Effect of micronutrient supplementation on linear growth of children

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This review summarizes the results of published, randomized clinical trials that have examined the impact of administration of micronutrients, singly or in combination to infants, preschool and school children on linear growth. Supplementation of single micronutrients resulted in small or no benefits on linear growth. A meta-analysis of zinc supplementation trials confirmed that zinc has a significant but small impact (0·22 SD units) on length gain in children 0–13 years of age. However, a recent study reported a substantially greater benefit (>1 SD) in stunted and non-stunted breast-fed infants 6–12 months of age. With iron supplementation, a beneficial effect was found only in anemic children. Vitamin A supplementation trials have reported little or no benefit on linear growth. Data currently available suggest some impact in children with clinical or biochemical vitamin A deficiency, but this issue needs confirmation. Few studies could be identified where a combination of micronutrients was given as a supplement or as fortified food; in the latter set of studies energy availability was assured. The impact on length without multiple micronutrient supplementation was no greater than that observed with single micronutrients. In conclusion, zinc and iron seem to have a modest effect on linear growth in deficient populations. Vitamin A is unlikely to have an important effect on linear growth. Limited available evidence does not allow us to conclude whether a combination of micronutrients, with or without additional food, would have a greater impact than that seen with zinc alone.

Linear growth: Iron: Vitamin A: Zinc: Micronutrients

Linear growth faltering is common in children belonging to the low socio-economic groups in developing countries. This faltering commences during the intrauterine period and extends to postnatal life, most strikingly in the initial 18–24 months. Subsequently, the rates of growth approach those of children in industrialized countries (Waterlow *et al.* 1980).

The aetiology of linear growth faltering is thought to be multi-factorial. Maternal malnutrition and low dietary intakes in infants, frequent infections and poor psycho-social environment are some factors known to be associated with retarded linear growth.

Macro or micronutrient deficiency during the prenatal period could potentially programme the fetus towards slower linear growth during postnatal life or result in low nutrient stores at birth. Low micronutrient intakes of young infants in developing countries could result from low levels of various micronutrients in breast milk due to maternal deficiency, and also from inadequate complementary feeding practices during the second half of infancy. Energy as well as micronutrient intakes of infants are usually low in many of these settings. Even when energy intakes are adequate, diets are often vegetarian and are low in content and poor in bioavailability of nutrients like iron, calcium, zinc and vitamin A. Developing country infants and children suffer frequent infections leading to decreased intake, impaired absorption, increased nutrient losses, hypercatabolism and other metabolic perturbations, all of which contribute to faltered linear growth.

The micronutrients associated with linear growth are those believed to be nutritionally significant or 'essential'; reduction in the availability of these micronutrients below a certain threshold consistently leads to a reduction in one or more physiologically important functions. These 'essential' micronutrients have been defined by a WHO Expert Committee to include iodine, zinc, selenium, copper, molybdenum, chromium, vitamin A and calcium (WHO, 1996).

This review is focused on the role of deficiency of micronutrients in linear growth faltering of developing country infants in postnatal life and the extent to which supplementation of these micronutrients, alone or in combination, improves growth. The evidence available from observational as well as experimental studies is examined. This issue assumes importance given the recent proposals to consider routine supplementation of multi-nutrient mixtures as a strategy to reduce stunting in developing country children.

Supplementation trials with individual micronutrients

Zinc

Zinc deficiency has long been known to be associated with high phytate, high fiber, low protein diets and with

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hookworm and schistosomiasis (Halstead *et al.* 1972). The initial zinc supplementation trials, conducted in the early 1980s did not result in improved linear growth possibly because of the short duration of supplementation and poor absorption of zinc due to vegetarian diets that impeded absorption (Allen, 1994). Recent studies, several of which were done in industrialized countries, have however shown improved linear growth following zinc supplementation.

