Infant Iron Deficiency and Iron Supplementation Predict Adolescent Internalizing, Externalizing, and Social Problems

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Objective To evaluate associations between iron supplementation and iron deficiency in infancy and internalizing, externalizing, and social problems in adolescence.

Study design The study is a follow-up of infants as adolescents from working-class communities around Santiago, Chile who participated in a preventive trial of iron supplementation at 6 months of age. Inclusionary criteria included birth weight ≥3.0 kg, healthy singleton term birth, vaginal delivery, and a stable caregiver. Iron status was assessed at 12 and 18 months of age. At 11-17 years of age, internalizing, externalizing, and social problems were reported by 1018 adolescents with the Youth Self Report and by parents with the Child Behavior Checklist.

Results Adolescents who received iron supplementation in infancy had greater self-reported attention-deficit/hyperactivity disorder but lower parent-reported conduct disorder symptoms than those who did not (*P*s < .05). Iron deficiency with or without anemia at 12 or 18 months of age predicted greater adolescent behavior problems compared with iron sufficiency: more adolescent-reported anxiety and social problems, and parent-reported social, post-traumatic stress disorder, attention-deficit/hyperactivity disorder, oppositional defiant, conduct, aggression, and rule breaking problems (*P*s < .05). The threshold was iron deficiency with or without anemia for each of these outcomes.

Conclusions Iron deficiency with or without anemia in infancy was associated with increased internalizing, externalizing, and social problems in adolescence. *(J Pediatr 2017;■■:■■-■■).*

Iron deficiency in infancy is associated with poorer cognitive functioning, behavioral disturbances, emotional difficulties, and lower motor scores,[1] with long-term effects despite iron therapy at diagnosis.[2] The longest follow-up study of early iron deficiency assessed young adults in Costa Rica who were treated for iron deficiency that was identified in the second year of life (termed "chronic" iron deficiency). When participants were 11-14 years of age, parents and teachers reported increased anxiety/depression, attention, and social problems for those with chronic iron deficiency in infancy.[3] At 25 years of age, these young adults reported poorer emotional health, including more negative emotions and greater dissociation/detachment than those who did not have chronic iron deficiency in infancy.[2] In this study, behavior problems in early adolescence were an important mediator of emotional health at 25 years of age,[2] indicating the persistence of problems following iron deficiency in infancy.

It is unknown whether associations between infant iron deficiency and emotion/behavior problems generalize to other populations or apply to infants with less chronic iron deficiency. To address these questions, we analyzed data from a large cohort of Chilean adolescents who participated as infants in an iron deficiency anemia preventive trial. At 10 years of age, children who received iron supplementation in the trial showed more adaptive behaviors, such as greater cooperation, confidence, persistence, and positive affect.[4] In adolescence, we predicted that iron supplementation in infancy would also be associated with more adaptive behaviors. We expected that individuals with iron deficiency in infancy would report more behavior problems than those who were iron-sufficient in infancy. However, we did not have a prediction about whether iron deficiency anemia or iron deficiency without anemia would be the threshold for symptoms.

Methods

This study was a follow-up of a project in Chile that included a clinical trial of preventing iron deficiency anemia in infancy. Infants were enrolled from 1991 to 1996 at clinics in 4 working-class communities outside of Santiago, Chile. Inclusion and exclusion criteria were chosen to enroll healthy infants without common

ADHD	Attention-deficit/hyperactivity disorder
CBCL	Child Behavior Checklist
Hb	Hemoglobin
PTSD	Post-traumatic stress disorder
SES	Socioeconomic status
YSR	Youth Self Report

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risk factors for developmental or behavioral problems. Inclusion criteria include birth weight >3.0 kg, singleton term birth, vaginal delivery, stable caregiver, and residence in the communities. Exclusion criteria included major congenital anomaly, birth complications, phototherapy, hospitalization longer than 5 days, illness, or iron therapy, another infant less than 12 months of age in the household, day care for the infant, or a caregiver who was illiterate or psychotic.[5]

At 6 months of age, qualifying infants were randomized in the double-blind preventive trial to receive high-iron formula (12 mg/L) or low-iron formula (2.3 mg/L) in the initial years of the study. Infants needed to be consuming at least 250 mL of formula or cow milk per day to be entered in the trial. From 1994 to 1996, this requirement was dropped, as national campaigns greatly increased breastfeeding rates. In addition, a no-added-iron group replaced the low-iron group, as originally planned.[5] Infants consuming ≥250 mL/day of cow milk or formula were randomized to high-iron formula or cow milk without added iron. Infants who were taking <250 mL/day of cow milk or formula were randomized to liquid vitamins with iron (10 mg/day) or without iron (study diagram shown in **Figure 1** (available at www.jpeds.com). A total of 1657 infants completed the preventive trial. Supplementation significantly reduced iron deficiency and iron deficiency anemia at 12 months of age and improved social behavior in infancy and at 10 years of age.[4,5] More details on study design and preventive trial results are described elsewhere.[4] Written informed consent was obtained at each assessment, and child assent was obtained from 10 years of age on. A flowchart of the timeline and measures related to the current analyses is included in **Figure 2** (available at www.jpeds.com). The study was approved by the institutional review boards of the corresponding universities.

