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ORIGINAL ARTICLE

# Benefits and Risks of Iron Interventions in Infants in Rural Bangladesh

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## ABSTRACT

### BACKGROUND

Universal provision of iron supplements (drops or syrup) or multiple micronutrient powders to young children in low-to-middle-income countries where anemia is prevalent is recommended by the World Health Organization and widely implemented. The functional benefits and safety of these interventions are unclear.

### METHODS

We conducted a three-group, double-blind, double-dummy, individually randomized, placebo-controlled trial to assess the immediate and medium-term benefits and risks of 3 months of daily supplementation with iron syrup or iron-containing multiple micronutrient powders, as compared with placebo, in 8-month-old children in rural Bangladesh. The primary outcome was cognitive development, as assessed by the cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition, immediately after completion of the assigned 3-month regimen; scores range from 55 to 145, with higher scores indicating better cognitive performance. Secondary outcomes included the cognitive composite score at 9 months after completion of the assigned regimen; behavioral, language, and motor development, as well as growth and hematologic markers, immediately after completion and at 9 months after completion; and safety.

### RESULTS

We randomly assigned 3300 infants to receive iron syrup (1101 infants), multiple micronutrient powders (1099), or placebo (1100) daily. After completion of the assigned 3-month regimen, no apparent effect on the cognitive composite score was observed with iron syrup as compared with placebo (mean between-group difference in change in score from baseline, −0.30 points; 95% confidence interval [CI], −1.08 to 0.48) or with multiple micronutrient powders as compared with placebo (mean between-group difference in change in score from baseline, 0.23 points; 95% CI, −0.55 to 1.00). No apparent effect on any other developmental or growth outcome was observed immediately after completion of the assigned regimen or at 9 months after completion. At 9 months after completion of the assigned regimen, the prevalences of anemia, iron deficiency, and iron deficiency anemia increased in all three trial groups but remained lower among the children who received iron syrup or multiple micronutrient powders than among those who received placebo. The risk of serious adverse events and incidence of symptoms of infection were similar in the three trial groups.

### CONCLUSIONS

In this trial involving infants in Bangladesh, 3 months of daily supplementation with iron syrup or multiple micronutrient powders did not appear to have an effect on child development or other functional outcomes as compared with placebo. (Funded by the National Health and Medical Research Council of Australia; BRISC Australian New Zealand Clinical Trials Registry number, ACTRN12617000660381.)

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Among children younger than 5 years of age worldwide, nearly 40% are anemic, most of whom reside in low-to-middle-income countries. This burden is highest in the World Health Organization (WHO) regions of South-East Asia and Africa, where anemia affects 49.0% and 60.2% of this age group, respectively.[1] Iron deficiency is considered to be the main cause of anemia in the public health context.[2] The WHO recommends that all children 6 to 23 months of age in regions with prevalent anemia receive iron through either home-based fortification of complementary foods with iron-containing multiple micronutrient powders (packets of lipid-encapsulated iron with other micronutrients that are sprinkled onto weaning foods)[3] or iron supplements in the form of drops or syrup.[4,5]

Prevention and treatment of iron deficiency and anemia in infancy have been considered essential to improving developmental outcomes (particularly cognitive development) in children. Although observational studies link anemia in children younger than 5 years of age to adverse developmental outcomes,[6] few randomized, controlled trials have assessed the immediate and sustained effects of iron interventions on cognitive, language, motor, or behavioral development, well-being, or growth in this age group.[7,8] Infection-related adverse effects, including increased rates of diarrhea[9,10] and malaria,[11] have been identified in trials of iron interventions in children who reside in areas where exposure to pathogens is intense. Although iron interventions are being scaled up (more than 18 million children across 61 countries received multiple micronutrient powders in 2018[12]), there is inadequate high-quality evidence regarding the benefits and safety of such interventions as a public health strategy for children in low-to-middle-income countries. We aimed to determine whether iron interventions (consistent with WHO anemia-prevention guidelines)[3,4] in infants produce meaningful beneficial or harmful clinical outcomes and whether iron syrup and multiple micronutrient powders produce differential effects.

## Methods

### Trial Design and Oversight

We conducted a three-group, double-blind, double-dummy, individually randomized, placebo-controlled trial (Benefits and Risks of Iron Interventions in Young Children [BRISC]) to assess immediate and medium-term benefits and risks of 3 months of daily supplementation with iron syrup or multiple micronutrient powders in 8-month-old children. The trial protocol was approved by ethics committees at the International Center for Diarrheal Disease Research, Bangladesh, and Melbourne Health, Australia, and by the Government of Bangladesh Directorate General of Drug Administration, and the trial was overseen by an independent data safety and monitoring board.

Parents or guardians of the participants provided written informed consent before both screening and enrollment in the trial. The statistical analysis plan, included with the protocol (available with the full text of this article at NEJM.org), was finalized before unblinding of the regimen assignments.[13,14] The first, penultimate, and last authors designed the trial, oversaw its implementation, and vouch for the accuracy and completeness of the data; the third and third-to-last authors analyzed the data; and the other authors collected the data. The first author wrote the initial draft of the manuscript, and all authors approved the final version for submission. There were no agreements regarding confidentiality of the data among the sponsor (the University of Melbourne), authors, and participating institutions.

*A Quick Take is available at NEJM.org*

### Participants

The trial took place in Rupganj Upazila, Narayanganj District, Bangladesh, a rural area 35 km northeast of Dhaka covering 235 km$^2$ and comprising approximately 82,000 households. The Upazila is divided into administrative units known as unions, of which we selected three (Rupganj, Golakandail, and Bhulta) for the trial. We undertook house-to-house enumeration of the entire study area to identify potentially eligible children. We screened children 7.5 to 8.5 months of age. Children with marked anemia (a hemoglobin level of <8.0 g per deciliter), current febrile illness, severe acute malnutrition, a known inherited red-cell disorder or previous transfusion, or known developmental delay were excluded. Bangladesh has areas where groundwater iron levels are high, which may affect iron intake[15]; however, the study area had generally low levels of iron in the groundwater. Furthermore, iron levels in drinking water were tested at screening, and children were excluded if the level exceeded 1 mg per liter.

