The Effect of Micronutrient Deficiencies on Child Growth: A Review of Results from Community-Based Supplementation Trials[1]

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ABSTRACT Several micronutrients are required for adequate growth among children. However, it has been unclear as to which nutrient deficiencies contribute most often to growth faltering in populations at risk for poor nutrition and poor growth. Therefore, evidence from community-based, randomized, placebo-controlled, micronutrient supplementation trials was reviewed to determine which micronutrient deficiencies have been found to be causal to growth faltering. Although correction of growth-limiting nutrient deficiencies may be achieved through provision of pharmacological nutrient supplements, it also was of interest to review evidence for the use of animal source food supplements to improved growth among children in at-risk populations. There is strong evidence for the contribution of zinc deficiency to growth faltering among children; even mild to moderate zinc deficiency may affect growth. Vitamin A and iron deficiencies also have been demonstrated to cause growth faltering, however only when the deficiency state of these nutrients is severe. Several controlled, community-based intervention trials that have included animal source foods, either together with additional micronutrient supplements or with other supplemental food sources, have demonstrated positive growth responses among children. Three trials that used an animal source food alone (skim milk powder) also resulted in a positive growth response. However, the geographic scope of the latter three trials was limited, and it remains unclear to what extent supplemental animal source foods alone and which types of animal source foods can be used to improve growth among children in at-risk populations. J. Nutr. 133: 4010S–4020S, 2003.

KEY WORDS: • *Micronutrients* • *animal source foods* • *growth* • *supplements*

Growth retardation is highly prevalent in developing countries (1) and is associated with several adverse outcomes throughout life (2). Inadequate intakes of dietary energy and protein and frequent infections are well-known causes of growth retardation (3–5). However, the role of specific micronutrient deficiencies in the etiology of growth retardation has gained attention more recently (6–8). Micronutrient deficiencies are highly prevalent in low-income countries, and the most probable causes are low content in the diet and poor bioavailability. More than half of preschool children are anemic, and an estimated 75 million and 140 million preschool children have clinical and subclinical vitamin A deficiencies, respectively (9). Less information is available on the prevalence of zinc deficiency, although it has been estimated recently that about half of the world's population is at risk of inadequate intake of absorbable zinc (10).

Attained height is the result of the interaction between genetic endowment and both macro- and micronutrient availability during the growth period. Longitudinal growth occurs through a process of cell proliferation, the addition of new cells to the growth plate of the bone and hypertrophy, resulting in the expansion of the growth plate (11). Although the control of bone growth in its different phases is not entirely understood, the key roles of growth hormone (GH)[3] and insulin-like growth factor I (IGF-I) have been identified. IGF-I receptors are found predominantly in proliferating bone chondrocytes (11), and IGF-I itself stimulates synthesis of collagen and proteoglycans. These physiological functions explain the role of IGF-I in linear growth. Furthermore, GH itself and its effect on IGF-I synthesis exert a direct effect on growth.

Nutrition plays a key role in the control of linear growth through a variety of mechanisms. Evidence from animal models indicates that energy and protein restriction reduces IGF-I plasma concentration, which returns to normal after

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[3] Abbreviations used: GH, growth hormone; IGF-I, insulin-like growth factor I; HAZ, height-for-age Z-score; WAZ, weight-for-age Z-score; WHZ, weight-for-height Z-score; RDA, Recommended Daily Allowance.

replenishment. The impact of reduced protein intake appears to be larger than that observed with energy restriction (12). The association between nutritional status and the IGF-I system also has been observed in humans: IGF-I is reduced during acute protein deficiency (kwashiorkor) and protein-energy malnutrition in children (12). Some micronutrients also affect the IGF-I system. For example, it is well documented that zinc deficiency in rats causes not only growth retardation but also a decrease in both IGF-I plasma concentration and GH receptors, which return to normal after zinc repletion (13). Additionally, through its influence on the GH/IGF-I system, zinc deficiency has been observed to affect bone metabolism (14). The role of zinc in growth also may be explained in part through its participation in DNA synthesis (15).

Studies on rats also have shown similar decreases in plasma IGF-I concentrations with depletion of potassium, magnesium or thiamine, which return to normal after repletion of these nutrients (12). Copper also is involved in growth through its role in cross-linking collagen fibers, and manganese deficiency is associated with skeletal abnormalities, including retarded growth, which may be mediated through defects in proteoglycan physiology in the growth plate (11). Vitamin D and calcium deficiencies also affect bone development, as manifested through the condition known as rickets (16).

Vitamin A was first identified as the growth-promoting factor "A." Studies in the 1920s–1930s demonstrated arrested growth, especially of weight in rats, after acute vitamin A depletion (17–20). However, even today effects of vitamin A on linear growth, bone formation and body composition in animals are less clear (21). Judisch et al. (22) found that anemic children were small for their age and that their growth rates accelerated when treated with iron. Since then, however, evidence for the effect of iron deficiency on growth has been equivocal.

Deficiencies of some micronutrients, such as iron, magnesium and zinc, result in anorexia (15,23). Therefore, these nutrient deficiencies also may contribute to growth retardation indirectly by reducing the intake of other growth-limiting factors, such as energy and protein. Also, several micronutrients, including zinc, iron and vitamin A, are associated with immune function and risk of morbidity, which in turn affect growth (4). Therefore, micronutrient deficiencies may have an indirect effect on growth by increasing the prevalence or severity of morbidity and anorexia.