Iron Status

All infants received a capillary hemoglobin (Hb) screening at 6 months of age. Infants with screening Hb ≤103 g/L and the next nonanemic infant received a venipuncture. Infants with iron deficiency anemia at 6 months (venous Hb ≤100 g/L[6] and 2 out of 3 abnormal measures as detailed below) and the next infant with venous Hb >115 g/L were excluded from the preventive trial and followed in a separate study. At 12 months of age, a venous blood sample was collected for all participants in the preventive trial. At 18 months of age, participants in the low-iron and no-added-iron groups received another venipuncture. Missing iron measures at 18 months of age for individuals who did not receive a venipuncture were imputed using multiple imputation techniques.[7] Anemia at 12 and 18 months of age was defined as Hb <110 g/L.[8] Iron deficiency was defined as 2 of 3 iron measures in the abnormal range[9] mean corpuscular volume <70 fL,[10] free erythrocyte protoporphyrin >100 μg/dL red blood cells,[11] and ferritin <12 μg/L.[11] Infants with iron deficiency anemia at any age received iron therapy. Based on each individual's poorest iron status at 12 or 18 months of age, we classified iron status as iron deficiency anemia, iron deficiency without anemia, or iron-sufficient (ie, not having iron deficiency anemia or iron deficiency without anemia at 12 and 18 months of age). We could not do so at 6 months because only 321 infants had an iron status assessment based on venipuncture. By 18 months, iron deficiency anemia was greatly reduced because of supplementation, slower growth, and a more diverse diet. After infancy, iron deficiency anemia was uncommon in the sample, with less than 1% iron deficiency anemia at the 5- and 10-year follow-ups and 2.5% at the adolescent assessment.

Adolescent Follow-Up

Youth Self Report and Child Behavior Checklist. All parents reported their adolescent's symptoms using the Child Behavior Checklist (CBCL).[12] All adolescents reported symptoms using the Youth Self Report (YSR), the self-report version of the CBCL. Both were administered in Spanish. The YSR and CBCL are widely used, valid, and reliable instruments for assessing symptoms in children and adolescents.[12,13] Internalizing symptoms were assessed by the following scales: depressive problems, anxiety problems, and post-traumatic stress disorder (PTSD) problems. Externalizing problems were assessed with the oppositional defiant problems, conduct problems, rule breaking, attention-deficit/hyperactivity disorder (ADHD) problems, and aggressive behavior scales. Social problems were assessed using the social problems scale. Correlations between the parent and adolescent report for each subscale ranged from $r = 0.16$ for anxiety problems to $r = 0.42$ for rule breaking ($Ps < .001$). T scores were used in analyses. Scales that were skewed (skewness value >1) were log-transformed prior to analysis; specifically, parent-reported rule breaking and conduct problems and adolescent-reported social, depressive, PTSD, aggressive, ADHD, and oppositional defiant problems were log-transformed.

Potential Covariates

To consider socioeconomic status (SES) effects, SES was measured in infancy using a modified Graffar Index.[14] Maternal age (in years), number of life stressors in the past year, birth weight and length, gestational age, and growth from 0 to 6 months in height and weight were also reported at the infancy assessment.[15] The Home Observation for Measurement of the Environment (HOME) measured home support for child development.[16] Because exclusion criteria changed during enrollment regarding breastfeeding, we controlled for feeding in infancy by including the mean daily formula/milk consumption (mL/day) between 6 and 12 months of age as a covariate. This variable was inversely correlated with all breastfeeding measures (ie, weaning age [if weaned], nursing at 1 year, and age at first bottle). Data on formula/milk consumption and breastfeeding was obtained from mothers at weekly home visits. Family stress in infancy was measured by a modified Social Readjustment Rating Scale.[17] Some participants were enrolled at 12 or 18 months of age in a study component examining neuromaturation in iron deficiency anemia compared with infants who were iron-sufficient; they all received medicinal iron.[9] Participation (with receipt of medicinal iron) was coded as 0 = not in neuromaturation study, 1 = in neuromaturation study. For control variables, missing values were imputed using multiple imputation techniques.[7]

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