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Linear and Ponderal Growth Trajectories in Well-Nourished, Iron-Sufficient Infants Are Unimpaired by Iron Supplementation[1,2]

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Abstract

Iron deficiency remains the most common nutritional deficiency worldwide and supplementation is recommended during periods of high risk, including infancy. However, questions have been raised about possible adverse effects of iron on growth in iron-sufficient (IS) infants and the advisability of across-the-board iron supplementation. This study examined whether short- or long-term growth was impaired in IS infants who received iron supplementation. From a longitudinal study of healthy, breast-fed, low- to middle-income Chilean infants randomly assigned to iron supplementation or usual nutrition at 6 or 12 mo, we retrospectively identified infants meeting criteria for iron sufficiency at the time of random assignment (n = 273). Using multilevel analysis, ponderal and linear growth were modeled before, during, and after iron supplementation up to 10 y in 3 comparisons: *1*) iron supplementation compared with usual nutrition from 6 to 12 mo; *2*) iron supplementation compared with usual nutrition from 12 to 18 mo; and *3*) 15 mg/d of iron as drops compared with iron-fortified formula (12 mg/L). Growth trajectories did not differ during or after supplementation indicating no adverse effect of iron in any comparison. These results suggest that, at least in some environments, iron does not impair growth in IS infants. J. Nutr. 139: 2106–2112, 2009.

Introduction

Iron deficiency remains the most common nutritional deficiency worldwide (1). The WHO recommends iron supplementation during periods of high risk for iron deficiency, such as in pregnancy and infancy, when iron needs often exceed iron sources (2). This is not only to prevent anemia and its associated morbidities but also to foster infant development and behavior. Preventing iron deficiency in infancy may be all the more important, because developmental and behavioral alterations in iron-deficient anemic infants may not be corrected following iron therapy (3–7).

The advisability of across-the-board prophylactic iron supplementation depends on the risk of adverse effects. This issue pertains especially to infants who are already iron-sufficient (IS)[7] and thus are unlikely to need additional iron. Early in infancy, iron regulation is not mature and iron absorption may occur in IS infants without the usual feedback mechanisms, raising concern about the potential for adverse effects (8–11).

A 2006 review of the health benefits and risks of iron supplementation during early childhood concluded that iron supplementation "may jeopardize optimal height and weight gains," (12) based on 3 reports of slower gain in length or weight during prophylactic or therapeutic iron in IS infants (13–15). A more recently published secondary analysis also found slower growth in IS infants treated with iron or iron and zinc compared with those given placebo or zinc alone (16). These 4 studies of IS infants had group sizes of 22–50. Another recent study of breast-fed infants, including some who were IS, found positive effects of iron on growth, especially for those who were undernourished or iron deficient (17). In addition, a recent study in Brazil showed no growth differences in 3 groups of nonanemic infants given different doses of iron for 16 wk beginning at 5–7 mo (iron sufficiency was not assessed) (18). Most other research on iron and growth has focused on iron-deficient children, in whom growth improves or is unaffected by iron (19,20).

This study provides information on how iron influences growth in the context of adequate energy intake, a high prevalence of iron deficiency, and infrequent parasitic infections. Our research adds new information about the influence of iron supplementation on growth related to dose, vehicle, and timing.

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[7] Abbreviations used: HAZ, height-for-age Z-score; Hb, hemoglobin; IS, iron-sufficient; SES, socioeconomic status; WAZ, weight-for-age Z-score.

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The study differs from others in that we assessed growth effects of iron administration at 2 different ages (6 and 12 mo) and compared 2 different iron vehicles (iron-fortified formula vs. iron drops). The duration of iron administration was also longer in our study (6–12 mo) compared with 3–5 mo in several other preventive trials (13–15). Most importantly, we considered long-term growth effects with follow-up to 10 y. For these analyses, we retrospectively identified infants who met criteria for IS at the time of their prospective randomization to iron supplementation or usual nutrition at 6 or 12 mo (21).

Methods

This study is a secondary data analysis of linear (length and height) and ponderal (weight) growth in IS Chilean infants from a randomized controlled trial of iron deficiency anemia prevention and a companion study of the neurodevelopment of treated anemic infants along with randomly selected nonanemic comparison infants who also received iron. We describe first the study and then the selection of the subsample for the analyses presented in this paper.