A meta-analysis of twenty-two zinc supplementation trials with concurrent controls that examined impact on linear growth was recently published (Brown *et al.* 1998). Most of the included studies were double-blind and placebo-controlled. The age range of children participating in these trials that examined the impact of zinc supplementation on linear growth was from birth to 13 years; the mean age was 3·6 years. The mean initial plasma zinc of children ranged from 42 to140 μg/dL (mean 83 μg/dL). The duration of supplementation varied from 10 days to 16 months, with an average of approximately 7 months. Between eleven and 191 subjects per group were enrolled in the trials. The initial height for age Z-scores ranged from −5·4 to +0·12 with a mean of −2·32. The mean daily zinc dose was 14 mg per day with a range of 1·5 mg to 50 mg. In most studies, zinc was administered 5 to 6 days a week.

The results of all studies were standardized as 'effect size' which was calculated as the mean change in length/height of the treatment group minus the mean change in the control group divided by the pooled standard deviation of change for both groups. Overall, zinc supplementation resulted in a significant but small average effect size of 0·22 SD units.

There was a significant heterogeneity in effect size in the studies. Initial height for age status of infants and children was found to be associated with treatment effect size in a multiple regression analysis. In studies with mean initial height for age Z-score less than −2, there was a larger effect size of 0·49 SD units. No impact of supplementation was observed in studies with mean initial height for age Z-score greater than −2.

In a recent randomized double-blind zinc supplementation trial, not included in the meta-analysis, 100 non-stunted and 100 stunted breast-fed infants, 6–12 months of age, received 10 mg zinc or placebo 6 days a week for 6 months. The effect size was 4·32 SD for stunted and 1·88 SD for non-stunted infants (Umeta *et al.* 2000). These 8–9 fold

greater effect sizes than those in the meta-analysis may be due to higher level of zinc deficiency, larger dose of zinc used and the supplemental period being that of rapid growth. These results, however, need to be confirmed in future studies.

In conclusion, zinc is an important linear growth limiting micronutrient in populations that are zinc deficient.

Vitamin A

Association between linear growth faltering and clinical vitamin A deficiency signs (night blindness, conjunctival xerosis) prompted intervention trials examining the impact of vitamin A supplementation on linear growth (Mele *et al.* 1991; Brink *et al.* 1979; Santos *et al.* 1983; Muhilal *et al.* 1988).

We identified ten vitamin A supplementation trials from published literature that have reported an impact on linear growth. Seven of these studies were double-blind, placebo-controlled and included children aged from 6 months to 5 years. Vitamin A was given weekly (Rahmathullah *et al.* 1991) as a single large dose (Bahl *et al.* 1997) or 4–6 monthly (Lie *et al.* 1993; Ramakrishnan *et al.* 1995; Fawzi *et al.* 1997; West *et al.* 1997; Donnen *et al.* 1998, Hadi *et al.* 2000) supplements, or as fortified monosodium glutamate (Muhilal *et al.* 1988). Two studies did not have random allocation; neighbouring villages (Muhilal *et al.* 1988) and alternate households (Fawzi *et al.* 1997) were given vitamin A or placebo in these. One study did not report the overall effect; there was however no benefit of supplementation in either males or females in terms of linear growth (West *et al.* 1988). In the remaining nine studies, effect sizes were calculated as SD shifts as suggested by Brown *et al.* (1998). The effect sizes ranged from −0·06 to +0·21 SD; the median was 0·05 SD (Table 1). Only two of the ten studies showed a significant but small benefit of 0·16 and 0·21 SD (Muhilal *et al.* 1988; Hadi *et al.* 2000). Both these studies were from Indonesia where vitamin A deficiency was very common; 1·24 % had Bitot's spots in one study and 67·4 % had serum retinol ≤0·7 μmol/L in the other. The latter study also showed that the benefit was 2–3 fold higher in infants who had serum retinol ≤0·35 μmol/L.