Several approaches may be taken to improve the intake of growth-limiting nutrients, including administration of micronutrient supplements, fortification of food with micronutrients or improved dietary intake. In populations where dietary quality is poor, it is likely that several micronutrient deficiencies co-occur (24–26), in which case growth may be affected by more than one growth-limiting nutrient. Therefore, interventions designed to increase the intake of several common growth-limiting nutrients may be more effective in preventing growth retardation than those that increase the intake of only one problem nutrient. In general, animal source foods contain higher concentrations of several micronutrients that may be limiting to growth (e.g., calcium, zinc, iron and certain amino acids), and micronutrients in animal source foods also tend to be more readily available than micronutrients from plant foods. Indeed, results from observational studies conducted in Mexico and Peru have suggested that intake of animal source foods is associated positively with growth. In Mexico, a higher consumption of animal products between 18 and 30 mo of age was associated with greater weight and length at 30 mo (27). In Peru, intake of animal source foods was associated with greater growth among infants who were either breastfed less frequently or weaned, or whose intake of complementary foods was low (28). These cross-sectional studies suggest that relatively small increases in the intake of animal source foods may reduce the prevalence of growth stunting in populations at risk. However, as these cross-sectional studies cannot confirm a direct impact of animal source food intake on growth, it will be necessary to consider results from experimental studies using animal source food supplements.

The objectives of this review are as follows: *1*) to summarize evidence in the literature regarding the effects of common micronutrient deficiencies on child growth derived from community-based, randomized controlled supplementation trials using either single or multiple micronutrients; and *2*) to summarize evidence of the effects of interventions that included animal source foods in the prevention of growth retardation in community-based intervention trials.

METHODS

We conducted a literature review using the PubMed electronic system. No language restriction was imposed on the search, and articles published after 1989 were identified. Relevant studies published before 1989 were identified through bibliographies of the obtained published articles. For the micronutrient studies, only randomized, placebo-controlled supplementation trials were included. The food-based intervention trials had to have included a concurrently enrolled control group. Only studies conducted for a minimum of 8 wk were accepted, as we consider this the minimum necessary to observe an impact of supplementation on growth.

RESULTS AND DISCUSSION

Randomized trials of the effect of micronutrient supplementation on child growth

Single micronutrients. Community-based, randomized controlled supplementation trials were identified for zinc, iron and vitamin A. The findings from these studies are described in detail below, and a summary of the results is presented in **Table 1**.

Zinc. A meta-analysis of the effects of zinc supplementation on the growth of prepubertal children was published recently (8); therefore, the results of this analysis are summarized here. The studies in this analysis included the following: *1*) randomized, placebo-controlled intervention trials in which the supplemented and controlled groups were enrolled concurrently; *2*) children <12 y of age or specifically stated to be prepubertal throughout the period of intervention; *3*) no premature infants; *4*) subjects free of chronic diseases (e.g., marasmus and cystic fibrosis); *5*) zinc as the only component of the supplement that differed between treatment groups; *6*) supplementation that was provided for at least 8 wk; and *7*) information on the body weight and/or height that was collected during the period of supplementation and reported in sufficient detail. A total of 33 studies were considered to be acceptable, where 13 of the studies were conducted in Latin America/Caribbean, 8 in Asia, 8 in North America/Europe and 4 in Africa. There were positive effect sizes for 25 out of 33 studies that measured height and 25 out of 32 studies that measured body weight. The overall effect size (expressed in standard deviation units) in height was 0.350 (CI = 0.189, 0.511; $p < 0.0001$) and weight was 0.309 (CI = 0.178, 0.439; $p < 0.0001$). The growth responses were greater in children with low initial weight-for-age Z-scores and in those aged ≥6 mo with initial low height-for-age Z-scores.

Results of one zinc supplementation trial conducted in West Java, Indonesia met the criteria described above and was

TABLE 1

Randomized, placebo-controlled, single-micronutrient supplementation trials and effects on child growth