Original study. Between 1991 and 1996, we recruited healthy low- to middle-income, urban Chilean infants weighing ≥3 kg at birth to enter a double-blind, randomized, controlled trial of iron supplementation between 6 and 12 mo of age. Infant health was generally excellent in Chile; generalized undernutrition, hemoglobinopathies, hookworm infection, and elevated lead concentrations were virtually absent. However, dietary iron deficiency was common and iron supplementation during infancy was not routine. In the trial, infants were randomized to iron supplementation or usual nutrition at 6 mo. The nature of study supplements depended on whether the infant had started bottle-feeding and was already taking at least 250 mL/d. Such infants received iron-fortified formula (12 mg/L) or "usual nutrition," study-provided, powdered whole cow milk (2930 kJ/L) plus vitamins without iron. To not interfere with breast-feeding, those taking <250 mL/d at 6 mo were randomized to vitamins with 10 mg/d of iron or vitamins without iron. Formula and cow milk were provided in identical containers and vitamins were in identical bottles.

All infants received a fingerstick hemoglobin (Hb) at 6 mo. Anemic infants (Hb <103 g/L) and randomly selected nonanemic infants (Hb ≥110 g/L) had venous Hb and iron studies. Iron-deficient anemic infants, defined as venous Hb ≤100 g/L at 6 mo, with 2 of 3 abnormal iron measures (mean cell volume <70 fL, erythrocyte protoporphyrin ≥1.77 μmol/L RBC, serum ferritin <12 g/L) (n = 73) were not eligible for the preventive trial. Rather, they entered into a treatment trial along with a comparison group of 62 nonanemic infants. All were treated for 1 y with 15 mg/d of iron as drops in a single daily dose, as recommended by Dallman (22–24).

At 12 mo, all infants completing the preventive trial received venous iron studies; 92 infants from the unsupplemented, usual nutrition group who met criteria (appropriate for age) for iron-deficiency anemia also entered the treatment trial, along with a comparison group of 89 randomly selected, nonanemic infants. They were treated with 30 mg/d of iron as drops for a minimum of 6 mo. Iron was provided as iron sulfate in all 3 vehicles (formula, vitamins with iron, and iron drops) and all iron doses refer to elemental iron. For all components of the study, project personnel made weekly home visits to review the infants' consumption of study-provided formula or milk, vitamins, or iron drops with the mothers.

The cohort continues to be followed with waves of data collection at 5 and 10y. Overall, participation was high with 69% of the infancy sample successfully followed up for a total of 1127 children assessed at 10 y. Parents provided written informed consent and participating children provided written assent at age 10 y. The protocols for the original infant study and follow-up studies have been approved annually by the Institutional Review Boards of the Universities of Michigan and Chile.

Secondary analysis of the influence of iron on growth. The focus of the original project was on preventing and treating iron-deficiency anemia and did not require establishing iron sufficiency. Therefore, only a subset of infants, described above, had a complete panel of iron measures at 6 mo. For our analyses, we retrospectively identified IS at 6 mo, based on venous measures if available and capillary Hb if not, by the following criteria: capillary Hb ≥128 g/L or venous Hb ≥110 g/L with at least 2 of 3 iron measures in the sufficient range (mean corpuscular volume ≥70 fL, erythrocyte protoporphyrin <1.77 μmol/L RBC, serum ferritin ≥12 mg/L), all ~2 SD from the mean in normative data (22,25,26). Using the criterion of Hb ≥128 g/L to indicate IS was based on our unpublished analysis of data from 321 infants who had both capillary Hb measurement and venous iron studies; 94% of those with Hb ≥128 g/L met criteria for IS with at least 2 of 3 iron measures in the sufficient range (21).

By these criteria, 142 infants from the preventive trial and 40 infants from the treatment trial were IS at 6 mo. All of the IS infants from the treatment trial and 118/142 (83%) from the preventive trial had growth data to 10 y. From the 534 infants assigned to usual nutrition in the preventive trial at 6 mo, 241 met criteria for IS at 12 mo; 115 were randomly assigned to iron or followed on usual nutrition. All had growth data to 10 y.

We conducted 3 analyses (**Table 1**): *1*) a comparison of 6-mo-old IS infants randomly assigned in the preventive trial to iron supplementation (n = 56) or usual nutrition (n = 62); *2*) a comparison of 12-mo-old IS infants randomly assigned to 30 mg iron/d (n = 48) and those on usual nutrition as part of surveillance after the preventive trial (n = 67); and *3*) a comparison of IS 6-mo olds randomly assigned to 15 mg/d of iron (n = 40) in the treatment study and IS infants taking iron-fortified formula (n = 43) in the preventive trial. There was no overlap between those in the 6- and 12-mo analyses (comparisons 1 and 2) because of our selection criteria. However, comparison 3 included some infants from comparison 1, specifically 43 of the 56 IS infants treated with iron in the preventive trial (all on iron-fortified formula). The 40 IS infants from the treatment component who were treated with iron drops in comparison 3 were not included in comparison 1 or comparison 2.

