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Early life adversity is associated with poor iron status in infancy

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Abstract

Exposure to early life adversity (ELA) and iron deficiency early in life are known risk factors for suboptimal brain and socioemotional development. Iron deficiency may arise from and co-occur with ELA, which could negatively affect development. In the present study, we investigated whether ELA is associated with iron deficiency in infants receiving no iron supplementation. This study is a secondary analysis of extant data collected in the 1990s; participants were healthy infants from working-class communities in Santiago, Chile (N = 534, 45.5% female). We measured stressful life events, maternal depression, and low home support for child development during infancy and assessed iron status when the infant was 12 months old. Slightly more than half of the infants were iron deficient (51%), and 25.8% were iron-deficient anemic at 12 months. Results indicated that ELA was associated with lower iron levels and iron deficiency at 12 months. The findings are consistent with animal and human prenatal models of stress and iron status and provide evidence of the association between postnatal ELA and iron status in humans. The findings also highlight a nutritional pathway by which ELA may impact development and present a nutritionally-focused avenue for future research on ELA and psychopathology.

Keywords

early life adversity; nutrition; stress; iron deficiency; infancy

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

Introduction

The micronutrient iron is notable for its role in the development and function of all body tissues and is especially important for brain development. Iron deficiency is one of the most common forms of malnutrition, affecting an estimated 4 in 10 children under five years of age globally (Stevens et al., 2013) and 15.1% of toddlers in the United States (Gupta et al., 2017). Developmentally, infants are especially at risk of becoming iron deficient (ID) at approximately 6–12 months of age, when prenatal iron stores become depleted (Georgieff, 2017). During the critical 6- to 24-month postnatal window of rapid brain development, iron deficiency is particularly damaging, as several areas of the brain require iron for normal development (Cusick & Georgieff, 2016). The high demand for iron in infancy coincides with the period of rapid growth and development of brain structure and functions that require iron, including the hippocampus, cortical regions, neuronal and glial energy metabolism, myelin synthesis, and neurotransmission (Lozoff & Georgieff, 2006). Iron is also essential for serotonin, norepinephrine, and dopamine neurotransmitter synthesis (Lozoff & Georgieff, 2006). Animal studies show associations between altered brain metabolism, myelination (Beard et al., 2003; Kwik-Uribe et al., 2000; Oloyede et al., 1992; Yu et al., 1986), and neurotransmitter function (Lozoff, Beard, et al., 2006) and early-life iron deficiency. Early ID also is associated with alterations to the developing hippocampus (de Deungria et al., 2000), with pervasive and long-lasting iron deficiency-induced metabolic (Rao et al., 2003) and dendritic structure changes (Jorgenson et al., 2003). Neurophysiologic studies of the effects of iron deficiency have found differences in the speed of neural transmission in the auditory system (Li et al., 1994; Roncagliolo et al., 1998), recognition memory (Burden et al., 2007; Siddappa et al., 2004), longer auditory brainstem response, and longer visual evoked potentials latencies (Algarin et al., 2003). Infants at high risk for ID show poorer recognition memory, possibly due to iron's effects on the hippocampus and central nervous system (Nelson et al., 2000). Iron deficiency during infancy is associated with children's socioemotional and behavioral problems and lower cognitive abilities (Georgieff, 2011; Lozoff, Beard, et al., 2006; Pivina et al., 2019). Thus, inadequate iron can negatively impact neurodevelopment across several domains and in different brain regions (Beard & Connor, 2003; Beard et al., 2006; Felt et al., 2006).

Iron deficiency may also be more likely to occur in the context of early life adversity (ELA) (Walker et al., 2011). ELA can include exposure to poverty, a harsh family environment, parental separation, caregiver mental illness, major illness, death of a family member, or other forms of psychosocial adversity (Lupien et al., 2009). ELA is also detrimental to optimal neurodevelopment, placing children at risk for psychopathology later in life (Lupien et al., 2009). There are biological and sociological reasons for their co-occurrence (Grantham-McGregor & Ani, 2001). Sociologically, children experiencing ELA in the form of poverty may be at higher risk of iron deficiency due to food insecurity or diets low in iron (e.g., (Skalicky et al., 2006)). Biologically, conditions of ELA may co-occur with conditions that increase an infant's exposure to infection and inflammation that impact iron status. Hepcidin, a hormone that responds to body iron status and inflammation to regulate intestinal absorption and tissue distribution, mediates iron absorption and sequestration. Hepcidin expression is modulated during infection and inflammation to decrease iron

availability to invading pathogens. Iron supply for red blood cell precursors is also restricted during inflammation and infection (Ganz & Nemeth, 2009).

Adversity might also put a child at risk for developing iron deficiency due to physiological processes arising from ELA. The stress of ELA can contribute to dysregulated neuroendocrine pathways that can disrupt nutrient absorption and utilization even in the context of adequate nutrient intake (Monk et al., 2013; Osterholm & Georgieff, 2015; Suchdev et al., 2017). Chronic disruptions to the stress response shape neurobiology and physiology during sensitive periods of development, leading to alterations in stress and immune system activity (Nusslock & Miller). The hypothalamic-pituitary-adrenocortical (HPA) plays a significant role in how an organism responds to stress and how stressful experiences are biologically embedded (Gunnar et al., 2015; Gunnar & Vazquez, 2006). Early-life exposure to stress and increased exposure to cortisol or its releasing hormone, corticotropic-releasing hormone (CRH), is thought to program the developing HPA axis and brain (Korosi & Baram, 2008). Disruptions to stress-mediating systems that arise from early life adversity can produce multi-system reactions (Danese & Baldwin, 2017). These include elevated cytokine levels, glucocorticoid resistance, and dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, among other stress-mediating systems (Miller et al., 2011). Psychological stress can negatively impact nutritional processes such as iron absorption, synthesis, and availability (Monk et al., 2013). Animal studies show evidence for changes in iron metabolism following stress exposure. Adult rodents exposed to psychological stress exhibit decreases in serum iron, hemoglobin, ferritin, and erythropoietin (Wei et al., 2008). In another study, exposure to acute and chronic stressors in rodents reduced whole blood iron concentration (Teng et al., 2008). Additionally, research from non-human primates shows that experimental stress to the pregnant monkey produced compromised iron status in the infant (Coe et al., 2007).