### RANDOMIZATION AND MASKING

After written informed consent was obtained and baseline data were collected, the children underwent randomization. An independent statistician prepared a computer-generated randomization list with block randomization, stratified according to union and the sex of the child, to link sequential participant identification numbers to trial groups; a hard-copy list was used for randomization in the field. The list of participant identification numbers with associated trial-group assignments was held by the independent statistician until the database was locked for analysis.

### TRIAL-GROUP ASSIGNMENTS

The participants were randomly assigned to receive 12.5 mg of elemental iron as ferrous sulfate syrup daily[4] plus placebo packets of multiple micronutrient powders that contained maltodextrin alone; packets of multiple micronutrient powders that contained 12.5 mg of iron as ferrous fumarate, 0.3 mg of vitamin A, 30 mg of vitamin C, 0.16 mg of folic acid, 5 mg of zinc, and maltodextrin[3] plus placebo syrup; or placebo syrup and placebo packets. The iron syrup, multiple micronutrient powders, and placebo products were taken daily. The iron syrup (purchased from ACME Laboratories) was administered through a syringe marked with the required volume, and the multiple micronutrient powders (donated by Renata) were sprinkled onto complementary foods. These interventions met the WHO recommendations.[3,4] The active agents and placebo were packaged identically and could be distinguished only by a finely printed, multidigit batch number. The iron content of active agents and placebo was independently tested at the International Center for Diarrheal Disease Research, Bangladesh. The trial drugs and placebo were initially administered at the time of randomization, when proper use of the products was demonstrated.

### OUTCOME ASSESSMENT

Data were entered in the field on handheld devices and uploaded to an SQL database. Children underwent detailed assessments at baseline, at the completion of the assigned 3-month regimen (up to 7 days before or 14 days after completion), and at 9 months after completion (with a window of ±14 days). During the intervention period, trained local data collectors visited the participants at home weekly to assess medical complications and adherence and to replenish trial drugs or placebo. Data collectors also visited the participants monthly during the postintervention period to assess medical complications.

Assessments of cognitive, behavioral, language, and motor development were conducted, anthropometric variables (crown–heel length, weight, and head circumference) were measured at least in duplicate by two trained persons, and z scores were calculated with the use of the 2006 WHO Child Growth Standards.[16] Sociodemographic and nutrition data were collected, and home stimulation was assessed with the use of the family care indicators tool[17] at baseline, immediately after completion of the assigned 3-month regimen, and at 9 months after completion. Venous blood samples of up to 3 ml were collected, and hemoglobin levels were measured with a HemoCue 301+ device (HemoCue). Serum was separated and frozen for analysis of ferritin and C-reactive protein levels.

The primary trial outcome was cognitive development, as assessed by the cognitive composite score on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III), immediately after completion of the assigned 3-month regimen. Using a locally adapted Bayley-III tool, trained testers, who had a master's degree in psychology or social sciences, evaluated each infant in the presence of the mother (or another caregiver if the mother was unavailable) in a quiet environment outside the family home.[18] The Bayley-III is a reference clinical and research tool for comprehensive assessment of neurodevelopment in early childhood that uses a structured set of tasks to assess function across various domains and takes approximately 1 hour to administer; scores range from 55 to 145 for cognitive development and from 45 to 155 for language and motor development, with higher scores indicating better performance (in U.S. populations, the standardized mean [±SD] score is 100±15).[19]

Key secondary outcomes were the Bayley-III cognitive composite score at 9 months after completion of the assigned regimen, the Bayley-III language composite and motor composite scores, length-for-age and weight-for-age z scores, hemoglobin level, and iron stores (measured as the ferritin level), each of which was assessed

immediately after completion of the assigned regimen and at 9 months after completion. Other secondary outcomes were behavior (as assessed with the use of Wolke's Behavior Rating Scale), temperament, anemia (defined as a hemoglobin level of <11 g per deciliter), iron deficiency (defined as a ferritin level of <12 $\mu$g per liter or <30 $\mu$g per liter if the C-reactive protein level was >5 mg per liter),[20] and iron deficiency anemia (concurrent anemia and iron deficiency), each of which was assessed immediately after completion of the assigned regimen and at 9 months after completion.

The quality of the Bayley-III measurements was monitored. Before the trial was initiated, intraobserver reliability for Bayley-III ratings ranged from 0.81 to 0.99 and interobserver reliability from 0.99 to 1 among the testers, except for one who had not performed as well as the other testers initially but was retrained before continuing involvement. During the trial, 9% of tests were observed by another tester: interobserver reliability ranged from 0.96 to 1 (Table S1 in the Supplementary Appendix, available at NEJM.org). Performance of testers was accounted for in alternative analyses of Bayley-III scores by incorporating rater and the interaction between rater and visit in the model.

During home visits, mothers or caregivers were asked whether the child had symptoms of infection (i.e., diarrhea [defined as at least 3 loose or liquid stools per day], bloody diarrhea, vomiting, fever, or cough or breathing difficulty) and the number of days in the previous week (during the intervention period) or previous 2 weeks (during the follow-up period) that they had occurred. Parents or caregivers could seek medical care for their infant from government or private providers; the receipt of such care was recorded as an unplanned clinic visit. Safety outcomes were symptoms of infection that were reported during home visits, as well as unplanned clinic visits and hospitalizations that were reported at any time; records of hospitalizations and deaths were confirmed by the trial pediatrician, who was also available to provide free advice for the participating families.

