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Associations among Infant Iron Deficiency, Childhood Emotion and Attention Regulation, and Adolescent Problem Behaviors

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Abstract

This study examined whether iron deficiency in infancy contributes to problem behaviors in adolescence through its influence on poor regulatory abilities in childhood. Chilean infants (N = 1,116) were studied when there was no national program for iron fortification (1991-1996), resulting in high rates of iron deficiency (ID, 28%) and iron-deficient anemia (IDA, 17%). Infants (54% male) were studied at childhood (M_{age} 10 years) and adolescence (M_{age} 14 years). IDA in infancy was related to excessive alcohol use and risky sexual behavior in adolescence through its effect on poor emotion regulation in childhood. Attentional control deficits at age 10 were also related to both infant IDA and heightened risk-taking in adolescence. Findings elucidate how poor childhood regulatory abilities associated with infant IDA compromise adjustment in adolescence.

Keywords

adolescent alcohol use; adolescent risk-taking; anemia; attention deficits; emotion regulation; iron deficiency; sluggish cognitive tempo

Iron-deficiency anemia during infancy is associated with poor neuromotor, behavioral, and socio-emotional development in children (Lozoff, 2011). Through alterations in striatal-frontal dopaminergic systems, iron deficiency and iron-deficiency anemia contribute to

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deficits in attention and executive function, which is responsible for emotion control, planning, and self-regulation (Georgieff, 2011). Understanding the developmental ramifications of poor attentional and emotion control associated with early iron deficiency is important given known associations between inattention and emotion dysregulation and a variety of problem behaviors (Eisenberg et al., 2000; Hill, Degnan, Calkins, & Keane, 2006). The current study examined whether poor iron status in infancy contributes to "downstream" problematic behaviors in adolescence through its influence on poor regulatory abilities in childhood. Specifically, we investigated whether iron deficiency (ID) and iron-deficiency anemia (IDA) in infancy are linked to poor emotion and attention regulation in childhood, and whether these factors in turn, contribute to risk-taking and rule-breaking behaviors in adolescence. We further examined the extent to which risk-taking and rule-breaking tendencies are associated with adolescent alcohol use and sexual risk behaviors. The connection between iron deficiency in infancy and subsequent problem behaviors has widespread significance given that iron deficiency affects 2.4 million U.S. children and 273 million children worldwide (Brotanek, Gosz, Weitzman, & Flores, 2007). In the U.S., Latino and low-income children are particularly vulnerable, as they have relatively higher prevalences of iron deficiency associated with rapid postnatal growth in Latinos (Brotanek et al., 2007) and food insecurity leading to nutritional deficiencies in low-income children (Alaimo, Olson, Frongillo, & Briefel, 2001).

The conceptual model that guides this study is based on several literatures and is shown in Figure 1. To test this model, we used longitudinal data on over one thousand Chilean children who were studied from infancy to adolescence as part of an iron-deficiency anemia preventive trial and follow-up study (Lozoff et al., 2003). The associations outlined in the model are based on three areas of research: (a) the effects of iron deficiency and iron-deficiency anemia on children's poor emotion regulation and inattention; (b) the roles of poor emotion regulation and inattentiveness in adolescent risk-taking and rule-breaking, and; (c) the associations between risk-taking and rule-breaking and adolescent alcohol use and high-risk sexual behavior. These literatures are reviewed briefly below.

Iron-Deficiency Anemia and Poor Emotion and Attention Regulation

Iron deficiency is a micro-nutrient deficiency characterized by depleted iron stores and reduced iron-dependent protein production. Iron deficiency is present when there is insufficient iron to maintain normal physiologic functions (Baker, Greer, & The Committee on Nutrition, 2010). Anemia, the most severe and end-stage form of deficiency, is characterized by depleted iron stores, reduced iron-dependent oxidative enzyme concentration, and reduced hemoglobin concentrations. Iron-deficiency anemia in infants and children presents behaviorally as listlessness, wariness, and fatigue (Lozoff, et al., 1998). Iron deficiency is most prevalent during infancy due to depletion of prenatal iron stores, very rapid growth and limited dietary sources of iron. ID-anemia generally resolves in childhood with the introduction of a wide variety of iron-rich foods.