Reference and country	*n*	Age group	Initial status[a]	Dose	Duration	Main findings
Zinc supplementation						
Brown et al., 2002 (8) Meta-analysis of 33 studies (Latin America/Caribbean, Asia, North America Europe and Africa)	21–210	3.1 ± 3.1 y (0–10 y)	Various	13 ± 17 mg/d (1–70 mg/d)	6.6 ± 3.8 mo (8 wk–15 mo)	• Effect size for change in height = 0.350 (CI: 0.189–0.511; $p < 0.0001$) • Effect size for change in weight = 0.309 (CI: 0.178–0.439; $p < 0.0001$) • Effects larger in children < -2 WAZ, and children ≥ 6 mo of age with < -2 HAZ
Dijkhuizen et al., 2001 (29) (Indonesia)	360	4 mo		10 mg/d	6 mo	• No difference in HAZ, WAZ, WHZ, prevalence of stunting or knee-heel length • Effect size for HAZ not significant (p = 0.09) • No difference in plasma IGF-I concentration
Iron supplementation						
Aukett et al., 1986 (30) (Indonesia)	97	1.5 y	Anemic	30 mg/d (+ 20 mg of vitamin C)	2 mo	• Significantly greater rate of weight gain after treatment • Rate of weight gain greater among those showing greatest increase in hemoglobin ($p \approx 0.05$)
Chwang et al., 1988 (31) (Indonesia)	119	8.2–13.5 y	Normal weight; anemic versus nonanemic	10 mg/d	12 wk	• Weight, height and arm circumference increased significantly in the anemic group after iron treatment • Morbidity scores significantly lower in anemic children after iron treatment • No growth effect among nonanemic children
Angeles et al., 1993 (32) (Indonesia)	76	2–5 y	WAZ −2 to −3; iron deficient/anemic	30 mg/d (+ 20 mg of vitamin C)	2 mo	• Change in height and HAZ significantly greater after treatment • Change in WHZ significantly greater in control group
Lawless et al., 1994 (23) (Kenya)	86	6–11 y	~75% anemic and ~95% with hookworm (severe anemia and heavy hookworm excluded)	55 mg/d	14 wk	• Mean changes in height, HAZ, weight and WAZ were significantly greater after iron treatment • Total food (g) and energy intake significantly increased after iron treatment—anorexia may have partly caused poor growth in untreated children
Latham et al., 1990 (33) (Kenya)	55	8 y	No heavy parasite loads (>50% anemic)	80 mg/d (received supplements 15/32 wk)	32 wk	• Changes in weight, weight-for-height, arm circumference and skinfolds were significantly greater after iron treatment • No change in height was observed
Rosado et al., 1999 (34) (Mexico)	335	18–36 mo	(73% anemic)	20 mg/d	1 y	• Linear growth and body composition indicators did not improve significantly after iron treatment • Multiple-micronutrient deficiencies were noted in the children (see Rivera et al., 2001)

Dossa et al., 2001 (35) (Benin)	68	3–5 y	(78% anemic and 58% stunted)	60 mg/d	3 mo	• No significant differences in changes in weight, height or arm circumference observed after iron treatment, nor among those initially stunted or anemic • Hemoglobin increased significantly after iron treatment • Parallel study with albendazole treatment also did not improve growth
Dijkhuizen et al., 2001 (29) (Indonesia)	360	4 mo	28% anemic in treatment group and 66% anemic in control group	10 mg/d	6 mo	• No difference in HAZ, WAZ, WHZ or knee-heel length after iron treatment
Idjradinata et al., 1994 (36) (Indonesia)	47	2–18 mo	Nonanemic; normal weight and height	3 mg/kg body weight/d (~30 mg/d)	4 mo	• The rate of weight gain was significantly greater in the placebo group • No significant differences in length gain or arm circumference
Rahman et al., 1999 (37) (Bangladesh)	223	6–71 mo	Nonanemic	15 mg/d (plus 400RE Vitamin A, 10 μg of cholecalciferol and 50 mg of Vitamin C)	1 y	• No significant differences in weight or height after treatment
Aguayo, 2000 (38) (Bolivia)	64	6–11.9 y	Nonanemic	3 mg/kg body weight weekly (~80 mg/wk)	18 wk	• No differences in weight, height or arm circumference • Significant decline in hemoglobin observed in controls but not in those treated with iron
Vitamin A supplementation						
Ramakrishnan & Martorell, 1998 (39) Review of 9 randomized trials (China, Ghana, India, Indonesia, Nepal and Tanzania)		<3 y		Biannual or 4/mo high dose (n=7/9), RDA equivalent (n=1/9), fortification of MSG (n=1/9)	~1 y	• Vitamin A supplementation unlikely to improve the growth of young children who have only mild to moderate vitamin A deficiency
Hadi et al., 2000 (49) (Indonesia)	1407	6–47 mo	15% very low serum retinol	206,000 IU, every 4 mo	~2 y	• Significant height and weight increases observed only in nonbreastfed children and those with low serum retinol
Fawzi et al., 1997 (50) Sudan	28740	6–72 mo	Free of eye signs of vitamin A deficiency	200,000 IU, 3 doses every 6 mo	>18 mo	• Significantly greater weight observed only in girls aged 1–3 y after vitamin A treatment • No reduction in the incidence of wasting
Villamor et al., 2002 (51) (Tanzania)	554	6–60 mo	Admitted with pneumonia	200,000 IU/d (>12 mo) or 100,000 IU/d (<12 mo) d 1 & 2, and mo 4 & 8	12 mo	• Linear growth increased significantly among children of low socioeconomic status or with HIV infection • Risk of stunting was significantly reduced among children with poor water supply, those who were exclusively breastfed 4–6 mo and those who had persistent diarrhea
Donnen et al., 1998 (52) Zaire	358	0–72 mo	Children stunted	60 mg of vitamin A, 2 doses every 4 mo	13 mo	• Significantly greater increases in weight and arm circumference increments in children with initially low serum retinol

[1] Initial status refers to nutritional status (biochemical or anthropometric) or physiological status (presence of infections) of the subjects at baseline, where this information was provided or relevant. Where no information is provided, this indicates that subjects were not selected on the basis of their initial status.

published after the meta-analysis was completed (29). No differences were found among the groups in height-for-age, weight-for-age or weight-for-height Z-scores (HAZ, WAZ and WHZ, respectively) and in plasma IGF-I concentrations in a subsample. The effect size for length was estimated by us to be 0.09 and was not significant. The authors concluded that there must have been additional underlying factors, including other nutritional deficiencies, that impaired the growth of these children. Nonetheless, the general conclusions of the meta-analysis remain valid, as the authors indicated that >500 studies with no effect of zinc supplementation on growth would be required to invalidate their findings (8).