### STATISTICAL ANALYSIS

We determined that a sample size of 3300 participants (1100 per group) would provide 80% power to detect a 2-point difference in cognitive composite score between each active intervention group and the placebo group immediately after completion of the assigned regimen, assuming a standard deviation of 15 points, a 20% loss to follow-up, and a two-sided type I error rate of 5%. With a Bonferroni-corrected two-sided alpha level of 0.025 for the comparisons between iron syrup and placebo and between multiple micronutrient powders and placebo, the trial would have at least 80% power to reject at least one of the two primary null hypotheses (no difference between iron syrup and placebo or between multiple micronutrient powders and placebo with respect to the primary outcome immediately after completion of the assigned regimen). In our previous systematic review of the effects of iron supplementation on cognitive development in young children, we estimated that iron supplementation would result in a 1.65-point higher cognitive composite score than placebo at the end of the intervention[7]; differences in the cognitive composite score of between 2 and 3 points in favor of iron supplementation have been reported in previous underpowered population trials.[21] The current trial was thus powered to detect a minimum effect size of a 2-point between-group difference in the cognitive composite score immediately after completion of the assigned regimen; a 2-point difference is probably smaller than a clinically meaningful effect.

Analyses were performed according to the intention-to-treat principle and followed a prespecified statistical analysis plan.[13] The cognitive composite score at 3 months (primary outcome) was analyzed with the use of a likelihood-based longitudinal data analysis model by Liang and Zeger,[22] with the randomization stratification factors union and sex of the child as covariates, and unstructured variance–covariance among repeated measurements (the Stata code used for analysis is provided in Text S1 in the Supplementary Appendix). Similar analyses were applied to the key secondary outcomes of Bayley-III language composite and motor composite scores, length-for-age z score, weight-for-age z score, hemoglobin level, and log-transformed ferritin level, as well as the secondary outcomes of weight-for-length z score and head circumference. Secondary outcomes of stunting (length-for-age z score of less than –2), underweight (weight-for-age z score of less than –2), wasting (weight-for-length z score of less than –2), ane-

mia, iron deficiency, and iron deficiency anemia were analyzed with the use of a Poisson regression model with a random intercept for the participant and robust error variance. Infection outcomes during the intervention period (number of days with a parent-reported symptom of infection) and follow-up period (number of days with a parent-reported symptom of infection during the last 14 days of each month) were analyzed with the use of a negative binomial regression model for each period separately with offset for time at risk. The multiple testing strategy consisted of testing the two primary null hypotheses at a significance level of 2.5%; testing the key secondary hypotheses involving the same comparisons was conditional on the rejection of the primary null hypotheses.[23]

Additional analyses of primary, key secondary, and secondary outcomes included covariate-adjusted analyses for baseline imbalance and a per-protocol analysis of participants with at least 70% adherence, to which we applied the previously described multiple-testing approach. The likelihood-based longitudinal analysis model was fitted under the missing-at-random assumption. An analysis based on a pattern-mixture model was performed for the primary outcome to assess sensitivity to data missing not at random.[24] Nine prespecified subgroup analyses of the primary and key secondary outcomes and three post hoc subgroup analyses of parent-reported symptoms of infection and clinic visits (according to baseline status with respect to anemia, iron deficiency, and iron deficiency anemia) were conducted to assess heterogeneity of the differences among the active interventions and placebo. Analyses were performed with the use of Stata/SE software, version 15.1 (StataCorp).

## RESULTS

### TRIAL POPULATION

Between July 6, 2017, and February 20, 2019, a total of 3300 children were enrolled and underwent randomization (Fig. S1). Follow-up was completed on February 10, 2020; unblinding of the data was delayed because of restrictions related to coronavirus disease 2019.[25] Baseline household and child characteristics were similar across trial groups (Table 1 and Table S2). At baseline, 1428 of 3188 children (44.8%) had anemia, 852 of 3080 (27.7%) had iron deficiency, and 594 of 3080 (19.3%) had iron deficiency anemia. Median adherence to iron syrup, multiple micronutrient powders, and placebo was 86.8%, 86.8%, and 87.9%, respectively (Table S3); 73.1% of children consumed at least 70% of their assigned active agent or placebo.

### CHILD DEVELOPMENT

Among the 3300 children who had undergone randomization, 2885 (87.4%) were assessed for the primary outcome immediately after completion of the assigned 3-month regimen. Loss to follow-up was similar among the trial groups. No apparent effect on the cognitive composite score was observed with iron syrup as compared with placebo (mean between-group difference in change in score from baseline, −0.30 points; 95% confidence interval [CI], −1.08 to 0.48) or with multiple micronutrient powders as compared with placebo (mean between-group difference in change in score from baseline, 0.23 points; 95% CI, −0.55 to 1.00) (Table 2). No evidence of a difference in cognitive composite score was found with iron syrup as compared with multiple micronutrient powders (mean between-group difference in change in score from baseline, −0.52 points; 95% CI, −1.31 to 0.26). No apparent differences in cognitive composite score were observed among the trial groups at 9 months after completion of the assigned regimen (Table 2). There were no apparent differences in baseline characteristics between the children with missing cognitive composite scores and those with at least 70% adherence to the assigned regimen (Tables S4 and S5). The absence of an evident effect of an active intervention on the primary outcome was confirmed with alternative models that accounted for missing data, baseline anemia, tester, and adherence (Table S6).

Neither iron syrup nor multiple micronutrient powders improved motor or language development, child behavior (Wolke's Behavioral Rating Scale), or temperament, either immediately after completion of the assigned regimen or at 9 months after completion (Table 2 and Table S7). Measurements of child growth (length-for-age z score, weight-for-age z score, weight-for-length z score, and head circumference) did not differ significantly among the three groups either immediately