Many important processes of brain development, such as myelination, dendritogenesis, and synaptogenesis, are highly dependent on iron-containing enzymes and hemoproteins (Georgieff, 2011). Because infancy is a period of rapid brain growth -- during which critical

iron-containing enzymes and hemoproteins are needed for hippocampal and cortical regional development -- iron deficiency during infancy can have serious, long-lasting and what many experts agree are irreversible effects on children's functioning (Beard, 2007; McCann & Ames, 2007). The striatum and hippocampus are two brain regions that undergo considerable maturation during the early postnatal period and are known to be adversely affected by early iron deficiency in animal studies (Beard, 2007). Alterations of processes associated with the striatum and related dopaminergic functioning in humans would be evidenced by a disruption of systems regulating emotion and attention (Georgieff, 2011; Lozoff, 2011). Emotion regulation has been defined in the child development literature as the ability to modulate one's emotional arousal to foster an optimal level of engagement with the environment (Kim-Spoon, Cicchetti, & Rogosch, 2013). Poor emotion regulation is characterized by emotional volatility, mood lability, emotional intensity and reactivity, and disruptive and angry outbursts (Cole, Martin, & Dennis, 2004). Children who have difficulty regulating emotions are apt to act out aggressively and have problems delaying gratification (Eisenberg et al., 2000).

Several studies suggest associations between early-life iron deficiency and children's emotion regulation deficits. For example, lower levels of neonatal hemoglobin and serum iron (and ferritin to a lesser degree) were correlated with higher levels of infant negative emotionality (distress) and reduced soothability (Wachs, Pollitt, Cueto, Jacoby, & Creed-Kanashiro, 2005), an early manifestation of self-regulatory processes. Significant linear relations also have been found between infants' severity of iron deficiency and lower soothability, and marginally, lower ability to regulate emotions (Lozoff et al., 2008). In a study of preschool Chinese children, those who had IDA in infancy showed lower frustration tolerance in a delay of gratification task than children with no history of IDA (Chang et al., 2011). Executive function impairments (i.e., poorer emotional regulation and inhibitory control) have also been found among young adults who experienced chronic and severe iron deficiency in infancy (Lukowski et al., 2010).

The link between early iron deficiency and subsequent attention problems is less firmly established. One study found that children who had severe chronic iron deficiency in infancy were less able to pay attention to a tester's requests and were rated by teachers and parents as having more attention problems (Lozoff, Jimenez, Hagen, Mollen, & Wolf, 2000). Higher levels of inattention were also observed by Fuglestad and colleagues (2013) in iron deficient post-institutionalized children. In addition, young adults who were iron deficient as infants exhibited less attention regulation, or the ability to shift attention (Lukowski et al., 2010). Taken together, these findings suggest that iron deficiency and iron deficiency anemia in infancy are associated with alterations in neurodevelopment that can contribute to deficits in emotion control and, possibly, attention.

Links between Poor Emotion and Attention Regulation and Adolescent Risk-Taking and Rule-Breaking

Deficient capacity to regulate emotion commensurate with situational demands has been documented in many studies to be associated with children's rule-breaking behaviors, such

as lying, cheating and stealing (Eisenberg et al., 2000, 2001). Indeed, theorists have argued that rule-breaking, by its very nature an act of undercontrol, would logically relate to weak or absent control regulatory processes (Bradley, 2000). Using this framework, research by Eisenberg has shown that children who have poor emotion regulation abilities (defined as more negatively emotionally labile and intense) exhibit higher rates of rule-breaking behaviors two years later (Eisenberg et al., 2000). Eisenberg and colleagues (2001) also found that children who engaged in frequent rule-breaking were more prone to anger, low emotion control, and impulsivity as rated by parents, teachers, and observers. Silk and colleagues (2003) also found, using an experience-sampling method, that adolescents' emotional intensity, lability and poor anger regulation were related to rule-breaking behaviors (Silk, Steinberg, & Morris, 2003).