Few studies in humans examine the effects of stress on iron status. One experiment in Navy SEAL trainees found that a week of psychological stress resulted in an acute disruption to iron status (Singh et al., 1991). From a population perspective, more impoverished countries have higher rates of iron deficiency (Black et al., 2017). However, studies assessing the association between ELA and iron status are primarily limited to adversity exposure in pregnancy. In studies of pregnant mothers, mothers exposed to higher levels of objective stressors and mothers who reported higher levels of stress in pregnancy were more likely to have offspring with worse iron status, including lower cord blood ferritin (Armony-Sivan et al., 2013; Campbell et al., 2020) and a higher cord blood zinc protoporphyrin/heme ratio (McLimore et al., 2013). Rendina and colleagues (Rendina et al., 2018) also found that pregnant women with higher stress levels had 1-year old infants with an increased risk of low plasma ferritin.

Currently, it is unknown how postnatal ELA impacts iron status in infants. The current study examines the extent to which cumulative adversity experienced during the first year of life relates to infants' iron status. Our outcomes of interest included infants' iron status at 12 months of age (i.e., iron deficiency with or without anemia) and hematological markers of poor iron status (ferritin, hemoglobin, mean corpuscular volume, free erythrocyte protoporphyrin). All infants studied here were randomized to the control (no-added iron)

arm of an iron deficiency anemia preventive trial from 6 to 12 months (Lozoff et al., 2003). We hypothesize that higher levels of adversity in the first year of life will be associated with poor iron status at 12 months and individual hematological markers of poor iron status at 12 months of age.

Methods

Participants

The current sample was part of a Chilean cohort that participated in a randomized controlled trial (RCT) in infancy to prevent iron deficiency anemia (IDA; see descriptive statistics in Table 1). The study is fully described (Lozoff et al., 2003). Infants were recruited from 1991–1996 at community clinics in four adjacent working-class communities in Santiago, Chile. In these communities, infants were primarily fed breastmilk and powdered milk ("Leche Purita") that was not iron-fortified. Screening infants for anemia was not a regular part of pediatric care, and routine iron supplementation was not the policy in Chile at the time of the study (Lozoff et al., 2003). Infants randomized (double-blind) into one of three iron supplementation groups: (1) iron-fortified formula (12.7 Fe mg/L, provided by Abbott-Ross Laboratories) or vitamins with iron (15 mg/d) if primarily breastfed, (2) low-iron formula (2.3 Fe mg/L, provided by Abbott-Ross Laboratories), and (3) the control group of no added iron formula or vitamins without iron if primarily breastfed. Infants received the intervention from 6 to 12 months of age.

Inclusion criteria in the trial were birth weight > 3.0 kg, singleton term birth, vaginal delivery, stable caregiver, and residence in the target communities. Exclusion criteria were a major congenital anomaly, birth complications, phototherapy, hospitalization longer than five days, illness, or iron therapy, another infant less than 12 months of age in the household, daycare for the infant, and a caregiver who was illiterate or psychotic, which was self-reported or reported by family members on a recruitment questionnaire. Until mid-1994, exclusive breastfeeding (<250 mL cow milk or formula/d) was also an exclusion criterion. However, given secular increases in breastfeeding, the study was modified to enroll qualifying infants even if they had not started any bottle-feeding. Between 1994–1996, to increase the size of the no-added iron group, infants who were consuming ≥250 mL/d cow milk or formula were randomly assigned in a 1-to-3 ratio to either (a) high-iron formula or (b) unmodified cow milk plus multivitamins without iron. Infants who were taking < 250 mL/d of formula (defined as "exclusively breastfed") were randomly assigned in a 1-to-2-ratio to liquid multivitamin preparation that (a) did contain iron or (b) did not contain iron (Lozoff et al., 2003). The no-added iron group consisted entirely of infants recruited after 1994.

Infants received capillary hemoglobin (Hb) screening at six months. Infants with low Hb (≤ 103 g/L) were further assessed by venipuncture. IDA at six months was defined as venous Hb ≤ 100 g/L and 2 of 3 iron measures in the deficient range: mean corpuscular volume (MCV) < 70 fL, free erythrocyte protoporphyrin (FEP) > 100 μg/dL red blood cells, and ferritin < 12 μg/L. At six months, infants with iron-deficiency anemia (IDA) were excluded from the preventive trial and given medicinal iron (n = 73 of 2,027 screened). All other (nonanemic) infants were invited to participate in the preventive trial.

The current study analyzed only those infants who were not anemic at six months to meet trial enrollment criteria, completed the trial, had iron status measured at 12 months, and were randomized to the control group, which received no iron supplementation from the study (n = 534). We selected only the no-added iron control group to understand how ELA is associated with iron status without supplementation. There were no differences between those who did or did not complete the study by group assignment, infant characteristics (birth weight, gestational age, sex, growth, and temperament [described below]), or family characteristics (household size, father absence, parental education, maternal depressed mood, and child development support provided in the home) (Lozoff et al., 2003). Table 1 displays the descriptive characteristics of the sample. The Institutional Review Boards at the relevant institutions in the US and Chile approved the study. The study's procedures were consistent with the Declaration of Helsinki. Additional details of the supplementation study have been previously published (Lozoff et al., 1996).