The evidence available to date suggests that routine vitamin A supplementation has little or no impact on linear

Table 1. Impact of vitamin A supplementation on linear growth

Author, year	Subjects' age (months)	Number† per group	Vitamin A	Comments on study design	Effect size (SD units)
Muhilal, 1988	12–23	322/361	Fortified monosodium glutamate	Non-random, five neighbouring villages selected as control	0·16*
Rahmathullah, 1991	12–23	1136/1171	2500 μg RE weekly for 1 year	Randomized, double-blind	0·12
Lie, 1993	6–36	94/94	60 000 μg RE; two doses. 6 months apart	Randomized, double-blind	0·19
Ramakrishnan, 1995	6–36	310/282	60 000 μg RE; three doses every 4 months	Randomized, double-blind	0·05
Fawzi, 1997	6–72	10625/10626	60 000 μg RE; three doses every 6 months	Alternate household allocation	0·03
West, 1997	12–60	1760/1617	60 000 μg RE; four doses every 4 months	Randomized, double-blind	0·03
Bahl, 1997	12–59	427/430	60 000 μg RE; single dose	Randomized, double-blind	0·05
Donnen, 1998	0–72	118/117	60 000 μg RE; two doses every 4 months	Randomized, double-blind	−0·06
Hadi, 2000	6–48	715/722	61 800 μg RE; six doses every 4 months	Randomized, double-blind	0·21*

* $P < 0.05$; † intervention/control.

Table 2. Impact of iron supplementation on linear growth

Author, year	Subjects		% Anaemic at baseline	Iron supplementation‡	Study design	Effect size (SD units)
	Age (months)	Number†				
Chwang, 1988	96–156	43/35	All	2 mg/kg per d for 12 wk	Stratified randomization, double-blind	0·28*
	96–156	16/25	None	2 mg/kg per d for 12 wk		−0·21
Bhatia, 1992	36–60	56/49	All	40 mg/d for 24 wk	Randomized trial, non stratified	−0·11*
	36–60	28/23	None	40 mg/d for 24 wk		0·09*
Angeles, 1993	24–60	39/37	All	30 mg/d for 8 wk	Randomized double-blind	0·99*
Lawless, 1994	72–132	44/42	80 %	45 mg for 14 wk	Randomized double-blind	0·6*
Rosado, 1997	12–18	22/22	None	3 mg/kg per d for 16 wk	Randomized double-blind	0·07
Rosado, 1997	18–36	50/47	~50 %	20 mg/d for 48 wk	Randomized double-blind	−0·07
Adish, 1999	24–60	192/206	All	Iron v. aluminium pots for cooking	Randomized community based	0·3*
Morley, 1999	9	133/135	?	Iron fortified (1·2 mg/L) v. non-fortified formula (0·9 mg/L) for 36 wk	Randomized double-blind	0·03
Rahman, 1999	6–71	107/116	?	15 mg/d for 48 wk	Randomized double-blind	−0·11

* $P < 0.05$; † intervention/control group; ‡ elemental iron.

growth. The data are not sufficient to allow any conclusion on impact of vitamin A in children with clinical or biochemical deficiency.

Iron

There are several small iron supplementation studies that have examined its impact on linear growth in young children. These studies appear to have mixed results with the effect sizes varying from −0·21 to +0·99 SD units (Adish *et al.* 1999; Angeles *et al.* 1993; Lawless *et al.* 1994; Morley *et al.* 1999; Rahman *et al.* 1999). The results become clearer when the studies are classified by baseline prevalence of anaemia (Table 2). Four of the five studies, where >80 % children were anaemic, showed significant benefits in linear growth following supplementation (median effect size 0·6 SD units). An Indian study reported a negative effect in anaemic children and a beneficial impact in those who were non-anaemic (Bhatia & Seshadari, 1992). The design of this study had several limitations. Four preschools were randomly allocated without stratification by haemoglobin status, but results were presented separately for anaemic and non-anaemic children. Further, there were important baseline differences in length, which were not adjusted for. In studies where the prevalence of anaemia was either not mentioned or was low, no impact was observed.