The field of risk-taking has been studied from multiple perspectives, yet a consistent focus within this area includes an emphasis on emotional volatility and poor emotion control as likely predisposing factors to engaging in high-risk behaviors (Boyer, 2006). Risk-taking behaviors are those that involve some potential for danger or harm and emanate from a desire for intensity, excitement and novelty (Zuckerman, 2007). Mager and colleagues (2008) describe risk-taking as occurring under conditions of high arousal, with emotional intensity and volatility increasing the propensity to take risks (Mager, Phillips, & Hosie, 2008). Cooper and colleagues also emphasize the importance of affective control and emotion regulation processes in risk-taking tendencies (Cooper, Agocha, & Sheldon, 2000). Impulsivity, a core component of emotion reactivity, also has been found to relate directly to risk-taking in adolescence (Romer et al., 2011). Additionaally, Steinberg (2008) proposes that the decline in risk-taking between adolescence and adulthood stems from a greater ability to inhibit impulsive behavior and improved emotion regulation.

In addition to emotion regulation, the current study examines inattentiveness as a mediator between infant iron deficiency and adolescent risk-taking and rule-breaking. Inattentiveness is operationalized in the current study as a low ability to focus, concentrate, or attend, or symptoms characteristic of a “sluggish cognitive tempo” (SCT; Carlson & Mann, 2002). It has been suggested that children and adolescents with sluggish cognitive tempo symptoms engage in high-risk, thrill-seeking behaviors to remedy the general low arousal level that accompanies inattentiveness (Diamond, 2005). Supporting this view, inattention (in the absence of hyperactivity and behavioral disinhibition) has been found to correlate with a variety of risky and reckless behaviors (Jerome, Segal, & Habinski, 2006). Given their sluggish and slow responsivity, children with SCT symptoms are less likely to exhibit externalizing behaviors than their hyperactive-inattentive counterparts (Bauermeister, Barkley, Bauermeister, Martinez, & McBurnett, 2012). However, compared to children without hyperactivity or inattentiveness, children with SCT symptoms are more likely to engage in delinquent-like behaviors (Carlson & Mann, 2002).

The Role of Risk-Taking and Rule-Breaking in Adolescent Alcohol Use and Sexual Risk Behaviors

There is a substantial body of literature linking risk-taking tendencies with adolescent alcohol use (Hittner & Swickert, 2006) and unsafe and indiscriminate sexual behavior (Hoyle, Fejfar, & Miller, 2000). Physiologically, risk-taking is believed to result from dopamine brain pathways responsible for attraction to rewarding behaviors and a desire for sensory stimulation (Zuckerman, 2007), which would explain its relation to alcohol use and sexual behavior. Other studies conceptualize risk proneness as an individual's preference for spontaneous decision making and motivation for excitement (Reyna & Farley, 2006). These studies find that adolescents' risk proneness is associated with risky sexual behavior and substance use (Crockett, Raffaelli, & Shen, 2006). Still other studies use decision-making and gambling tasks in risk/reward scenarios to assess risk taking, with findings showing links between risky decision-making and a broad range of safety risk behaviors, including frequency of unprotected sex and alcohol and substance use (Galvan et al., 2007).

Rule-breaking behavior also has been discussed as contributing to adolescent alcohol use and high-risk sexual behavior. Jessor's problem behavior theory outlined a syndrome of problematic behaviors (including early drinking and indiscriminate sexual activity) that is preceded by a greater tolerance for deviance and a disregard for rules and social conventions (Costa, Jessor, Donovan, & Fortenberry, 1995). Much research has confirmed these relations, with rule-breaking tendencies linked with teenage drinking (Chassin, Pitts, & Prost, 2002) and sexual risk behaviors (Schofield et al., 2008).