Data analysis. Data were analyzed with SAS 9.1 (SAS Institute). The baseline characteristics of the IS infants randomized to iron or usual nutrition at each age were compared using t tests for continuous variables and chi-square tests for categorical ones.

Individual weight and length growth curves were modeled for each infant using a hierarchical linear modeling approach with random coefficients for intercepts, slopes, and quadratic terms, implemented through Proc Mixed in SAS. As expected, the growth trajectory in infancy was nonlinear, with growth rate being higher in the early months and decelerating later. Thus, growth from birth to 12 mo was modeled using quadratic growth curves. Birth weight or birth length was included as the first data point in the infancy weight and length models, respectively. Growth during the 12- to 18-mo period and the 1- to 10-y period was modeled using linear models. Intercepts were set at the midpoints (by centering age at these points) for analyses, assessing growth from birth to 6 mo, 6 to 12 mo, and 12 and 18 mo. Thus, for analysis in infancy the slope represents the growth rate at midpoints where age is centered. For analyses assessing growth from 1 to 10 y, 10 y was set as the intercept, because we were interested in assessing the influence of iron during infancy on long-term weight and height. Outcomes included weight and length (height), growth rate for all

TABLE 1 Comparisons of IS infants

Group	Age, *mo*	Treatment (*n*)	Comparison (*n*)
1[1]	6–12	10 mg/d iron (56)[4]	Usual nutrition (62)
2[2]	12–18	30 mg/d iron (48)	Usual nutrition (67)
3[3]	6–12	15 mg/d iron (40)	Iron-fortified formula (43)

[1] 6-mo olds randomized to iron or usual nutrition.
[2] 12-mo olds randomly selected to receive iron or continued on usual nutrition.
[3] 6-mo olds taking iron-fortified formula or iron drops.
[4] 10 mg/d iron for those taking <250 mL of supplementation to breast-feeding (19) or iron-fortified formula (12 mg/L) for those receiving at least 250 mL of supplemental milk (43).

models and growth deceleration (quadratic) for growth during the first year. Birth weight and birth length were used as controlling covariates when assessing growth from 1 to 10 y but were included in the growth curve from birth to 12 mo. Iron supplementation status as well as its interaction with growth parameters, slope, and quadratic term (quadratic for infancy trajectories only) were included in the models to test for different growth trajectories related to iron supplementation.

Growth points (weight and length) were plotted based on age in days at each measurement. The longitudinal models of individual growth over time were fitted using mixed models with random effects. Such models are based on the restricted likelihood function that uses all available data and gives valid results under the assumption that missing data are missing at random. Only interactions significant at $P < 0.10$ were retained in the final models. We tested but did not include interactions between iron and feeding method and iron and iron vehicle, because they were nonsignificant in the models.

Outcome variables. Unclothed infant weight, using an electronic scale (to the nearest 0.01 kg), and length, on a recumbent length board (to the nearest 0.1 cm), were measured monthly at well-baby visits until 1 y and bimonthly from 1 to 1.5 y. At 5 and 10 y, weights and heights in minimal clothing without shoes were measured at laboratory visits by an experienced nurse,using digital scales (0.1 kg precision, 150 kg capacity) and stadiometers (0.1 cm precision) according to standardized methods. BMI was calculated at 1, 5, and 10 y as weight (kg)/height squared (m).

Covariates. Sex and socioeconomic status (SES) were included as covariates in all analyses, because we previously found them to be related to growth in this cohort (27,28). SES was measured using a modified Graffar index, which included 13 items concerning family structure, schooling, occupation, and social security of the head of the family, structural quality and health conditions of the home, and the existence of home appliances and car ownership. The Graffar is designed to differentiate strata within relatively homogeneous lower-SES populations (29). We analyzed this scale as a continuous variable. The range in our cohort was 14–47 with an overall possible range of 0–65; a higher score indicates lower SES. Birth weight and length were included as covariates in the models of growth from 1 to 10 y, because birth size is related to both growth (30,31) and iron stores at birth (32–34). The parameter estimates for iron supplementation and its interactions with growth rate and deceleration terms assess differences in weight, length, growth rates, and growth deceleration based on whether the infant was given iron or usual nutrition. To achieve more parsimonious models, we removed other covariates that were not significantly related to growth rate or deceleration ($P < 0.10$) as recommended by Raudenbush and Bryk (35).