Iron. Twelve iron supplementation trials were identified, which provided sufficient information to determine whether there was a statistically significant difference in growth response. These studies included children between 2 mo and 13.5 y of age, receiving 10–80 mg of iron/d for at least 2 mo and up to 1 y. These studies were conducted in Asia ($n = 5$), Africa ($n = 4$) and Latin America ($n = 2$). Three of these studies selected children who were anemic (30–32). All three studies showed that provision of iron supplements to the anemic infants or young children resulted in improved growth. The two studies that measured length or height demonstrated greater linear growth (31,32), whereas the third study that did not measure length showed significantly greater weight gain (30). It also was noted in the Indonesian study (31) that a decrease in morbidity was observed among the anemic children who received iron.

Four studies enrolled children from communities that were not selected based on their iron status, but baseline measurements indicated that at least 50% of the children were anemic (23,33,34,35). One group of Kenyan schoolchildren demonstrated significant gains in height and weight, as well as increased food intake, after 14 wk of treatment with iron (23). Another study, also conducted among Kenyan schoolchildren, resulted in increased weight, weight-for-height, arm circumference and skinfolds, but no increase in height was observed after 7 mo of intermittent iron supplementation (33). A study conducted in Benin among preschool children showed no change in height or weight, although hemoglobin concentration was noted to increase significantly after treatment (35). Treatment for intestinal helminthes with albendazole also had no effect on growth in the latter study; therefore, it is possible that some other growth-limiting nutrient was severely deficient in this group. Rosado et al. (34) also reported no effect of iron treatment on growth among preschoolers in Mexico. However, it was noted that several multiple-micronutrient deficiencies were present, including zinc, vitamin A and vitamin B-12. One further study conducted in Indonesia did not measure baseline prevalence of anemia, but after 6 mo of iron treatment, 66% of infants in the placebo group were anemic compared to 28% in the group that received iron (29). No effect on growth was observed in the iron-supplemented group nor were any differences in IGF-1 concentrations found. Zinc supplementation in the same study also did not improve growth. The authors concluded that there must have been other underlying growth-limiting deficiencies present.

There also were four iron supplementation trials that selected only children who were nonanemic (31,36–38). None of these studies demonstrated an effect of iron on growth. In fact, the study conducted in Indonesia demonstrated a significantly lower rate of weight gain among children who received iron compared to controls (36).

In summary, 11 trials that reported information necessary to judge the effect of iron supplementation on growth were reviewed. Four selected anemic infants or young children and one analyzed the subgroup of anemic infants separately. The three that selected only anemic subjects all demonstrated positive effects on growth. Two of five studies that did not select for iron status but noted a high (>50%) prevalence of anemia showed a growth response after iron supplementation. On the other hand, none of the four trials that selected only nonanemic children showed an effect on growth. We concluded that there is substantial evidence indicating that iron supplementation of anemic infants or young children has effects on growth. Although the mechanisms by which anemia causes growth retardation are not clear, it may result from reduced oxidation reactions that occur when the functional iron compartment is depleted, from increased morbidity or from decreased appetite. Discrepancies in results in some of the trials conducted in communities with a high prevalence of anemia may be due to the presence of concurrent deficiencies of other growth-limiting nutrients. Available evidence suggests that iron supplementation has no effect on the growth of nonanemic children.

Vitamin A. Ramakrishnan and Martorell (39) conducted a literature review of vitamin A supplementation trials that measured impact on growth. They reported on nine randomized, double-blind trials (40–48), seven of which were placebo-controlled. The trials were conducted in India (n=3), Indonesia (n=2), China, Tanzania, Ghana and Nepal. Seven of the trials provided high vitamin A doses every 4 or 6 mo, and two of them provided daily amounts that were close to the recommended daily allowance (RDA). All trials were conducted among children <3 y of age in populations with evidence of vitamin A deficiency and high risk of growth retardation. The follow-up period (~1 y) would have been sufficient to find impacts on growth. Most of these trials found that vitamin A reduced mortality; however, eight of the nine studies did not find any effects on length or weight. The two studies that reported effects on growth, one in length (40) and one in weight (46), were the only ones that did not have placebo groups.

Since the publication of the review, results of four additional vitamin A supplementation trials meeting the requirements for inclusion in this review were published from Indonesia (49), Sudan (50), Tanzania (51) and Zaire (52). These studies were community-based, high-dose vitamin A supplementation trials that followed children under 6 y of age for 1–2 y. Two of these studies examined the effects of supplementation on growth according to initial serum retinol concentrations in the children (49,52). Children with severe vitamin A deficiency (serum retinol <0.35 μmol/L) demonstrated improved growth among those who received the vitamin A supplement compared to control children with severe vitamin A deficiency. The third study (50) observed the impact of vitamin A supplementation on weight gain only in girls 1–3 y of age but not in the other age groups (6 mo–1 y and 3–6 y) or in boys, but results were not analyzed according to baseline serum retinol concentrations. The study conducted in Tanzania (51) was the only study prospectively designed to evaluate factors that modify the effect of vitamin A supplementation on growth. Children hospitalized with pneumonia were admitted to the study and received either repeated high-dose vitamin A treatment over 8 mo or a placebo. No overall effect of the treatment was observed in these children. However, treatment had a significant positive effect on the linear growth in subgroups of children of low socioeconomic status and in children with HIV infection. Among those who received vitamin A treatment, risk of stunting after 1 y was significantly lower among children with poor water supply, and in those who were exclusively breastfed for 4–6 mo (but not <4 mo). Finally, treatment attenuated the negative effect of persistent diarrhea on stunting.