The Current Study

The current study examined how regulatory deficits associated with iron deficiency (ID) and iron-deficiency anemia (IDA) in infancy might contribute to “downstream” problematic behaviors in adolescence. Specifically, we examined whether ID and IDA in infancy are associated with poor emotion and attention regulation in childhood, and whether these deficits contribute to risk-taking and rule-breaking behaviors in adolescence which, in turn, contribute to alcohol use and high-risk sexual behaviors. As an indicator of alcohol use, we studied excessive and problematic alcohol use in adolescence given that moderate alcohol use within this Chilean cohort of youth might be normative and not necessarily problematic.

Longitudinal, follow-up studies conducted on infants diagnosed as iron-deficient anemic are few and often suffer from small sample sizes and quality control issues (McCann & Ames, 2007). The current sample of Chilean children was studied when there was no national program for iron fortification, resulting in a sample with relatively high iron deficiency and iron-deficiency anemia rates, thereby allowing for a robust test of effects associated with these conditions. To take advantage of these relatively high rates, as well as to better understand how iron deficiency and, separately, iron-deficiency anemia relate to children's regulatory abilities, we analyzed infant iron status using three comparisons: **1)** we compared children who were iron sufficient (IS) in infancy to those who were iron-deficient anemic (IDA); **2)** we compared children who were iron sufficient in infancy to those who were iron-

deficient only (ID-only), and; **3)** we compared children who were ID-only to those who were IDA.

The analysis comparing children who were IS to those who were ID-only is particularly important because ID without anemia is roughly 2.5 times more common than ID with anemia, is asymptomatic and, therefore, often goes undetected (Centers for Disease Control and Prevention, 2002). Very few studies have addressed the effects of ID-only, and of these, findings indicate that ID without anemia has a negative effect on brain development and can contribute to poor developmental outcomes (Akman et al., 2004; Doom et al., 2014). The comparison involving children who were IDA and ID-only in infancy will reveal whether iron-deficiency anemia is associated with deficits above and beyond those associated with iron deficiency. Again, very few studies have examined this issue, with results indicating more severe socio-emotional impairment (increased shyness, lower soothability) associated with ID-anemia compared to ID only (Akman et al., 2004; Lozoff et al., 2008). Given that the key distinguishing characteristic between ID and IDA is lower concentrations of serum hemoglobin, the oxygen-carrying protein found in red blood cells (Zimmermann & Hurrell, 2007), in IDA, understanding whether ID with anemia is associated with more severe impairments on children's regulatory capacities than ID-only would be important to investigate.

In this study's analyses we controlled for several child and family background factors given that iron deficiency is more likely to occur in disadvantaged family circumstances (Alaimo et al., 2001). We also controlled for children's stressful life events during infancy given its known association with children's emotion and attention regulation abilities and with adolescents' risk-taking and problem behaviors. Additionally, we controlled for whether infants were given iron supplementation as part of the preventive trial and whether infants were exclusively breastfed, given that these factors are related to iron deficiency and anemia in young children (Baker et al., 2010). We also tested whether the pathways outlined in our analytic model differ for boys and girls, because males are known to have higher rates of ID and IDA during infancy (Domellof et al., 2002), as well as higher levels of emotional dysregulation (Hill et al., 2006), attention difficulties (Gershon, 2002), and risk-taking tendencies (Byrnes, Miller, & Schafer, 1999). To take into account the possibility that model pathways are influenced by pubertal development, we considered if controlling for age at menarche alters the model pathways for girls. (Adequate data on pubertal timing was not available for boys.) Additionally, given that the variables of rule-breaking, risk-taking, alcohol use, and risky sexual behavior were assessed at adolescence, we tested an alternate model that specifies alcohol use and risky sexual behavior as mediators and rule-breaking and risk-taking as endogenous variables. This test was conducted so as to potentially rule out this competing order of effects and to derive evidence that rule-breaking and risk-taking are best understood as mediators linking children's regulatory deficits and subsequent problem behaviors. Finally, our analytic model included all direct paths between distal variables (e.g., poor emotion control → risky sexual behavior), including the direct effects of infant iron status on all model variables. Evidence of significant direct-distal paths has been suggested by studies linking poor emotion control with excessive alcohol use (Mager et al., 2008), SCT

symptoms with risky sexual behavior (Flory et al., 2006), and poor infant iron status with problem behaviors at adolescence (Corapci, Calatroni, Kaciroti, Jimenez, & Lozoff, 2010).