Measures

Iron status—At 12 months, all participants provided a venous blood sample to determine iron status based on Hb (Hb, g/L), mean corpuscular volume (MCV, fL), free erythrocyte protoporphyrin (FEP), and serum ferritin (μg/L). The focal iron status variable of interest was iron status, defined as iron sufficient, iron deficient without anemia, or iron-deficiency with anemia. For the categorical iron status assessment, infants were iron deficient (ID) if they had 2 of 3 iron measures in the abnormal range (described in the Participants section above) (Oski, 1993). Infants were categorized as having iron-deficiency anemia (IDA) with 2 of 3 iron measures in the abnormal range and Hb < 110 g/L. Infants without ID or IDA were categorized as iron sufficient (IS). Iron status was coded as an ordinal variable, with iron sufficient coded as 1, iron deficient without anemia coded as 2, and iron-deficient anemic coded as 3. We also analyzed continuous measures of Hb, MCV, FEP (FEP was reverse-scored and log-transformed), and ferritin (ferritin was log-transformed due to right-skew) in a latent variable with structural equation modeling (detailed below). All iron measures are reported in Table 1.

Early life adversity—Early life adversity (ELA) was a composite variable created by the sum of three indices (further explained below) of ELA in infancy: (1) stressful life events that occurred during the infants' first year, (2) frequent maternal depressive symptoms, and (3) low support for child development in the home. When their infants were 6–12 months old, mothers completed self-report questionnaires to assess these various adversities. All measures were extensively pilot tested in Chile before conducting the study. Spanish versions were used for all measures and found to have good reliability and high equivalence to the English versions (Wu et al., 2019). A native Spanish speaker translated measures into Spanish before a Chilean psychologist back-translated the measures to verify comparability with the English version (Wu et al., 2019). The original translations were also adjusted to accommodate subtle regional differences in Chilean Spanish (Ceballo et al.). The sum of each separate ELA index was standardized (z-score) and then summed to form an overall ELA index, with higher scores indicating higher levels of early-life adversity (Table 1).

(1) Stressful life events.: Mothers reported stressful life events with a modified Social Readjustment Rating Scale (Holmes & Rahe, 1967) when the target infant was 11 months old, capturing stressful life events in the last year. The measure was a maternal self-report of 30 possible stressors (e.g., chronic illness of a family member, marital separation, financial instability, etc.) occurring during the last year. Items were coded "0" if the event did not happen and "1" if the event did happen, with scores summed across the 30 items (range: 0 – 30).

(2) Maternal depressive symptoms.: Maternal depressive symptoms were assessed via the Center for Epidemiological Studies Depression scale (CES-D) (Radloff, 2016) when the infant was seven months old. The CES-D has been widely used in cross-cultural research and has demonstrated reliability and validity across ethnic groups within the US and internationally (Naughton & Wiklund, 1993; Roberts et al., 1990). Research-trained psychologists administered the scale to mothers via private interview. The 20-item scale asks about the frequency of depressive symptoms within the past three months, with response options ranging from "rarely or none of the time" (coded as 0) to "most or all the time" (coded as 3). The Cronbach alpha of the CES-D items at infancy was .85 (Wu et al., 2019). Scores on the CES-D reflect the frequency of maternal depressive symptoms in the last three months. We used the raw sum score of maternal depressive symptoms in this analysis, with higher scores indicating more frequent depressive symptoms (range: 0 – 60).

(3) Support for child development in the home.: We assessed support for child development with the Home Observation for Measurement of the Environment Inventory (HOME), which evaluates the quality of stimulation and support available to a child in their home environment (Caldwell & Bradley, 1984). HOME is well-established and has been used in several Latin American countries (Bradley & Corwyn, 2016). Scores from the HOME in studies conducted in Chile are comparable to studies conducted in the U.S. (Bradley & Corwyn, 2016; Bulnes, 1979; Lozoff et al., 2003). The HOME assessment was conducted by a trained researcher through home observation when the infant was nine months old. The HOME measures support for child development, including variety in daily stimulation, provision of play materials, organization of the environment, and the parent's responsivity and involvement with the child. The HOME score was reverse-scored, such that higher scores indicate less support for child development.

Covariates—Covariates determined *a priori* related to study outcomes include gestational age, birth weight (obtained from hospital records), and weight from 6 to 12 months (measured monthly on an electronic scale to the nearest 10 g by the study team). Researchers recorded the amount of formula or cow milk that the infant ingested at weekly home visits from 6 to 12 months. To control for differences in feeding behavior (formula vs. breastfeeding), we used the average daily intake (mL/d) of cow milk or formula as a covariate. This average daily intake of milk/formula (milliliters per day) is inversely related to breastfeeding status. Of the 359 participants with data on breastfeeding at one year, 44.6% were still breastfeeding. The mean age at weaning from breastfeeding was 5.9 months (SD: 3.3 months). Sex (0 = female, 1 = male) was included as a covariate given previous research has found that male infants are more likely to have poorer iron status in the no-added-iron

group even after control for birth weight and growth (Lozoff, Beard, et al., 2006), which also supports evidence that sex differences in iron status are independent of more rapid postnatal growth in males (Domellof et al., 2002).

Analytic Approach.

First, ordinal logistic regression models were used to predict iron status (the severity of iron deficiency at 12 months; coded as 0 to 2 for iron sufficient, iron-deficient, and iron-deficient anemic) from ELA exposure (the sum standardized z-score of stressful events, maternal depressive symptoms, and low support in the home). We controlled for the impact of growth velocity on infant iron status by including change in body weight from 6 to 12 months in the ordinal logistic regression model. All analyses included all covariates.

