinc only interventions. This may be due to the improved nutritional status of children in the more recent studies. Multiple micronutrient interventions improve linear growth, but the benefits are small. Other strategies are needed to prevent stunting.

INTRODUCTION

Recent estimates indicate that 20% of young children are underweight, 32% are stunted, and 10% are wasted, which places these children at an increased risk of dying as well as at risk for a range of adverse consequences over the life cycle and hinders them from meeting their full potential (1, 2). Although significant progress has been made over the past few decades in reducing the prevalence of malnutrition, recent data show that the prevalence of underweight and stunting has more than doubled in Sub-Saharan Africa, and South Asia continues to be home to nearly half of the world’s undernourished children (2).

Adequate access to food, health, and care are well recognized as necessary to ensure optimal growth and development during the early years, but interventions that address these underlying causes have not always been successful in large-scale programs. Apparently, simple strategies such as ensuring adequate frequency of feeding, ie, at least 5 times/d for young children, provision of high-quality complementary foods that are rich in both macro- and micronutrients, and promotion of exclusive breastfeeding, require behavior change that is often difficult to accomplish (2, 3). It is in this context that the potential of micronutrient interventions as cost-effective measures to prevent child undernutrition has recently received considerable attention (3–5).

Several studies have been conducted to explore the link between micronutrient deficiencies and growth failure, but there is considerable variability in the nature of the interventions, choice of control groups, age group, study setting, and other key explanatory variables that make it difficult to provide unquestionable evidence-based advice to policy makers and program implementers. Although several reviews have been published, to date few meta-analyses have been published on this topic (6–9). The earlier and widely known meta-analysis is the one by Brown et al (6) that evaluated studies of zinc supplementation and child growth. This analysis included children of all age groups (<18 y) and found evidence of a small-to-medium effect of zinc supplementation in improving height among children, especially among those who were younger and stunted at baseline. Another meta-analysis concluded that whereas iron and vitamin A interventions do not improve child growth, there was a suggestion of benefit for multiple micronutrient (MM) interventions (8). Since these meta-analyses, several more trials have been conducted, including the large multi-country International Research on Infant Supplementation Initiative (IRIS) trials that evaluated the effect of a MM intervention in very young children (10–13). The purpose of this review was to identify well-designed randomized controlled trials (published and unpublished) that have been conducted to date in young children <5 y old with selected micronutrients, both single and combined interventions, and conduct meta-analyses to evaluate the effect of these interventions in improving child growth, measured as changes in height, weight, and weight-for-height z scores (WHZ).

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METHODS

Identification of studies

The studies considered for possible inclusion in the current meta-analyses were identified by combining the results of 2 separate search strategies that were completed by April 15, 2008, with the PubMed (National Library of Medicine, Bethesda, MD) database (1966 to present). The first search for each intervention included the word vitamin A or iron or zinc or multi-micronutrients in the title and the words growth, infant, or child or children in any field. The second search contained all articles that had the word supplement or supplemental in the title and the words growth or weight or length or height in any field. The results of these 2 searches were then merged and examined for inclusion and exclusion as described below. Using similar specifications, we repeated the search using EMBASE (Elsevier, Amsterdam. Netherlands) and the Cochrane review for randomized controlled trials (Wiley InterScience, Hoboken, NJ). Additional studies that were identified through the bibliographies of review articles were also included.

Exclusion criteria

Exclusion criteria were as follows: 1) animal studies; 2) studies not in English; 3) review articles, commentary, editorial, or letter; 4) non-intervention studies; 5) inappropriate age (children >5 y old, adults, pregnant women); 6) micronutrients not unique factors in treatment; 7) studies that had subjects with chronic diseases such as sickle cell diseases, cystic fibrosis, and other conditions such as severe energy-protein malnutrition, Down syndrome, and beta-thalassemia that might independently affect growth; 8) duration of follow-up <8 wk; 9) lack of control groups; and 10) lack of sufficient data on growth to calculate effect size.

Inclusion criteria

Inclusion criteria were as follows: 1) randomized, placebo-controlled intervention trial; 2) children had to be ≤5 y old; and 3) intervention provided to treatment and control children differed only in the inclusion of the micronutrients of interest (vitamin A, iron, zinc, or multiple micronutrients). Initially, the first 3 exclusion criteria were applied by using the appropriate search terms in the electronic databases, after which complete citations (title and abstract) were reviewed to identify the studies that were most likely to meet the inclusion criteria. The complete publications of this subsample of studies were then read to ensure that they met the inclusion criteria. Most of the information was obtained from the published articles. In a few cases (n = 3), we also contacted the authors directly.

