REVIEW

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The Impact of Nutritional Interventions beyond the First 2 Years of Life on Linear Growth: A Systematic Review and Meta-Analysis[1–3]

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ABSTRACT

A large body of evidence suggests that the first 1000 d from conception is a critical window in which interventions to address malnutrition will be most effective, but little is known about the impact on linear growth of nutritional interventions in children ≥2 y of age. The aim of this analysis was to evaluate the effectiveness of several nutrition-based interventions, specifically iron, zinc, calcium, iodine, vitamin A, multiple (≥2) micronutrients, protein, and food, at improving growth in children ≥2 y of age. A systematic search of MEDLINE and EMBASE retrieved 7794 articles. A total of 69 studies met prespecified inclusion criteria. Baseline height-for-age *z* score, age, nutrient dose, and study duration were examined as potential sources of heterogeneity. Zinc (mean effect size: 0.15; 95% CI: 0.06, 0.24), vitamin A (0.05; 95% CI: 0.01, 0.09), multiple micronutrients (0.26; 95% CI: 0.13, 0.39), and protein (0.68; 95% CI: 0.30, 1.05) had significant positive effects on linear growth, with baseline height-for-age *z* score as a significant inverse predictor of the effect size. Iron, calcium, iodine, and food-based interventions had no significant effect on growth. Age at baseline, study duration, and dose were not related to effect size for any nutrient examined. These findings suggest that zinc, vitamin A, multiple micronutrients, and protein interventions delivered after 24 mo of age can have a positive effect on linear growth, especially in populations that have experienced growth failure. *Adv Nutr* 2017;8:323–36.

Keywords: zinc, iron, calcium, vitamin A, protein, multiple micronutrient, stunting, 1000 days

Introduction

The global prevalence of linear growth stunting has steadily declined from 1990 (40%) to 2014 (24%), yet ~159 million children <5 y old remain affected (1). This highlights the critical need to identify effective strategies to address the global burden of linear growth failure.

The etiology of linear growth faltering is multifactorial (2). More than 2 billion people and 800 million people suffer from vitamin and mineral deficiencies and energy deficiency, respectively (3, 4). Growth faltering may stem from deficiencies in single nutrients, multiple micronutrients (MMs)[6], macronutrients, energy, or more commonly, a combination of many nutritional deficiencies.

Increasingly, the foci of nutritional interventions are pregnancy and the first 2 y of life. This period, also coined the first 1000 d, is widely accepted as a window of opportunity in which interventions will affect child growth, with interventions outside of this window often considered unlikely to have any significant effect. However, based on evidence suggesting that catch-up growth occurs even in the absence of interventions, an opportunity to promote catch-up growth beyond the first 1000 d has been proposed (5, 6).

Most previous meta-analyses have restricted their analysis to single nutrients and to children <5 y of age (including both children <2 y of age and those ≥2 y of age), thereby limiting the conclusions that can be made regarding the impact of interventions on growth after age 24 mo. To address these issues, we conducted a systematic review and meta-analysis of clinical trials to evaluate the effect of a range of nutrition-based interventions beyond the first 2 y of life on child growth.

Methods

Data sources and searches. We searched MEDLINE (1966–2016) and EMBASE (1947–2016) on 14 January 2016 and 26 February 2016, respectively.

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[3] Supplemental Figures 1–5 and Supplemental Table 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://advances.nutrition.org.

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[6] Abbreviations used: HAZ, height-for-age *z* score; LMICs, low- and middle-income countries; MM, multiple micronutrient.

For MEDLINE, the search ("linear growth or height" and "intervention or child nutritional physiological phenomena") was used. For EMBASE, the search "nutrition and height and growth" was used. To be included, trials had to meet the following criteria: *1*) study subjects were humans; *2*) the study was available in English; *3*) subjects were children aged ≥2 y but <20 y; *4*) subjects were free of chronic disease, such as Crohn's disease and HIV; *5*) the study was a randomized controlled trial or quasirandomized controlled trial; 6) the intervention was nutritional; and *7*) height was measured and reported both before and after intervention. Titles and abstracts of retrieved studies were scanned to exclude irrelevant studies. Full texts of remaining articles were reviewed, and studies that met inclusion criteria were included. Reference lists of included articles and relevant literature reviews were hand-searched for additional relevant articles. The search process is illustrated in **Figure 1**.

Review of studies and extraction of summary data. Key descriptive data, including the sample size, location of intervention, baseline and endline characteristics of the study subjects, dose and duration of intervention, height outcome, and significance of findings were extracted into a standardized form. The reported sample size corresponds to the number of subjects who completed the intervention. The included studies were grouped into 8 intervention categories: *1*) iron, *2*) zinc, *3*) calcium, *4*) iodine, *5*) vitamin A, *6*) multiple MMs (≥2 MMs), *7*) protein, and *8*) food. Studies with >1 intervention group were treated as independent studies. For studies that did not report baseline height-for-age *z* score (HAZ) or stunting prevalence but provided mean age and height data, HAZ was calculated by using WHO Anthro software (version 3.2.2) from reference data for the majority sex by using the mean age. In studies that used a delivery schedule other than daily, the average dose provided was converted to a daily dose. The Jadad test (a validated instrument that independently assesses the method of randomization, blinding, and report of subject withdrawal and dropout) was used to assess methodological quality, which was classified as high (score 5), moderate (score 4), or low (scores 1–3) (7). All data were entered twice and inconsistencies resolved.

Data synthesis and analysis. The primary response variable was change in height, expressed in centimeters or HAZ. We utilized adjusted estimates of linear growth when available. Interquartile ranges, 95% CIs, and SEs were converted to SDs by using standard equations provided in the Cochrane Handbook for Systematic Reviews of Interventions (8). If only the baseline and endline values were reported, we calculated the crude mean change in height by subtracting baseline mean from the endline mean. For studies that did not report the SD for linear growth changes, we calculated the SD for change, assuming the baseline and endline were highly correlated ($\rho = 0.8$). In studies with multiple intervention groups and a single control group, the sample size of the control group was divided equally by the number of intervention groups while retaining the same value for the change in linear growth and its SD to avoid multiple counting of the control group.

A sensitivity analysis to assess the effect of assumptions regarding correlation between growth measures pre- and postintervention was conducted by using the following: *1*) assuming a correlation of 0.5, 0.8, or 0.9; *2*) assuming no correlation; and *3*) calculating effect size only for the subsample of studies that reported the changes and SD of change (**Supplemental Table 1**). Additional sensitivity analyses were conducted by excluding studies in which there was no stunting (mean study baseline HAZ >−2) and in which dietary intake was adequate.

Effect sizes for each individual study were computed by dividing the mean change in the intervention and control groups by the pooled SD. Data were consolidated by using an inverse variance method. I^2 statistics were used to measure the heterogeneity of the studies. If the I^2 value was <50%, a fixed-effects model was applied. If the I^2 value was >50%, a random-effects model was used (8). We visually assessed funnel plots to investigate potential publication bias (9). Data were analyzed by using RevMan (version 5.0.25), and figures were prepared by using RevMan and GraphPad Prism (version 5.01) software.

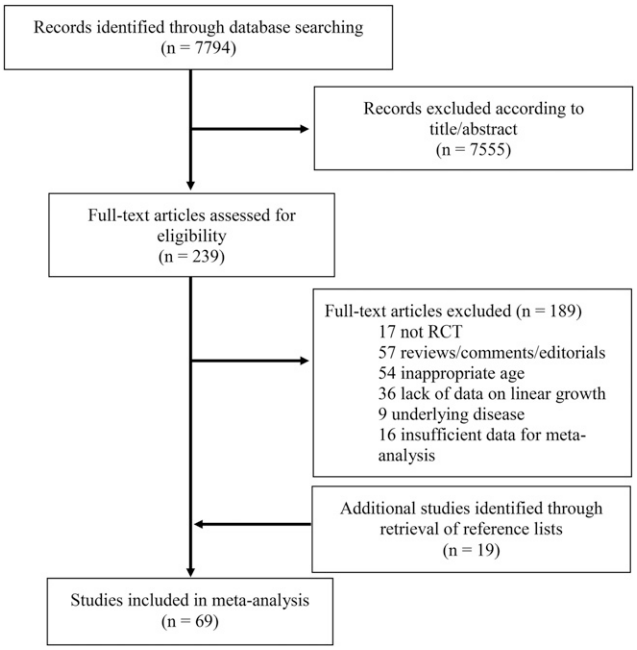

FIGURE 1 Flowchart illustrating the selection of trials for inclusion in the systematic review and meta-analysis. RCT, randomized controlled trial.

Results

Study selection

The literature search yielded 7794 references (Figure 1), of which 7555 were excluded on the basis of title and abstract, and 189 studies were excluded following full review. An additional 19 articles were identified from reference lists. A total of 69 articles were included in the systematic review and meta-analysis.

Baseline characteristics and risk of bias

The baseline characteristics for single-micronutrient and other nutrition-based interventions are reported in **Tables 1** and **2**, respectively. Using the Jadad test, 37 studies were classified as high quality, 19 were of medium quality, and 13 were of low quality. Symmetric funnel plots suggested a low chance of publication bias in zinc, iodine, and food-based analysis. Asymmetrical funnel plots for iron, calcium, vitamin A, MMs, and protein suggest potential publication bias (**Supplemental Figure 1**). The key effects of nutritional interventions administered after age 24 mo on linear growth are summarized in **Table 3**.