Then, we conducted a separate analysis with structural equation modeling (SEM) to test the extent to which ELA was associated with the continuous hematological measures of iron status at 12 months. As previously described (Lozoff, Kaciroti, et al., 2006), we created a latent variable (iron status) with MCV, hemoglobin, FEP (reverse-coded, log-transformed), and ferritin (log-transformed). A higher value on this continuous latent variable indicates better iron status. We conducted linear regressions within the SEM framework to predict the latent iron status variable from ELA, controlling for birth weight, gestational age, sex, and daily cow milk/formula intake. We fit the structural equation model with the SEM package *Lavaan* in R studio Version 1.456 (Rosseel, 2012) with full information maximum likelihood estimates. We assessed the goodness of fit of the model using the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Missing data in exposure variables were imputed using multiple imputation techniques (Rubin, 1987) with IVEWARE software within SAS using available demographic, anthropometric, and environmental data in infancy and early childhood (as described in (Doom et al., 2020; Newman, 2016)).

Results

Of the 534 infants analyzed here, 23% were iron sufficient at 12 months, approximately half were iron deficient (51.1%), and 25.8% met the criteria for iron deficiency anemia (Table 1). Drawing from historical data and estimates from Latin American countries from 1995 to 2011 for children <5 years, the mean hemoglobin concentrations from the present sample fall within the expected population hemoglobin concentration ranges (Stevens et al., 2013). The mean maternal depressive symptom score was 14.6 (SD = 2.6), mothers reported an average of 4.8 stressful life events in the last year (SD = 2.6), and the mean HOME support for child development was 39.6 (SD = 7.6). The overall ELA score mean was −.47 (SD = 1.9) and ranged from −4.7 to 6.6, with higher scores indicating higher levels of adversity.

The ordinal logistic regression results showed a significant association between ELA in infancy and 12-month iron status (p=.003), such that higher levels of psychosocial adversity were associated with increased odds of iron deficiency and iron deficiency anemia (Table 2, Figure 1). For every one-unit increase in the ELA score, the odds of being iron deficient or iron-deficient anemic at 12 months was 1.16 (i.e., an increase of 16%), holding constant all other variables. Table 3 displays the correlation matrix of key variables.

For the structural equation model, model fit indices demonstrated that the model was an acceptable fit for the data (CFI: .96, RMSEA: .059, SRMR: .032). Full model results are displayed in Table 4 and Figure 2. Structural equation modeling with the latent variable of hematological iron measures demonstrated a significant association between ELA and 12-month iron status composite, such that higher levels of ELA were associated with poorer iron status (Figure 2 and Table 3; standardized $\beta = -.09$; $\beta = -.375$; 95% CI = −708 – −.005; $p = .047$). Table 5 provides additional information on the early life adversity characteristics by iron status at 12 months.

Discussion

This study's results demonstrate that greater ELA exposure in the first year of life was associated with poorer iron status at 12 months of age, analyzed both as a categorical iron status variable and as a continuous hematologic composite. This finding is consistent with animal and prenatal human models of stress and iron status, such that postnatal ELA was associated with iron status in infancy. To our knowledge, this is the first study to examine postnatal stress in the first year of life and iron status in infants.

This study found evidence for poor iron status with clinical cut-offs (iron deficient, iron deficiency anemia) and a continuous composite of iron status across multiple iron markers. The continuous hematologic assessment is critical. There is a risk for harmful effects of compromised iron status that may arise from exposure to ELA even before an infant reaches a clinical iron-deficient state. During the rapid growth period of infancy, the body prioritizes iron to red blood cells and other organs over the brain (Georgieff, 2017; Zamora et al., 2016). Thus, brain iron is reduced even before the infant becomes anemic (Georgieff et al., 1990; Petry et al., 1992). After iron treatment, red blood cells become iron-replete before the brain (Geguchadze et al., 2008; Rao et al., 2003). Therefore, even before clinical diagnoses of iron deficiency or anemia, disruptions to iron status are likely to influence early brain development (Rao & Georgieff). Inadequate iron can negatively impact neurodevelopment across several domains and in different brain regions, as evidenced by animal studies (Beard & Connor, 2003; Beard et al., 2006; Felt et al., 2006). Maintaining sufficient iron early in life is vital to optimal neurodevelopment and reducing psychopathology risk (Georgieff, 2017). ELA, an exposure that poses a threat to both neurodevelopment and psychopathology, is found here to be additionally associated with iron insufficiency. Studying ELA and iron status simultaneously may help identify which children could benefit from iron supplementation and additional psychosocial services.

Several explanations exist for the associations found. The association between ELA and iron deficiency found in this study may arise from a bidirectional associations between HPA-axis functioning and iron status early in life. For example, there is evidence that iron deficiency (ID) and iron deficiency anemia (IDA) impacts the developing HPA system. (Felt et al., 2012; Golub et al., 2006; Saad et al., 1991; Yehuda & Yehuda, 2006). Non-infectious psychosocial stress may operate along similar pathways of infection and inflammation (Cohen et al., 2012), leading to the risk of IDA even in the context of adequate iron intake. Non-infectious psychological stress responses utilize many of the same pathways as infectious stress to alter basic processes of nutrient metabolism, including absorption

