Provision of Multiple Rather Than Two or Fewer Micronutrients More Effectively Improves Growth and Other Outcomes in Micronutrient-Deficient Children and Adults¹–³

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Abstract

Deficiencies of multiple micronutrients (MMN) usually coexist in developing countries, but supplements have usually provided only 1 or 2 micronutrients (MN). To inform policy, in this article we compared the relative benefits of supplying MMN vs. a placebo or 1 or 2 MN on the following: children’s growth, health, and development; pregnancy outcome; nutritional status; and HIV/AIDS mortality and morbidity in adults. Sufficient data were available to perform random-effects meta-analyses of randomized controlled trials (RCT) for the effects of MMN on child growth and nutritional status. Results for other outcomes are presented as effect sizes (ES) when available. In children, MMN interventions resulted in small but significantly greater improvements in length or height (ES = 0.13; 95% CI: 0.055, 0.21) and weight (ES = 0.14; 95% CI: 0.029, 0.25), hemoglobin (ES = 0.39; 95% CI: 0.25, 0.53), serum zinc (ES = 0.23; 95% CI: 0.18, 0.43), serum retinol (ES = 0.33; 95% CI: 0.050, 0.61), and motor development. A Cochrane review reported that compared with no supplementation or a placebo, MMN supplementation during pregnancy reduced the relative risk of low birth weight (0.83), small-for-gestational age (0.92), and anemia (0.61); however, MMN were not more effective than iron + folic acid alone. There is some evidence that MMN supplementation improves CD4 counts and HIV-related morbidity and mortality in adults. The efficacy of MMN varies across trials, but overall there is evidence that outcomes are better than when providing ≤2 MN. The policy implications of these studies are discussed. J. Nutr. 139: 1022–1030, 2009.

Introduction

Multiple micronutrient (MMN)⁶ deficiencies are very common, usually resulting from poor-quality diets. The most prevalent micronutrient (MN) deficiencies, iron, vitamin A, zinc, vitamin B-12, riboflavin, vitamin D, and vitamin E, usually occur together due to a low intake of animal source foods (1,2).

During the last few decades there has been strong interest in the adverse effects of MN deficiencies on health, growth, and development, although much of the research has focused on the effects of single MN. Interventions to improve the status of MMN simultaneously makes sense from both a biological and a programmatic perspective, and the cost of adding additional MN to supplements or fortificants is relatively low. Thus, in the last 5–10 y, the effects of MMN interventions on health and development have been evaluated in pregnant women, infants, preschool and school-aged children, and persons with HIV/AIDS in efficacy trials primarily as well as in a few complementary feeding programs.

To date there has been no comprehensive review of the effects of MMN on multiple outcomes, to our knowledge. A few meta-analyses have been conducted on selected outcomes, including child growth (3), HIV/AIDS (4), and pregnancy (5). The purpose of this paper is to review the efficacy of interventions with MMN supplements or fortified foods on growth, nutrient status, morbidity, and cognitive and motor development in children, and on HIV/AIDS and pregnancy outcomes in adults. Meta-analyses were conducted for outcomes with sufficient data and effect sizes (ES) calculated for other outcomes where appropriate.
Methods

Search strategy. We indentified published articles using PubMed and the ISI Web of Science, with no language or date restriction. Key words used to search the literature were: MN(s), vitamins, minerals, pregnancy, growth, morbidity, mortality, child development, cognitive development, motor development, HIV, and AIDS. Additional studies were identified from review articles and personal communications.