Results

Baseline characteristics. Infants had above average birth weight (compared with Chilean or U.S. CDC norms) due to the preventive trial entrance criterion of birth weight ≥3 kg (~15th percentile in Chile between 1991 and 1996) (21,36,37) (**Table 2**). The mean SES index of 27 reflected the low- to-middle SES of study families. The samples for these analyses did not differ from the original preventive trial and treatment study cohorts for birth weight, birth length, SES, weight-for-age Z-score (WAZ), or height-for-age Z-score (HAZ) at 1, 5 or 10 y. For infants randomized at 6 mo, the iron-supplemented and usual nutrition groups were similar in SES, sex, birth weight, and birth length. For those randomly assigned at 12 mo, sex, birth weight, birth length, and WAZ at 1 y were similar, but the iron-supplemented group was from a higher SES (0.4 effect size) and taller (higher HAZ) at 1 y (0.3 Z) than the usual nutrition group ($P < 0.05$).

Comparison 1: growth with iron supplementation compared with usual nutrition from 6 to 12 mo. For IS infants randomized in the preventive trial at 6 mo, the iron-supplemented and usual nutrition groups showed similar weight and weight gain before (birth to 6 mo), during (6–12 mo), and after supplementation (1–10 y) (**Table 3**) (**Fig. 1***A*). For length, there was a difference in growth prior to the preventive trial; those who would be selected for iron supplementation were growing 0.1 cm/mo faster than those who would receive usual nutrition, controlling for SES and sex ($P < 0.05$) (Table 3; Fig. 1*B*). During supplementation and after, until 10 y, linear growth did not differ between the 2 groups. In addition, the deceleration in weight or length gain was equivalent in the iron-supplemented and usual nutrition groups. As expected, boys were heavier and taller than girls during the first year of life ($P < 0.0001$).

Comparison 2: growth with iron supplementation compared with usual nutrition from 12 to 18 mo. For IS infants randomly selected for iron supplementation in the treatment study or followed without supplementation as part of the preventive trial, the 2 groups showed similar weight, weight gain, length, and growth in length prior to supplementation in the adjusted growth models (birth to 12 mo). Growth parameters continued to be comparable between 12 and 18 mo, when the iron-supplemented group received 30 mg/d iron. Weight and weight gain continued to be similar between 1 and 10 y. All models controlled for birth weight or length, sex, and SES. Birth weight and birth length were related to weight and height at 10 y ($P < 0.05$) in the respective models. Group differences in height were apparent at 10 y. Children who received iron in the second year of life were 0.7 cm taller at 10 y than those receiving usual nutrition ($P < 0.05$) (**Table 4**).

Comparison 3: growth with iron-fortified formula compared with iron drops. IS infants treated with iron drops (15 mg of elemental iron daily) beginning at 6 mo as part of the treatment trial ($n = 40$) were compared with 43 IS infants in the preventive trial who received iron-fortified formula (reference group). Baseline characteristics were equivalent. Comparing those receiving iron drops to those consuming iron-fortified formula, mean weight, length (or height), and growth in weight or length (or height) did not differ before, during, or after iron supplementation up to 10 y. Estimates and 95% CI for differences in weight (kg) were as follows: −0.02 (−0.39, 0.35) measured at 9 mo, the midpoint during supplementation, and 0.3 (−1.9, 2.5) after completion of iron administration, measured at 10 y. Estimates and 95% CI for differences in height (cm) for iron as drops compared with iron in fortified formula were as follows: −0.1 (−1.1, 0.9) at the midpoint during supplementation and −2.6 (−6.9, 1.6) at 10 y (we have not included a table illustrating these data, as the estimates are very similar to those in Table 3). Neither weight nor length differed based on vehicle of iron delivery.

Discussion

In this longitudinal analysis of well-nourished Chilean IS infants, we found no evidence that iron adversely influenced ponderal or linear growth during supplementation or afterwards until age 10 y. The vehicle for delivering iron did not appear to matter. In fact, children who received iron from 12 to 18 mo were minimally taller and growing faster at 10 y than those who had not received iron, controlling for SES and birth weight and length. Because this group had higher SES during infancy and there may have been other unmeasured differences, we offer the conservative interpretation that there was no adverse influence of iron supplementation on growth.