Statistical analyses

The primary outcomes were change in height (expressed in cm/y or height-for-age z score; HAZ), change in weight (measured in kg/y or weight-for-age z score; WAZ), and change in WHZ. We used change in HAZ or WAZ for studies that did not report changes in absolute height or weight in light of the high correlation between height and HAZ or weight and WAZ (r = 0.8–0.9). For studies that had different sample sizes at the beginning and end of the intervention, the lower value was assumed to be the sample size for the change. If the studies did not report the mean change, we calculated it as the difference of mean post- and pre-intervention measurements. If the study reported only SE or 95% CI, the SD was calculated from SE or 95% CI. If studies did not report the SD of the anthropometric changes, we calculated the SD for change, assuming that the correlation between the pre- and post-test variances was equal to the average correlation found in available studies.

To make sure our assumptions did not bias the results, we performed the sensitivity analysis noted by Sachdev et al (9) using the following different assumptions for the correlation between the pre- and post-test variances: 1) using the average correlation in data sets from available studies, 2) assuming a correlation = 0.5 (14), 3) assuming no correlation (14), 4) using postintervention values to calculate the effect size, and 5) calculated effect size only for the subsample of studies that reported the changes and SD of change.

Effect sizes were calculated for individual studies by dividing the difference between the mean change in treatment and control groups by the pooled SD. This value is known as Cohen’s effect size or Cohen’s d, and it is useful in meta-analyses because it eliminates the problems of units of measurement and duration, which may vary across studies (15). The overall mean effect size and 95% CI across studies was then estimated by assuming a random effects model that used the weighted mean effect size for each study where the weight was the inverse of the intrastudy variance.

Weighted mean effect sizes were calculated with and without outliers. We tested for heterogeneity of effect sizes by using the chi-square test of homogeneity as described by Hedges and Pigott (16). On evidence of significant heterogeneity (P < 0.05), we assessed the role of several potential predefined effect modifiers: mean initial age of children (age <24 or ≥24 mo), duration of intervention (duration <24 or ≥24 wk), baseline nutritional status (defined as HAZ <−2 or ≥−2, WAZ <−2 or ≥−2, WHZ <0 or ≥0) and baseline hemoglobin (hemoglobin <110 or ≥110 g/L only for iron intervention trials). For studies that did not provide baseline z scores, we calculated the z scores from baseline height and weight by using the World Health Organization/National Center for Health Statistics growth standards (17) to be comparable to the studies that reported z scores. In the case of MM interventions, we also stratified by mode of administration (supplementation or fortification) and combinations of MM (the ones that have similar combination as IRIS and those with fewer micronutrients). Weighted mean effect sizes were calculated in each subgroup that contained at least 2 studies.

The presence of publication bias was evaluated by the funnel plot, which is a plot of a measure of study size (usually SE or precision) on the vertical axis as a function of effect size on the horizontal axis (18). Egger’s test of the intercept and the Begg and Mazumdar rank correlation test were used for statistical testing of funnel plot asymmetry (19).

All statistical tests were 2-sided, and significance was reported for P values <0.05. All statistical analyses were done by using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

The flow of the number of studies that were included in the various meta-analyses is shown in Table 1.

Single micronutrients

Vitamin A

The characteristics of the 19 data sets from the 17 studies (20–36) included in the vitamin A meta-analysis are summarized in
### Table 1

Studies excluded and included in the meta-analyses of the effects of micronutrients on growth in children aged <5 y old.

<table>
<thead>
<tr>
<th></th>
<th>Vitamin A</th>
<th>Iron</th>
<th>Zinc</th>
<th>MM</th>
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<td><strong>Potential studies</strong></td>
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<tr>
<td>PubMed search</td>
<td>214</td>
<td>563</td>
<td>602</td>
<td>378</td>
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<tr>
<td>Other sources</td>
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<td>6</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total potential studies</strong></td>
<td>216</td>
<td>569</td>
<td>605</td>
<td>386</td>
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<tr>
<td><strong>Excluded studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal study^2</td>
<td>36</td>
<td>78</td>
<td>64</td>
<td>208</td>
</tr>
<tr>
<td>Studies not in English^2</td>
<td>9</td>
<td>45</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>Review paper, editorial, letter^2</td>
<td>27</td>
<td>74</td>
<td>80</td>
<td>27</td>
</tr>
<tr>
<td>Meta-analysis^2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nonintervention study^2</td>
<td>99</td>
<td>259</td>
<td>293</td>
<td>64</td>
</tr>
<tr>
<td>Inappropriate age^4</td>
<td>10</td>
<td>37</td>
<td>42</td>
<td>37</td>
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<tr>
<td>Intervention trials in children aged &lt;5 y</td>
<td>33</td>
<td>73</td>
<td>89</td>
<td>42</td>
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<td>Ineligible studies in children aged &lt;5 y</td>
<td>2</td>
<td>20</td>
<td>7</td>
<td>9</td>
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<td>Micronutrients not unique factors in treatment</td>
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<td>12</td>
<td>31</td>
<td>1</td>
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<td>Underlying diseases or severe malnutrition</td>
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<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of follow-up &lt;8 wk</td>
<td>—</td>
<td>1</td>
<td>2</td>
<td>—</td>
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<tr>
<td>Lack of control group</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lack of data on growth</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Eligible studies</td>
<td>17</td>
<td>27</td>
<td>43</td>
<td>20</td>
</tr>
<tr>
<td>Number of data sets in eligible studies</td>
<td>19</td>
<td>36</td>
<td>56</td>
<td>27</td>
</tr>
</tbody>
</table>