Based on these clinical trials, we conclude that vitamin A supplementation is unlikely to improve the growth of young children who are only mildly to moderately vitamin A deficient. On the other hand, severe vitamin A deficiency does appear to cause growth retardation, which may be alleviated after vitamin A supplementation. Effects of vitamin A deficiency on growth may be mediated through morbidity, as suggested by the results of the study in Tanzania, where stunting vitamin A deficiency appeared to contribute to stunting among children with serious infections such as HIV or persistent diarrhea. The interaction of breastfeeding with the effect of supplemental vitamin A on growth is equivocal. The results from Tanzania suggest that additional vitamin A enhanced the protective effects of breastfeeding against stunting, whereas the Indonesian study suggested that nonbreastfed children benefited more from supplemental vitamin A in terms of growth.

Other single micronutrients. We did not find randomized supplementation trials with other micronutrients. There is a theoretical basis to consider potassium, manganese, thiamin and copper as other micronutrients besides zinc, vitamin A and iron as being growth-limiting nutrients in populations. However it is possible that these nutrients are more often consumed in adequate quantities and/or that there is a lack of information available on the occurrence of these deficiencies in populations.

Multiple micronutrients. To date, limited information is available on the effects of multiple-micronutrient supplementation on growth. For the purpose of this review, multiple-micronutrient supplements were considered to be those that contained at least iron, zinc and a form of vitamin A. Five placebo-controlled trials of supplementation with multiple micronutrients were identified and are summarized in **Table 2**. Two of these studies were published in peer-reviewed journals, two were published abstracts and another was submitted recently to a journal for peer review. The studies were conducted in Botswana, Tanzania, Guatemala, Mexico and Vietnam. The studies in Botswana and Tanzania were conducted among schoolchildren, whereas the others included infants and preschoolers aged between 6 and 30 mo.

The three studies conducted among infants and preschool children varied somewhat in design. The study in Mexico (26) supplemented 8- to 14-mo-old children daily for 1 y with a flavored beverage containing 1–1.5 times the RDA of six minerals and 13 vitamins. This population of children was reported to have multiple-micronutrient deficiencies. Supplemented infants initially aged $<$12 mo had significantly greater length gains than the placebo group, with a difference of 0.29 length-for-age Z-score at the end of supplementation, whereas no effects were observed in children aged $\geq$ 12 mo at baseline. The study in Vietnam (53) supplemented children 6–24 mo of age for 3 mo with either of the following: *1*) daily supplements with 8 mg of iron, 5 mg of zinc, 333 μg of retinol and 20 mg of vitamin C, 5 d/wk; *2*) weekly supplements with 20 mg of iron, 17 mg of zinc, 1700 μg of retinol and 20 mg of vitamin C; or *3*) a placebo. Positive impacts on HAZ were documented both in the daily (+0.48, $p < 0.001$) and weekly (+0.37, $p < 0.001$) groups, but only in infants who were stunted at baseline. Limited information is as yet available for the study conducted in Guatemala (54). The supplements provided either whey protein concentrate or bovine serum concentrate, both with or without multiple micronutrients (composition not reported), for ~7 mo. There were no differences in length or weight between the protein-supplemented groups and the groups containing micronutrients.

The two African trials provided schoolchildren with beverages with or without multiple-micronutrient mixtures. In the study in Botswana (55), schools were randomized to receive either the fortified or the nonfortified beverage, where seven servings (100 kcal) of the beverage were provided 5 d/wk. The fortified beverage contained varying proportions of RDA for four minerals and eight vitamins. This treatment was provided for 8 wk, and change in weight, but not height, was included as a growth outcome. The children receiving the fortified beverage gained significantly more weight than those receiving the unfortified beverage. The trial conducted in Tanzania reported various outcomes of a similarly designed trial in a series of abstracts (56,57,58). The fortified or nonfortified beverages contained 30–120% of the RDA for three minerals and seven vitamins and were provided on school days for a period of 6 mo. High prevalences of anemia and severe vitamin A deficiency were reported at baseline in this population (56). Children who received the fortified beverage had significantly greater weight and height increments over the study period (58) and a reduced risk of stunting (57) compared to children who received the nonfortified beverage.

Another study worth noting is one conducted among low-income, Chinese schoolchildren aged 6–9 y (59), which looked at the effects of daily supplementation with zinc (20 mg) versus multiple micronutrients (half of the RDA for seven minerals and 10 vitamins and one-quarter of the RDA for folate) with and without zinc for 10 wk. A placebo group was not included, iron was not included in the multiple-micronutrient treatment and only knee height was reported as a growth outcome. The differences in knee height among groups were reported to be statistically significant ($p < 0.01$), and the largest growth increments occurred in the zinc + micronutrients groups, followed by the group of micronutrients alone and finally, the group of zinc alone. These results suggest that micronutrients other than zinc were limiting bone growth in the study population.

In summary, of the five trials examined, four demonstrated a positive growth response to multiple-micronutrient supplementation. The positive growth response found in the two studies conducted among infants and preschool children was significant only among certain subgroups of children (i.e. those under 12 mo of age in Mexico and those initially stunted in Vietnam). The effect size for change in linear growth in the subgroups for which positive responses were found in these studies (Mexico, 0.29; Vietnam, daily 0.48, weekly 0.37) was in the range of that found in the meta-analysis of zinc supplementation for initially stunted children. The abstract reported from Guatemala did not report specifically on effects among possible vulnerable subgroups of children, but suggested that these factors were controlled for in the analysis.