and prioritization. Like infection, psychosocial stress activates and, if chronic, dysregulates the HPA axis and increases proinflammatory cytokines (Hantsoo et al., 2019). Through glucocorticoid regulation and the HPA axis, ELA and chronic psychological stress may lead to iron sequestration and decreased iron absorption. Hepcidin may mediate these effects. Hepcidin, its receptor, and iron channel ferroportin work in concert to control the dietary absorption, storage, and tissue distribution of iron. Hepcidin is upregulated in response to inflammatory states to decrease iron availability and control infection. During infection and inflammation—and potentially psychosocial stress—hepcidin and ferroportin expression are modulated to reduce iron availability. Iron supply for red blood cell precursors is also restricted, contributing to the anemia associated with infections and inflammatory conditions (Ganz & Nemeth, 2009). ELA and HPA dysregulation are associated with increases in proinflammatory cytokines IL-6 and CRP that regulate hepcidin. Dysregulated neuroendocrine pathways that arise from contexts of psychosocial stress can disrupt iron absorption and utilization even in the context of adequate intake (Monk et al., 2013; Suchdev et al., 2017). The hepcidin-mediated reduction in gut absorption may also worsen total body iron deficiency in chronic stress. Thus, when increased inflammation is due to psychological stress, the impact of increased hepcidin activity is increased risk of IDA, without the benefit of controlling infection. Currently, the treatment response to ID or IDA is to increase iron with supplementation. However, suppose stress and neuroendocrine dysregulation is altering iron prioritization and loading through hepcidin. In that case, the answer is a non-nutritional solution, which fundamentally shifts how ID and IDA are assessed and treated.

Alternatively, there may be bidirectional associations between HPA-axis functioning and iron status early in life. A prior study on adults found that patients with iron deficiency experienced reduced cortisol secretion in response to an adrenocorticotropic hormone (ACTH) challenge. Other studies have found an impact of ID on HPA functioning in prenatal and postnatal models (Saad et al., 1991). In a study of rhesus monkeys randomly assigned to prenatal iron deprivation, infants born to mothers that were iron deprived showed elevated cortisol levels in response to novel contexts at four months (equivalent in age to older infancy/toddlerhood in humans) even though the animals were never anemic (Golub et al., 2006). This suggests that the effects of iron deprivation on the HPA axis can occur in the absence of anemia. Pregnant guinea pigs on an iron-deficient diet during gestation and lactation had offspring with significantly elevated basal cortisol levels at postnatal day 24 than the iron-sufficient control group (Shero et al., 2018). Postnatal studies of iron deficiency in humans are sparse but also suggest that ID could have long-term impacts on the developing neuroendocrine system. In one study, infants treated for IDA showed lower morning salivary cortisol levels as children (Yehuda & Yehuda, 2006), suggestive of a later hypo-responsive HPA system. Another study found that ten-year-old children who had IDA in infancy exhibited a blunted cortisol response to venipuncture and catheter placement (Felt et al., 2012). Given the potential for a bidirectional connection between iron status early in life and the developing stress response system, infants exposed to higher levels of ELA be experiencing changes to HPA-axis functioning to impact later iron status. Or their stress-response systems may be altered from worse iron status to make them more sensitive to conditions of ELA. Without more research, it is impossible to disentangle the two. Unfortunately, this study does not have measures of the stress response system (such

as cortisol), inflammation markers, or hepcidin measures. Future studies should consider focusing on biomarkers of the stress response to understand if the stress-mediating systems are involved in the associations between ELA exposure and iron status in infancy.

The association found between ELA exposure and infant iron status may be due to family background factors. In this sample, mothers who were younger, less educated, and of lower socioeconomic status were also more likely to have higher ELA scores (Table 3). These factors could influence nutrition during pregnancy and nursing and the money available for infant food. Families experiencing higher levels of stress and depression may be less able to provide iron-rich complementary food for infants. Conversely, the lack of ability to provide food for their family may also drive rates of stress and depression higher. This alternate explanation for the associations found herein may also inform interventions focusing on nutrition and stress mechanisms.

Several additional considerations of the current study should be noted. For example, ELA was measured as a sum of three forms of family-level adversities, some of which may have been present during mothers' pregnancies. Prenatal adversity was not assessed in this study and may have had residual effects on children's iron status at one year (Armony-Sivan et al., 2013; Campbell et al., 2020) (McLimore et al.; Rendina et al., 2018). A significant limitation to the present study is the lack of data on maternal iron status during pregnancy or postpartum, maternal dietary intake of iron throughout pregnancy and lactation, and infant iron stores at birth. Iron deficiency is common among women of childbearing age, and poor maternal iron status has been linked to depression and adversity. It is thus possible that maternal iron status may have contributed to both infant iron status during pregnancy and to infant iron status at 12 months, indirectly through higher levels of maternal depression (Beard et al., 2005; Black et al., 2011; Corwin et al., 2003). As a significant amount of iron is stored before birth via placental transfer in the third trimester (Winzerling & Kling, 2001), disruptions to maternal iron status or placental transfer arising from maternal psychosocial adversity may be partially responsible for the postnatal adversity-iron associations found in this study (Monk et al., 2013). However, suppose iron transfer and iron stores were inadequate during pregnancy. In that case, research suggests that infants would have developed iron deficiency anemia before recruitment into the iron supplementation trial at six months of age (Chaparro, 2008). As infants with iron deficiency anemia at six months were excluded from the iron supplementation trial (Lozoff et al., 2003), the strength of the association might have even been greater if infants with IDA were included.

The current study also did not have information on mothers' alcohol consumption, maternal obesity, or gestational diabetes during pregnancy (Lozoff et al., 2003), which could have impacted infant iron status (Rao & Georgieff, 2002). However, the current study excluded unhealthy pregnancies, growth-restricted or small-for-gestational-age infants, and infants <3kg, who often have rapid catch-up growth. These exclusions limit the confounding of iron status from those conditions. We also do not have information on the introduction of complementary foods or types of foods other than formula and breastmilk fed to infants, limiting our ability to ascertain if differences in iron status arose from differences in other food consumption.