Inclusion criteria. Studies varied in many aspects of the MMN interventions (Supplemental Table 1). These included: duration and frequency of supplementation, number and type of MN supplemented, control group (e.g. for pregnancy studies, the control group was usually given iron or iron + folic acid), age of subjects, and delivery system (supplement or fortified food). Only randomized controlled trials (RCT) lasting at least 4 wk were included in the analysis. The control group could be a placebo (including unfortified control food or beverage), riboflavin, iron alone, zinc alone, riboflavin + iron, riboflavin + zinc, or iron + folic acid (the latter most often in pregnancy), and the intervention could be a supplement or a fortified food. “Supplements” are defined here as tablets, powders, or beverages that contain ≤419 kJ/d (100 kcal/d) of cereal or milk, whereas the term “fortified foods” refers to MMN preparations containing more energy and macronutrients, which could theoretically affect MN (MN) absorption and other outcomes. “Multiple” MN were defined as those providing >3 MN, because studies containing less than this were usually designed to explore the individual effects of 1 or 2 MN.

Outcomes. Some studies measured multiple outcomes, but to compare data across studies, the effects of MMN interventions on specific outcomes were examined separately. Outcomes included growth of children (change in length or weight, and height), morbidity of infants and children, child development, pregnancy outcome, effects on HIV/AIDS, and anemia and nutritional status. For each outcome, previous reviews and meta-analyses are referred to when available, followed by the presentation of the current meta-analysis for each outcome (except pregnancy) using data from studies meeting the inclusion criteria. For outcomes with insufficient data to conduct a meta-analysis, the results of individual studies are described and presented in table format.

Analytical approach. The ES of all interventions meeting the inclusion criteria were calculated in the current meta-analysis and are shown in Figure 1 for length and height and in Figure 2 for weight. The values are presented in order of the age of the children, from youngest on the left to oldest on the right. Most of the studies were on infants and preschoolers, with only 5 on school children (7,8,19,21,22). Overall, MMN improved length or height, and weight compared with a control group, with an ES of 0.13 (95% CI: 0.05, 0.21; P = 0.0015) for length or height and 0.14 (95% CI: 0.029, 0.25; P = 0.015) for weight. Study type, baseline HAZ, WAZ, and age did not influence the ES for changes in growth.

Five individual studies showed a significant effect of MMN on increases in height, for all children in 3 studies (8,14,23) and only in subgroup analyses in 2 studies (10,11); in Mexico, MMN increased linear growth only in the children aged <12 mo (10) and in Vietnam, only children who were stunted at baseline had a greater increase in linear growth with a daily or weekly MMN supplement compared with a placebo (11). The 2 largest ES were in a subgroup analysis on stunted children (HAZ < −2) in Vietnam (11) (data not shown). None of the other studies investigated whether the response was greater in stunted children. Our meta-regression analysis did not show that children with lower initial HAZ scores would benefit more than those with higher scores.

Morbidity and mortality of children

MMN interventions were effective in reducing morbidity in some studies (28,29), but not others (13,17,18,27,30), and data were unsuitable for use in a meta-analysis. There was a small, 15% increase in diarrhea in Bangladesh when MMN were compared with a placebo and (not shown) a 29% increase in severe diarrhea in Peru when MMN were compared with a zinc control (18). Two studies, in India (28) and Pakistan (29), reported a significant reduction in diarrhea (18 and 11%, respectively). The study in India also found a significant reduction in fever (7%) and respiratory infections (26%). There were no studies, to our knowledge, of the effect of MMN on child mortality.

Mental and motor development of children

A series of papers recently published in The Lancet (31–33) identified stunting, iodine, and iron deficiency as risk factors for
poor child development and cognitive stimulation as a protective factor. The impact of MMN interventions was suggested as an area that needed further research (33).

Although investigators have studied the effects of single nutrient interventions on the mental and motor development of children, very few RCT have evaluated the effects of MMN on these outcomes. The 4 studies all show a positive effect of MMN on motor development (15,34–36) (Table 1). The interventions differed in each study, including weekly supplements to young children (34), a fortified complementary food (15), a MN powder or a fortified spread (36), or supplementation of HIV-positive pregnant women followed by assessment of the effects on development of their children (35). In contrast, neither of the studies that reported effects on mental development demonstrated a significant effect of the intervention (34,35).