**Table 1. Household and Child Characteristics at Baseline.***

| Characteristic | Iron Syrup (N=1101) | MNPs (N=1099) | Placebo (N=1100) |
|---|---|---|---|
| **Household** | | | |
| Median maternal education (IQR) — yr | 8 (5–10) | 8 (5–10) | 8 (5–10) |
| Median paternal education (IQR) — yr | 8 (5–10) | 7 (5–9) | 8 (5–10) |
| Household wealth index — no./total no. (%) | | | |
| Quintile 1: relative poorest | 222/1101 (20.2) | 224/1098 (20.4) | 215/1099 (19.6) |
| Quintile 3: relative middle | 213/1101 (19.3) | 230/1098 (20.9) | 211/1099 (19.2) |
| Quintile 5: relative wealthiest | 222/1101 (20.2) | 221/1098 (20.1) | 212/1099 (19.3) |
| Household with food-secure status — no./total no. (%)† | 884/1099 (80.4) | 877/1093 (80.2) | 866/1094 (79.2) |
| **Child** | | | |
| Demographic characteristic | | | |
| Female sex — no./total no. (%) | 550/1101 (50.0) | 548/1099 (49.9) | 550/1100 (50.0) |
| Age — mo | 8.0±0.3 | 8.0±0.3 | 8.0±0.3 |
| Laboratory measure | | | |
| Hemoglobin level — g/dl | 11.0±1.0 | 11.0±1.0 | 11.0±1.0 |
| Anemia — no./total no. (%)‡ | 495/1072 (46.2) | 461/1053 (43.8) | 472/1063 (44.4) |
| Median ferritin level (IQR) — μg/liter | 21.7 (11.7–38.5) | 23.1 (13.1–38.5) | 23.8 (12.8–39.3) |
| Iron deficiency — no./total no. (%)§ | 307/1033 (29.7) | 273/1021 (26.7) | 272/1026 (26.5) |
| Iron deficiency anemia — no./total no. (%)¶ | 225/1033 (21.8) | 181/1021 (17.7) | 188/1026 (18.3) |
| Median C-reactive protein level (IQR) — mg/liter | 0.68 (0.32–2.02) | 0.77 (0.32–2.49) | 0.76 (0.34–2.18) |
| Inflammation — no./total no. (%)‖ | 112/1033 (10.8) | 147/1021 (14.4) | 128/1027 (12.5) |
| Child growth | | | |
| Length-for-age z score | −1.23±1.04 | −1.20±1.00 | −1.27±1.00 |
| Weight-for-age z score | −0.58±1.04 | −0.57±1.01 | −0.63±1.01 |
| Weight-for-length z score | 0.24±1.03 | 0.22±1.02 | 0.21±1.01 |
| Child development according to the Bayley-III scores** | | | |
| Cognitive composite score | 96.2±7.8 | 96.0±7.8 | 96.6±7.7 |
| Language composite score | 88.3±7.2 | 88.1±7.1 | 88.8±7.0 |
| Motor composite score | 92.0±10.1 | 92.1±10.2 | 92.7±10.4 |

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and MNPs multiple micronutrient powders.
† Food-secure status was defined as an answer of "no" or "rarely" to question 1 and "no" to questions 2 through 9 on the Household Food Insecurity Access Scale.
‡ Anemia was defined as a hemoglobin level of less than 11 g per deciliter.
§ Iron deficiency was defined as a ferritin level of less than 12 μg per liter or less than 30 μg per liter if the C-reactive protein level was higher than 5 mg per liter.
¶ Iron deficiency anemia was defined as concurrent anemia and iron deficiency.
‖ Inflammation was defined as a C-reactive protein level of more than 5 mg per liter.
** Child development was assessed with the use of the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III). The Bayley-III is a reference clinical and research tool for comprehensive assessment of neurodevelopment in early childhood that uses a structured set of tasks to assess function across various domains and takes approximately 1 hour to administer. Scores range from 55 to 145 for cognitive development and from 45 to 155 for language and motor development, with higher scores indicating better performance.[19]

**Table 2. Efficacy of Iron Interventions Immediately after Completion of the 3-Month Regimen and at 9 Months after Completion (Intention-to-Treat Population).***