Effects of nutrition-based interventions on linear growth

Iron. A total of 14 studies were included in the meta-analysis. All studies were conducted in low- and middle-income countries (LMICs) located in East Asia and the Pacific ($n = 4$), South Asia ($n = 5$), Africa ($n = 4$), and Latin America or the Caribbean ($n = 1$). The number of subjects in each study ranged from 41 to 374, with mean ages ranging from 34 to 167 mo. Approximately 82% of datasets had a baseline HAZ <−1, and 5 of 17 datasets had a baseline HAZ <−2. One study (21) did not have

TABLE 1 Baseline study characteristics of single-micronutrient interventions in children ≥2 y of age[1]

Study	Year	Country	Subjects, *n*	Mean initial age, mo	Dose	Duration, mo	Mean initial HAZ	Quality
Iron								
Aguayo (10)	2000	Bolivia	64	111	3 mg/kg bw	4	−1.48	High
Angeles et al. (11)	1993	Indonesia	76	37	30 mg	2	−2.26	Medium
Bhatia and Seshadri 1 (12)	1992	India	105	47	40 mg	6	−2.3	Medium
Bhatia and Seshadri 2 (12)	1992	India	51	54	40 mg	6	−1.56	Medium
Chen et al. (13)	2008	China	132	48	8.57 mg	6	−0.23	Medium
Chwang et al. (14)	1988	Indonesia	41	128	10 mg/kg bw	3	−1.52	Medium
Dossa et al. (15)	2001	Benin	68	47	60 mg	3	−2.26	Medium
Hettiarachchi et al. (16)	2008	Sri Lanka	374	167	35.71 mg	6	−1.19	Medium
Latham et al. (17)	1990	Kenya	55	96	285.7 mg	1	−0.88	High
Lawless et al. (18)	1994	Kenya	86	105	150 mg	3	−1.23	High
Mwanri et al. 1 (19)	2000	Tanzania	68	132	85.7 mg	3	−2.2	High
Mwanri et al. 2 (19)	2000	Tanzania	68	126	85.7 mg	3	−1.56	High
Palupi et al. (20)	1997	Indonesia	187	42	4.29 mg	2	−1.82	Medium
Pereira et al. (21)	1979	India	44	42	10 mg	5	—	Low
Rahman et al. (22)	1999	Bangladesh	147	34	15 mg	12	−2.2	High
Sungthong et al. 1 (23)	2002	Thailand	200	116	300 mg	4	−1.55	High
Sungthong et al. 2 (23)	2002	Thailand	190	116	42.86 mg	4	−1.49	High
Zinc								
Castillo-Durán et al. 1 (24)	1994	Chile	19	169	10 mg	12	−2.58	High
Castillo-Durán et al. 2 (24)	1994	Chile	18	138	10 mg	12	−2.61	High
Cavan et al. (25)	1993	Guatemala	156	82	7.14 mg	6	−1.38	High
Friis et al. (26)	1997	Zimbabwe	276	134	40 mg	12	−1.18	High
Gibson et al. (27)	1989	Canada	60	75	10 mg	12	−1.39	High
Hettiarachchi et al. (16)	2008	Sri Lanka	382	161	10 mg	6	−1.1	High
Kaseb and Fallah (28)	2013	Iran	95	146	5 mg	4	−0.6	High
Kikafunda et al. (29)	1998	Uganda	113	56	10 mg	6	−0.7	High
Mozaffari-Khosravi et al. 1 (30)	2009	Iran	47	39	5 mg	6	−1.58	Medium
Mozaffari-Khosravi et al. 2 (30)	2009	Iran	38	40	5 mg	6	−1.65	Medium
Nakamura et al. (31)	1993	Japan	21	70	5 mg	6	−2.44	Low
Ronaghy et al. (32)	1969	Iran	27	156	28 mg	5	−2.73	Low
Ronaghy et al. (33)	1974	Iran	39	156	40 mg	12	−3.02	Low
Rosado et al. (34)	1997	Mexico	95	29	20 mg	12	−1.7	High
Ruz et al. (35)	1997	Chile	53	40	10 mg	14	−0.52	High
Sayeg Porto et al. (36)	2000	Brazil	18	116	5 mg/kg bw	6	−2.67	Medium
Sempértegui et al. (37)	1996	Ecuador	48	42	10 mg	2	−2	High
Taneja et al. (38)	2010	India	421	27	20 mg	4	—	High
Walravens et al. (39)	1983	United States	40	50	10 mg	12	−2.07	High
Calcium								
Bass et al. 1 (40)	2007	Australia	47	109	800 mg	9	0.47	High
Bass et al. 2 (40)	2007	Australia	41	109	800 mg	9	0.36	High
Bonjour et al. (41)	1997	Switzerland	108	95	850 mg	12	0.3	High
Cameron et al. (42)	2004	Australia	48	124	1200 mg	24	0.3	High
Chevalley et al. (43)	2005	Switzerland	174	89.3	850 mg	12	0.2	High
Courteix et al. 1 (44)	2005	France	54	119.3	800 mg	12	—	High
Courteix et al. 2 (44)	2005	France	31	119.3	800 mg	12	—	High
Dibba et al. (45)	2000	Gambia	160	124	714.3 mg	12	−1.09	High
Ekbote et al. (46)	2011	India	58	33	357.1 mg	12	−1.96	High
Iuliano-Burns et al. 1 (47)	2003	Australia	34	106	434 mg	9	−0.08	High
Iuliano-Burns et al. 2 (47)	2003	Australia	32	106	434 mg	9	0.27	High
Lloyd et al. (48)	1993	United States	94	143	500 mg	18	−0.23	High
Nowson et al. (49)	1997	Australia	56	168	1000 mg	18	−0.9	High
Pettifor et al. (50)	1981	South Africa	60	121	500 mg	3	−1.09	Medium
Specker and Binkley 1 (51)	2003	United States	90	48	714.3 mg	12	0	High
Specker and Binkley 2 (51)	2003	United States	88	39	714.3 mg	12	−0.15	High
Iodine								
Zimmerman et al. 1 (52)	2007	Albania	310	137	400 mg[2]	6	−1.13	Medium
Zimmerman et al. 2 (52)	2007	South Africa	188	110	200 mg[3]	6	−0.54	Medium
Vitamin A								
Fawzi et al. 1 (53)	1997	Sudan	2166	24 to <36[4]	200,000 IU	17	—	High
Fawzi et al. 2 (53)	1997	Sudan	2033	36 to <48[4]	200,000 IU	17	—	High
Fawzi et al. 3 (53)	1997	Sudan	1975	48 to <60[4]	200,000 IU	17	—	High
Fawzi et al. 4 (53)	1997	Sudan	1756	60 to <72[4]	200,000 IU	17	—	High

(Continued)

TABLE 1 (*Continued*)

Study	Year	Country	Subjects, *n*	Mean initial age, mo	Dose	Duration, mo	Mean initial HAZ	Quality
Fawzi et al. 5 (53)	1997	Sudan	2079	>60[4]	200,000 IU	17	—	High
Fawzi et al. 6 (53)	1997	Sudan	1991	24 to <36[4]	200,000 IU	17	—	High
Fawzi et al. 7 (53)	1997	Sudan	2023	36 to <48[4]	200,000 IU	17	—	High
Fawzi et al. 8 (53)	1997	Sudan	1985	48 to <60[4]	200,000 IU	17	—	High
Fawzi et al. 9 (53)	1997	Sudan	1875	60 to <72[4]	200,000 IU	17	—	High
Fawzi et al. 10 (53)	1997	Sudan	2120	>60[4]	200,000 IU	17	—	High
Hadi et al. 1 (54)	2000	Indonesia	377	≥24[4]	206,000 IU	24	—	Medium
Hadi et al. 2 (54)	2000	Indonesia	2263	≥24[4]	206,000 IU	24	—	Medium
Lin et al. (55)	2009	China	86	37	100,000 IU	3	−0.46	High
Mwanri et al. 1(19)	2000	Tanzania	68	131	5000 IU	3	−2.13	High
Mwanri et al. 2 (19)	2000	Tanzania	68	127	5000 IU	3	−1.39	High
Yang et al. (56)	2002	China	63	48	667 IU	12	−1.55	High

[1] bw, body weight; HAZ, height-for-age *z* score; IU, international unit.
[2] Single dose.
[3] Two doses delivered 3 mo apart.
[4] Age range.

extractable baseline height data. The daily dose of iron ranged from 10 to 286 mg/d. In 2 studies, the daily dose of iron could not be determined because administration of the mineral was based on body weight (10, 14). The duration of supplementation lasted from 1 to 12 mo.

Effect sizes for change in height were calculated from 17 datasets ($n = 14$ studies) and ranged from −0.30 to 0.89 (**Figure 2A**). There was significant heterogeneity ($P = 0.003$). The overall standard mean effect was not statistically significant (0.10; 95% CI: −0.04, 0.24) (Figure 2A). Sensitivity analyses excluding studies in which no children were stunted (0.13; 95% CI: −0.24, 0.51) and in which serum hemoglobin was ≥110 g/L (0.27; 95% CI: −0.13, 0.67) did not alter the conclusions. Baseline HAZ ($r = -0.34$; $P = 0.22$), age ($r = 0.20$; $P = 0.46$), study length ($r = -0.41$; $P = 0.10$), dose ($r = -0.03$; $P = 0.91$), and hemoglobin ($r = -0.15$; $P = 0.60$) were not predictors of the effect size (**Supplemental Figure 2A–E**).

Zinc. We identified 17 studies that examined the effect of zinc on height. The majority of included studies were conducted in LMICs located in South Asia ($n = 2$), Africa ($n = 2$), the Middle East ($n = 4$), and Latin America or the Caribbean ($n = 3$). The number of subjects in each study ranged from 18 to 421, with mean ages of subjects ranging from 27 to 169 mo. At baseline, 74% of datasets had HAZ scores <−1, and 8 of the 17 study populations had HAZ scores <−2. One study (38) did not have extractable baseline height data for children aged ≥24 mo. The daily dose of zinc ranged from 5 to 40 mg/d for 2 to 12 mo.

Effect sizes for change in height were calculated from 19 datasets ($n = 17$ studies) and ranged from −0.16 to 0.97 (Figure 2B). The majority of datasets (89%) had a positive effect size, and the overall standard mean effect was statistically significant (0.15; 95% CI: 0.06, 0.24) (Figure 2B). Sensitivity analyses excluding studies in which no children were stunted (0.49; 95% CI: 0.19, 0.79) and in which serum zinc was >12 μmol/L (0.13; 95% CI: 0.02, 0.24) did not alter the conclusions. The regression model showed a significant negative relation ($r = -0.51$; $P = 0.03$) between baseline HAZ and effect size for height gain (**Figure 3A**). Baseline age ($r = 0.17$; $P = 0.48$), study length ($r = -0.11$; $P = 0.65$), dose ($r = 0.09$; $P = 0.72$), and serum zinc ($r = 0.19$; $P = 0.56$) were not predictors of the effect size (Figure 3B–E).