It is not possible to determine which micronutrients in these studies were limiting to growth, and clearly, this would depend on the existence and severity of various micronutrient deficiencies. Based on the results of the meta-analysis of zinc supplementation on growth, it is clear that zinc is a common growth-limiting nutrient. The conclusions of the single-micronutrient trials confirm that zinc deficiency and severe iron and vitamin A deficiencies are causal to growth retardation. However, the study conducted among schoolchildren in China (59) and others (60) suggest that zinc alone was not the primary growth-limiting nutrient. It is possible that micronutrient deficiencies other than zinc, iron and vitamin A also cause growth faltering as the latter studies did not select for anemia or severe vitamin A deficiency.

Supplementation and/or nutrition education trials including foods of animal origin and their influence on child growth

Perhaps the main question to be asked by the review in this section is whether animal source foods can be used to provide

TABLE 2

Randomized, placebo-controlled, single-micronutrient supplementation trials and effects on child growth

Reference and country	*n*	Age group	Level of randomization	Dose	Duration	Main findings
Abrams et al. (in press) (55) (Botswana)	263	5–11 y	Schools	7 mg of Fe, 3.8 mg of Zn, 2400 μg of β-carotene (+ 9–133% RDA for 2 other minerals and 7 other vitamins)	8 wk	• Weight and weight-for-age Z-scores increased significantly after supplementation with the multiple micronutrient–containing beverage (effect size for weight-for-age Z-score = 0.36)
Ashe et al., 1998 (56), 1999 (57); Latham et al., 1998 (58) (Tanzania)	830	primary school age	Individual	30–120% RDA for 3 minerals and 7 vitamins, including Fe, Zn and vitamin A		• Mean change in weight was 0.8 kg greater ($p < 0.001$) and mean change in height was 0.7 cm greater ($p < 0.001$) in the group that received micronutrients compared to controls • Stunting was significantly reduced (odds ratio 0.52) after treatment
Brown et al., 2000 (54) Preliminary analysis (Guatemala)	171	6–14 mo	Individual	Daily multiple micronutrients plus purified protein (whey or bovine serum)	>7 mo	• No difference among groups in changes in length, weight or arm circumference
Rivera et al., 2001 (26) (Mexico)	319	8–14 mo	Individual	1–1.5 RDA/d of 13 vitamins and 6 minerals	1 y	• Impact of supplementation on length-for-age in infants <12 mo of age at recruitment (effect size = 0.30; $p < 0.05$) • Effect size on children ≥12 mo of age: 0.10 (N.S.)
Dai Thu et al., 1999 (53) (Vietnam)	163	6–24 mo	Individual	Daily: 8 mg of Fe, 5 mg of Zn, 333 μg of retinol and 20 mg of vitamin C; weekly: 20 mg of Fe, 17 mg of Zn, 1700 μg of retinol and 20 mg vitamin C	3 mo	• No significant differences in growth among groups • Among those stunted at baseline, HAZ increased significantly after daily (effect size 0.48) and weekly (effect size 0.37) treatment

additional micronutrients sufficient to prevent or limit growth faltering in children living in high-risk environments. Very few studies have been designed to answer this question directly. Several studies have used interventions that included increased intake of animal source foods. However, the intervention designs varied greatly and most included components other than provision of animal source foods, such as additional micronutrients or nutrition education, to improve young child feeding practices. The studies included in this review are randomized intervention trials with a concurrently enrolled control group and they lasted at least 8 wk.

Food supplements containing animal source foods plus additional micronutrients. Two studies were identified that provided food supplements plus additional micronutrients in the intervention (2,61). One study was conducted in Guatemala, where four villages received either a skim milk–based, high-protein, high-energy supplement (atole) or a no-protein, low-energy supplement (fresco), where both supplements contained additional micronutrients (2,62). The supplements were distributed in a central location in each village and were available on demand to all members of the community. Intake of the supplements was registered daily for all children under 7 y of age. Supplementation with atole resulted in 2.45 ± 0.10 cm greater length at 3 y of age than in the group receiving fresco. In Colombia, women in their first trimester of pregnancy living in an urban area were selected from low income families in which 50% of the children under 5 y of age in the family had a weight-for-age that was >85% of the Colombian standards (61). Mothers were followed through pregnancy and infants resulting from that pregnancy were followed for 3 y. The families were randomly assigned to receive either no supplement or food supplements consisting of dry skim milk, enriched bread and vegetable oil, plus iron and vitamin A supplementation for the enrolled children. At 3 mo, a difference in weight of 197 g in favor of the supplemented group and at 6 mo a difference in length of 0.9 cm were documented. By 36 mo, the supplemented group had a mean weight that was 476 g ($p < 0.05$) higher and a mean length that was 2.2 cm ($p < 0.005$) greater than the control group. Among unsupplemented children, diarrhea was significantly negatively associated with length; however, supplementation completely offset the negative effect of diarrheal disease on growth.