Method

Participants and Study Design

Participants were 1,116 children (54% male) who have been studied since infancy as part of an iron-deficiency anemia preventive trial and follow-up study in Santiago, Chile (Lozoff et al., 2003). The study originally involved 1,657 infants in a double-blind, randomized controlled trial designed to assess the effects of iron supplementation (described below). Infants were recruited from community clinics surrounding Santiago between 1991 and 1996, a period during which iron deficiency in infancy was widespread and there was no national program for iron fortification. At infancy, children's mothers had an average of a 9^{th}-grade education (only 9 years of schooling was compulsory in Chile at the time of the study), and 85% of fathers were present in the home. All infants who participated were healthy, full-term (birth weight ≥ 3.0 kg), and had no perinatal complications or acute or chronic illnesses. Participants were from low- to middle-income families, for whom most heads of households held stable skilled jobs (e.g., carpenter; 22%), stable semi-skilled jobs (e.g., taxi driver; 37%), or sporadic unskilled jobs (house painter; 29%). Almost all families had running water, sewage, and electricity. Chile is a South American democracy with a highly literate population and a comprehensive health care system where infant health is generally excellent and generalized undernutrition is virtually absent.

The preventive trial was designed to test the preventive effects of supplemental iron on iron-deficiency anemia. Non-anemic 6-month-old infants who were taking ≥ 250 ml of no-iron formula or cow milk were randomized to receive iron-supplemented formula (or iron drops for primarily breast-fed infants) or no iron. The preventive trial occurred when infants were 6- to 12- months of age, lasting 6 months. Assignment involved 1123 infants to the iron-supplemented group, and 534 infants to the no-added iron group. Results showed that iron supplementation was associated with significant reductions in ID and IDA at 12 months, but it did not eradicate such cases completely (Lozoff et al., 2003). Of those studied at 12 months, iron-deficiency anemia was present in 34 children (3.1%) in the iron-supplemented group and 116 children (22.6%) in the no-added-iron group. Iron deficiency (without anemia) was observed in 252 children (23.5%) and 157 children (30.7%) in the iron-supplemented and no-added-iron groups, respectively. Detailed description of the study design and findings related to the preventive trial have been published elsewhere (Lozoff, Castillo, Clark, Smith, & Sturza, 2014).

At 10 years of age, 1,127 of the study children were assessed on various measures of behavioral and social-emotional functioning (from 2001 to 2007; Lozoff et al., 2014). Parents and testers also rated the children's behavior. In adolescence, (M = 14.6 years; range 11.9-17.8 years; 2007 and 2010), 1,116 youth completed assessments of their mental health and aspects of their alcohol use and sexual behavior. These 1,116 youth form the core sample for analysis. At the adolescent follow up, 42% of youth were 11 to 13 years old, 50% were 14 or 15 years old, and 8% of youth were 17 years.

At recruitment, 6% of those eligible to participate refused; 7.3% refused at 10 years (primarily due to family moves); and less than 1% refused at the adolescent follow-up. Children who were or were not assessed at 10 years were similar in infant background characteristics, such as gender, birth weight, breastfeeding, and family characteristics, such as maternal education (Lozoff et al., 2014). Youth who did and did not participate at adolescence were comparable on all child characteristics, family background factors, and study variables with one exception. Youth who participated in adolescence were born somewhat later during the infancy recruitment than those who did not participate. Given this (as well as other reasons, described below), youths' age was included as a covariate on the variables assessed at adolescence.