| Outcome | Iron Syrup | MNPs | Placebo | Estimate (95% CI)† | | |
|---|---|---|---|---|---|---|
| | | | | Iron Syrup vs. Placebo | MNPs vs. Placebo | Iron Syrup vs. MNPs |
| **Immediately after completion of the 3-mo regimen** | | | | | | |
| Primary outcome: change in cognitive composite score from baseline | −1.16±9.97 | −0.57±10.39 | −1.27±10.25 | −0.30 (−1.08 to 0.48)‡ | 0.23 (−0.55 to 1.00)§ | −0.52 (−1.31 to 0.26) |
| Key secondary outcomes | | | | | | |
| Change in language composite score from baseline | −2.43±10.98 | −1.83±11.40 | −2.79±11.24 | −0.23 (−1.11 to 0.66) | 0.25 (−0.64 to 1.13) | −0.47 (−1.36 to 0.41) |
| Change in motor composite score from baseline | 1.55±10.41 | 1.24±10.84 | 0.80±10.73 | 0.31 (−0.46 to 1.09) | 0.11 (−0.66 to 0.88) | 0.20 (−0.57 to 0.98) |
| Change in length-for-age z score from baseline | −0.01±0.55 | −0.01±0.57 | −0.02±0.63 | 0.01 (−0.04 to 0.07) | 0.01 (−0.04 to 0.06) | 0.01 (−0.05 to 0.06) |
| Change in weight-for-age z score from baseline | −0.03±0.52 | −0.00±0.47 | −0.03±0.45 | 0.00 (−0.04 to 0.05) | 0.03 (−0.01 to 0.07) | −0.03 (−0.07 to 0.02) |
| Change in hemoglobin level from baseline — g/dl | 0.55±0.93 | 0.47±0.93 | −0.13±0.81 | 0.69 (0.60 to 0.77) | 0.60 (0.52 to 0.69) | 0.08 (0.00 to 0.17) |
| Median change in ferritin level from baseline (IQR) — μg/liter | 35.41 (20.59–53.14) | 30.16 (18.07–45.86) | 17.56 (8.77–31.25) | 1.85 (1.72 to 1.99) | 1.62 (1.50 to 1.73) | 1.15 (1.07 to 1.23) |
| Other secondary outcomes | | | | | | |
| Anemia — no./total no. (%) | 157/671 (23.4) | 172/672 (25.6) | 326/662 (49.2) | 0.48 (0.41 to 0.56) | 0.52 (0.45 to 0.60) | 0.92 (0.76 to 1.11) |
| Iron deficiency — no./total no. (%) | 94/651 (14.4) | 100/656 (15.2) | 258/649 (39.8) | 0.36 (0.29 to 0.45) | 0.38 (0.31 to 0.47) | 0.95 (0.73 to 1.23) |
| Iron deficiency anemia — no./total no. (%) | 50/651 (7.7) | 56/656 (8.5) | 191/649 (29.4) | 0.26 (0.20 to 0.35) | 0.29 (0.22 to 0.38) | 0.91 (0.63 to 1.30) |
| **At 9 mo after completion of the assigned regimen** | | | | | | |
| Key secondary outcomes | | | | | | |
| Change in cognitive composite score from baseline | −3.61±10.39 | −3.54±10.81 | −3.73±10.27 | −0.34 (−1.10 to 0.42) | −0.26 (−1.02 to 0.51) | −0.09 (−0.85 to 0.68) |
| Change in language composite score from baseline | 4.35±11.20 | 4.42±10.96 | 4.46±11.02 | −0.76 (−1.64 to 0.11) | −0.72 (−1.59 to 0.16) | −0.04 (−0.92 to 0.83) |
| Change in motor composite score from baseline | 4.14±11.36 | 3.71±11.95 | 3.05±11.84 | 0.27 (−0.37 to 0.92) | 0.11 (−0.54 to 0.75) | 0.17 (−0.48 to 0.81) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Change in length-for-age z score from baseline | −0.12±0.68 | −0.14±0.70 | −0.17±0.66 | 0.05 (−0.01 to 0.11) | 0.04 (−0.01 to 0.10) | 0.01 (−0.05 to 0.07) |
| Change in weight-for-age z score from baseline | −0.16±0.66 | −0.18±0.68 | −0.19±0.73 | 0.03 (−0.03 to 0.09) | 0.01 (−0.06 to 0.07) | 0.02 (−0.04 to 0.08) |
| Change in hemoglobin level from baseline — g/dl | 0.41±1.03 | 0.37±1.09 | 0.03±1.23 | 0.39 (0.28 to 0.49) | 0.31 (0.20 to 0.42) | 0.08 (−0.03 to 0.18) |
| Median change in ferritin level from baseline (IQR) — μg/liter | 16.18 (8.43–27.92) | 14.84 (8.13–27.37) | 11.39 (6.04–21.37) | 1.34 (1.24 to 1.45) | 1.31 (1.21 to 1.42) | 1.02 (0.94 to 1.11) |
| Other secondary outcomes | | | | | | |
| Anemia — no./total no. (%) | 198/684 (28.9) | 227/666 (34.1) | 280/686 (40.8) | 0.71 (0.61 to 0.82) | 0.83 (0.72 to 0.95) | 0.85 (0.73 to 1.00) |
| Iron deficiency — no./total no. (%) | 284/672 (42.3) | 294/649 (45.3) | 378/678 (55.8) | 0.76 (0.68 to 0.85) | 0.81 (0.73 to 0.90) | 0.94 (0.83 to 1.06) |
| Iron deficiency anemia — no./total no. (%) | 144/672 (21.4) | 166/649 (25.6) | 227/678 (33.5) | 0.64 (0.53 to 0.76) | 0.75 (0.63 to 0.89) | 0.85 (0.70 to 1.03) |

* Plus–minus values are means ±SDs. Analyses of Bayley-III scores included available data from all 3300 participants: 12% had baseline data only, 74% had complete data, and 15% had incomplete data. Anthropometric analyses included data from 3299 participants: 12% had baseline data only, 74% had complete data, and 15% had incomplete data. Analyses of the hemoglobin level included data from 3270 participants: 24% had baseline data only, 46% had complete data, and 30% had incomplete data. Analyses of the ferritin level included data from 3215 participants: 23% had baseline data only, 45% had complete data, and 32% had incomplete data.

† The Bayley-III scores (cognitive composite, language composite, and motor composite), z scores, and hemoglobin level were analyzed with the use of a likelihood-based longitudinal data analysis model that adjusted for union (i.e., administrative region) and sex of the child; the estimated values represent the mean between-group difference in the change in score from baseline to the time point of evaluation. The log-transformed ferritin level was analyzed with the use of a likelihood-based longitudinal data model that adjusted for union and sex of the child; the estimated values represent the geometric mean ratio of the relative change from baseline to the time point of evaluation between the groups. Anemia, iron deficiency, and iron deficiency anemia were analyzed with the use of a Poisson regression model with robust error variance that adjusted for union and sex of the child with a random intercept for the participant because of nonconvergence of the log-binomial model; the estimated values represent the prevalence ratio of the relative change from baseline to the time point of evaluation between the groups. Owing to imbalance at baseline, the model for iron deficiency anemia was adjusted for baseline imbalance by removing the constraint of a common baseline mean across the three trial groups. The 95% confidence intervals and P values were not adjusted for multiple testing. The significance threshold for the comparisons between iron syrup and placebo and between MNPs and placebo immediately after completion of the assigned regimen was 2.5% for the two primary null hypotheses (no difference between iron syrup and placebo or between multiple micronutrient powders and placebo with respect to the primary outcome immediately after completion of the assigned regimen).

‡ P=0.45.

§ P=0.57.

after completion of the assigned regimen or at 9 months after completion (Table S8), and these results were similar in additional analyses (Table S9).

### HEMATOLOGIC OUTCOMES

The effects of the assigned regimens on hematologic outcomes immediately after completion of the assigned regimen and at 9 months after completion are shown in Table 2. Among the 3300 participants who had undergone randomization, data on the venous hemoglobin level were available for 2094 (63.5%) immediately after completion of the assigned regimen and for 2104 (63.8%) at 9 months after completion. Three months of supplementation with iron syrup or multiple micronutrient powders resulted in a lower prevalence of anemia than placebo (prevalence ratio with iron syrup vs. placebo, 0.48 [95% CI, 0.41 to 0.56], and with multiple micronutrient powders vs. placebo, 0.52 [95% CI, 0.45 to 0.60]). The prevalence of anemia was similar in the iron-syrup group and the multiple-micronutrient-powder group, with a prevalence ratio of 0.92 (95% CI, 0.76 to 1.11). At 9 months after completion of the assigned regimen, the prevalence of anemia increased in all three trial groups but remained lower among the children who received iron syrup or multiple micronutrient powders than among those who received placebo (prevalence ratio with iron syrup vs. placebo, 0.71 [95% CI, 0.61 to 0.82], and with multiple micronutrient powders vs. placebo, 0.83 [95% CI, 0.72 to 0.95]). The prevalences of iron deficiency anemia and iron deficiency were also lower with either active intervention than with placebo (Table 2). Further analyses confirmed these results (Table S10).