Calcium. A total of 12 studies contributed 16 data sets. Three of the studies were conducted in LMICs located in South Asia ($n = 1$) and Africa ($n = 2$). The remaining studies were conducted in high-income countries, including 2 in the United States, 4 in Australia, 2 in Switzerland, and 1 in France. The number of subjects in each study ranged from 31 to 174, with mean ages of subjects ranging from 33 to 168 mo. Four studies enrolled both boys and girls, 6 studies enrolled only girls, and 2 enrolled only boys. At baseline, 3 of 8 study populations had HAZ scores <−1, and no population had HAZ scores <−2. There was insufficient data to calculate baseline HAZ in the study by Courteix et al. (44). The daily dose of calcium ranged from 357 to 1200 mg/d for 3 to 24 mo.

Effect sizes for change in height ranged from −0.37 to 0.61 (Figure 2C). The overall standard mean effect was not statistically significant (0.03; 95% CI: −0.09, 0.14) (Figure 2C). Sensitivity analyses excluding studies in which dietary intake was ≥400 mg/d did not alter the conclusions (−0.08; 95% CI: −0.35, 0.18). Baseline HAZ ($r = 0.33$; $P = 0.25$), age ($r = 0.29$; $P = 0.08$), study length ($r = -0.29$; $P = 0.27$), dose ($r = -0.07$; $P = 0.79$), and baseline dietary calcium ($r = 0.14$; $P = 0.63$) were not predictors of the effect size (**Supplemental Figure 3A–E**).

Iodine. Two studies that examined the impact of iodine supplementation on linear growth were identified. One study contributing 2 data sets was included in the meta-analysis. The data were obtained from studies conducted in Albania and South Africa, both LMICs. The number of subjects was 188 and 310, with mean ages 110 and 137 mo, respectively. Both studies had a baseline mean HAZ >−2,

TABLE 2 Baseline study characteristics of multiple-micronutrient, protein, and food-based interventions in children ≥2 y of age[1]

Study	Year	Country	Subjects, *n*	Mean initial age, mo	Form	Duration, mo	Mean initial HAZ	Quality
Multiple micronutrient								
Ash et al. (57)	2003	Tanzania	750	120	5.4 mg Fe, 1750 IU vitamin A, 45 μg I, 5.25 mg Zn, 72 mg vitamin C, 0.6 mg riboflavin, 0.15 mg folic acid, 3 μg vitamin B-12, 0.7 mg pyridoxal, 10.5 mg vitamin E	6	−2.1	Medium
Hall et al. (58)	2007	Vietnam	1080	83	Biscuits fortified with 18 vitamins and minerals; supplemented food provided 1400 IU retinol, 60 μg I, 5 mg Fe, 6 mg Zn	17	−1.47	Low
Hettiarachchi et al. (16)	2008	Sri Lanka	380	159	50 mg Fe, 14 mg Zn	6	−1.08	Medium
Hyder et al. (59)	2007	Bangladesh	837	144	7 mg Fe, 1296 IU vitamin A, 75 μg I, 7.5 mg Zn, 120 mg vitamin C, 0.91 mg riboflavin, 120 μg folic acid, 1 μg vitamin B-12, 1 mg vitamin B-6, 10 mg vitamin E, 5 mg niacin	12	−1.97	High
Vinod Kumar and Rajagopalan (60)	2006	India	159	90	3,000 IU vitamin A, 1 mg vitamin B-12, 1 mg Ca, 15 mg niacin, 1 mg pyridoxal, 100 μg folic acid, 1 μg vitamin B-12, 30 IU vitamin E, 30 mg vitamin C, 10 mg Fe, 250 mg lysine	9	−1.23	Low
Lopriore et al. (61)	2004	Algeria	209	50	1000 mg Ca, 1134 mg K, 635 mg P, 156 mg Mg, 42 mg Fe, 41 mg Zn, 2 mg Cu, 2000 μg vitamin A, 50 μg vitamin D, 20 mg vitamin E, 125 mg vitamin C, 4 mg thiamin, 4 mg riboflavin, 4 mg pyridoxal, 4 μg vitamin B-12, 500 μg folate, 25 mg pantothenic acid, 60 mg niacin	6	−2.85	Medium
Manger et al. (62)	2008	Thailand	563	111	5 mg Fe, 5 mg Zn, 50 μg I, 270 μg vitamin A	7	−1	High
Muthayya et al. (63)	2009	India	277	104	500 μg vitamin A, 0.9 mg riboflavin, 1 mg pyridoxal, 1.8 μg vitamin B-12, 300 μg folate, 227.1 mg vitamin C, 231 mg Ca, 100 μg I, 18 mg Fe, 10.5 mg Zn, 0.93 g α-linolenic acid, 0.10 g docosahexaenoic acid	12	−1.32	High
Mwanri et al. (19)	2000	Tanzania	68	143	5,000 IU vitamin A, 200 mg Fe	3	−1.9	High
Ronaghy et al. (32)	1969	Iran	30	156	10 g dried egg white, 6,000 IU vitamin A, 500 IU vitamin D, 50 IU α-tocopherol, 2 mg thiamin, 2.5 mg riboflavin, 25 mg niacin, 20 mg panthothenic acid, 0.3 mg biotin, 4 mg pyridoxal, 10 μg vitamin B-12, 90 mg vitamin C, 0.1 mg folic acid, 100 mg Ca, 100 mg Fe, 5 mg Mn, 0.1 mg Co, 1.1 mg Cu, 0.15 Cr, 2 mg Mb, 0.5 mg Ni, 0.1 mg Se, 0.15 mg I, 1 mg F	20	−2.96	Low
Ronaghy et al. (33)	1974	Iran	25	156	6,000 IU vitamin A, 500 IU vitamin D, 50 IU vitamin E, 2 mg thiamin, 2.5 mg riboflavin, 25 mg niacin, 20 mg panthothenic acid, 0.1 mg folic acid, 0.3 mg biotin, 4 mg pyridoxal, 10 μg vitamin B-12, 90 mg vitamin C, 100 mg Ca, 120 mg Mg, 100 mg Fe, 5 mg Mn, 0.1 mg Co, 40 mg Zn, 1.1 mg Cu, 0.15 mg Cr, 2 mg Mb, 0.5 mg Ni, 0.1 mg Se, 0.15 mg I, 1 mg F	5	−2.74	Low

(Continued)

TABLE 2 (*Continued*)

Study	Year	Country	Subjects, *n*	Mean initial age, mo	Form	Duration, mo	Mean initial HAZ	Quality
Rosado et al. (34)	1997	Mexico	96	29	20 mg Fe, 20 mg Zn	12	−1.65	High
Sarma et al. (64)	2006	India	695	122	7.3 g protein, 2 g fat, 576 mg Ca, 14 mg Fe, 1.6 mg riboflavin, 2 mg pyridoxal, 1 μg vitamin B-12, 200 μg folic acid, 80 mg vitamin C, 400 μg vitamin A, 2.5 μg vitamin D, 0.7 mg thiamin, 0.9 mg niacin, 75 μg I, 2.3 mg Zn	14	−0.62	High
Shatrugna et al. (65)	2006	India	184	138	14 mg Fe, 1.6 mg riboflavin, 2 mg pyridoxal, 1 μg vitamin B-12, 200 μg folic acid, 80 mg vitamin C, 400 μg vitamin A, 2.5 μg vitamin D, 0.7 mg thiamin, 0.9 mg niacin, 400 mg Ca, 75 μg I, 2.3 mg Zn	14	−0.86	High
Solon et al. (66)	2003	Philippines	831	119	4.8 mg Fe, 700 IU vitamin A, 48 μg I, 3.75 mg Zn, 75 mg vitamin C, 0.46 mg riboflavin, 0.06 mg folic acid, 0.5 μg vitamin B-12, 0.5 mg pyridoxal, 2.5 mg vitamin E, 2.5 mg niacin	4	−1.81	Medium
Zadik et al. (67)	2004	Israel	37	173	10 mg Fe, 11 mg Zn, 10,000 IU vitamin A	6	−2.65	Medium
Zadik et al. (68)	2010	Israel	37	77	12 mg Fe, 6,000 IU vitamin A	6	−2.75	Medium
Protein								
Grillenberger et al. 1 (69)	2003	Kenya	178	91	Ground beef added to githeri	24	−1.4	Medium
Grillenberger et al. 2 (69)	2003	Kenya	190	88	Cow milk	24	−1.3	Medium
Kabir et al. (70)	1998	Bangladesh	69	33	Protein-supplemented diet	1	−1.87	Low
Lampl et al. 1 (71)	1978	New Guinea	45	124	Skim milk powder added to diet	8	−3.85	Low
Lampl et al. 2 (71)	1978	New Guinea	41	124	Skim milk powder added to diet	8	−3.95	Low
Larnkjær et al. 1 (72)	2014	Denmark	61	161	Skim milk	3	0.84	High
Larnkjær et al. 2 (72)	2014	Denmark	53	161	Casein protein	3	0.78	High
Larnkjær et al. 3 (72)	2014	Denmark	59	160	Whey protein	3	0.89	High
Malcolm 1 (73)	1970	New Guinea	43	94	Skim milk powder	2	−3.75	Low
Malcolm 2 (73)	1970	New Guinea	66	97	Skim milk powder	3	−3.64	Low
Pereira et al. (74)	1969	India	35	42	Rice supplemented with lysine and threonine	6	−2.07	Medium
Pereira et al. 1 (75)	1973	India	63	42	Rice supplemented with lysine and threonine	6	−2.22	Low
Pereira et al. 2 (75)	1973	India	46	42	Wheat supplemented with lysine	6	−1.88	Low
Food								
Alarcon et al. (76)	2003	Philippines and Taiwan	91	49	Pediasure (Abbott Laboratories)	3	−1.38	Low
Grillenberger et al. (69)	2003	Kenya	246	87	Fat added to githeri	24	−1.35	Medium
Malcolm (73)	1970	New Guinea	57	126	5 meals of taro and sweet potato instead of 3	3	−3.6	Low
Maleta et al. (77)	2004	Malawi	61	51	RTUF (high in micronutrient) or maize or soy flour	23	−3.1	Low
Prasad Mp et al. 1 (78)	2016	India	137	134	Sorghum supplementation	8	−1.64	Low
Prasad Mp et al. 2 (78)	2016	India	125	119	Sorghum supplementation	8	−1.2	Low

[1] HAZ, height-for-age *z* score; RTUF, ready to use food; IU, international unit.

with 1 study having a mean HAZ <−1. Supplemental iodine was delivered as iodized oil in one large bolus (400 mg) or 2 smaller doses (200 mg every 3 mo). The duration of both studies was 6 mo.