**Pregnancy outcome**

A review of RCT of MN efficacy concluded that the only supplements that affected birthweight were magnesium (which reduced small-for-gestational age births by 30%) and calcium (which reduced the risk of low birthweight) (37). No MMN interventions were included. A Cochrane analysis conducted in 2005 (5) reviewed 9 trials that provided MMN (defined as ≥3 MN) in pregnancy with a total of 15,378. The review concluded that MMN significantly reduce risk of low birthweight [relative risk (RR) = 0.83], small-for-gestational age (RR = 0.92), and anemia (RR = 0.61) compared with no supplementation or a placebo. However, these benefits were not significantly better than those obtained with iron + folic acid alone.

An updated meta-analysis of pregnancy intervention trials was not conducted here, because the Systematic Review Team of Multiple Micronutrient Supplements During Pregnancy, under the Micronutrient Working Group of the Standing Committee on Nutrition of the United Nations, is currently completing a pooled analysis of data from trials that used the UNICEF/UNU/WHO international MMN preparation “UNIMMAP” supplement designed for pregnant and lactating women. They are expected to provide further information about whether MMN increase perinatal and neonatal death, a concern raised by an analysis that combined the outcomes of 2 separate MMN trials in Nepalese pregnant women (38).

**FIGURE 1** Effect of MMN supplementation compared with the control group on children’s linear growth in individual studies and combined in the meta-analysis. Values are weighted mean ES ± 2 SE, n = 36. All interventions contained >3 MN provided for ≥4 wk. If the control group was not a placebo, the MN control is given in parentheses.

**FIGURE 2** Effect of MMN supplementation compared with the control group on children’s weight gain in individual studies and combined in the meta-analysis. Values are weighted mean ES ± 2 SE, n = 35. All interventions contained >3 MN provided for ≥4 wk. If the control group was not a placebo, the MN control is given in parentheses.
In cervicovaginal secretions or semen have been measured in 3 studies (42,50,51). One reported an increase in cervical shedding of HIV in the MMN vs. placebo group, which was not significant in women who were selenium deficient at baseline (42). Neither of the other 2 studies found a significant effect of MMN on this outcome (50,51).

In summary, there is some evidence that supplementation with MMN reduces mortality, and possibly morbidity, in adults with HIV/AIDS, although additional studies are needed in other populations.

**Hb, anemia, and nutritional status**

Most (17/19) studies that included child growth as an outcome (29,30,52–58). Most studies used a placebo control, some studies included both iron and placebo controls (23–26,30), and 2 (53) included an iron + folic acid control. MMN were given daily, several times a week, or weekly, with some trials comparing different dosing frequencies. The iron content of the MMN ranged from 5 to 22 mg/d, but most commonly was 5 to 10 mg.

### Table 2 Efficacy of MMN for improving HIV/AIDS indicators and associated outcomes in adults

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Population</th>
<th>n</th>
<th>Mortality (RR) 1</th>
<th>Viral load (ES) 1</th>
<th>Other significant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(48,51)</td>
<td>Thailand</td>
<td>Adults</td>
<td>481</td>
<td>0.53*</td>
<td>−0.11</td>
<td>—</td>
</tr>
<tr>
<td>(42)</td>
<td>Kenya</td>
<td>Nonpregnant women</td>
<td>400</td>
<td>—</td>
<td>−0.11</td>
<td>CD4, CD8, ↑ genital shedding</td>
</tr>
<tr>
<td>(46,47)</td>
<td>Tanzania</td>
<td>Pregnant and lactating women</td>
<td>1083</td>
<td>0.72*</td>
<td>−0.19*</td>
<td>↑ CD4, CD8, CD3, ↓ risk of diarrhea and ↓ mortality in infants; ↓ MTCT 2</td>
</tr>
<tr>
<td>(43,44)</td>
<td>Tanzania</td>
<td>Pregnant and lactating women</td>
<td>1083</td>
<td>—</td>
<td>—</td>
<td>↓ Maternal wasting, ↑ infant growth</td>
</tr>
<tr>
<td>(41)</td>
<td>USA</td>
<td>Adults taking HAART</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>↑ CD4 (24%)</td>
</tr>
</tbody>
</table>

1 * P < 0.05.