^1 MM, multiple micronutrients.
^2 Search limitation terms.
^3 Title or abstract reviews.
^4 Complete article reviews.

### Table 2

Characteristics of 19 data sets from 17 intervention studies included in the meta-analyses of vitamin A and child growth of children aged <5 y old.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Subjects</th>
<th>Mean initial age</th>
<th>Dose</th>
<th>Doses</th>
<th>Duration</th>
<th>Mean initial height</th>
<th>Mean initial weight</th>
<th>Mean initial WAZ</th>
<th>Mean initial HAZ</th>
<th>Mean initial WHZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fahrmi^2 (20)</td>
<td>2007</td>
<td>Indonesia</td>
<td>378</td>
<td>5</td>
<td>30</td>
<td>1</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alarcon^2 (21)</td>
<td>2004</td>
<td>Peru</td>
<td>229</td>
<td>17</td>
<td>60</td>
<td>1</td>
<td>18</td>
<td>76.8</td>
<td>10.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pangaribuan (22)</td>
<td>2003</td>
<td>Indonesia</td>
<td>400</td>
<td>36.5</td>
<td>60</td>
<td>1</td>
<td>16</td>
<td>89.2</td>
<td>12.1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Villaros (23)</td>
<td>2002</td>
<td>Tanzania</td>
<td>687</td>
<td>18.7</td>
<td>60</td>
<td>4</td>
<td>52</td>
<td>76.1</td>
<td>9.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Yang^2 (24)</td>
<td>2002</td>
<td>China</td>
<td>63</td>
<td>48</td>
<td>0.2</td>
<td>260</td>
<td>52</td>
<td>95.15</td>
<td>13.78</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rahman (I) (25)</td>
<td>2002</td>
<td>Bangladesh</td>
<td>317</td>
<td>23.7</td>
<td>60</td>
<td>1</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rahman (II)^2 (25)</td>
<td>2002</td>
<td>Bangladesh</td>
<td>336</td>
<td>23.7</td>
<td>60</td>
<td>1</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hadi (26)</td>
<td>2000</td>
<td>Indonesia</td>
<td>1407</td>
<td>27</td>
<td>60</td>
<td>6</td>
<td>16</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Smith (27)</td>
<td>1999</td>
<td>Central America</td>
<td>251</td>
<td>44</td>
<td>3</td>
<td>24</td>
<td>24</td>
<td>92</td>
<td>13.9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

^1 WAZ, weight-for-age z score; HAZ, height-for-age z score; WHZ, weight-for-height z score.
^2 Intervention group received vitamin A + iron + zinc; control group received iron + zinc.
^3 Intervention group received vitamin A + calcium + zinc; control group received calcium + zinc.
^4 Intervention group received vitamin A + zinc; control group received zinc.

Two data sets (“Health” and “Survival”) from one publication.
suggested weight loss (effect size = −0.34; 95% CI: −0.66, −0.01) among those who received vitamin A compared with placebo in the subsample of studies conducted in underweight children (baseline WAZ < −2; n = 3) compared with no effect (effect size 0.00; 95% CI: −0.17, 0.17) among the studies where baseline WAZ ≥ −2 (n = 10). There was no overall effect on change on WHZ (weighted mean effect size was 0.01; 95% CI: −0.06, 0.09), but data were available for only 5 studies.

Iron

Sufficient information was available from the 36 data sets from 27 studies (10–13, 20, 37–58) for calculating the effect of iron supplementation on child growth (Table 3). Most of the studies were conducted in developing countries since the 1990s with more than half (n = 17) in Asia, followed by Africa (n = 3) and Latin America and the Caribbean (n = 3). Two studies were conducted in North America and 3 in Europe. Most studies delivered iron in the form of a tablet or syrup taken daily, and the most common dosage was 10 mg/d; higher doses (20–60 mg/d) were used in some of the studies with children older than 15 mo. A weekly dose was used in 2 studies (40, 51). Seven studies (20, 37–40, 46, 50) also used different combinations of iron and zinc and therefore yielded 2 data sets each, namely, comparisons of iron only to placebo and iron + zinc to zinc only. Three studies used fortification-based strategies, namely, comparisons of iron-fortified formula with non-fortified formula (48, 52, 56); the one by Adish et al (49) compared cooking in an iron pot with cooking in an aluminum pot. The duration of intervention varied from 8 to 52 wk (x ± SD: 24.3 ± 10.4 wk). The initial ages of the children ranged from 1 to 48 mo.