Effect sizes for change in height were calculated from 2 datasets (n = 1 study) and were 0.00 and 0.11 (Figure 2D). The overall standard mean effect was not statistically significant (0.07; 95% CI: −0.10, 0.25) (Figure 2D). Because of limited data, effect modification by baseline HAZ, age, and study length was not examined.

Vitamin A. We identified 5 studies that assessed the effect of vitamin A on linear growth. The studies contributed 16 datasets for analysis. The studies were conducted in Sudan

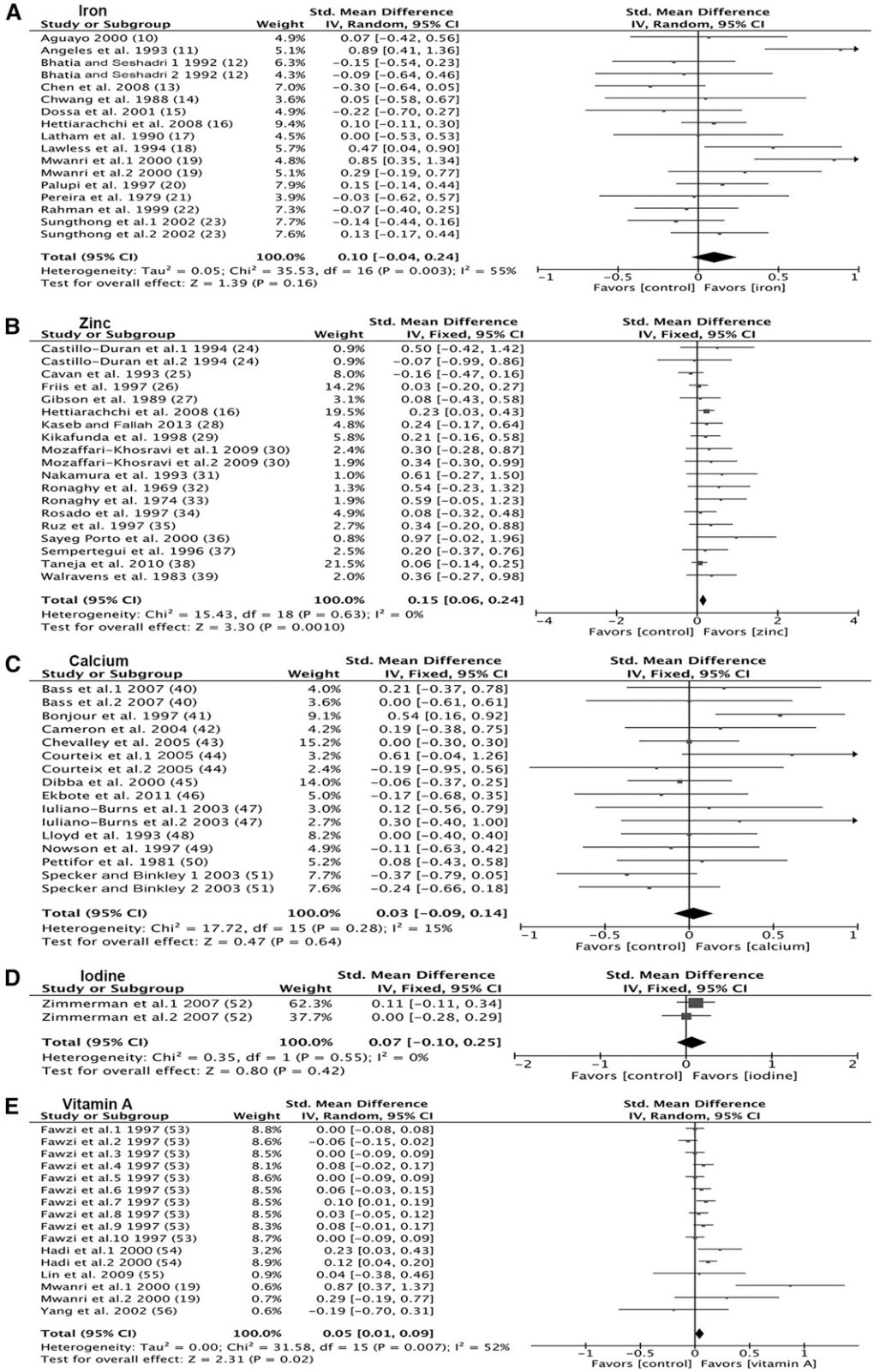

FIGURE 2 Forest plots of the effect on linear growth of single micronutrient interventions in children ≥2 y of age. Data derived from systematic literature review of nutrient interventions administered after age 2 y. (A) Iron. (B) Zinc. (C) Calcium. (D) Iodine. (E) Vitamin A. Fixed, fixed-effects model; IV, inverse variance; random, random-effects model; std., standard.

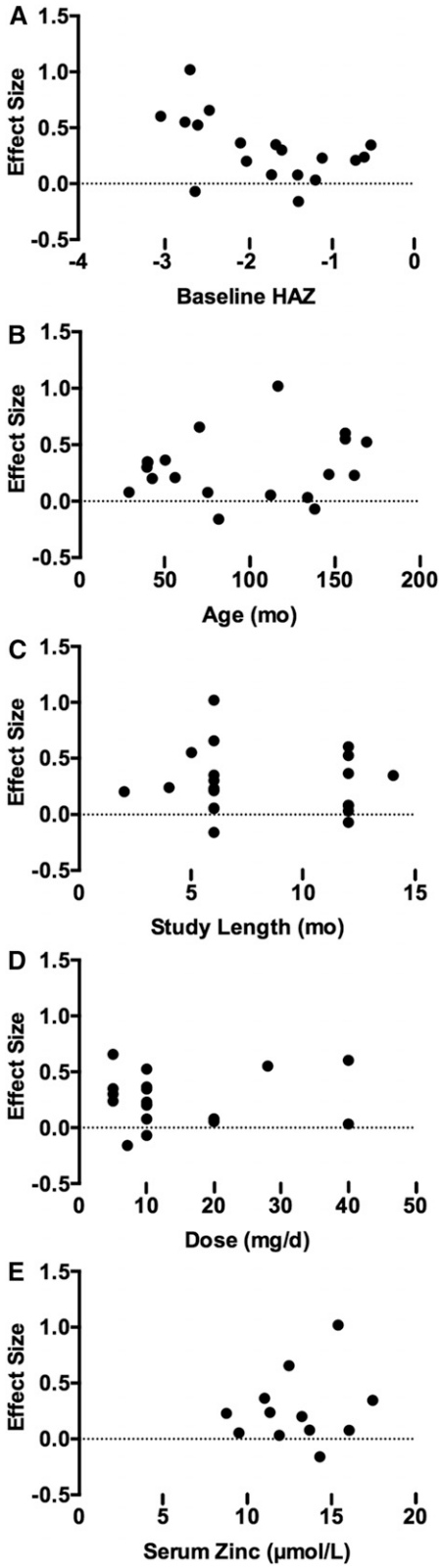

FIGURE 3 Relation between potential sources of heterogeneity and the standard mean effect of zinc intervention on linear growth in children ≥2 y of age. (A) Baseline HAZ was a significant predictor of the effect size ($r = -0.51$; $P < 0.05$). (B) Age ($r = 0.17$; $P > 0.05$), (C) study duration ($r = -0.11$; $P > 0.05$), (D) dose ($r = 0.09$; $P > 0.05$), and (E) serum zinc ($r = 0.19$; $P > 0.05$) were not predictors of the effect size. Each point represents one study estimate. HAZ, height-for-age *z* score.

(53), Tanzania (19), China (55, 56), and Indonesia (54). The study in Sudan (53) was stratified by age group and sex, the study in Tanzania (19) had 2 treatment groups, and the study in Indonesia (54) was stratified by breastfeeding status. The number of subjects in each study ranged from 63 to 2166, with mean ages of subjects ranging from 2 to 12 y. A majority (75%) of the study populations had a baseline HAZ <−1, of which 1 study population had HAZ <−2. The study by Fawzi et al. (53) did not provide sufficient data to calculate baseline HAZ for the stratified sex and age groups. The dose of vitamin A ranged from 5000 to 206,000 international units, and duration of supplementation lasted from 3 to 17 mo. Larger doses (≥100,000 international units) were administered with larger time intervals between doses (monthly to biannually); whereas smaller vitamin A supplements were administered more frequently (3 d/wk to weekly).

Effect sizes for change in height were calculated from 16 datasets ($n = 5$ studies) and ranged from −0.19 to 0.87 (Figure 2E). There was significant heterogeneity ($P = 0.007$). One dataset by Mwanri et al. (19) was identified as a potential outlier because of its effect size being 3 times higher than that of the next largest effect size. The overall standardized mean effect was statistically significant with (0.05; 95% CI: 0.01, 0.09) and without (0.04; 95% CI: 0.01, 0.07) the outlier (Figure 2E). Baseline HAZ ($r = -0.62$; $P = 0.38$), age ($r = 0.83$; $P = 0.17$), and study duration ($r = -0.43$; $P = 0.10$) were not predictors of effect size for height gain (**Supplemental Figure 4A–C**).

MMs. Seventeen trials were identified. All studies were conducted primarily in LMICs: 3 in Africa, 3 in East Asia and the Pacific, 4 in the Middle East, 6 in South Asia, and 1 in Latin America and the Caribbean. The number of subjects in each study ranged from 25 to 1080, with mean ages of subjects ranging from 29 to 173 mo. At baseline, 14 study populations had a mean HAZ <−1, of which 6 had a mean HAZ <−2. MM interventions were administered as either supplements (e.g., pills) or fortified foods and beverages. The composition and dose of the MM supplements varied among studies. All interventions contained iron, whereas the inclusion of zinc (76.5%), vitamin A (88.2%), calcium (41.2%), and iodine (52.9%) was more variable. The duration of supplementation ranged from 3 to 20 mo.