The current study cohort was recruited from low- and middle-class neighborhoods (Doom et al., 2018). Thus, the ability to assess how adversity contributes to iron status in a full range of socioeconomic contexts was not possible. It is also important to remember that eligibility into the preventive trial may have limited the generalizability of study findings. Children with anemia at six months were treated with iron and excluded, as were children with major health problems. Thus, all infants studied here were healthy and nonanemic at six months.

It is also important to note the particular context in Chile at the beginning of the study in 1991. From a nutritional and pediatric practice perspective, feeding practices and government-provided formula have since changed. In the current study, infants were generally well-nourished at enrollment because general undernutrition was nearly eradicated in Chile at the time of the study. As part of a legally-mandated initiative to combat universal undernutrition, health clinics provided unmodified powdered milk as part of the National Complementary Feeding Program (PNAC). The feeding program was available to all children from birth to age five regardless of their territorial location, nationality, or socioeconomic status. Accordingly, the prevalence of iron-deficiency anemia in Chile's population of otherwise healthy, well-nourished infants not receiving routine iron supplementation was conservatively estimated at between 20% to 30% (Brito et al., 2013; Lozoff et al., 2003; Stevens et al., 2013). In addition to the successful public health campaigns for exclusive breastfeeding noted above during the study, the decades after the study saw changes in the government-distributed powdered milk product, "Purita." In 1999, Purita was fortified with iron, zinc, copper, and vitamin C, though caregivers still needed to add sugar and other additives to the milk. A series of cross-sectional studies in Chile using data collected before and after the national introduction of iron-fortified milk found that the introduction of the iron-fortified product was associated with lower anemia and improved iron status in 11 to 18-month-olds (Brito et al., 2013). In 2021, a new infant starter formula was introduced that reduced the need for additives in bottle preparation and more closely matched national and international nutrient recommendations for infant formula (Chile Ministerio de Salud).

Socio-politically, this study occurred just after the return to democracy, after 13 years of military dictatorship in which government-enforced violence reached high levels (National Research Council, 1985). This may have been a particularly salient time for maternal depressive symptoms. During this time, sociopolitical violence experienced by pregnant women was associated with a five-fold increase in pregnancy complications (Zapata et al., 1992), and domestic violence was associated with increased rates of depression in Chilean women (Quelopana, 2012). Analysis of a subset of study mothers (N=215) when children were age five years showed that greater economic hardship and more stressful life events were positively associated with domestic abuse, which was itself associated with higher reports of depressive and posttraumatic stress disorder symptoms in study mothers (Ceballo et al., 2016). Given the widespread sociopolitical violence in Santiago in the years preceding the start of this study, the levels of maternal depressive symptoms reported here may potentially reflect heightened levels of depressive symptoms compared to other historical periods. In addition, studies of depressive symptoms in Chilean women have found that women of lower socioeconomic status are at greater risk of developing depression (Jadresic & Araya, 1995). Thus, the historical context during data collection may limit the

generalizability of the study's findings to other contexts and serve as an example for future studies on ELA and infant iron status to take the sociopolitical context into account when examining associations between ELA and iron status. Nonetheless, the rates of anemia in this sample and mean hemoglobin concentrations are comparable with those in populations in the Latin American region in the early to mid-1990's and more recently in 2011 (Stevens et al., 2013), suggesting that the study's findings may continue to be relevant for more contemporary cohorts.

Future Directions.

Though the current burgeoning literature on the associations between adversity and iron status is intriguing, more work is needed to clarify how these exposures relate to each other and their downstream effects on children's socioemotional and cognitive development. ELA is associated with a host of later psychopathologies and neurobehavioral development that mirror exposure to early iron deficiency. Adversity is not randomly assigned or changed easily in human studies. Still, animal models that study iron and stress exposures with proper control groups could help understand how the HPA-axis influences iron status early in life. Human studies that take advantage of natural experiments (e.g., natural disaster studies) and experiments to either reduce adversity burden or increase iron status could also be used. For instance, if maternal depressive symptoms are a modifiable area of ELA through interventions (e.g., (Rojas et al., 2007)) this may be one way to reduce the ELA burden on children and reduce the risk of child iron deficiency in the first year of life. Future work should also investigate whether ELA influences the response to iron treatment as well as the risk of becoming iron deficient early in life. If physiological changes arising from ELA impact iron prioritization and sequestration, then treating iron deficiency through oral supplementation may be less effective in contexts of ELA. As this study is the first that examines how ELA is associated with iron status in infancy, it lays the groundwork for future work to elucidate why this association exists, and how to intervene to prevent subsequent risk to socioemotional and cognitive development. A better understanding of the synergies of ELA and early nutritional adversities will encourage dual-focused interventions, rather than interventions singularly focused, and could help numerous children around the world reach their developmental potential.