Effect sizes for change in height were calculated for 34 data sets (Figure 2) and ranged from −5.00 to 0.99. The weighted mean effect size for height was −0.01 (95% CI: −0.17, 0.15) and increased to 0.01 (95% CI: −0.08, 0.10) after excluding the study by Majumdar et al (41) that was considered an outlier because its effect size (−5.00; 95% CI: −5.80, −4.20) was more than 5 times smaller than the next smallest effect size.

Effect sizes for weight gain ranged from −8.14 to 2.18 and, similar to height, the study by Majumdar et al (41) was defined an outlier because of its extreme value. The overall weighted mean effect size with and without the outlier was 0.07 (95% CI: −0.17, 0.30) and 0.08 (95% CI: −0.11, 0.27), respectively. Fourteen studies had sufficient data to calculate effect sizes for WHZ; the effect sizes ranged from −0.56 to 1.21 and the weighted mean effect size was −0.02 (95% CI: −0.15, 0.12).

For all outcomes, there was significant heterogeneity (P < 0.001), but the stratified analysis did not find any predictors that could explain the variation in effect sizes. Sensitivity analysis using different assumptions did not alter the overall conclusions; however, when we restricted the analysis to the subset of 18 studies that reported only change in weight gain, we found a significant negative effect on weight (effect size = −0.11; 95% CI: −0.20, −0.02).

**Zinc**

Of the 602 potential studies identified from the database search and 3 studies from bibliographies of review articles, only 89 were zinc intervention trials among young children; an additional 46 studies were excluded because of zinc not being a unique factor in treatment (n = 7), underlying diseases or severe malnutrition (n = 31), lack of growth data (n = 6), or short duration of intervention and follow up (n = 2), resulting in a final sample of 43 studies (20, 21, 24, 27, 37–40, 46, 50, 59–91) with 56 data sets for inclusion in the zinc meta-analysis (Table 1). Selected characteristics of the studies included in this meta-analysis are described in Table 4. All studies were published between 1976 and 2008, of which 15 were conducted in Asia, 13 in Latin America and the Caribbean, 8 in North America and Europe, and 7 in Africa. Mean initial age ranged from 0 to 48 mo with most of the studies being conducted in younger children (initial age < 24 mo). Eight studies were conducted in newborns that were either term or small-for-gestational age infants. The intervention was provided daily as a liquid supplement (syrup mixed into a beverage); the dosage, however, varied from as low as 20 mg/wk to 20 mg/d. A few studies also provided zinc in fortified formula (24, 68, 91) or as a fortified cereal porridge (60).

Similar to iron, several studies had more than one intervention resulting in 2 or 3 data sets each. For example, Wuehler et al (59) compared 3 different doses (3, 7, and 10 mg) of zinc with placebo, and Brown et al (60) compared 2 modes of interventions allowing us to compare zinc fortification in iron-fortified cereal porridge plus MM versus MM alone, and zinc supplementation added in MM versus MM alone. Similarly, several studies used different
combinations of zinc and iron (20, 37–40, 46, 50) that yielded 2 data sets each, namely, comparisons of zinc only to placebo and zinc + iron to iron only. The duration of intervention varied from 8 to 64 wk with a median of 24 wk.

Effect sizes for change in height were calculated for 53 data sets (n = 40 studies) and ranged from −0.80 to 1.12 (Figure 3). Thirty (56.6%) studies had a positive effect size and 11 were statistically significant; however, the overall weighted mean effect (0.07; 95% CI: −0.03, 0.17) was small and not statistically significant. Sensitivity analyses using different assumptions did not alter the observed effect sizes and conclusions (results not shown). There was significant heterogeneity (P < 0.001), but the stratified analysis did not identify any predictors that could explain the variation in effect sizes.