Procedure

The infant study, the 10-year follow-up, and the adolescent follow-up were approved by the relevant institutional review boards in the U.S. and Chile. Signed informed consent was obtained from parents at all time points; assent was obtained from children at 10 years and at adolescence. At the adolescent follow-up, youth completed a two-hour, interviewer-administered questionnaire in a private room. The questionnaire was administered by a Chilean psychologist who was trained on the administration of standardized questionnaires.

Measures

At all study time points, Spanish versions of the study measures were used, which have good reliability and high equivalence to the English-language measures. Measures administered at the adolescent follow-up were back-translated to verify comparability with the English version and pilot-tested with the study population prior to conducting the study. Table 1 presents descriptive statistics of the sample and study variables.

Infant iron deficiency and iron-deficiency anemia—At 6 months, children underwent a finger stick to determine hemoglobin levels. Infants with hemoglobin values ≤ 103 g/L, had a venipuncture performed to determine anemia status. Anemia at 6 months was defined as a venous hemoglobin concentration ≤ 100 g/L. Iron deficiency at 6 months was defined as two or more iron measures in the deficient range (mean corpuscular volume < 70 fL, erythrocyte protoporphyrin > 100 μg/L red blood cells, and serum ferritin < 12 mg/L) (Baker et al., 2010). All infants diagnosed as iron-deficient anemic at 6 months were treated orally for 1 year and did not take part in the preventive trial; however, they participated in all other aspects of the study and are included in this study's sample.

At 12 months of age, venipuncture blood specimens were drawn on all infants; at 18 months, venipuncture was peformed for roughly half of the sample. Anemia at 12 and 18 months was defined as venous hemoglobin < 110 g/L. Iron deficiency at 12 and 18 months was defined as two of three iron measures in the iron-deficient range (detailed above; Baker et al., 2010). Infants with iron-deficiency anemia at 12 or 18 months of age were treated with therapeutic doses of oral iron and followed up (through venipuncture) for maintenance of improvement. Because testing and treatment of IDA occurred every 6 months, the longest an 18-month old child could have been iron-deficient anemic was typically 6 months. However, a child could have been iron deficient at any of the three time points, or at 6, 12, or 18 months of age.

Since iron status fluctuated across infancy, we categorized infants' iron status as the most severe diagnosis at any of the time points, or as: ever ID, ever IDA, or IS (iron sufficient, or not iron deficient or iron-deficient anemic at any time point during infancy). The various iron groups are mutually exclusive, such that no child was ever coded as both ever ID or ever IDA. The rates of the iron status groups are shown in Table 1. Iron measures were tested again at 10 years and during adolescence. All children within the current sample had good iron status in childhood and adolescence.

10-year poor emotion regulation and sluggish cognitive tempo symptoms— The Spanish-version of the Child Behavior Checklist (CBCL; Achenbach & Ruffle, 2000) was administered to parents when children were 10 years of age. The Spanish-CBCL has good equivalence with the English version and good internal consistency and concurrent validity (Rubio-Stipac, Bird, Canino, & Gould, 1990). Poor emotion regulation has been operationalized in the literature as mood lability, emotional intensity and reactivity, and difficulty regulating affect (Cole et al., 2004). Eleven items assess these characteristics on the CBCL and were used in the current study: mood changes, temper tantrums, is loud, argues, screams, irritable, destroys own things, destroys other's things, disobedient at home, disobedient at school, and impulsive. These behaviors are represented on several existing measures of poor emotion regulation (e.g., the Difficulties in Emotion Regulation Scale; Gratz & Roemer, 2014). The Cronbach alpha of these items within the current sample was . 85, and principal component analysis yielded a 1-factor solution with loadings ≥ .52.