The effect sizes for change in height ranged from −0.14 to 2.56 (**Figure 4A**). The majority of datasets (94%) had a positive effect size, and 7 were statistically significant. There was significant heterogeneity ($P < 0.00001$). The studies by Zadik et al. (67, 68) and Ronaghy et al. (33) were identified as possible outliers because of extreme effect sizes. The overall weighted mean effect was 0.26 (95% CI: 0.13, 0.39) and 0.15 (95% CI: 0.06, 0.24) with and without the potential outliers, respectively. Excluding studies in which no children were stunted at baseline did not alter these conclusions (0.96; 95% CI: 0.46, 1.46). The regression model showed a significant negative relation ($r = -60$; $P = 0.0117$) between

TABLE 3 Summary estimates of the weighted mean effect sizes (95% CIs) for each nutritional intervention

Outcome	Iron	Zinc	Calcium	Iodine	Vitamin A	MM[1]	Protein	Food
n	1953	1966	1175	498	22,928	6258	939	717
Linear growth	0.10	0.15	0.03	0.07	0.05	0.26	0.68	0.19
	(−0.04, 0.24)	(0.06, 0.24)	(−0.09, 0.14)	(−0.10,0.25)	(0.01, 0.09)	(0.13, 0.39)	(0.30, 1.05)	(−0.28, 0.66)

[1] MM, multiple micronutrient.

baseline HAZ and effect size for height gain (Figure 5A). Age (r = 0.45; P = 0.067) and study length (r = −0.14; P = 0.6) were not predictors of the effect size for height gain (Figure 5B–C).

Protein. A total of 7 protein-based intervention trials that provided data to calculate an effect on linear growth were identified. Five studies contained multiple treatment groups, each providing either 2 (69, 73, 75) or 3 data sets (72). A majority of the studies were conducted in LMICs, including 1 in Africa, 2 in East Asia and the Pacific, and 3 in South Asia. The number of subjects in each study ranged from 35 to 190, with mean ages of subjects ranging from 33 to 161 mo. At baseline, 10 study populations had a mean HAZ of <−1, of which 6 had a mean HAZ <−2. Protein supplements were administered as either meat (69), cow milk (liquid or powder) (69, 71–73), amino acid–supplemented rice or wheat (74, 75), casein (72), whey (72), or high-protein diets (70). The duration of supplementation ranged from 0.69 to 24 mo.

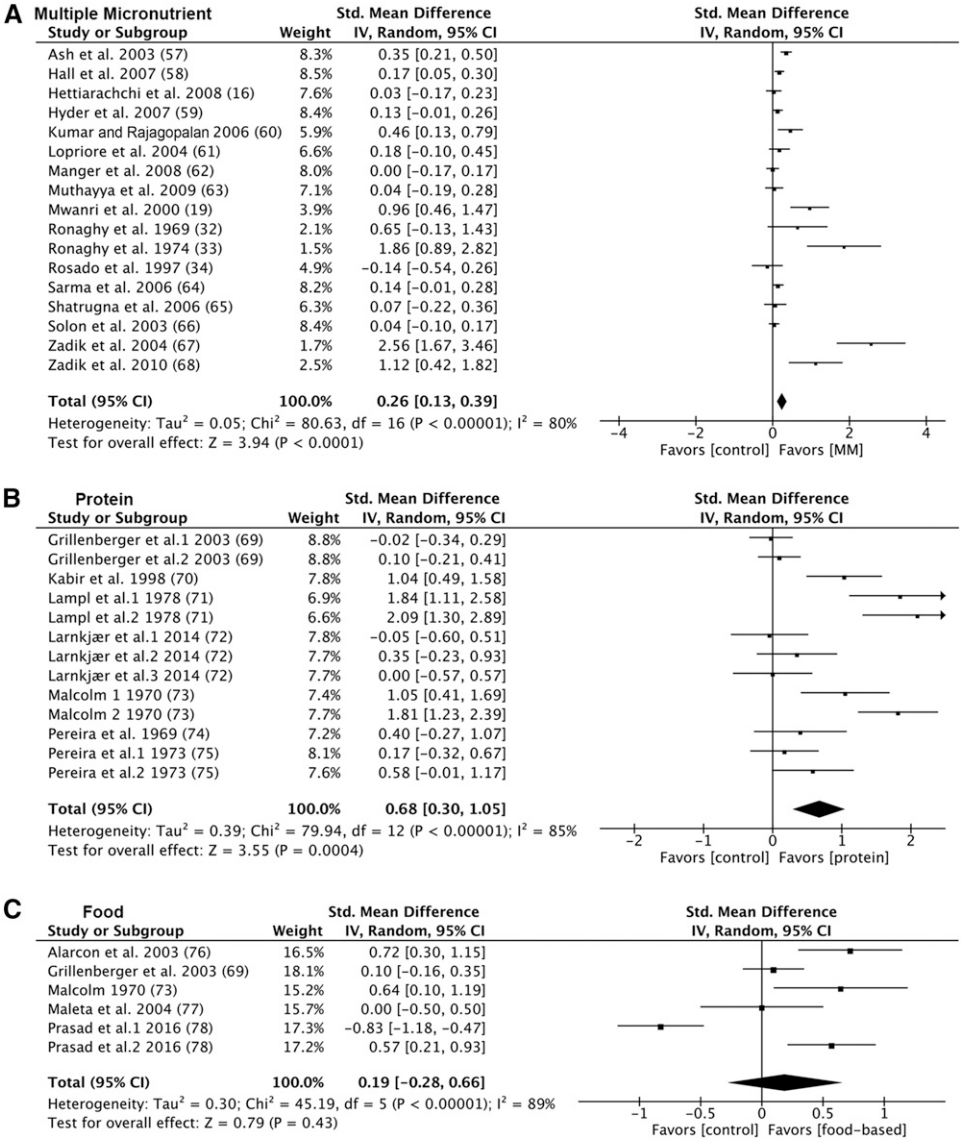

FIGURE 4 Forest plots of the effect on linear growth of multiple-micronutrient, protein, and food-based interventions in children ≥2 y of age. Data derived from systematic literature review of nutrient interventions administered after age 2 y. (A) Multiple micronutrient. (B) Protein. (C) Food-based. Fixed, fixed-effects model; IV, inverse variance; MM, multiple micronutrient; random, random-effects model; std., standard.

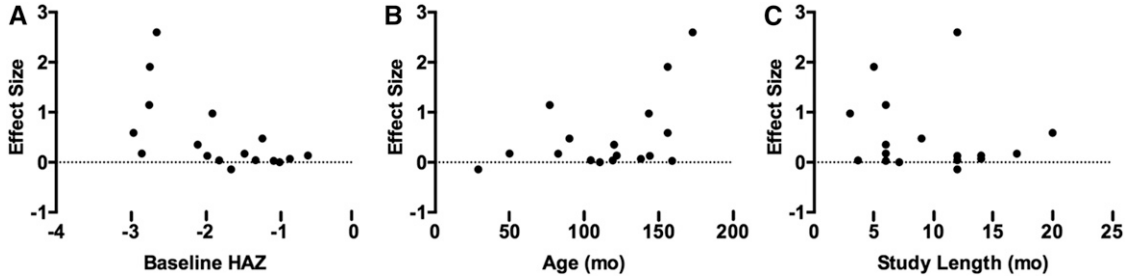

FIGURE 5 Relation between potential sources of heterogeneity and the standard mean effect of multiple-micronutrient interventions on linear growth in children ≥2 y of age. (A) Baseline HAZ was a significant predictor of the effect size ($r = -0.60$; $P < 0.05$). (B) Age ($r = 0.45$; $P > 0.05$) and (C) study duration ($r = -0.14$; $P > 0.05$) were not predictors of the effect size. Each point represents 1 study estimate. HAZ, height-for-age *z* score.

The effect sizes for change in height ranged from −0.05 to 2.09 (Figure 4B). The majority of datasets (85%) had a positive effect size, but only 5 were statistically significant. There was significant heterogeneity ($P < 0.00001$). The data sets extracted from Lampl et al. (71), Malcolm (73), and 1 data set from Kabir et al. (70) were possible outliers because of the large effect size. The overall weighted mean effect was 0.68 (95% CI: 0.30, 1.05) and 0.13 (95% CI: −0.03, 0.29) with and without the potential outliers, respectively. Excluding studies in which no children were stunted at baseline did not alter the conclusions (1.21; 95% CI: 0.53, 1.88). The regression model showed a significant negative relation ($r = -0.80$; $P = 0.001$) between baseline HAZ and effect size for height gain (**Figure 6**A). Age ($r = -0.02$; $P = 0.94$) and study length ($r = -0.29$; $P = 0.34$) were not predictors of the effect size for height gain (Figure 6B–C).

Food-based intervention. Sufficient data were available from 6 data sets from 5 studies (69, 73, 76–78) for calculation of the effect of food-based supplementation on height. All of the studies were conducted in LMICs, including 2 in Africa, 1 in East Asia and the Pacific, and 1 in South Asia. The number of subjects in each study ranged from 57 to 246, with mean ages of subjects ranging from 49 to 134 mo. At baseline, all study populations had a HAZ score <−1, of which 33% had a HAZ score of <−2. Food-based supplements were delivered in many forms including Pediasure (Abbott Laboratories) (76), fat (69), ready-to-use therapeutic food (77), additional meals (73), or the addition of sorghum to the diet (78).

The effect sizes for change in height ranged from −0.83 to 0.72 (Figure 4C). There was significant heterogeneity ($P < 0.001$). The overall weighted mean effect was not statistically significant (0.19; 95% CI: −0.28, 0.66) (Figure 4C). Furthermore, excluding studies in which no children were stunted at baseline did not alter the conclusions (0.31; 95% CI: −0.32, 0.94). Baseline HAZ ($r = -0.11$; $P = 0.84$), age ($r = -0.28$; $P = 0.59$) and study length ($r = -0.23$; $P = 0.66$) were not predictors of the effect size for height gain (**Supplemental Figure 5A–C**).

Discussion

This systematic review and meta-analysis was conducted to investigate the impact of nutrition-based interventions on linear growth in children aged ≥2 y. A few notable observations may have programmatic implications. Specifically, interventions containing iron, calcium, or iodine or those providing food do not improve linear growth, whereas interventions containing zinc (0.15; 95% CI: 0.06, 0.24), vitamin A (0.05; 95% CI: 0.01, 0.09), MMs (0.26; 95% CI: 0.13, 0.39), or protein (0.68; 95% CI: 0.30, 1.05) had a significant positive effect on height. A range of sensitivity analyses with the use of different assumptions for the SD for the change in height did not alter these conclusions (**Supplemental Table 1**).