Effect sizes for zinc intervention on weight gain were calculated for 54 data sets (n = 41 studies) and ranged from −0.78 to 3.89. Approximately 61% of the data sets (n = 33) had positive effect sizes, and 10 were statistically significant. The study by Shrivastava et al (86) was considered an outlier because of the large effect size (3.89; 95% CI: 2.95, 4.83) that was at least 2 times larger than the next largest effect size. The overall weighted mean effect sizes were 0.09 (95% CI: −0.11, 0.25) and 0.06 (95% CI: −0.10, 0.23) with and without the outlier, respectively, indicating no statistically significant effect of zinc on weight gain. Sensitivity
The overall weighted mean effect sizes for the combination of vitamin A and zinc were 0.10 (95% CI: −0.41, 0.61) for height, 0.11 (95% CI: −0.58, 0.80) for weight, and 0.05 (95% CI: −0.12, 0.22) for WHZ. The overall weighted mean effect sizes for the combination of iron and folic acid were 0.16 (95% CI: −0.05, 0.38) for height and 0.79 (95% CI: −0.35, 1.94) for weight.

Multiple micronutrients (3 micronutrients or more)

We identified 33 intervention trials that were conducted in young children and allowed us to isolate the effects of multiple micronutrients, of which 20 had growth data. A description of the 27 data sets from the 20 studies (10–13, 20, 24, 40, 62, 67, 92–102) included in the meta-analysis is shown in Table 5. All the studies were published between 1993 and 2008 and were conducted primarily in developing countries: 8 in Asia, 7 in Africa, and 5 in Latin America and the Caribbean. The initial ages of the children ranged from 3 to 50 mo. The study by Begin (93) compared MM + bovine serum concentrate versus bovine serum concentrate and MM + whey protein concentrate versus whey protein concentrate, resulting in 2 data sets. The studies by Hople et al (12), Lopez de Romana et al (13), Smuts et al (10), Uronto et al (11), and Thu et al (100) compared both daily and weekly MM supplementation with placebo; thus, each yielded 2 data sets. The study by Ramakrishnan et al (102) also yielded 2 data sets because the intervention was nested within a prenatal intervention trial in which the mothers received either multiple micronutrients or iron only during pregnancy.

MM interventions were administered either as daily or weekly supplements or as fortified foods. The supplements were given in several forms such as a foodlets (10–13), syrup (20, 40, 67, 98, 100, 102), or tablets (24, 62). MM fortificants were delivered in the form of sprinkles that were added to food (92), fortified complementary food (96, 99), or a fortified maize-meal or spread food (10, 93, 95, 97, 101). The intervention was given ≥5 d/wk in all studies. In addition, the interventions were also given weekly in the IRIS trials (10–13) and by Thu et al (100). All interventions contained at least 3 micronutrients, and 80% of them contained vitamin A, iron, and zinc. Some interventions also contained iodine (40, 73), selenium (10, 40, 67, 73), and copper (67, 73). In most cases, the daily supplements provided 1–2 times the Recommended Dietary Allowance for the various micronutrients. Details of the micronutrient composition of the supplements and fortified products will be provided on request.

The effect sizes for change in height ranged from −0.64 to 0.63 (Figure 5). Using the random effects model, the overall weighted mean effect size was 0.09 (95% CI: 0.008, 0.17). The mean effect size was similar (0.11; 95% CI: 0.02, 0.18) when we restricted the analysis to studies that provided at least vitamin A, iron, and zinc.

The effect sizes for change in weight ranged from −0.28 to 1.52, and the overall weighted mean effect size was small (0.04; 95% CI: −0.05, 0.12). Restricting the analyses to studies in which the MM intervention contained at least vitamin A, iron, and zinc showed a similar mean effect size of 0.03 (95% CI: −0.04, 0.10).

Effect sizes for change in WHZ were calculated for 19 data sets and ranged from −0.70 to 0.29. The overall mean weighted effect size of MM interventions on change in WHZ was −0.001 (95% CI: −0.07, 0.07; P = 0.98). Restricting the analyses to the subsample of studies in which the MM intervention contained at least vitamin
TABLE 4
Selected characteristics of 56 data sets from 43 intervention studies included in the meta-analyses of zinc on growth of children aged <5 y old