Four CBCL items assess sluggish cognitive tempo symptoms (Achenbach & Ruffle, 2000): daydreams, stares, confused–seems in a fog, and lacks energy-slow moving (Cronbach alpha = .67; principal component loadings = .45 - .80). These items are an often-used measure of SCT in children and adolescents (e.g., Bauermeister et al., 2012) and have demonstrated good internal consistency as well as convergent and discriminant validity with other parent- and self-reported symptoms scales and with DSM-IV diagnoses as determined by clinical interviews (Nakamura, Ebesutani, Bernstein, & Chorpita, 2009). However, the current scoring of SCT symptoms is not intended to indicate a clinical diagnosis of attention deficit disorder as the study did not routinely involve psychiatric evaluations of children. Response options on the CBCL are: "*not true*" (coded as 0), "*somewhat or sometimes true*" (1) and "*very true or often true*" (2). Scores were summed across items to yield a possible score range of 0 to 22 for poor emotion regulation, and 0 to 8 for sluggish cognitive tempo symptoms. High scores indicate poor emotion regulation and persistent sluggish cognitive tempo symptoms.

Adolescent rule-breaking—At the adolescent follow-up, youth completed the self-report youth version of the Child Behavior Checklist (YSR; Achenbach, 1991), which includes a 15-item rule-breaking scale (e.g.," I break rules at home, school or elsewhere," "I lie or cheat," "I steal"; α = .69). Response options were: 0 = "*not true*," 1 = "*somewhat or sometimes true*," and 2 = "*very true or often true*." An item, "I drink alcohol without my parents' approval" was excluded due to its overlap with the endogenous variable of adolescent alcohol use. Principal component analyses showed a 1-factor solution, with factor

loadings ranging from .38 to .61. Scores were added across items to yield a possible score range of 0 to 28, with high scores indicating frequent rule-breaking.

Adolescent risk-taking—The individual risks scale from the Spanish version of the Child Health and Illness Profile-Adolescent Edition (CHIP-AE; Starfield et al., 1993) assessed risk-taking. The Spanish-version of the CHIP-AE has good reliability and construct validity (Rajmil et al., 2003). Seven items ask about the adolescent's engagement in risk behaviors (e.g., "I did something risky or dangerous on a dare," "I willingly rode in a car with someone who I knew would drive dangerously"). Response options asked about the recency of engaging in these types of behaviors (0 = "*I never did this*" to 5 = '*I did this in the past week*"). Because we were interested in youths' predisposition to risky behaviors (rather than the recency of the behavior), all responses were dichotomized into 0 (never did this) or 1 (did this). The scale was then constructed by summing the number of risky behaviors the adolescent had ever engaged in (range 0 to 7; $\alpha = .67$), with high scores indicating a proclivity toward risk-taking.

Excessive and problematic alcohol use—Adolescents completed an extensive alcohol use inventory in which they responded to questions about their alcohol use and problems resulting from their alcohol use. Excessive alcohol use was indexed by three items: "*had five or more drinks at one sitting within last 30 days*," "*got drunk two or more times within last 30 days*," and "*first got drunk at age 14 or younger.*" Each affirmative response was coded as 1 and all items were summed for a range of 0 – 3. Youth also responded to 15 questions about problems resulting from their alcohol use (e.g., "*Your use of alcohol has … hurt your relationship with your friends; hurt your relationship with your parents; hurt your school or job performance; caused physical health problems?*"). Affirmative responses were coded as 1 and all items were summed for a possible range of 0 to 15.

Adolescent sexual risk behaviors—Youth answered several questions about their sexual activity as part of the CHIP-AE (Starfield et al., 1993), including whether they had had heterosexual intercourse, their age at first sex, and number of sexual partners. To avoid a large number of missing values for age at first sex, age 20 was imputed for those who had not yet had sex. (Without imputation, age at first sex ranged from 12.2-17.8, $M = 15.3$ years.) The items used here are a commonly-used measure of risky sexual behaviors that can lead to unhealthy reproductive health outcomes, such as early, unwanted pregnancy and sexually transmitted disease.