Similarly, none of the studies in anaemic iron replete children reported a beneficial impact of iron supplementation. On the contrary there is some suggestion that growth might be adversely affected under these circumstances (Idjradinata *et al.* 1994). Non significant negative effects were reported for length (−0·21 SD units) in a study by Chwang *et al.* 1988 and on weight in a recent Indonesian study (−0·45 SD units, Idjradinata *et al.* 1994).

In conclusion, iron supplementation of anaemic children has significant impact on linear growth only in anaemic children. The adverse impact observed in supplementation of non-anaemic children needs further confirmation.

Copper

Copper deficiency during infancy and childhood is caused by low birth weight, low copper intake because of a predominantly cow's milk-based diet, malabsorption and diarrhea. We could not locate any randomized supplementation trials that examined impact on linear growth. Observational studies suggest that stunted children are copper deficient (Singla *et al.* 1996; Chuwa *et al.* 1996; Tanzer & Ozalp, 1988; Subotzky *et al.* 1992). In a study from Chile, copper deficient (plasma copper <70 μg/dL and ceruloplasmin <200 mg/L) infants 6–12 months of age and controls matched by age, sex and nutritional status were supplemented with 80 mg/kg per day copper for one month. Supplementation improved length for age by 0·34 SD units in the copper deficient group and by 0·09 SD in controls but the difference was not significant (Castillo-Duran & Uauy, 1988).

Copper supplementation trials in infants and children with sample size and period of supplementation adequate to examine impact on linear growth are required.

Table 3. Randomized double-blind controlled trials examining the impact of multiple micronutrient supplementation on linear growth

Author, year	Age (months)	Number per group†	Study group	Baseline nutrition status	Effect size (SD units)	Subgroup effect size (SD units)
Rosado, 1997	18–36	49/47	Zinc and iron v. placebo × 12 months	HAZ −1·6±0·8	−0·13	–
Thu, 1999	6–24	55/54	Zinc, iron, vitamin A, vitamin C v. placebo × 3 months daily	<12 months, 15 % stunted 12–18 months, 36 % stunted	0·20	1·04* stunted at baseline
		54/54	Same as above but weekly	>18 months, 66 % stunted	0·38	0·57* stunted at baseline
Stuijvenberg, 1999	72–132	115/113	Fortified (iron, iodine, carotene) v. unfortified biscuits × 10.75 months	14·8 % stunted	No difference (data not shown)	–
Rosado, 1999	8–14	168/167	Fortified v. unfortified beverage × 12 months‡	?	0·14*	0·24* low/medium SES

* P < 0·05; † intervention/control; ‡ fortified with iron, zinc, retinol, vitamin C, riboflavin, B₁₂, vitamins D, E and K, niacin, folic acid, panthothenic acid, iodine, calcium, phosphorus, manganese, fluoride, selenium.

Iodine

Observational studies suggest that severe as well as marginal iodine deficiency is associated with linear growth retardation (Greene, 1980; Neumann *et al.* 1992). There are however, no controlled studies of iodine supplementation with linear growth as the outcome. Such trials are unlikely to be conducted in future because of universal salt iodization recommendations for iodine deficient populations.

Calcium, phosphorus and magnesium

Evidence from animal studies and observational studies in children suggest that inadequate dietary intakes of calcium may contribute to linear growth retardation. An Indian study conducted in 1938 reported a height gain of 0·36 cm in 3·6-year-old children supplemented with 65 mg calcium per day for 4–5 months (Aykroyd & Krishnan, 1938). The same investigators reported 0·53 cm greater height gain in 6–12-year-old children supplemented with 130 mg calcium for 3 months (Aykroyd & Krishnan, 1939). These findings were however not confirmed in subsequently conducted controlled supplementation trials in India, China and South Africa (Bansal *et al.* 1964; Lee *et al.* 1994; Pettifor *et al.* 1981). A recent review concluded that calcium supplementation alone or together with phosphorus does not improve height or weight gain of children in developing countries with low to medium calcium intakes (Prentice & Bates, 1994).