Several observational studies have reported associations between iron-deficiency anemia and impaired linear growth

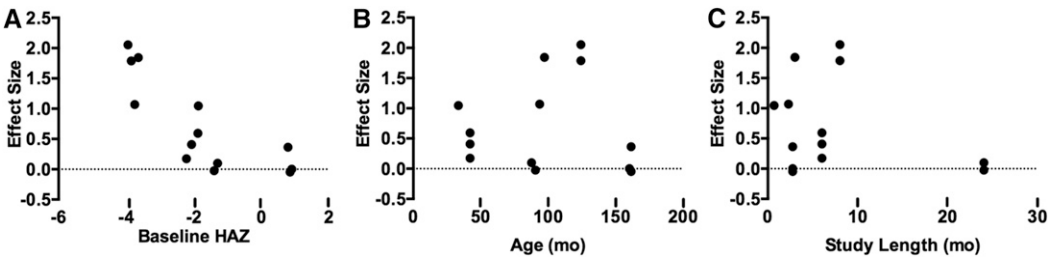

FIGURE 6 Relation between potential sources of heterogeneity and the standard mean effect of protein interventions on linear growth in children ≥2 y of age. (A) Baseline HAZ was a significant predictor of the effect size ($r = -0.80$; $P < 0.05$). (B) Age ($r = -0.02$; $P > 0.05$) and (C) study duration ($r = -0.29$; $P > 0.05$) were not predictors of the effect size. Each point represents 1 study estimate. HAZ, height-for-age *z* score.

that may stem from impaired immunity, appetite, and thyroid hormone metabolism (18, 79, 80). As such, the impact of iron supplementation on linear growth has been the subject of a number of systematic reviews and meta-analyses (81–83). The review by Ramakrishnan et al. (81) restricted their analysis to children <5 y old, which excludes a large number of trials included in this study. Three systematic reviews examined iron-supplementation trials conducted in all children (aged <18 y) and did not identify a statistically significant effect on linear growth (82–84). Despite methodological differences, our findings were consistent with those of earlier reviews. When we excluded studies with normal hemoglobin, the effect size increased (0.10 compared with 0.27) but did not reach statistical significance (11, 12, 15, 19, 21). Our study further contributes to the growing body of evidence suggesting that iron is ineffective at promoting linear growth.

Zinc is an essential transition metal that plays a critical role in normal linear growth via mechanisms involving growth-hormone release, insulin-like growth factor I, chondrogenesis, collagen synthesis, osteoblast function, and calcification of bone (85). Thus, it is no surprise that moderate-to-severe zinc deficiency in children depresses growth and skeletal maturation (85). For this reason, the effect of zinc supplementation on linear growth has been the topic of several meta-analyses (2, 81, 86–88). In contrast to our study, the systematic reviews by Ramakrishnan et al. (81), Stammers et al. (86), and Das et al. (87) reported no significant effect of zinc supplementation on height; however, it is not appropriate to compare our review and the aforementioned studies because of considerable variability in inclusion criteria. Our findings confirm those of Brown et al. (88) who found a statistically significant positive effect (0.35; 95% CI: 0.19, 0.51) of zinc supplementation on linear growth in children aged <12 y. Interestingly, this systematic review reported a weighted mean effect size that was 2-fold higher than the standard mean difference of our review (0.35 compared with 0.15), likely a consequence of differing inclusion criteria and statistical techniques. Only baseline HAZ was a significant inverse predictor of the effect of zinc supplementation on height. We also did not find any evidence that linear growth was more responsive to zinc supplementation in individuals with baseline serum zinc ≤12 μmol/L. However, the small number of trials with baseline zinc deficiency likely limited this analysis (16, 26, 28, 38, 39). Collectively, our study suggests that zinc supplementation after age 24 mo will have a positive effect on linear growth, principally in stunted children.

Bone is the principal reservoir for body calcium, where it is stored as a component of hydroxyapatite. Calcium deficiency will induce bone resorption, which may impair linear growth. The majority of the studies included in this analysis measured height secondary to bone outcomes, the primary variable of interest. It is also likely that baseline calcium intake can influence the effect of calcium supplementation on height; however, few studies included in this review had a low baseline calcium intake (<400 mg/d) (45, 46), which limits our ability to assess effect modification by baseline status. Overall, our findings confirm those of Winzenberg et al. (89), who found no significant effect of calcium supplementation on linear growth in children aged <18 y. Taken together, there is no evidence to support the use of calcium supplements in children ≥2 y of age as a public health strategy to reduce stunting.

Iodine deficiency remains a major public health problem, despite successful strategies to prevent deficiency (e.g., fortification of salt). Iodine is an essential component of thyroid hormones that are required for skeletal growth (90). There were few studies that met our inclusion criteria. One study that provided 2 datasets was included in the meta-analysis, which showed no effect of iodine supplementation on linear growth. The sparsity of randomized, placebo-controlled iodine intervention trials is a limitation of this analysis, and the conclusions that can be made regarding the impact of iodine supplementation in children ≥2 y of age on height remain limited.

Vitamin A is essential for growth, and clinical vitamin A deficiency has been linked to poor growth performance (91). Supplemental vitamin A is thought to promote growth by reducing infection and diarrhea, both predictors of growth faltering. Our results suggest that vitamin A supplementation does have an effect on linear growth in children ≥2 y of age. Our findings contradict those of 2 meta-analyses by Ramakrishnan et al. (84, 81) in which the authors conclude that vitamin A supplementation does not have a positive effect on height gain. These conflicting findings likely stem from different inclusion criteria, because the reviews by Ramakrishnan et al. (81, 84) included children aged <2 y. Taken together, the evidence suggests that vitamin A supplementation may be a strategy to address linear-growth faltering in children.

Nutrient deficiencies are unlikely to occur in isolation; thus, MM supplementation has been promoted as a more holistic strategy to address malnutrition and stunting. Interestingly, our findings (0.26; 95% CI: 0.13, 0.39) were nearly identical to the effect of MM interventions reported in a meta-analysis of four studies conducted by Ramakrishnan et al. (84) (0.28; 95% CI: 0.16, 0.41). However, in a subsequent review by Ramakrishnan et al. (81), the effect of MMs on height in children aged <5 y was considerably smaller, although the results remained statistically significant (0.09; 95% CI: 0.01, 0.17). Similar to zinc, baseline HAZ was a significant predictor of the effect of MM supplementation on height. It is important to note that the studies by Zadik et al. (67, 68) and Ronaghy et al. (33) had individual effect sizes that were considerably higher than the other included studies. A possible explanation for the large effect sizes is that the subjects in the studies by Zadik et al. (67, 68) were diagnosed with constitutional delay of growth and puberty and born small-for-gestational age, respectively, whereas the subjects in the study by Ronaghy et al. (33) were malnourished. Excluding these studies from our analysis reduced the overall standardized mean effect size (0.15; 95%: CI: 0.06, 0.24), but it remained statistically significant. Overall, our results are consistent with previous meta-analyses and provide evidence in support of MM supplementation

after age 24 mo as a strategy to promote linear growth during childhood.

It is well documented that severe protein malnutrition in children mechanistically drives linear growth retardation through a reduction of insulin-like growth factor I (92). The results of our review suggest a statistically significant positive effect of protein supplementation on linear growth in children ≥2 y of age. Baseline HAZ was a significant inverse predictor of the effect of protein supplementation on height. The studies by Lampl et al. (71), Malcolm (73), and Kabir et al. (70) had individual effect sizes that were nearly double that of the next highest effect, and excluding those studies from our analysis substantially reduced the overall standardized mean effect size (0.13; 95% CI: −0.03, 0.29). The subjects in the studies by Lampl et al. (71) and Malcolm (73) were severely stunted (HAZ <−3) at baseline and had a deficiency of 14–25 g protein/d, whereas those in the study by Kabir et al. (70) were recovering from shigellosis infection, which may explain the large effect of protein supplementation on linear growth. Nonetheless, we believe that the studies should remain in the meta-analysis because they both represent situations in which protein malnutrition would be present. Overall, our findings provide evidence in support of protein-based interventions after age 24 mo as an effective strategy to address stunting, especially in children who are severely stunted.

Growth faltering is also associated with overall poor diet quality that includes low intake of animal foods and high intakes of foods that contain inhibitors that impede the bioavailability of nutrients essential for growth. However, the results from our systematic review suggest that food interventions are ineffective at improving linear growth. This analysis is limited by the small number of studies ($n = 6$) and suffered from significant heterogeneity, which is to be expected because food-based interventions can take many forms. Additional well-designed trials are warranted to truly elucidate the growth-promoting potential of food-based interventions.

This review highlights several limitations of the extant literature. Approximately half of the included trials were of medium-to-low quality as assessed by Jadad scoring. However, influence analyses, or the effect of omitting single studies, did not reveal an overwhelming effect of any single trial, suggesting that no one study was influencing the results. A second limitation is the duration of interventions and length of follow-up of the included studies. Stunting is indicative of long-term nutritional status; the short duration of most trials (≤12 mo) may have corrected the nutritional deficiency but may not have been sufficiently long enough to observe a significant effect on height. Future intervention trials should have longer durations and/or include extended periods of subject follow-up. It is also worth noting that the inclusion of females >16 y and males >18 y of age may have reduced the potential impact of intervention effect because of the cessation of linear growth after the pubertal growth spurt. Across studies included in this review, the oldest mean age of subjects was 14 y. Furthermore, the studies reported that children aged >13 y showed no evidence of puberty, had recently reached menarche, or had not completed pubertal development as assessed by Tanner stages. Thus, the inclusion of older children is unlikely to have influenced our results. Lastly, consistent data on baseline nutritional status of subjects were available only for iron, zinc, and calcium interventions. Restricting our analysis to subjects deficient in the respective nutrient did not alter our conclusions but may have been limited by the small number of studies with baseline deficiency. Ultimately, our ability to draw conclusions regarding conditions that are more responsive to nutritional interventions is limited by a lack of extractable data and represents a critical gap that should be addressed in future trials.

In conclusion, this review indicates that nutritional interventions, namely zinc, vitamin A, MMs, and protein, delivered to children ≥2 y of age have the potential to improve linear growth, particularly in children who have experienced growth failure. The results suggest that the window of opportunity to address stunting does not completely close at 2 y of age.