Two other studies that provided food supplements containing animal source foods plus additional micronutrients were identified. Although these did not meet the criteria for inclusion in the review, their results are worth mentioning. A study conducted in a peri-urban area in Guinea-Bissau aimed to determine the effects of a dietary supplement (millet gruel with egg, milk powder, banana, margarine and sugar) plus micronutrients given to children <3 y of age with diarrhea ($n = 120$) versus the children's typical diet. The supplement was given during the diarrheal episode and for 1 wk during convalescence (63). Although the intervention was administered for a median of only 17 d, the children's growth response was monitored for a median of 6.6 mo. The treatment group had a weight gain exceeding that of the control group by 61.5 g/wk during the intervention period and by 12.5 g/wk during follow-up. Not surprisingly, there was no significant increase in knee-heel height during the intervention period. However, it was significantly greater in the treatment group (7.5 mm/y, $p < 0.0001$) after the follow-up. Another study was conducted among Ghanaian infants to evaluate the effect of feeding centrally produced infant cereals of varying nutritional composition on nutritional status (64). Unfortunately, it was not possible to include a concurrently enrolled control group, so a separate cross-sectional study was used as a comparison. Breastfed infants received one of the following porridges: a cereal-legume blend (Weanimix), Weanimix + vitamins and minerals, Weanimix + fish powder or koko (a traditionally used fermented maize porridge) + fish powder. No differences were observed in length or weight among the four intervention groups. However, LAZ and WAZ among all of the supplemented infants (pooled) were greater than among those in the cross-sectional study group. It is possible that all of the supplemental food types tested were equally sufficient to increase the intake of growth-limiting nutrients. However, the authors also suggested that the provision of the hygienically prepared supplemental foods in vacuum flasks may have reduced exposure to diarrheal pathogens and that more prompt use of clinic facilities may have been encouraged indirectly due to frequent morbidity monitoring during the intervention. It was not possible to assess the contribution of decreased morbidity rates to the apparently improved growth among the supplemented children.

The three controlled trials described above produced positive effects on growth, and two of the studies (61,63) suggested that the growth impact was at least partially mediated through attenuation of the negative effects of diarrheal morbidity on growth. The main difference between these studies and those that provided micronutrient supplements alone is that these trials also included supplementary energy and protein, which also may be limiting to growth and may contribute to improved catch-up during convalescence. As both food supplements and micronutrients were provided simultaneously in the intervention, it is not possible to ascertain whether the nutritious food supplement alone could produce similar benefits without the provision of additional micronutrients.

Nutrition education interventions that included increased intake of animal source foods. Two studies conducted nutrition education interventions that included a component to increase the intake of animal source foods. A year-long intervention was conducted in China that assessed the impact of nutrition education and growth monitoring activities on growth among children from their first year of life (65). The educational component included specific messages to encourage exclusive breastfeeding for 4–6 mo, after which time, hard-boiled egg yolk should be offered to the infant daily. It was reported that more women in the intervention group could cite important foods to include in the complementary diet and appropriate patterns of breastfeeding, and more children in the intervention group received egg yolk daily. Infants in the intervention group had significantly better growth in weight and length than the control group. (WAZ: −1.17 vs. −1.93, $p = 0.004$; HAZ: −1.32 vs. −1.96, $p = 0.002$). The increase in intake of egg yolk by young children may have contributed to increased intake of growth-limiting nutrients in this population. However, it cannot be determined to what extent this, or the other intervention activities, contributed to the greater growth observed.

An intervention conducted in India offered a milk- and cereal-based supplement plus nutrition counseling, or visitation only, for 8 mo among infants recruited at 4 mo of age (66). Children receiving the supplement had a weight increment 0.25 kg greater than that of the control group, but no change in length was observed. However, children in the intervention group also had higher rates of diarrhea and were breastfed less frequently than the control children. In this case, the increased diarrheal infections may have been caused by use of contaminated water needed to dilute the food supplement and possibly by the displacement of breast milk. This study suggests that, in addition to providing increased nutritional intake, simultaneous interventions to improve water quality also may be needed to achieve more effective prevention of morbidity and associated growth faltering.

Interventions with animal source foods alone. Only four studies were identified where a single food supplement was provided to children in the form of milk powder or formula without additional micronutrients, three of which were conducted in the same population group. Malcolm (67) reported results of two food-supplementation trials conducted among children in a boarding school in Bundi, New Guinea. The first study compared changes in height, weight and skinfold thickness between two classes of children receiving their regular diet of 3 meals daily of taro and sweet potato (tubers) or a skim milk powder supplement providing 25 g of protein daily for 5 mo. The schoolchildren receiving the supplement demonstrated significantly greater gains in height (+2.42 cm) and weight (+0.73 kg) compared to the control class (+1.18 cm, $p < 0.001$ and –0.13 kg, $p < 0.01$). The second study used a similar design to compare growth response of the schoolchildren to supplemental skim milk powder (270 kcal/d), margarine (270 kcal/d) or two additional meals of taro and sweet potato daily, each provided 5 d/wk for 13 wks. The skim milk–supplemented group demonstrated the largest height and weight increases (+2.32 cm, +1.21 kg) relative to the control group (+1.10 cm, +0.50 kg). Only a small increase in weight (+1.05 kg) occurred in the margarine-supplemented group but skinfolds increased substantially in this group compared to controls. The additional taro and sweet potato resulted in a small increase in height (+1.54 cm) relative to controls. Because the children's normal diet was based almost exclusively on tubers with relatively low protein content, it was hypothesized that protein was limiting to the growth of these children. These results are consistent with protein, or other growth-limiting nutrients in milk, being limiting to the accrual of lean tissues, whereas additional energy provided as fat apparently contributed to fat accumulation. These results were corroborated by a later trial conducted in the same area where children receiving a skim milk powder supplement also demonstrated improvements in indices of skeletal development (68). Walker et al. (69) conducted a randomized intervention trial in Jamaica where a milk-based formula was provided for 1 y to children (9–24 mo) who were initially stunted, and their growth was compared to age- and sex-matched stunted controls who received no food supplement. Supplemented children gained an additional 0.9 cm and 0.31 kg more than that of control children during the first 6 mo of the study, whereas no further benefit was observed in the latter half of the study. It was noted that the gains in growth were greater among younger children than they were among older children. Based on the results of these three trials, it appears that milk supplements may provide a good source of nutrients that are limiting to growth in some settings, although the specific growth-limiting nutrients were not identified.