TABLE 2 Unadjusted characteristics of IS infants randomly selected for iron supplementation or usual nutrition at 6 or 12 mo[1]

	6 mo			12 mo	
	Preventive trial		Neuromaturation study	Preventive trial	Neuromaturation study
Characteristics	Usual nutrition	Iron supplemented[2]	Iron (15 mg/d)	Usual nutrition	Iron (30 mg/d)
n	62	56	40	67	48
Birth weight, *kg*	3.61 ± 0.43	3.58 ± 0.39	3.65 ± 0.43	3.62 ± 0.34	3.64 ± 0.39
Birth length, *cm*	50.8 ± 1.7	50.5 ± 1.5	51.2 ± 1.8	50.9 ± 1.5	51.1 ± 1.6
SES index[3]	26.9 ± 6.8	27.1 ± 6.0	27.7 ± 6.3	27.6 ± 6.1	24.9 ± 6.0
Male, *n* (%)	27 (43.5)	25 (44.6)	18 (45.0)	34 (50.7)	17 (35.4)
Female, *n* (%)	35 (56.5)	31 (53.4)	22 (55.0)	33 (49.3)	31 (64.6)
WAZ, 6 mo	0.42 ± 0.73	0.43 ± 0.84	0.23 ± 0.77	0.43 ± 0.91	0.56 ± 0.86
HAZ, 6 mo	0.02 ± 0.86	0.10 ± 0.68	−0.08 ± 0.87	0.20 ± 0.71	0.27 ± 0.68
WAZ, 1 y	−0.05 ± 0.91	0.04 ± 1.00	−0.18 ± 0.95	−0.09 ± 0.93	0.07 ± 0.98
HAZ[3], 1 y	−0.14 ± 0.70	−0.08 ± 0.80	−0.22 ± 0.99	−0.11 ± 0.70	0.19 ± 0.76
WAZ, 5 y	0.63 ± 0.93	0.60 ± 0.86	0.69 ± 0.87	0.45 ± 0.94	0.60 ± 0.95
HAZ[3], 5 y	0.21 ± 0.81	0.16 ± 0.77	0.14 ± 1.08	0.05 ± 0.88	0.45 ± 0.87
WAZ, 10 y	0.51 ± 0.98	0.49 ± 1.04	0.33 ± 1.09	0.33 ± 0.97	0.57 ± 1.24
HAZ[3], 10 y	−0.35 ± 0.66	−0.16 ± 0.82	0.00 ± 0.85	−0.36 ± 0.82	0.07 ± 1.06

[1] Values are mean ± SD or *n* (%).
[2] Iron was given as iron-fortified formula if the infant was taking at least 250 mL of formula or as vitamins with iron if the infant was taking <250 mL of formula.
[3] SES at 6 mo, HAZ score at 1, 5, 10 y were higher in the infants randomized to receive iron at 12 mo than in those who received usual nutrition, $P < 0.05$.

The reasons that our results contrast with 4 previous reports of poorer growth with routine iron supplementation in IS infants and young children are unclear (13–16). Although the studies differed methodologically from each other and ours, such factors do not offer likely explanations for the differing results. For example, we used a post hoc analysis of a prospective, randomized study, but so did 3 of the other studies (13,15,16). Our sample sizes were comparable to those of previous research (13–16), providing ample power to detect smaller magnitude effect size differences than those previously reported, especially given the methodology of longitudinal analysis with longer duration of observation and more time points. The amount of iron in our study paralleled previous studies; in the preventive trial, infants received low doses, similar to the Swedish/Honduran study (14) and a recent large Indonesian study (16), whereas those in the treatment study from 12 to 18 mo received somewhat higher doses, more comparable to an earlier Indonesian study (13). Furthermore, if dose explained the difference in findings, studies using higher doses of iron might show greater growth impairment, but this has not been the case. Specifically, the greatest effect size was found in an Indian study using a daily iron dose of 2 mg/kg (14). The 12- to 18-mo olds in our

TABLE 3 Multilevel longitudinal growth models from birth to 10 y in IS infants, randomized to iron supplementation or usual nutrition at 6 mo[1]