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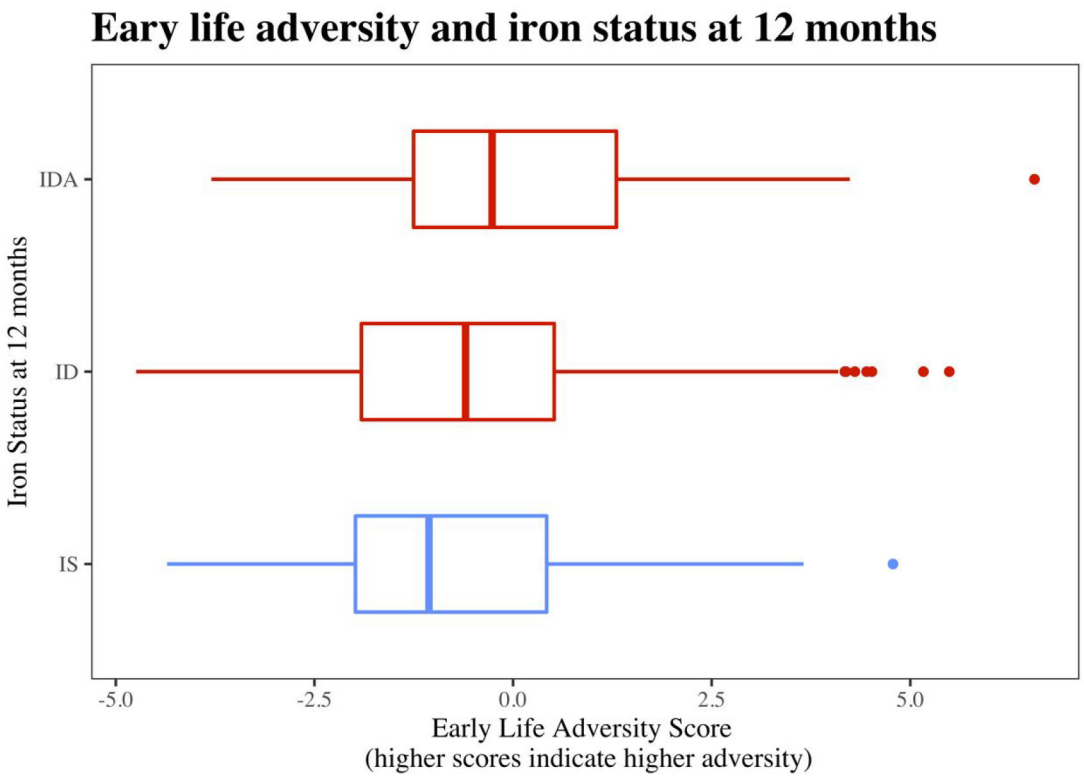

Figure 1.

Note. Early life adversity was significantly associated with iron status at 12 months. IDA = iron deficiency anemia, ID = iron deficiency, IS = iron sufficient

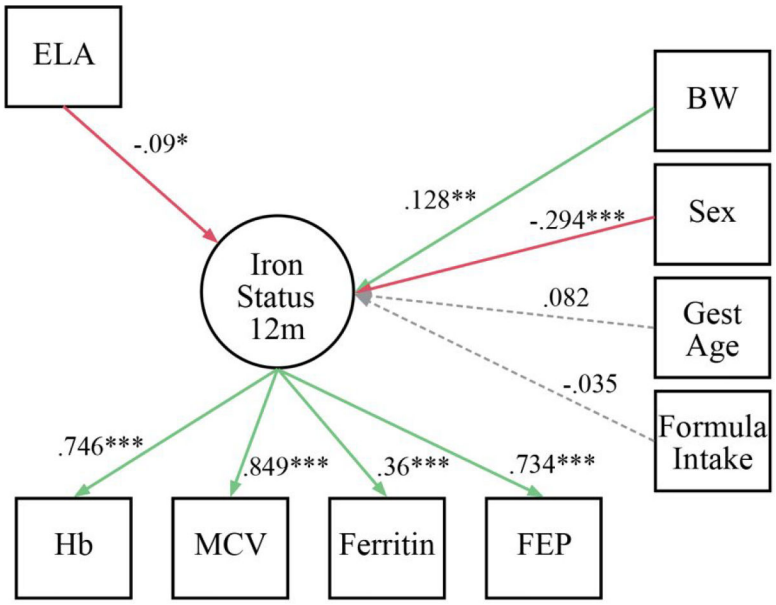

Figure 2.

Higher early life adversity scores were associated with worse continuous iron status at 12 months Note. Model fit indices suggest model fit was acceptable (CFI: .96, RMSEA: .059 (90% CI .041 – .079), SRMR = .032). All coefficients are standardized. Dotted lines indicate non-significant paths. ELA = early life adversity, Hb = hemoglobin, MCV = mean corpuscular volume, FEP = free erythrocyte protoporphyrin (reversed), Gest Age = gestational age in weeks, BW = birthweight (g). Sex coded as 0 = female, 1 = male. Formula intake was average intake in ml/d 6–12 months of no-added iron cow milk. *** = Correlation is significant at the 0.001 level (2-tailed). ** = Correlation is significant at the 0.01 level (2-tailed). * = Correlation is significant at the 0.05 level (2-tailed).

Table 1.

Participant Characteristics

	Mean (SD) or N (%)
	(N=534)
Sex	
Female	243 (45.5%)
Male	291 (54.5%)
Maternal age (years)	26.4 (6.25)
Mother's education (years)	9.51 (2.64)
Gestational age (weeks)	39.5 (1.07)
Birthweight (kilograms)	3.58 (.37)
Weight at 12 months (kilograms)	10.10 (1.10)
Formula/milk intake (ml/day)	404 (249)
Feeding style at 6 months	
Exclusively breastfeeding	170 (31.8%)
Mixed breast and bottle feeding	202 (37.8%)
Exclusive bottle feeding	153 (28.7%)
Iron Status at 12 months	
Iron sufficient	123 (23.0%)
Iron deficient	273 (51.1%)
Iron deficient-anemia	138 (25.8%)
Ferritin (ug/L)	8.74 (8.61)
Hb (g/L)	116 (10.1)
MCV (fl)	71.3 (5.18)
FEP (ug/dL RBC)	115 (51.2)
HOME support for child development	
Reverse-coded z-score	−0.43 (0.92)
Raw score	39.7 (7.6)
Maternal depressive symptoms (CESD)	
Z-score	−0.08 (0.99)
Raw score	14.6 (11.6)
Stressful events	
Z-score	0.03 (0.98)
Raw score	4.8 (2.6)
Early life adversity sum score *	−0.47 (1.90)

Note:

* higher scores reflect greater adversity

Table 2.