Malnourished children have been reported to have low magnesium levels (Singla *et al.* 1998). Hypomagnesemia in malnourished children may be due to inadequate intake, malabsorption, diarrhea and other infections. In twenty-three Guatemalan children with edematous protein caloric malnutrition following magnesium supplementation (2·7 mg/kg per day) for a period of 9–35 days, the rate of recovery from malnutrition was accelerated by two weeks (Nichols *et al.* 1978). However, more trials are needed to show whether malnourished children will have accelerated linear growth if supplemented with magnesium.

Individual micronutrient supplementation studies in humans have generally observed a smaller impact than that anticipated by the results of animal experiments. One reason is that the deficiency that is achieved in animals is severe as compared to the marginal deficiency observed in humans. Another important factor may be that multiple nutrient deficiencies are likely to occur in children in developing countries and supplementation with individual micronutrients can be expected to have only a limited impact on growth. Studies in various settings have shown that deficiencies of iron, vitamin A, zinc and other micronutrients often coexist (Rosado *et al.* 1997; Rosado, 1999; Hautvast *et al.* 1999; Neumann & Harrison, 1994). The subsequent section therefore, reviews available literature on randomized controlled trials where multiple micronutrients were administered as supplements to observe their impact on linear growth. In another set of studies, foods were fortified with micronutrients to understand the likely impact of micronutrient supplementation on

linear growth if energy and protein availability were assured.

Interventions examining the impact of multiple micronutrients administered as supplements

Few randomized placebo controlled trials were identified (Table 3, Rosado *et al.* 1997; Rosado 1999; Thu *et al.* 1999; Stuijvenberg *et al.* 1999). No differences in linear growth were observed between the group supplemented with zinc and iron when compared to the placebo in Mexico after 12 months of supplementation (Rosado *et al.* 1997). The investigators, concluding that lack of impact was probably due to concurrent deficiencies of other micronutrients, conducted another study in the same setting (Rosado, 1999). In the second study, a mixture of micronutrients was given as a supplement to children over a period of 12 months. There was a small significant overall impact (effect size 0·14 SD units) and a greater benefit was observed in supplemented children belonging to the low and medium socio-economic status (effect size 0·24 SD units; Rosado, 1999).

In Vietnam (Thu *et al.* 1999), children aged 6–24 months received iron (8 mg elemental), zinc (5 mg), retinol (333 μg) and vitamin C (20 mg) for 3 months. Heights were measured at baseline and 3 months post supplementation. In the overall study population, the impact on growth was not significant. Children who were stunted (HAZ < −2) at the baseline had greater benefit; 0·57 SD units with weekly and 1·04 SD units with daily supplementation.

In only one study (Sandstead *et al.* 1998) was a direct comparison made between multiple micronutrients and zinc alone. In this study, school children in China were supplemented at three sites with micronutrients without zinc, micronutrients with zinc and zinc alone. The impact was measured as a change in knee height. The impact observed with multiple micronutrients containing zinc seemed larger than that obtained with zinc alone. The results comparing the impact of micronutrients without zinc and with zinc alone were inconsistent. However, these results need to be interpreted with caution as they pertained to only two study sites; the results from the third site were not presented because of local technical problems in measuring heights.

Supplementation with micronutrient fortified foods

Even when children are provided with micronutrients in adequate amounts, low energy and protein intakes may limit growth. This issue could be studied in food supplementation trials where food was fortified with micronutrients (Table 4). However, in these trials, the comparison groups differed in energy and protein intakes in addition to differences in micronutrient intake. The impact of micronutrients cannot therefore be separated from that of the additional energy or protein quantity or quality.

Four similar randomized controlled trials were conducted in Congo, Senegal, Bolivia and New Caledonia (Simondon *et al.* 1996, Table 4). Four-month-old infants were randomly allocated to supplement or control groups. The supplemented infants received a cereal-based precooked porridge offered twice daily for 3 months and consumption was monitored. The mean daily consumption of the supplement at different sites varied between 558 and 790 kJ/d. The length increment was higher in supplemented children by 0·44 SD units in Senegal; no significant impact was observed in other countries. The authors concluded that one of the reasons for not observing an impact was probably the short period of supplementation.