	Weight			Length/height		
Characteristics	Before supplementation birth–6 mo	During supplementation 6–12 mo	After supplementation 1–10 y	Before supplementation birth–6 mo	During supplementation 6–12 mo	After supplementation 1–10 y
Intercept						
Weight, *kg*, or length, *cm*	5.98 (5.83, 6.13)	8.99 (8.76, 9.22)	36.1 (34.1, 38.2)	58.8 (58.3, 59.2)	70.2 (69.6, 70.7)	142.2 (140.0, 144.4)
Iron	−0.06 (−0.25, 0.13)	0.06 (−0.26, 0.38)	0.5 (−2.1, 3.0)	0.1 (−0.4, 0.7)	0.4 (−0.3, 1.1)	−0.7 (−3.5, 2.1)
Slope						
Growth rate, *kg or cm/mo*	0.70 (0.67, 0.73)	0.30 (0.27, 0.33)	0.2 (0.15, 0.25)	2.5 (2.4, 2.6)	1.31 (1.25, 1.36)	0.62 (0.59, 0.64)
Slope × iron	0.02 (−0.03, 0.06)	0.02 (−0.01, 0.06)	0.01 (−0.01, 0.04)	0.1 (0.05, 0.2)*	0.0 (−0.1, 0.1)	0.0 (−0.01, 0.01)
Quadratic						
Deceleration, *kg*^{2} *or cm*^{2}*/mo*	−0.03 (−0.04, −0.025)	−0.03 (−0.04, −0.025)	—	−0.1 (−0.15, 0.05)	−0.1 (−0.15, 0.05)	—
Quadratic × iron	0.0 (−0.01, 0.01)	0.0 (−0.01, 0.01)	—	0.0 (−0.01, 0.01)	0.0 (−0.01, 0.01)	—
Covariates[2]						
SES index	0.01 (0.00, 0.03)*	0.01 (0.00, 0.03)*	−0.1 (−0.2, 0.0)	0.0 (0.0, 0.1)	0.03 (0.0, 0.1)	−0.1 (−0.2, 0.1)
Male	0.37 (0.23, 0.51)**	0.37 (0.23, 0.51)**	−0.7 (−2.2, 0.8)	1.4 (0.9, 1.9)**	1.4 (0.9, 1.9)**	0.3 (−1.2, 1.9)
Birth weight	—	—	1.7 (−0.2, 3.5)	—	—	0.3 (−0.2, 0.8)

[1] Values are estimate (95% CI) at 3 mo, 9 mo, and 10 y, $n = 56$ (iron-supplemented) and 62 (usual nutrition group). *SES related to weight at 3 and 9 mo in the model, $P < 0.05$. **Male sex associated with higher weight and height at 3 and 9 mo in the models, $P < 0.0001$.
[2] Covariates were included for estimation of weight or length.

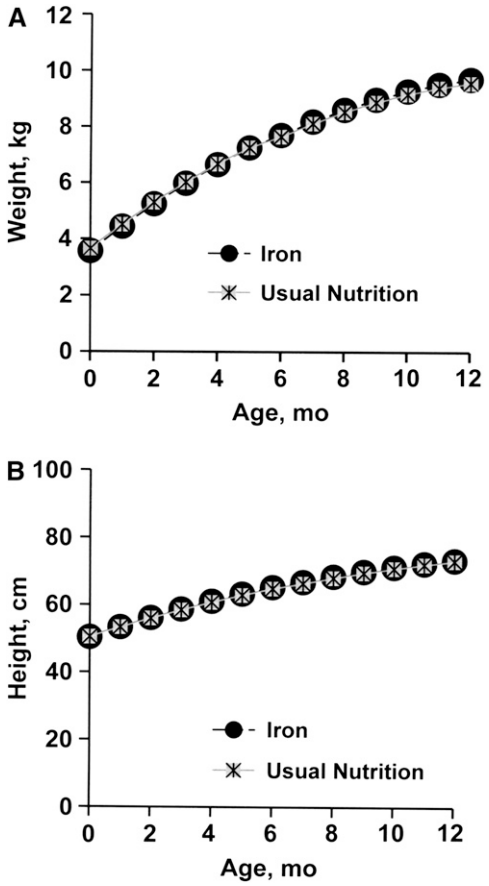

FIGURE 1 Mean weight (*A*) and length (*B*) growth trajectories for IS infants randomized to iron supplementation (n = 56) or usual nutrition (n = 62) between 6 and 12 mo of age.

treatment study received on average 3 mg/kg daily. The iron delivery vehicle is another consideration if the adverse growth effects in previous studies were due to the use of iron drops in contrast to iron-fortified formula. Yet we found no differences related to iron vehicle. The wide age range in 2 studies from 14 to 73 mo (14) and 6 to 24 mo (13) could contribute to differing findings, because growth velocity differs by age. However, the Swedish/Honduran study (15), 1 Indonesian study (16), and ours began with infants of uniform age and are comparable in this respect.