### SAFETY

The percentage of participants with at least one serious adverse event (hospitalization or death) was similar in the three trial groups, as was the percentage of participants who had unplanned clinic visits during the intervention period or immediately after completion of the assigned regimen (Table 3 and Table S11). Parental reports of symptoms of infection (diarrhea, fever, or respiratory symptoms) were similar in the three trial groups, both during the intervention period and during the follow-up period. Tables S12 through S17 report the results of descriptive post hoc subgroup analyses of safety outcomes according to baseline status with respect to anemia, iron deficiency, and iron deficiency anemia. Neither iron intervention had an effect on the prevalence of corneal lesions (Bitot's spots) (Table S18).

### SUBGROUP ANALYSES

The results of the prespecified subgroup analyses of the primary and key secondary outcomes are provided in Figure 1 and Table S19. There was no evidence of a subgroup effect on the cognitive composite score according to baseline status with respect to anemia or iron deficiency immediately after completion of the assigned regimen (Fig. 1) or at 9 months after completion. The increases in hemoglobin and ferritin levels at completion of the assigned regimen were greater among the children who had anemia, iron deficiency, or iron deficiency anemia at baseline, and there was no evidence of a difference between the two iron interventions.

## DISCUSSION

In a rural, low-income, South Asian region where anemia in young children is a severe public health problem, 3 months of daily supplementation with iron syrup or multiple micronutrient powders in 8-month-old infants, as recommended in the WHO guidelines, did not have an effect on the primary outcome of child cognitive development, despite a markedly lower prevalence of anemia or iron deficiency in the active intervention groups than in the placebo group. The iron interventions were not associated with evidence of immediate or sustained improvements in other measures of child development, behavior, temperament, or growth. Reductions in anemia were partly sustained at 9 months after completion of the assigned regimen. Neither intervention was associated with an increase in parental reports of symptoms of infection or clinic visits or hospitalizations, and each led to a similar short-term reduction in the prevalence of anemia or iron deficiency.

The key rationale for preventive iron interventions in young children is the presumed benefit with respect to functional health outcomes,[26] particularly child development and growth[27]; this presumption is based on observational studies that have consistently linked anemia to suboptimal

**Table 3. Safety Outcomes during the Intervention Period (Safety Population).**

| Outcome | Iron Syrup | | MNPs | | Placebo | | Iron Syrup vs. Placebo* | | MNPs vs. Placebo* | | Iron Syrup vs. MNPs* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total No. of Infants | No. with Event (%) | Total No. of Infants | No. with Event (%) | Total No. of Infants | No. with Event (%) | Relative Risk (95% CI) | P Value | Relative Risk (95% CI) | P Value | Relative Risk (95% CI) | P Value |
| **Serious adverse event** | | | | | | | | | | | | |
| Death | 1101 | 0 | 1099 | 1 (0.1) | 1100 | 1 (0.1) | — | — | — | — | — | — |
| ≥1 Serious adverse event | 1101 | 20 (1.8) | 1099 | 23 (2.1) | 1100 | 21 (1.9) | 0.95 (0.52–1.75) | 0.88 | 1.10 (0.61–1.97) | 0.76 | 0.87 (0.48–1.57) | 0.64 |
| ≥1 Hospitalization† | 1101 | 20 (1.8) | 1099 | 22 (2.0) | 1100 | 20 (1.8) | 1.00 (0.54–1.85) | 1.00 | 1.10 (0.60–2.01) | 0.75 | 0.91 (0.50–1.66) | 0.76 |
| **≥1 Clinic visit according to reason‡** | | | | | | | | | | | | |
| Any reason | 1101 | 243 (22.1) | 1099 | 252 (22.9) | 1100 | 226 (20.5) | 1.08 (0.92–1.26) | 0.37 | 1.10 (0.94, 1.29) | 0.21 | 0.97 (0.84–1.13) | 0.73 |
| Fever | 861 | 104 (12.1) | 856 | 112 (13.1) | 849 | 109 (12.8) | 0.96 (0.75–1.22) | 0.72 | 1.02 (0.80–1.29) | 0.89 | 0.94 (0.74–1.20) | 0.62 |
| Diarrhea§ | 861 | 42 (4.9) | 856 | 41 (4.8) | 849 | 30 (3.5) | 1.42 (0.90–2.24) | 0.13 | 1.37 (0.86–2.16) | 0.18 | 1.04 (0.69–1.58) | 0.85 |
| Bloody stool | 861 | 4 (0.5) | 856 | 1 (0.1) | 849 | 6 (0.7) | 0.68 (0.19–2.39) | 0.55 | 0.17 (0.02–1.39) | 0.10 | 4.05 (0.45–36.05) | 0.21 |
| Vomiting | 861 | 57 (6.6) | 856 | 58 (6.8) | 849 | 50 (5.9) | 1.16 (0.81–1.66) | 0.43 | 1.17 (0.81–1.67) | 0.40 | 0.99 (0.70–1.41) | 0.97 |
| Cough or difficulty breathing | 861 | 96 (11.1) | 856 | 93 (10.9) | 849 | 93 (11.0) | 1.05 (0.81–1.37) | 0.72 | 1.00 (0.77–1.31) | 0.98 | 1.05 (0.80–1.36) | 0.74 |
| Other reason¶ | 861 | 119 (13.8) | 856 | 121 (14.1) | 849 | 124 (14.6) | 0.97 (0.77–1.21) | 0.76 | 0.97 (0.77–1.21) | 0.77 | 1.00 (0.79–1.26) | 0.99 |
| **Parent-reported symptoms of infections** | | Median Days (IQR)‖ | | Median Days (IQR)‖ | | Median Days (IQR)‖ | Incidence Rate Ratio (95% CI) | | Incidence Rate Ratio (95% CI) | | Incidence Rate Ratio (95% CI) | |
| Fever | 1091 | 4.3 (0.0–8.8) | 1092 | 4.4 (0.0–9.2) | 1087 | 4.4 (0.0–9.9) | 0.97 (0.87–1.08) | 0.56 | 1.00 (0.90–1.12) | 0.93 | 0.96 (0.86–1.08) | 0.50 |
| Diarrhea§ | 1091 | 0.0 (0.0–2.2) | 1092 | 0.0 (0.0–2.2) | 1087 | 0.0 (0.0–1.1) | 1.13 (0.89–1.42) | 0.31 | 1.17 (0.93–1.48) | 0.18 | 0.96 (0.76–1.21) | 0.73 |
| Bloody stool | 1091 | 0.0 (0.0–0.0) | 1092 | 0.0 (0.0–0.0) | 1087 | 0.0 (0.0–0.0) | 1.00 (0.58–1.72) | 0.99 | 0.86 (0.50–1.49) | 0.60 | 1.15 (0.67–1.99) | 0.61 |
| Vomiting | 1091 | 0.0 (0.0–4.4) | 1092 | 0.0 (0.0–3.3) | 1087 | 0.0 (0.0–3.3) | 1.19 (1.00–1.41) | 0.05 | 1.07 (0.90–1.27) | 0.44 | 1.11 (0.94–1.32) | 0.23 |
| Cough or difficulty breathing | 1091 | 3.3 (0.0–12.5) | 1092 | 4.4 (0.0–12.1) | 1087 | 4.4 (0.0–11.0) | 1.03 (0.90–1.18) | 0.68 | 1.04 (0.90–1.19) | 0.61 | 0.99 (0.87–1.14) | 0.93 |