It is difficult to summarize interventions studying the efficacy of supplementary animal source foods on prevention of growth faltering because of the many different study designs used and because most of the interventions included other components that may have contributed to the effects observed. The only examples of animal source foods solely contributing to growth promotion are the trials that provided milk supplements alone: all four trials produced positive effects on growth; however, it is not possible to determine what specific micro- or macronutrients contributed to the growth response. It also is unclear to what extent additional micronutrients would have provided further benefits to growth. In any case, all of the trials that included food supplements, with or without additional micronutrients, reported positive impacts on growth.

Conclusions

The essential role for several micronutrients in growth has been demonstrated clearly by both animal- and clinical-based human trials of supplementation with single micronutrients. The three micronutrients with the strongest relationship to growth, iron, zinc and vitamin A, are commonly deficient in low-income populations where dietary quality often is poor. The positive impact of community-based supplementation trials reviewed in this article indeed confirms that iron, zinc and vitamin A are common growth-limiting nutrients. However, iron and vitamin A appear to be limiting to growth only when deficiencies of these nutrients are severe, whereas growth may be limited only by mild to moderate deficiency of zinc. This is consistent with the known metabolic and physiologic activity of these nutrients: zinc has direct effects on the primary hormonal system (IGF-I/GH) that controls growth in the postnatal phase when the majority of stunting occurs. On the other hand, iron and vitamin A do not appear to influence this system directly, but more likely exert their effects on growth when their functional stores have been depleted and/or when deficiencies of these nutrients result in increased morbidity, which in turn contributes to growth faltering. Although single-micronutrient supplementation trials have been useful to confirm the effects of specific micronutrients on growth outcomes, programs that provide supplements of only one nutrient may not be the most cost-effective way of preventing growth faltering and associated adverse health outcomes because of the co-existence of multiple-micronutrient deficiencies in many populations.

Multiple-micronutrient supplements are expected to be more efficacious in preventing growth faltering in at-risk populations, as all possible growth-limiting micronutrient deficiencies may be corrected simultaneously. Although the few available multiple-micronutrient supplementation trials have demonstrated positive effects on growth, in some cases these effects were limited to specific subgroups of the study population. Also, the interaction of various micronutrients and the potential negative effect of some minerals on the absorption of others (e.g., iron, zinc and copper, calcium) when combined in a single supplement requires further assessment.

From a programmatic perspective, it may be more desirable to consider intervention options other than supplement use. Food-based interventions may have several advantages, including the provision of additional nutrients in a familiar form that can be integrated with the usual diet and the provision of an additional source of energy and high-quality protein, which also have direct effects on the IGF-I/GH hormone system (70). Animal source foods provide the richest and most bioavailable sources of several micronutrients. Some of the food-based trials have demonstrated that at least part of the positive effects of the intervention on growth occurred by improving catch-up growth after diarrheal illness (61,63). Although it is conceivable that the additional micronutrients (provided by the pharmacological supplements or animal source food) supported catch-up growth during convalescence, the supplemental foods also would have provided additional energy and protein, which may contribute to improved growth in the face of frequent infections (71,72).

Unfortunately, very few studies have been reported that confirm the evidence from cross-sectional studies suggesting that intake of animal source foods is associated with better growth in children. Several intervention studies have included both food supplements and additional multiple micronutrients,

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but it remains uncertain as to whether the supplemental food source alone could have been equally effective at preventing growth faltering. The few interventions that provided animal source foods alone were restricted to those that provided milk powder. Although milk powder may provide some additional micronutrients, it is not as good a source of readily available iron and zinc or of vitamin A, as compared to beef for example. Most of the studies that reported positive effects of milk-powder supplementation were conducted in Papua, New Guinea, where protein was likely to be a major growth-limiting nutrient in this population because low-protein tubers are the main staple food. However, in many populations where protein intakes are sufficient, such as those that rely on cereal grains, milk powder may not be as effective in preventing growth faltering. Clearly, more studies are needed to determine the efficacy of different animal source foods, including meat and fish, in a variety of geographical settings.

With respect to program development, it would be useful to compare directly the relative impact of micronutrients and nutritious food supplements in the prevention of growth faltering. If food supplements prove to be comparably effective for many children in a particular setting, greater confidence may be placed in the efficacy of food-based approaches, thus providing another feasible option. A useful study design to determine whether micronutrients from animal source foods can improve growth relative to pharmacological micronutrients alone would be to employ a four-cell design with an animal source food, micronutrients alone, an animal source food supplement plus additional micronutrients and a parallel control group.

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