Although the factors discussed above do not seem to explain the differing results, preexisting growth differences might. The infants in our sample were considerably heavier at birth and continued to be bigger than most infants in the other reports. For example, at study entry at 5–6 mo, their WAZ scores averaged 0.4 in contrast to about −0.4 in the most recent Indonesia study (16). In addition, other studies did not report prior growth velocities, only that iron and placebo groups were similar in weight and length at study entry. The issue of growth velocity is particularly relevant in the Swedish cohort (15), because the infants were comparable in size to those in Chile. We therefore examined published data from that study in more detail. Data in the tables suggest that IS Swedish infants receiving iron drops between 6 and 9 mo, who showed slower linear growth, were gaining weight more slowly prior to iron administration than the placebo group. The group that began iron supplementation at 4 mo had the highest linear growth between 4 and 6 mo, followed by some slowing between 6 and 9 mo. Those receiving iron the longest (for 5 mo) had higher linear growth velocity during the period of supplementation than those who received iron for only 3 mo. Furthermore, the HAZ scores of the 3 groups did not differ significantly at 4, 6, or 9 mo. These observations point to the importance of considering growth trajectories before and after iron supplementation using multiple data points to construct individual growth curves to detect differences in growth velocities during different periods (35).

The prevalence of iron sufficiency in specific populations could be another preexisting difference that might contribute to different outcomes. However, direct comparison across studies is difficult, as every study used different criteria, even those that relied on Hb and ferritin. To try to understand our differing results, we estimated the prevalence of IS in the Chile sample in 2 different ways using the criteria in the most recent Indonesia

TABLE 4 Multilevel longitudinal growth models from birth to 10 y in IS infants, randomly selected for iron or usual nutrition at 12 mo[1]

	Weight			Length//height		
Characteristics	Before supplementation birth–12 mo	During supplementation 12–18 mo	After supplementation 1–10 y	Before supplementation birth–12 mo	During supplementation 12–18 mo	After supplementation 1–10 y
Intercept						
Weight, *kg*, or length, *cm*	7.97 (7.75, 8.20)	11.1 (10.7, 11.5)	33.8 (31.3, 36.2)	66.4 (65.9, 66.9)	80.8 (80.0, 81.6)	149.4 (146.5, 152.2)
Iron[1]	0.11 (−0.18, 0.40)	0.0 (−0.4, 0.5)	−0.8 (−4.1, 2.4)	0.4 (−0.2, 1.0)	0.5 (−0.6, 1.5)	0.7 (0.3, 1.1)*
Slope						
Growth rate, *kg or cm/mo*	0.51 (0.48, 0.53)	0.02 (0.15, 0.3)	0.2 (−0.2, 0.3)	−0.1 (−0.15, −0.05)	1.0 (0.9, 1.1)	0.7 (0.65, 0.75)
Slope × iron	0.01 (−0.02, 0.04)	0.0 (−0.05, 0.15)	0.0 (−0.1, 0.1)	0.1 (0.05, 0.15)	0.0 (−0.2, 0.1)	0.1 (0.05, 0.15)
Quadratic						
Deceleration, kg^2 *or* cm^2*/mo*	−0.03 (−0.04, −0.025)	—	—	−0.1 (−0.15, −0.05)	—	—
Quadratic × iron	0.00 (−0.0–5, 0.01)	—	—	0.0 (−0.05, 0.05)	—	—
Covariates[2]						
SES index	−0.01 (−0.02, 0.00)	0.0 (−0.0, 0.0)	0.0 (−0.05, 0.02)	0.0 (−0.1, 0.0)	0.0 (0.0, 0.0)	0.0 (−0.1, 0.1)
Male	0.20 (0.05, 0.34)	0.2 (−0.2, 0.6)	0.4 (−0.1, 0.8)	1.0 (0.5, 1.5)	0.8 (0.1, 1.5)	0.9 (0.1, 1.7)
Birth weight	First point in model	1.0 (0.5, 1.6)**	0.9 (0.4, 1.5)**	First point in model	0.7 (0.5, 1.0)**	0.8 (0.5, 1.1)**