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Subjects</th>
<th>Mean initial age</th>
<th>Mean initial height</th>
<th>Mean initial weight</th>
<th>Mean initial WAZ</th>
<th>Mean initial HAZ</th>
<th>Mean initial WHZ</th>
<th>Mean initial zinc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wuehler (I) (59)</td>
<td>2008</td>
<td>Ecuador</td>
<td>251</td>
<td>21</td>
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<tr>
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<td>Ecuador</td>
<td>253</td>
<td>21</td>
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<td>11.96</td>
</tr>
<tr>
<td>Wuehler (III) (59)</td>
<td>2008</td>
<td>Ecuador</td>
<td>253</td>
<td>21</td>
<td>9.70</td>
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<tr>
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<td>Peru</td>
<td>302</td>
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<td>Peru</td>
<td>302</td>
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<tr>
<td>Berger (I) (38)</td>
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<td>2006</td>
<td>Vietnam</td>
<td>391</td>
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<td>6.9</td>
<td>0.58</td>
<td>1.07</td>
<td>0.31</td>
<td>0.31</td>
<td>14.18</td>
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</tr>
<tr>
<td>Olney (II) (62)</td>
<td>2006</td>
<td>Zanzibar</td>
<td>433</td>
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<td>7.0</td>
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<td>1.45</td>
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<tr>
<td>Olney (II) (62)</td>
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<td>Zanzibar</td>
<td>443</td>
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<td>7.0</td>
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<td>1.45</td>
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<td>0.15</td>
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<td>Brazil</td>
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<td>1.20</td>
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<tr>
<td>Walravens (89)</td>
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<td>USA</td>
<td>50</td>
<td>15</td>
<td>5.7</td>
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<td>1.76</td>
<td>0.18</td>
<td>0.18</td>
<td>15.30</td>
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<tr>
<td>Walravens (91)</td>
<td>1976</td>
<td>USA</td>
<td>68</td>
<td>0</td>
<td>4</td>
<td>0.57</td>
<td>1.25</td>
<td>0.63</td>
<td>0.63</td>
<td>15.30</td>
</tr>
</tbody>
</table>

In data set I, the intervention group received 1 mg Zn/d. In data set II, the intervention group received 5 mg Zn/d.

1 WAZ, weight-for-age z score; HAZ, height-for-age z score; WHZ, weight-for-height z score.

2 In data set I, the intervention group received 3 mg Zn/d. In data set II, the intervention group received 7 mg Zn/d. In data set III, the intervention group received 10 mg Zn/d.

3 In data set I, the intervention group received multiple micronutrients (MM) + zinc as fortification; the control group received MM without zinc. In data set II, the intervention group received MM + zinc as supplementation; the control group received MM without zinc.

4 The intervention group received zinc and iron; the control group received iron alone.

5 The intervention group received zinc + iron and folic acid; the control group received iron and folic acid.

6 The intervention group received zinc + calcium and vitamin A; the control group received calcium and vitamin A.

7 Data set I for nonstunted children; data set II for stunted children.

8 In data set I, the intervention group received 1 mg Zn/d. In data set II, the intervention group received 5 mg Zn/d.
A, iron, and zinc showed a similar mean effect size of $-0.002$ (95% CI: $-0.08, 0.07$).

For all 3 outcomes, there was no evidence of heterogeneity ($P = 0.08$ for height and weight and $P = 0.51$ for WHZ). Sensitivity analyses using different assumptions confirmed the overall findings.

**Publication bias**

Except for the studies of effects of zinc on WHZ, the funnel plot in each meta-analysis was relatively symmetrical, thus indicating the absence of publication bias (data not shown). The Egger’s weighted regression method and Begg’s rank correlation method further confirmed the symmetrical observation of the funnel plot with $P$ values $>0.05$. For the effect of zinc on WHZ, the funnel plot was quite asymmetrical, indicating evidence of publication bias ($P$ of Egger’s method $= 0.01$ and $P$ of Begg’s method $= 0.02$). The effects of zinc on WHZ were reported in only 22 studies (32 data sets); many studies that reported effects of zinc on height and weight change did not report WHZ, which may explain some of the observed publication bias.

**DISCUSSION**

The key findings of this review are summarized in Table 6. Interventions containing iron only, vitamin A only, and combinations of iron and zinc, iron and vitamin A, and zinc and vitamin A do not improve growth in height, weight, or WHZ in children aged $<5$ y. Interventions containing zinc only have a small positive effect ($0.06; 95\% \text{ CI: } 0.006, 0.11$) on change in WHZ but do not improve height or weight gain in young children. Finally, MM interventions have a small effect only on growth in height ($0.09; 95\% \text{ CI: } 0.008, 0.17$).

A major strength of the current review is the sample size for the various meta-analyses, except for the 2-way combinations. This is especially true for MM interventions, because several studies were completed since the previous review that had only 5 studies, of which only 3 were conducted in young children (98, 99, 101). The present review included 20 studies that contributed 27 data sets, and many of them were conducted in infants. Although most of these studies (19 data sets) provided the intervention as “supplements,” some used food-based approaches and the findings did not differ by mode of delivery (results not shown).
TABLE 5
Selected characteristics of 27 data sets from 20 intervention studies included in the meta-analyses of multiple micronutrients on growth of children aged <5 y old