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References

1. UNICEF, WHO, World Bank. 2014 Joint child malnutrition estimates: levels and trends 2014. [cited 2016 Jun 17]. Available from: http://www.who.int/nutgrowthdb/jme_brochure2015.pdf?ua=1.
2. Bhandari N, Bahl R, Taneja S. Effect of micronutrient supplementation on linear growth of children. Br J Nutr 2001;85 Suppl 2:S131–7.
3. WHO, FAO. Guidelines on food fortification with micronutrients. In: Allen L, de Benoist B, Dary O, Hurrell R, editors. Geneva (Switzerland): WHO; 2009.
4. FAO, IFAD, WFP. The state of food insecurity in the world 2015. Meeting the 2015 international hunger targets: taking stock of uneven progress. Rome (Italy): FAO; 2015.
5. Prentice AM, Ward KA, Goldberg GR, Jarjou LM, Moore SE, Fulford AJ, Prentice A. Critical windows for nutritional interventions against stunting. Am J Clin Nutr 2013;97:911–8.
6. Lundeen EA, Behrman JR, Crookston BT, Dearden KA, Engle P, Georgiadis A, Penny ME, Stein AD. Growth faltering and recovery in children aged 1–8 years in four low- and middle-income countries: Young Lives. Public Health Nutr 2014;17:2131–7.
7. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
8. Higgins J, Green S., editors. Cochrane handbook for systematic reviews of interventions version 5.0.2. London: The Cochrane Collaboration, 2009.
9. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
10. Aguayo VM. School-administered weekly iron supplementation–effect on the growth and hemoglobin status of non-anemic Bolivian school-age children: a randomized placebo-controlled trial. Eur J Nutr 2000; 39:263–9.
11. Angeles IT, Schultink WJ, Matulessi P, Gross R, Sastroamidjojo S. Decreased rate of stunting among anemic Indonesian preschool children through iron supplementation. Am J Clin Nutr 1993;58:339–42.
12. Bhatia D, Seshadri S. Growth performance in anemia and following iron supplementation. Indian Pediatr 1992;30:195–200.
13. Chen L, Liu YF, Gong M, Jiang W, Fan Z, Qu P, Chen J, Liu YX, Li TY. Effects of vitamin A, vitamin A plus zinc, and multiple micronutrients on anemia in preschool children in Chongqing, China. Asia Pac J Clin Nutr 2008;21:3–11.

14. Chwang LC, Soemantri AG, Pollitt E. Iron supplementation and physical growth of rural Indonesian children. Am J Clin Nutr 1988;47:496–501.
15. Dossa RAM, Ategbo EAD, de Koning FLHA, van Raaij JMA, Hautvast JGAJ. Impact of iron supplementation and deworming on growth performance in preschool Beninese children. Eur J Clin Nutr 2001;55:223–8.
16. Hettiarachchi M, Liyanage C, Wickremasinghe R, Hilmers DC, Abrams SA. The efficacy of micronutrient supplementation in reducing the prevalence of anaemia and deficiencies of zinc and iron among adolescents in Sri Lanka. Eur J Clin Nutr 2008;62:856–65.
17. Latham MC, Stephenson LS, Kinoti SN, Zaman MS, Kurz KM. Improvements in growth following iron supplementation in young Kenyan school children. Nutrition 1990;6:159–65.
18. Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. J Nutr 1994;124:645–54.
19. Mwanri L, Worsley A, Ryan P, Masika J. Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. J Nutr 2000;130:2691–6.
20. Palupi L, Schultink W, Achadi E, Gross R. Effective community intervention to improve hemoglobin status in preschoolers receiving once-weekly iron supplementation. Am J Clin Nutr 1997;65:1057–61.
21. Pereira SM, Begum A, Mathan VI, Baker SJ. A preliminary simulated iron fortification trial in South Indian preschool children. Br J Nutr 1979;41:413–7.
22. Rahman MM, Akramuzzaman SM, Mitra AK, Fuchs GJ, Mahalanabis D. Long-term supplementation with iron does not enhance growth in malnourished Bangladeshi children. J Nutr 1999; 129:1319–22.
23. Sungthong R, Mo-suwan L, Chongsuvivatwong V, Geater AF. Once weekly is superior to daily iron supplementation on height gain but not on hematological improvement among schoolchildren in Thailand. J Nutr 2002;132:418–22.
24. Castillo-Durán C, García H, Venegas P, Torrealba I, Panteón E, Concha N, Pérez P. Zinc supplementation increases growth velocity of male children and adolescents with short stature. Acta Paediatr 1994;83:833–7.
25. Cavan KR, Gibson RS, Grazioso CF, Isalgue AM, Ruz M, Solomons NW. Growth and body composition of periurban Guatemalan children in relation to zinc status: a longitudinal zinc intervention trial. Am J Clin Nutr 1993;57:344–52.
26. Friis H, Ndhlovu P, Mduluza T, Kaondera K, Sandstrom B, Michaelsen KF, Vennervald BJ, Christensen NO. The impact of zinc supplementation on growth and body composition: a randomized, controlled trial among rural Zimbabwean schoolchildren. Eur J Clin Nutr 1997;51:38–45.
27. Gibson RS, Vanderkooy PD, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc-deficiency syndrome in some southern Ontario boys with low height percentiles. Am J Clin Nutr 1989;49:1266–73.
28. Kaseb F, Fallah R. Efficacy of zinc supplementation on improvement of weight and height growth of healthy 9–18 year children in Iran. World Appl Sci J 2013;26:89–93.
29. Kikafunda JK, Walker AF, Allan EF, Tumwine JK. Effect of zinc supplementation on growth and body composition of Ugandan preschool children: a randomized, controlled, intervention trial. Am J Clin Nutr 1998;68:1261–6.
30. Mozaffari-Khosravi H, Shakiba M, Eftekhari M-H, Fatehi F. Effects of zinc supplementation on physical growth in 2–5-year-old children. Biol Trace Elem Res 2009;128:118–27.
31. Nakamura T, Nishiyama S, Futagoishi-Suginohara Y, Matsuda I, Higashi A. Mild to moderate zinc deficiency in short children: effect of zinc supplementation on linear growth velocity. J Pediatr 1993;123:65–9.
32. Ronaghy H, Fox MRS, Garn SM, Israel H, Harp A, Moe PG, Halsted JA. Controlled zinc supplementation for malnourished school boys: a pilot experiment. Am J Clin Nutr 1969;22:1279–89.
33. Ronaghy HA, Reinhold JG, Mahloudji M, Ghavami P, Fox MRS, Halsted JA. Zinc supplementation of malnourished schoolboys in Iran: increased growth and other effects. Am J Clin Nutr 1974;27:112–21.
34. Rosado JL, López P, Muñoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican preschoolers. Am J Clin Nutr 1997;65:13–9.
35. Ruz M, Castillo-Duran C, Lara X, Codoceo J, Rebolledo A, Atalah E. A 14-mo zinc-supplementation trial in apparently healthy Chilean preschool children. Am J Clin Nutr 1997;66:1406–13.
36. Sayeg Porto MA, Oliveira HP, Cunha AJ, Miranda G, Guimarães MM, Oliveira WA, Santos DM. Linear growth and zinc supplementation in children with short stature. J Pediatr Endocrinol Metab 2000;13:1121–8.
37. Sempértegui F, Estrella B, Correa E, Aguirre L, Saa B, Torres M, Navarrete F, Alarcón C, Carrión J, Rodríguez A, et al. Effects of short-term zinc supplementation on cellular immunity, respiratory symptoms, and growth of malnourished Equadorian children. Eur J Clin Nutr 1996;50:42–6.
38. Taneja S, Strand TA, Sommerfelt H, Bahl R, Bhandari N. Zinc supplementation for four months does not affect growth in young North Indian children. J Nutr 2010;140:630–4.
39. Walravens PA, Krebs NF, Hambidge KM. Linear growth of low income preschool children receiving a zinc supplement. Am J Clin Nutr 1983;38:195–201.
40. Bass SL, Naughton G, Saxon L, Iuliano-Burns S, Daly R, Briganti EM, Hume C, Nowson C. Exercise and calcium combined results in a greater osteogenic effect than either factor alone: a blinded randomized placebo-controlled trial in boys. J Bone Miner Res 2007;22:458–64.
41. Bonjour JP, Carrie AL, Ferrari S, Clavien H, Slosman D, Theintz G, Rizzoli R. Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. J Clin Invest 1997;99:1287–94.
42. Cameron MA, Paton LM, Nowson CA, Margerison C, Frame M, Wark JD. The effect of calcium supplementation on bone density in premenarcheal females: a co-twin approach. J Clin Endocrinol Metab 2004;89:4916–22.
43. Chevalley T, Bonjour JP, Ferrari S, Hans D, Rizzoli R. Skeletal site selectivity in the effects of calcium supplementation on areal bone mineral density gain: a randomized, double-blind, placebo-controlled trial in prepubertal boys. J Clin Endocrinol Metab 2005;90:3342–9.
44. Courteix D, Jaffré C, Lespessailles E, Benhamou L. Cumulative effects of calcium supplementation and physical activity on bone accretion in premenarchal children: a double-blind randomised placebo-controlled trial. Int J Sports Med 2005;26:332–8.
45. Dibba B, Prentice A, Ceesay M, Stirling DM, Cole TJ, Poskitt EME. Effect of calcium supplementation on bone mineral accretion in Gambian children accustomed to a low-calcium diet. Am J Clin Nutr 2000;71:544–9.
46. Ekbote VH, Khadilkar AV, Chiplonkar SA, Hanumante NM, Khadilkar VV, Mughal MZ. A pilot randomized controlled trial of oral calcium and vitamin D supplementation using fortified laddoos in underprivileged Indian toddlers. Eur J Clin Nutr 2011;65:440–6.
47. Iuliano-Burns S, Saxon L, Naughton G, Gibbons K, Bass SL. Regional specificity of exercise and calcium during skeletal growth in girls: a randomized controlled trial. J Bone Miner Res 2003;18:156–62.
48. Lloyd T, Andon MB, Rollings N, Martel JK, Landis JR, Demers LM, Eggli DF, Kieselhorst K, Kulin HE. Calcium supplementation and bone mineral density in adolescent girls. JAMA 1993;270:841–4.
49. Nowson CA, Green RM, Hopper JL, Sherwin AJ, Young D, Kaymakci B, Guest CS, Smid M, Larkins RG, Wark JD. A co-twin study of the effect of calcium supplementation on bone density during adolescence. Osteoporos Int 1997;7:219–25.
50. Pettifor JM, Ross P, Moodley G, Shuenyane E. The effect of dietary calcium supplementation on serum calcium, phosphorus, and alkaline phosphatase concentrations in a rural black population. Am J Clin Nutr 1981;34:2187–91.
51. Specker B, Binkley T. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. J Bone Miner Res 2003;18:885–92.
52. Zimmermann MB, Jooste PL, Mabapa NS, Mbhenyane X, Schoeman S, Biebinger R, Chaouki N, Bozo M, Grimci L, Bridson J. Treatment of iodine deficiency in school-age children increases insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations and improves somatic growth. J Clin Endocrinol Metab 2007;92:437–42.