2 Significant (P < 0.05) decrease in mortality and MTCT in women with low baseline nutritional and immunological status.
The overall ES across the trials show that MMN are certainly effective at increasing Hb compared with a control group, with a mean ES of 0.39 (95% CI: 0.25, 0.53; \( P < 0.001 \)) (Fig. 3). Studies that used a fortified food were significantly more effective in improving Hb (ES = 0.60, 95% CI: 0.32, 0.88, \( P \)-value for fortified compared with other study types = 0.001). Younger children had a larger increase in Hb due to MMN than did older children (\( P = 0.0063 \)). Baseline Hb, HAZ, and WAZ were unrelated to the ES.

Fewer studies reported change in the prevalence of anemia. The mean reduction in the point prevalence of anemia with MMN vs. a noniron placebo ranged from 10 to 40%. There was a greater reduction in anemia with a higher amount of iron in the MMN (Fig. 4A), and in populations with a higher prevalence of anemia at baseline (Fig. 4B).

In the MMN interventions that reported changes in serum (or plasma) zinc and retinol, the control contained neither of these nutrients. MMN had a significant effect on serum zinc in 8 of the 12 studies where MMN were given daily. The mean ES was 0.23 overall (95% CI: 0.18, 0.43; \( P = 0.034 \)) (Fig. 5). There was no difference in the change in serum zinc by type of study (\( P = 0.006 \)). Daily supplementation compared with either placebo or iron was significantly better at improving serum zinc compared with the other study types (ES = 0.45, 95% CI: 0.18, 0.43, \( P \) for difference = 0.001 and ES = 0.42, 95% CI: −0.70, 1.54, \( P \) for difference = 0.013, respectively). In the meta-regression model, lower HAZ and higher serum zinc at baseline predicted a larger response to MMN (\( P = 0.0059 \) and \( P = 0.024 \), respectively).

One paper only reported the effects of MMN on changes in serum retinol (59); the overall ES was 0.33 (95% CI: 0.05, 0.61; \( P = 0.023 \)) (Fig. 6), with no significant difference due to the type of study. However, children with lower baseline HAZ, WAZ, and serum retinol had a larger retinol response (\( P < 0.001 \), \( P = 0.002 \) and \( P < 0.007 \), respectively).

### Discussion

This review shows that the efficacy of MMN varies across trials and outcomes, but that overall there is substantial evidence that outcomes are improved compared with 0–2 MN.

Providing MMN vs. 0–2 MN improves growth (in length and weight) and young child motor development. In addition MMN reduce anemia, and improve the zinc and vitamin A status of infants, children and school children. However, the ES of MMN on Hb and serum zinc differ depending on the type of study. Somewhat surprisingly fortified food (compared with unfortified food) had a significantly larger effect on Hb compared with other interventions, including daily or weekly MMN vs. placebo and daily MMN vs. iron. For improving serum zinc, daily MMN supplements were more effective than fortified food or weekly supplements. Few studies have been conducted on the effects of MMN on morbidity, and none on mortality. Given our overall conclusion that MMN interventions support better child growth, nutritional status and motor development than a placebo, with no reported adverse effects, it may, however be unnecessary to conduct more large mortality trials.

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**FIGURE 3** Effect of MMN supplementation compared with the control group on children’s Hb concentration in individual studies and combined in the meta-analysis. Values are weighted mean \( \pm 2 \) SE, \( n = 46 \). All interventions contained \( \geq 3 \) MN provided for \( \geq 4 \) wk. If the control group was not a placebo, the MN control is given in parentheses.