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Subjects</th>
<th>Mean initial age</th>
<th>Duration</th>
<th>Mean initial height</th>
<th>Mean initial weight</th>
<th>Mean initial ZWA</th>
<th>Mean initial HAZ</th>
<th>Mean initial WHZ</th>
<th>Mean initial Hb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begin (I) (93)</td>
<td>2008</td>
<td>Guatemala</td>
<td>69</td>
<td>6.8</td>
<td>32</td>
<td>64.0</td>
<td>6.89</td>
<td>-1.07</td>
<td>-1.52</td>
<td>0.18</td>
<td>115.5</td>
</tr>
<tr>
<td>Begin (II) (93)</td>
<td>2008</td>
<td>Guatemala</td>
<td>63</td>
<td>6.8</td>
<td>32</td>
<td>64.1</td>
<td>6.94</td>
<td>-1.05</td>
<td>-1.54</td>
<td>0.22</td>
<td>115.5</td>
</tr>
<tr>
<td>Fahmidah (20)</td>
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<td>Indonesian</td>
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<td>-0.59</td>
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<td>0.28</td>
<td>95.6</td>
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<tr>
<td>Giovannini (92)</td>
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<td>Cambodia</td>
<td>127</td>
<td>6</td>
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<td>—</td>
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<td>-0.87</td>
<td>-0.79</td>
<td>-0.38</td>
<td>101.2</td>
</tr>
<tr>
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<td>-1.25</td>
<td>-1.50</td>
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<tr>
<td>Faber (94)</td>
<td>2005</td>
<td>South Africa</td>
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<td>68.8</td>
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<td>111.0</td>
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<tr>
<td>Hop Le (I) (12)</td>
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<td>Vietnam</td>
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<tr>
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<td>Vietnam</td>
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<td>-2.78</td>
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<tr>
<td>Smuts (I) (10)</td>
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<td>South Africa</td>
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</tr>
<tr>
<td>Smuts (II) (10)</td>
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<td>South Africa</td>
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<td>8.4</td>
<td>24</td>
<td>68.25</td>
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<td>1.24</td>
<td>112.4</td>
</tr>
<tr>
<td>Urioto (I) (11)</td>
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<td>Indonesia</td>
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<td>9.2</td>
<td>23</td>
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<tr>
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<td>23</td>
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<tr>
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<td>China</td>
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<td>70.7</td>
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<td>6.08</td>
<td>0.3</td>
<td>-0.22</td>
<td>0.43</td>
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</tr>
</tbody>
</table>

1 WAZ, weight-for-age z score; HAZ, height-for-age z score; WHZ, weight-for-height z score; Hb, hemoglobin.
2 In data set I, the intervention group received multiple micronutrients (MM) + bovine serum concentrate; the control group received bovine serum concentrate. In data set II, the intervention group received MM + whey protein concentrate; the control group received whey protein concentrate.
3 In data set I, the intervention group received daily MM supplementation. In data set II, the intervention group received weekly MM supplementation.
4 In data set I, the intervention children and their mothers received MM. In data set II, the intervention children received MM but their mothers received placebo.

Overall, our findings confirm the results of the earlier meta-analyses conducted by Ramakrishnan et al (8) but contradict the findings presented by Brown et al (6) regarding the benefits of zinc supplementation. The findings for vitamin A are not surprising; we added 2 new studies (20, 21) and only one study (103) in the earlier review was not eligible because it was conducted in older children (9–12 y). In the case of iron, although the results are similar, the current meta-analyses included 13 new studies (10–13, 20, 37, 38, 40, 42, 44, 52, 54, 56), and 7 studies (103–109) included in the earlier review were ineligible for the current meta-analyses because they were conducted among older children. Our findings are also consistent with the conclusions by Sachdev et al (9), who conducted a meta-analysis of iron supplementation trials on physical growth and found no positive effect. That study included 25 studies, of which 15 were conducted among children <5 y old, in contrast to the 27 studies that contributed 36 data sets in the current meta-analysis. Many of these were the recently completed IRIS trials that were not included in the earlier meta-analyses. It is important to note that there were no significant differences when we stratified by baseline hemoglobin level for the various study populations (results not shown).