* Serious adverse events and clinic visits were analyzed with the use of a log-binomial regression model that adjusted for union and sex of the child. Death was not analyzed owing to small numbers. For infection-related outcomes, the participant's total number of days with infection during the 13-week intervention period was analyzed with the use of a negative binomial regression model adjusted for union and sex of child and with the time at risk (total number of days) as offset. The analyses of infection-related outcomes excluded participants with missing data on infection symptoms for the entire intervention period (9 [0.8%] in the iron-syrup group, 7 [0.6%] in the MNP group, and 13 [1.2%] in the placebo group). In all the analyses reported in the table, the 95% confidence intervals and P values were not adjusted for multiple testing.

† Hospitalization was defined as at least a one-night stay in the hospital.

‡ Clinic visit was defined as an unplanned visit to the clinic that did not result in hospitalization. The reason for the clinic visit was collected for 78% of the trial population during the intervention period and for 94% of the trial population during the follow-up period.

§ Diarrhea was defined as three or more watery stools in 24 hours.

¶ Other reasons include runny nose, skin problem, eye problem, oral problem, ear problem, constipation, and other symptoms not otherwise specified.

‖ The median number of days with a parent-reported symptom of infection is reported per 100 person-days.







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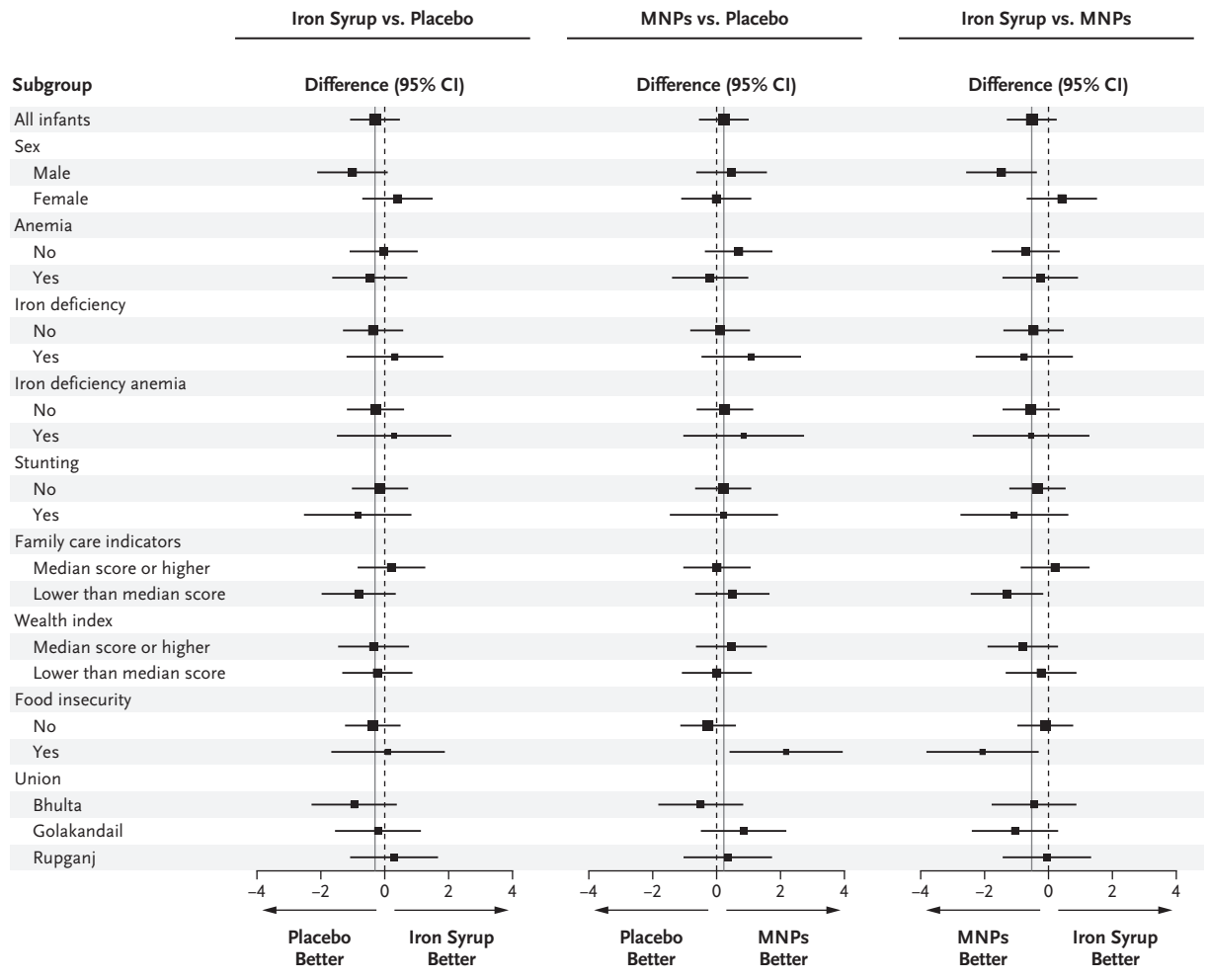