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53. Fawzi WW, Herrera MG, Willett WC, Nestel P, El Amin A, Mohamed KA. The effect of vitamin A supplementation on the growth of preschool children in the Sudan. Am J Public Health 1997;87:1359–62.
54. Hadi H, Stoltzfus RJ, Dibley MJ, Moulton LH, West KP Jr., Kjolhede CL, Sadjimin T. Vitamin A supplementation selectively improves the linear growth of Indonesian preschool children: results from a randomized controlled trial. Am J Clin Nutr 2000;71:507–13.
55. Lin J, Lai X, Qin J, Song F, Zhang Y, Yao P, Yang X, Liu L. Effect of beta-carotene supplementation on health and growth of vitamin A deficient children in China rural villages: a randomized controlled trial. e-SPEN 2009;4:e17-e21.
56. Yang YX, Han JH, Shao XP, He M, Bian LH, Wang Z, Wang GD, Men JH. Effect of micronutrient supplementation on the growth of preschool children in China. Biomed Environ Sci 2002;15:196–202.
57. Ash DM, Tatala SR, Frongillo EA, Jr., Ndossi GD, Latham MC. Randomized efficacy trial of a micronutrient-fortified beverage in primary school children in Tanzania. Am J Clin Nutr 2003;77:891–8.
58. Hall A, Hanh TTM, Farley K, Quynh TPN, Valdivia F. An evaluation of the impact of a school nutrition programme in Vietnam. Public Health Nutr 2007;10:819–26.
59. Hyder SMZ, Haseen F, Khan M, Schaetzel T, Jalal CSB, Rahman M, Lönnerdal B, Mannar V, Mehansho H. A multiple-micronutrient-fortified beverage affects hemoglobin, iron, and vitamin A status and growth in adolescent girls in rural Bangladesh. J Nutr 2007;137:2147–53.
60. Vinod Kumar M, Rajagopalan S. Impact of a multiple-micronutrient food supplement on the nutritional status of schoolchildren. Food Nutr Bull 2006;27:203–10.
61. Lopriore C, Guidoum Y, Briend A, Branca F. Spread fortified with vitamins and minerals induces catch-up growth and eradicates severe anemia in stunted refugee children aged 3–6 y. Am J Clin Nutr 2004;80:973–81.
62. Manger MS, McKenzie JE, Winichagoon P, Gray A, Chavasit V, Pongcharoen T, Gowachirapant S, Ryan B, Wasantwisut E, Gibson RS. A micronutrient-fortified seasoning powder reduces morbidity and improves short-term cognitive function, but has no effect on anthropometric measures in primary school children in northeast Thailand: a randomized controlled trial. Am J Clin Nutr 2008;87:1715–22.
63. Muthayya S, Eilander A, Transler C, Thomas T, van der Knaap HC, Srinivasan K, van Klinken BJW, Osendarp SJ, Kurpad AV. Effect of fortification with multiple micronutrients and n−3 fatty acids on growth and cognitive performance in Indian schoolchildren: the CHAMPION (Children's Health and Mental Performance Influenced by Optimal Nutrition) study. Am J Clin Nutr 2009;89:1766–75.
64. Sarma KVR, Udaykumar P, Balakrishna N, Vijayaraghavan K, Sivakumar B. Effect of micronutrient supplementation on health and nutritional status of schoolchildren: growth and morbidity. Nutrition 2006; 22(1 Suppl)S8–14.
65. Shatrugna V, Balakrishna N, Krishnaswamy K. Effect of micronutrient supplement on health and nutritional status of schoolchildren: bone health and body composition. Nutrition 2006; 22(1 Suppl)S33–9.
66. Solon FS, Sarol JN, Bernardo ABI, Solon JAA, Mehansho H, Sanchez-Fermin LE, Wambangco LS, Juhlin KD. Effect of a multiple-micronutrient-fortified fruit powder beverage on the nutrition status, physical fitness, and cognitive performance of schoolchildren in the Philippines. Food Nutr Bull 2003; 24(4 Suppl 2)S129–40.
67. Zadik Z, Sinai T, Zung A, Reifen R. Vitamin A and iron supplementation is as efficient as hormonal therapy in constitutionally delayed children. Clin Endocrinol (Oxf) 2004;60:682–7.
68. Zadik Z, Sinai T, Zung A, Golander A, Reifen R. "Functional food" for acceleration of growth in short children born small for gestational age. J Pediatr Endocrinol Metab 2010;23:435–41.
69. Grillenberger M, Neumann CG, Murphy SP, Bwibo NO. Van'T Veer P, Hautvast JGAJ, West CE. Food supplements have a positive impact on weight gain and the addition of animal source foods increases lean body mass of Kenyan schoolchildren. J Nutr 2003; 133(11 Suppl 2)3957S–64S.
70. Kabir I, Rahman MM, Haider R, Mazumder RN, Khaled MA, Mahalanabis D. Increased height gain of children fed a high-protein diet during convalescence from shigellosis: a six-month follow-up study. J Nutr 1998;128:1688–91.
71. Lampl M, Johnston FE, Malcolm LA. The effects of protein supplementation on the growth and skeletal maturation of new Guinean school children. Ann Hum Biol 1978;5:219–27.
72. Larnkjær A, Arnberg K, Michaelsen KF, Jensen SM, Mølgaard C. Effect of milk proteins on linear growth and IGF variables in overweight adolescents. Growth Horm IGF Res 2014;24:54–9.
73. Malcolm LA. Growth retardation in a new Guinea boarding school and its response to supplementary feeding. Br J Nutr 1970;24:297–305.
74. Pereira SM, Begum A, Jesudian G, Sundararaj R. Lysine-supplemented wheat and growth of preschool children. Am J Clin Nutr 1969;22:606–11.
75. Pereira SM, Jones S, Jesudian G, Begum A. Feeding trials with lysine- and threonine-fortified rice. Br J Nutr 1973;30:241–50.
76. Alarcon PA, Lin L-H, Noche M, Hernandez VC, Cimafranca L, Lam W, Comer GM. Effect of oral supplementation on catch-up growth in picky eaters. Clin Pediatr (Phila) 2003;42:209–17.
77. Maleta K, Kuittinen J, Duggan MB, Briend A, Manary M, Wales J, Kulmala T, Ashorn P. Supplementary feeding of underweight, stunted Malawian children with a ready-to-use food. J Pediatr Gastroenterol Nutr 2004;38:152–8.
78. Prasad Mp R, Benhur D, Kommi K, Madhari R, Rao MV, Patil JV. Impact of Sorghum supplementation on growth and micronutrient status of school going children in Southern India — a randomized trial. Indian J Pediatr 2016;83:9–14.
79. Rao KVRG, Raju SV. Association of growth status and the prevalence of anaemia in preschool children. Indian J Med Res 1980;71:237–46.
80. Beard J, Haas J, Gomez LH. The relationship of nutritional status to oxygen transport and growth in highland Bolivian children. Hum Biol 1983;55:151–64.
81. Ramakrishnan U, Nguyen P, Martorell R. Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions. Am J Clin Nutr 2009;89:191–203.
82. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on physical growth in children: systematic review of randomised controlled trials. Public Health Nutr 2006;9:904–20.
83. Vucic V, Berti C, Vollhardt C, Fekete K, Cetin I, Koletzko B, Gurinovic M, van't Veer P. Effect of iron intervention on growth during gestation, infancy, childhood, and adolescence: a systematic review with meta-analysis. Nutr Rev 2013;71:386–401.
84. Ramakrishnan U, Aburto N, McCabe G, Martorell R. Multimicronutrient Interventions but not vitamin A or iron interventions alone improve child growth: results of 3 meta-analyses. J Nutr 2004; 134:2592–602.
85. Hambridge KM, Casey CE, Krebs NF. Zinc. In: Mertz W, editor. Trace elements in human and animal nutrition. New York: Academic Press; 1986.
86. Stammers AL, Lowe NM, Medina MW, Patel S, Dykes F, Perez-Rodrigo C, Serra-Majam L, Nissensohn M, Moran VH. The relationship between zinc intake and growth in children aged 1–8 years: a systematic review and meta-analysis. Eur J Clin Nutr 2015;69:147–53.
87. Das JK, Kumar R, Salam RA, Bhutta ZA. Systematic review of zinc fortification trials. Ann Nutr Metab 2013;62 Suppl 1:44–56.
88. Brown KH, Peerson JM, Rivera J, Allen LH. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2002;75: 1062–71.
89. Winzenberg T, Shaw K, Fryer J, Jones G. Calcium supplements in healthy children do not affect weight gain, height, or body composition. Obesity (Silver Spring) 2007;15:1789–98.
90. Markou KB, Tsekouras A, Anastasiou E, Vlassopoulou B, Koukkou E, Vagenakis GA, Mylonas P, Vasilopoulos C, Theodoropoulou A, Rottstein L, et al. Treating iodine deficiency: long-term effects of iodine repletion on growth and pubertal development in school-age Children. Thyroid 2008;18:449–54.
91. West KP, Jr., LeClerq SC, Shrestha SR, Wu LSF, Pradhan EK, Khatry SK, Katz J, Adhikari R, Sommer A, Pokhrel RP, et al. Effects of vitamin a on growth of vitamin A-deficient children: field studies in Nepal. J Nutr 1997;127:1957–65.
92. Estívariz CF, Ziegler TR. Nutrition and the insulin-like growth factor system. Endocrine 1997;7:65–71.

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