[1] Values are estimates (95% CI) at 6 mo, 15 mo, and 10 y, n = 48 (iron-supplemented) and 67 (usual nutrition). *At 10 y, children who were randomized to iron supplementation at 12 mo were taller than those in the usual nutrition group, $P < 0.05$. **Birth weight associated with higher height and weight at 15 mo and 10 y in the models, $P < 0.0001$.
[2] Covariates were included for estimation of weight or length.

study (16) (extrapolating from those in our sample with venous Hb and ferritin determinations) and our criterion of a screening Hb ≥ 128 g/L. By both methods, the prevalence of IS in our cohort was only 7–8% compared with 24% in Lind et al. (16). The differing rates may relate to growth differences between studies, because the iron needs for growth can deplete iron stores. The rapid growth in the Chilean infants, combined with early introduction of powdered cow milk formula even for breast-fed infants, help explain why iron deficiency was so widespread and so few infants were IS. Conversely, poor growth might have contributed to more iron sufficiency in Lind et al. (16), because iron needs are lower with smaller size and slower growth. It is also possible that iron supplementation may have impaired growth indirectly in the Indonesian study if iron supplementation promoted infection, as some studies indicate (38–42). Children with parasitic (malarial) or bacterial infections may experience decreased appetite or poorer growth through other mechanisms.

The fact that there is currently no standard way to define iron sufficiency in the first 6 mo is a serious problem for the field. Ferritin may be of limited value in assessing iron status in such young infants, as processes regulating iron storage are not fully mature and ferritin may not adequately capture iron status early on (9,10,43,44). Furthermore, ferritin, an acute-phase reactant, can be elevated with infection or inflammation. This means that some infants identified as iron-replete may have high ferritin concentrations due to other conditions, some of which adversely affect growth and might interact deleteriously with iron. Nonetheless, it might be informative for investigators with existing infancy iron-trial data sets to collaborate in comparing results using more uniform iron sufficiency criteria.

Although our study provides the only available data on long-term growth effects of iron supplementation in IS infants and the vehicle of iron delivery, it has several important limitations. These include the generalizability and definition of IS. The Chilean infants were growing well, unlike the infants in the Indian and Indonesian studies (13,14,16). But unlike the well-nourished sample of Swedish infants reported in Dewey et al. (15), the Chilean infants came from a cohort in which iron deficiency was prevalent. In addition, lower-birth weight infants were excluded and they might have different responses to iron in the face of iron sufficiency compared with normal- or high-birth weight infants. Classifying infants as IS could not be based on venous blood or a full panel of iron measures for all infants, because these were obtained only for a subset. Therefore, IS was probably under-ascertained. Some infants with capillary Hb < 128 g/L who did not have iron measures may have had ≥2 normal iron measures. Although including more IS infants would have given greater power, we do not think that failure to identify some of the IS infants introduced systematic bias in relationship to our question. Only if identified IS infants had systematically different growth trajectories from unidentified IS infants would under-ascertainment of IS infants bias the results of our analyses and this seems implausible. In addition, ~17% of the retrospectively identified IS infants did not have adequate growth data for these analyses. However, the infants who were lost to follow-up did not differ in anthropometry or SES from those included in the analyses. These limitations notwithstanding, in a sample of full-term breast-fed IS Chilean infants, growth was not adversely affected during the period of supplementation in the first or second year or later during childhood and growth rates did not differ for iron provided in fortified formula or drops.

Iron supplementation for prevention of iron deficiency is implemented in most settings without determining infant iron status. Differing growth effects in IS compared with iron-deficient children would have implications for public health practice and policy. If it were necessary to determine iron status before giving iron in populations where iron deficiency is common, the logistics and cost might interfere with providing iron to many children who would benefit. On the other hand, if certain groups of IS infants are at risk for adverse growth with iron supplementation, then it might be necessary to develop new strategies for screening prior to supplementation. Thus, further information is needed on the growth effects of giving iron to IS infants. It is possible that iron per se is not the culprit. Rather, the contrasting results in 4 other studies challenge us to consider whether there are specific circumstances under which there could be adverse effects. Relevant data have likely been collected in several large trials. These data should be analyzed and published, whether or not they show adverse effects of iron in IS infants. Future studies should have adequate sample size, collect data on growth prior to and after supplementation, and consider timing and method of iron administration. New and ongoing iron supplementation studies should include careful growth monitoring with planned discontinuation of supplementation if growth falters with iron administration.

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