**Figure 1. Subgroup Analyses of the Treatment Effect on the Cognitive Composite Score Immediately after Completion of the Assigned Regimen According to Baseline Characteristics.**

The cognitive composite scores on the Bayley Scales of Infant and Toddler Development, third edition, were analyzed in the intention-to-treat population with the use of a likelihood-based longitudinal data analysis model that adjusted for union and sex of the child and included subgroup-by-regimen and subgroup-by-visit interactions. The 95% confidence intervals were not adjusted for multiple comparisons. Anemia was defined as a hemoglobin level of less than 11 g per deciliter. Iron deficiency was defined as a ferritin level of less than 12 μg per liter or less than 30 μg per liter if the C-reactive protein level was higher than 5 mg per liter. Iron deficiency anemia was defined as concurrent anemia and iron deficiency. Stunting was defined as a length-for-age z score lower than –2. The median total score on the family care indicators tool was 13, on a scale from 0 to 42, with higher scores indicating more activities involving play and reading materials.[17] The median wealth index score was 0.49; households with a score below 0.49 comprised relatively poorer households, and those with a score above 0.49 relatively wealthier households. The wealth index is derived from an asset-based measure of a household's living standard calculated from a principal component analysis. Food security was assessed with the use of the Household Food Insecurity Access Scale questionnaire; food-secure status was defined as an answer of "no" or "rarely" to the initial question regarding worry over the previous 4 weeks that the household would not have enough food and an answer of "no" to further questions regarding change in food availability or eating behaviors due to food access. MNPs denote multiple micronutrient powders.

child cognitive development.[6] However, meta-analyses of randomized, controlled trials evaluating iron supplementation revealed limited and inconclusive data with regard to functional outcomes.[7,8] Individual trials were underpowered,[21] involved patient groups (not populations),[28] or had an open-label design,[10] limitations that the current trial was designed to

overcome. Given that iron interventions produced sustained improvements in the hemoglobin level and iron stores but did not improve developmental, behavioral, or growth outcomes in the immediate or medium term, our results address this knowledge gap. Our conclusions were consistent across all additional primary intention-to-treat analyses.

We administered the iron syrup and multiple micronutrient powders for 3 months, as recommended by the WHO. Although a longer duration of supplementation may have further increased iron stores, it is uncertain whether this would have had an effect on functional outcomes, because iron deficiency anemia was virtually eliminated after 3 months. Previous studies that involved longer interventions (e.g., 6 months[21] and 18 months[10,29,30]) have not shown benefits with respect to cognitive development. In addition, a longer intervention may have exacerbated the risk of diarrhea. Future studies may explore whether prolonged iron interventions in infants can have a benefit with regard to functional outcomes; alternatively, improvement of neurodevelopment in children may require an earlier intervention (e.g., antenatal supplementation).[31]

There are concerns that iron interventions may increase risks of infections, such as those that cause diarrhea.[9,10] The rates of parent-reported diarrhea and unplanned clinic visits for diarrhea were not higher in the groups that received iron syrup or multiple micronutrient powders than in the placebo group. Although the subgroup analyses indicated an increased risk of unplanned clinic visits because of diarrhea in nonanemic or non–iron-deficient children while they were receiving iron syrup or multiple micronutrient powders, these findings are not conclusive because the analyses were post hoc, did not include adjustment for multiple comparisons, and showed no significant difference between subgroups.

Our data showed that iron syrup and multiple micronutrient powders were associated with similar adherence, had similar effects in reducing the prevalences of anemia and iron deficiency, and did not differ significantly with respect to functional or infection-related outcomes. The prevalences of anemia, iron deficiency, and iron deficiency anemia were lower among the children in the active intervention groups than among those in the placebo group for up to 9 months after completion of the assigned regimen, although the prevalences in all three groups had increased from the time immediately after completion of the intervention. Repeated cycles of the intervention, which is recommended for multiple micronutrient powders[3] but not for iron supplements (drops or syrup), may be needed to sustain hematologic responses.

We did not identify an effect on developmental outcomes in subgroups defined according to baseline anemia, iron deficiency, and iron deficiency anemia. These findings inform the rationale for screening and therapy for asymptomatic iron deficiency in children in clinical practice.[32,33]

The strengths of our trial were that it was designed with cognitive development as the primary outcome, was powered to detect a small effect size, minimized the risk of bias, and ensured high interobserver concordance between assessors. The limitations of our trial were that 36 to 37% of the infants at each postbaseline visit did not have a measurement of the venous hemoglobin concentration for reasons such as unwillingness of the parents to allow collection of a venous blood sample, which limited the data used in the secondary hematologic analyses but not the data used for the primary or other functional outcome analyses. We found no important differences in baseline characteristics between those for whom consent to a blood test was provided and those for whom consent was not provided. Per-protocol analyses were adjusted for key prognostic baseline factors, as were the intention-to-treat analyses; however, bias due to unmeasured postrandomization factors associated with adherence is possible.

In our trial, 3 months of daily supplementation with iron syrup or multiple micronutrient powders in 8-month-old children reduced the prevalence of anemia but did not improve cognitive development or other functional health outcomes immediately after completion of the regimen or at 9 months after completion.

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## APPENDIX

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