The supplementation period was longer in a recently concluded trial in New Delhi (Bhandari *et al.* unpublished). A precooked milk cereal mixture fortified with micronutrients was fed to infants from 4 to 12 months of age. Although higher energy and micronutrient intakes were reported in the supplemented children as compared to those not supplemented, no impact was observed on linear growth.

In a Ghanaian study, infants were randomly assigned to receive one of the four foods from 6 to 12 months of age. These foods were weanimix, fortified weanimix (with vitamin A, iron, zinc, copper, calcium, phosphorus and potassium), weanimix enriched with fish powder and fermented maize porridge plus fish powder. No significant

Table 4. Randomized controlled trials examining the impact of micronutrients given along with food on linear growth in children

Author, year	Subject age at starting supplement (months)	Number/group†	Intervention	Effect size (SD units)
Simondon, 1996	4	Congo 53/67	Precooked mixture *v.* usual home foods × 3 months‡	−0·13
		Senegal 53/57		0·44*
		Bolivia 65/62		0·29
		New Caledonia 43/47		0·04
Lartey, 1999	6	51/53	Fortified v/s unfortified weanimix × 6 months§	0
Bhandari, unpublished	4	86/90	Precooked milk cereal mixture *v.* usual home foods × 8 months¶	0·14

* $P < 0.05$; † intervention/control; ‡ precooked wheat, maize, millet, soy bean, milk powder soybean oil, sugar mixture, enriched with calcium, phosphorus, potassium, magnesium, iron, copper, manganese, zinc, iodine, selenium. Vitamins A, B, E, C, B_6, B_{12}, thiamin, riboflavin, niacin, folic acid and pantothenic acid; § weanimix (cereal legume blend of maize, soybean and groundnuts) fortified with vitamin A, iron, zinc, copper, calcium, phosphorus and potassium; ¶ precooked wheat, milk powder, sugar mixture enriched with vitamins A, B, C, E, K, B1, B_2, B_6, B_{12}, folic acid, nicotinamide, Ca- panthenate, niacin, $CaPO_4$, iron, copper, iodine, manganese, zinc and selenium.

differences were reported between the four intervention groups in linear growth. However weight and length Z-scores in all the four intervention groups were higher between 9 and 12 months of age when compared to infants who had not participated in the intervention but resided in the same setting (Lartey *et al.* 1999).

In conclusion, from the limited data available, it does not appear that micronutrients when supplemented in addition to food have a greater benefit on linear growth than when given alone. It may be noted that in a majority of the trials, food availability but not intake could be assured.

Conclusions

Among individual micronutrients, there is good evidence that zinc supplementation has a modest but significant linear growth impact in preschool and school going children. A beneficial impact of iron supplementation on linear growth seems likely only in anaemic children. On the other hand, a substantial impact by vitamin A on linear growth in children is unlikely.

Few investigators have examined the impact of multiple micronutrient supplementation on linear growth; comparisons between multiple and single micronutrient supplementation are even more uncommon. The limited available evidence from published studies does not allow us to conclude that supplementation with multiple micronutrients will have a greater impact on growth than is seen, for instance, with zinc alone in developing countries. More double-blind randomized controlled trials with adequate sample sizes and duration of supplementation, and with provision to examine impact on relevant subgroups are required.

Based on the current evidence of the impact on cognition, morbidity and mortality respectively, iron and vitamin A supplementation should be continued. Zinc supplementation or fortification may be considered in populations where the prevalence of deficiency is high, given the observed impact on morbidity and growth; the case would become stronger if mortality trials proposed to be conducted in the near future also show a beneficial impact on child mortality. The feasibility of providing iron and zinc in the same formulation needs to be explored, if necessary, with addition of trace amounts of copper.

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