**FIGURE 4** The percentage point difference in anemia reduction compared with a placebo group depends on the mg Fe/d supplied by the MMN (A) and the baseline anemia prevalence (B). Data are from 9 studies in children.
There is some evidence of benefits of MMN supplements for reducing adult morbidity and mortality, improving birth outcomes, and increasing CD4 counts. These results need to be confirmed in other populations. To date, no studies of MMN have been conducted, to our knowledge, in children with HIV/AIDS. More studies are needed to examine patients receiving HAART and also the effects on MTCT.

For pregnant women, the published meta-analysis shows a reduction in low birthweight, small-for-gestational age, and anemia when MMN were compared with no supplementation or a placebo, but no greater response to MMN when compared with iron + folic acid alone. The important issue of possibly increased perinatal and neonatal mortality due to maternal MMN supplementation during pregnancy in some populations will be addressed in the forthcoming publication of the pooled analysis of the UNIMMAP supplements.

It is undoubtedly necessary to increase the dose of at least some MMN delivered, both in pregnancy and in other population groups, to reduce the remaining high prevalence of deficiency and possibly improve the impact. Only 1 RCT has compared the effect of supplementing pregnant women with twice the Recommended Daily Allowance (2RDA) (except for iron) or 1RDA of 15 MN compared with iron + folic acid (60). The 2RDA supplement caused a significant reduction in birthweights < 3000 g and in low birthweight infants of women who were anemic (and presumably more deficient in several MN) at baseline, whereas the 1RDA supplement was no more effective than the control. Different doses should be tested systematically in future trials with MMN supplements, fortified foods, and lipid-based nutrient spreads. More data are needed on the effects of MMN on other nutritional status outcomes and cognitive development. In addition, more attention should be given to the issues of targeting (e.g. whether we should target stunted children), optimal delivery vehicles (including supplements, fortified foods, dry MMN powders, and fortified spreads), and program efficacy and effectiveness. The benefits from maternal supplementation in lactation should also be investigated.

**Implications for policy.** Only 2 current policies on the use of MMN were identified. WHO’s “Guiding Principles on Feeding Non-Breastfed Children 2 to 24 Months of Age” states: “as needed, use fortified foods or vitamin-mineral supplements (preferably mixed with or fed with food) that contain iron.” Also, “if adequate amounts of animal-source foods are not consumed, these fortified foods or supplements should also contain other MN, particularly zinc, calcium and vitamin B-12” (61). More recently, UNICEF/WHO recommended the use of MMN supplements in populations affected by an emergency (62). In addition to these specific recommendations, WHO/FAO recommends the fortifi-
cation of food staples with MMN. The selection of MMN rather than 0–2 MN? In total, they provide considerable evidence for relatively small benefits for child growth and development, pregnancy outcome, reduced mortality, and CD4 counts in HIV/AIDS (but with few studies conducted); a substantial reduction in anemia (but not compared with iron + folic acid alone), and improvements in vitamin A and zinc status. These may be the greatest benefits it is reasonable to expect and MMN are relatively cheap and feasible to supply. On the other hand, we are still lacking evidence of major impacts on child mortality and morbidity and the important question of whether MMN provided during pregnancy increase perinatal mortality needs to be resolved. If it is still necessary to obtain such evidence, perhaps by testing different formulations and amounts of MN, this needs to be decided and research focused on this question. Agencies and scientists need to develop a coordinated, systematic plan that prioritizes research and optimizes and assesses program efficacy and effectiveness. A huge investment has already been made in testing MMN interventions, but we still need to answer important questions such as: when is supplementation or fortification with only 1 or 2 MN justified or should MMN always be supplied; what doses should be delivered; and how do we prioritize, integrate, and monitor the many available approaches for delivering MMN? In addition, those responsible for the delivery of MN should establish a coordinated, systematic plan for providing and delivering them to relevant population groups in ways that are effective, cost-effective, feasible, and safe.

Literature Cited