The most surprising result of the current review is the one for zinc interventions. We did not find the significant positive effects that were seen both in height and weight gain in the earlier meta-analyses by Brown et al (6). Our findings are timely and important in light of the fact that the Lancet series on Maternal and Child Undernutrition recommended zinc supplementation as an effective intervention to reduce morbidity and prevent stunting (3). The Lancet series estimated that universal coverage with zinc supplementation in the 36 countries with the highest burden of undernutrition would reduce the prevalence of stunting by 9.1% at 12 mo, by 15.5% at 24 mo, and by 17% at 36 mo (3). The recommendation of zinc supplementation as an effective intervention to reduce morbidity rates was based on a new meta-analysis that showed very large preventive effects, namely, reductions of 14% and 20% in episodes of diarrhea and lower respiratory infections, respectively (3). In the case of zinc supplementation as an intervention to prevent stunting, no new analyses were carried out; instead, the Lancet series accepted the results of the meta-analysis by Brown et al (6), which reported an effect of zinc supplementation on growth rates in height of 0.35 (95% CI: 0.15–0.55).
studies that were in the earlier review: the studies by Hong et al (110, 111), which were in Chinese, and the one by Matsuda et al (112) that provided zinc + copper and did not allow us to isolate the specific of zinc; however, including or excluding these studies did not account for the observed differences between the 2 meta-analyses. Another difference between the older and more recent studies is that the latter have a lower prevalence of stunting, reflecting secular improvements in many parts of the world. Although Fischer-Walker and Black (113) recently confirmed the results reported by Brown et al (6), their meta-analysis was not restricted to children <5 y of age and did not include any studies published after 2005. It may be that the response to zinc supplementation in the more recent trials was attenuated by improvements in baseline nutritional status. However, we do not find evidence in our analysis that effects sizes were modified by baseline anthropometric characteristics (results not shown). Whether it has been easier to publish null results over time as the result of efforts to combat publication bias remains a possibility. In short, we do not have an explanation for the contrasting results between older and newer studies of zinc supplementation. What is important is that the combined weight of evidence indicates no effect of zinc supplementation on growth of children <5 y of age.

Another contribution of the present review was the inclusion of studies that provided combinations of 2 micronutrients. We identified very few studies for iron-folic acid and vitamin A-zinc combinations. In contrast, we did identify 7 studies for iron-zinc combinations and found no improvements in child growth. Most of these studies were done among infants and these interventions improved micronutrient status, namely, hemoglobin and zinc status (results not shown), and may result in other benefits such as reduced morbidity and mortality (3).

The main limitations relate to the nature of the studies that were available for inclusion in these meta-analyses. The limited variability in the dosage used and lack of data on baseline nutrient status, especially zinc, make it difficult to identify the conditions under which these interventions might be beneficial (113). Other limitations include the dearth of well-designed trials that evaluate the benefits of micronutrients in the context of food-based approaches or examine the long-term effects of these interventions.

In conclusion, this review demonstrates that micronutrient interventions, whether single or multi-nutrient, can do little to prevent stunting, a problem with major, adverse, long-term consequences for cognition, education, and income (114). Although there is no doubt that micronutrient interventions such as supplementation with vitamin A, iron, and zinc have important benefits for child survival and health that amply justify their implementation, more comprehensive approaches that improve the diets of small children are needed to promote child growth and development. The Lancet series on maternal and child undernutrition underscored the importance of exclusive

0.19, 0.51). Our meta-analysis indicates that zinc supplementation would not prevent stunting.

What explains the differences between our meta-analysis and that of Brown et al (6)? Comparison of the studies included in the 2 meta-analyses reveals that the results from studies that were published after the study by Brown et al (6) account for the differences. Specifically, we find significant effects of zinc supplementation on both height (0.26; 95% CI: 0.08, 0.43) and weight gain (0.33, 95% CI: 0.04, 0.62) if we restrict our analysis to the 21 data sets included in both our analysis and that of Brown et al (6). On the other hand, restricting our analysis to recent studies, that is, to those 32 data sets included in our meta-analysis but not in the earlier analysis by Brown et al (6), indicates no effect on growth in height (0.02; 95% CI: −0.07, 0.11) or weight (−0.003; 95% CI: −0.15, 0.14). Note that we also excluded a few limitations include the dearth of well-designed trials that evaluate the benefits of micronutrients in the context of food-based approaches or examine the long-term effects of these interventions.

In conclusion, this review demonstrates that micronutrient interventions, whether single or multi-nutrient, can do little to prevent stunting, a problem with major, adverse, long-term consequences for cognition, education, and income (114). Although there is no doubt that micronutrient interventions such as supplementation with vitamin A, iron, and zinc have important benefits for child survival and health that amply justify their implementation, more comprehensive approaches that improve the diets of small children are needed to promote child growth and development. The Lancet series on maternal and child undernutrition underscored the importance of exclusive

![FIGURE 5. Effect sizes for height gain in multiple micronutrient intervention trials among children aged <5 y old. Data are presented as means with 95% CIs.](https://www.ajcn.org)
breastfeeding for survival and reduced morbidity but at the same time noted that breastfeeding promotion interventions do not improve growth. Of the nutrition interventions that we have at our disposal, only direct efforts to improve complementary feeding have been shown to improve growth. On the basis of a limited number of studies, it is known that education and counseling of caretakers in food-secure populations can improve growth in height (0.25; 95% CI: 0.01, 0.49) and providing complementary food, with or without education and counseling, can improve height in food-insecure populations (0.41; 95% CI: 0.05, 0.76) (3). What we do not know is whether education and counseling alone can be effective in food-insecure populations. Thus, while we move forward to correct micronutrient deficiencies to improve child survival and health, we must, at the same time, focus on interventions to improve complementary feeding.

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