Predictors of Iron Deficiency at 12 months

	OR	CI 2.5%	CI 97.5%	p
ELA z-score[a]	1.163	1.054	1.285	.003
Sex[b]	2.670	1.822	3.943	<.001
Gestational age	0.766	NA	NA	<.001
Formula intake (mL/day)	1.000	0.999	1.001	.689
Weight gain from 6 to 12m	1.000	1.000	1.000	.671

Note. Iron deficiency is coded as an ordinal categorical variable, where 0 = iron sufficient, 1 = iron deficient, 2 = iron deficient anemia.

[a]Higher ELA scores reflect greater early-life adversity

[b]Coded as 0 = female, 1 = male.

Table 3.

Correlation matrix of key variables

	Correlations															
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
1	Gestational Age	--															
2	Birthweight (g)	.26**	--														
3	12 month weight (g)	−.04	.34**	--													
4	Formula/milk intake (ml/day)	−.08	−.03	.09	--												
5	Maternal Education (years)	−.01	−.02	.05	.02	--											
6	Maternal Age	.06	.19**	.05	.01	−.17**	--										
7	Maternal Socioeconomic Status (Graffar) [a]	−.05	−.11*	−.08	.04	−.06	−.14**	--									
8	Maternal CESD	−.08	−.09*	−.00	.05	−.10*	−.02	.12**	--								
9	Stressful Events Score	−.01	.01	.03	.05	−.07	−.17**	.09	.37**	--							
10	HOME score (reversed)	−.02	−.06	−.03	.02	−.07	−.33**	.25**	.01	.04	--						
11	ELA z-score	−.05	−.07	0	.06	−.12**	−.26**	.23**	.719**	.73**	.51**	--					
12	12m Hb (g/L)	.06	.10*	−.05	0	.16**	.12**	−.15**	−.01	−.07	−.16**	−.12**	--				
13	12m MCV (fl)	.09*	.11*	−.14**	−.06	.22**	.07	−.17**	−.04	−.06	−.08	−.09*	.63**	--			
14	12m FEP (ug/dL)	−.17**	−.14**	.14**	.09*	−.09	−.05	.13**	.06	.04	.07	.09*	−.57**	−.64**	--		
15	12m Ferritin (ug/L)	.08	.005	−.17**	−.06	.05	−.03	−.06	−.06	−.12**	−.03	−.11*	.17**	.26**	−.24**	--	
16	12m Iron status category [b]	−.15**	−.12**	.09	.02	−.24**	−.03	.13**	.09*	.17**	.14**	.20**	−.69**	−.67**	.62**	−.35**	--

Note. ** = Correlation is significant at the 0.01 level (2-tailed). * = Correlation is significant at the 0.05 level (2-tailed). CESD = Center for Epidemiological Studies Depression scale, HOME = Support for child development in the home, ELA = early life adversity, Hb = hemoglobin, MCV = mean corpuscular volume, FEP = free erythrocyte protoporphyrin.

[a] Higher values represent worse socioeconomic status.

[b] Coded as 0 = iron sufficient, 1 = iron deficient, 2 = iron deficient anemia.

* $p < .05$

** $p < .01$

$^{***}p < .001$

Table 4.

Predicting hematological iron status at 12 months in a structural equation model

	Estimate	95% CI Lower	95% CI Upper	Std. Estimate	Std. Err.	p
	Factor Loadings					
Iron Status at 12 months						
Hb	1.00+			0.746		
MCV	0.585	0.515	0.655	0.849	0.036	< **.001**
Ferritin (log)	0.044	0.033	0.055	0.360	0.006	< **.001**
FEP (log)	0.054	0.047	0.060	0.734	0.003	< **.001**
	Regression Slopes					
Iron Status at 12 months ~						
ELA	−0.357	−0.708	−0.005	−0.090	0.18	**0.047**
Sex [a]	−4.431	−5.804	−3.059	−0.294	0.7	< **.001**
Gestational Age	0.573	−0.068	1.213	0.082	0.33	0.08
Birthweight	0.003	0.001	0.004	0.128	0	**0.006**
mL/day of formula or cow milk	−0.001	−0.004	0.002	−0.035	0	0.439
	Intercepts					
Hb	86.36			8.586	12.57	< **.001**
MCV	54.21			10.484	7.31	< **.001**
Ferritin (log)	0.48			0.522	0.58	0.408
FEP (log)	2.95			5.378	0.68	< **.001**

[a]Coded as 0 = female, 1 = male.

Table 5.

Early life adversity characteristics by Iron Status at 12 months (Mean (SD))

	Iron sufficient (N=123)	Iron deficient (N=273)	Iron-deficient anemic (N=138)	*Total* (N=534)
HOME support for child development				
Reverse-coded z-score	−0.36 (0.89)	−0.61 (0.89)	−0.13 (0.94)	−0.43 (0.92)
Raw score	39.2 (7.33)	41.2 (7.35)	37.2 (7.73)	39.7 (7.6)
Maternal depressive symptoms (CES-D)				
Z-score	−0.22 (0.96)	−0.03 (1.02)	−0.04 (0.96)	−0.08 (0.99)
Raw score	12.9 (11.2)	15.1 (11.9)	15.1 (11.2)	14.6 (11.6)
Stressful events				
Z-score	−0.26 (0.85)	0.10 (0.99)	0.17 (1.03)	0.03 (0.98)
Raw score	4.03 (2.22)	4.97 (2.58)	5.17 (2.70)	4.8 (2.6)
Early life adversity sum z-score *	−0.85 (1.75)	−0.55 (1.93)	0.01 (1.88)	−0.47 (1.90)

Note:

* high scores reflect greater adversity