Controls

Socioeconomic status—Socioeconomic status (SES) was based on parents' responses to 13 questions on the Graffar instrument (Graffar, 1956) when the participants were infants. This measure asks about the family's housing conditions, material possessions (own a T.V., car, etc.), source of income, and parents' type of occupation, and is an often-used instrument to assess poverty in developing countries. Thirteen categories of living conditions and possessions were coded as absent (1) to plentiful (6), for a possible score range of 13 to 78, with higher scores indicating lower poverty or a higher SES. The average Graffar score for

the current sample was 38, indicating that most children's families were working class (Graffar, 1956).

Family stressors—A modified Social Readjustment Rating Scale (Holmes & Rahe, 1967) assessed family stressors when participants were infants. Mothers were interviewed by research staff and asked to indicate the presence of 30 stressful life events (e.g., illness of a family member, death of a family relative). Stressful events were coded as present (1) or absent (0) and summed, for a possible score range of 0 to 30.

Home environment—The Home Observation for Measurement of the Environment Inventory (HOME Infant-Toddler version; Bradley, Corwyn, & Whiteside-Mansell, 1996) was used to measure the quality of the development-fostering support in the home environment during infancy. The HOME is a well-established measure that is sensitive to variations in family life, including in Latin American countries (Bradley et al., 1996). The infant-toddler version consists of 45 binary-choice items clustered into subscales that assess parents' emotional and verbal responsivity, parental involvement, and opportunities for variety in daily stimulation. The total HOME score is the sum of all items, yielding a possible score range of 0 to 45.

Iron supplementation—As stated above, iron supplementation was associated with infant iron status. Thus, whether iron supplementation was given as part of the preventive trial was included as a covariate; coded as 0 = received no iron supplementation, and 1 = received some form of iron supplementation.

Breastfeeding at 6 months—Beginning at 4 months, breastfeeding status was assessed weekly at home visits by research personnel. In the current analyses, we controlled for breastfeeding as the sole source of milk at 6 months of age (0 = no; 1 = yes).

Age at menarche—At the adolescent follow-up, girls were asked whether they had begun to menstruate and, if so, their age at their first menstrual period (in years and months).

Analytic Strategy

We conducted structural equation modeling using Mplus 6.0 (Muthén & Muthén, 2010) to evaluate our analytic model (Fig. 1). The main predictor, iron status, was dummy coded into 3 categories: IDA, ID and IS. IS was the omitted category because it served as the reference group. Thus, the two exogenous variables in this analysis were: IDA vs IS and ID vs IS. To compare the IDA and ID groups directly, we specified new parameters derived from parameter estimates for the two dummy variables in the full model. The standard errors for these new parameters were produced using the delta method (Muthén, 2011). The model was estimated using latent variables. Excessive-problematic alcohol use was estimated by the two indicators of excessive alcohol use and problematic alcohol use. Risky sexual behavior was estimated by the indicators of: ever had sex, number of sexual partners, and age at first sex (subtracted from 20 so that higher ages connote a greater risk behavior). Sluggish cognitive tempo symptoms were estimated using the four items on the CBCL that assess SCT symptoms. Risk-taking was first indicated by the seven items from the CHIP

risk-taking scale, but two items had low factor loadings (< .25) and were subsequently dropped ("raced on a bike, skateboard, or boat for excitement" and "rode a motorbike, motorcycle, minibike or ATV"). The remaining five items were used as indictors of risk-taking. Latent variables for emotion regulation and rule-breaking were estimated using the parceling procedure of randomly selected items outlined by Bandalos and Finney (2001). Emotion regulation was indicated by two parcels of five and six items, and rule-breaking was indicated by two parcels of seven items each. The measurement model using these latent varibles was tested using the total sample and by gender to assess invariance across gender. Model fit was examined by reviewing indices of good model fit (Kline, 2011), such as a nonsignificant chi-square, the comparative fit index (CFI; > .93), the root mean square error of approximation (RMSEA; < .06), and the standardized root mean square residual (SRMR; < .08). Missing data (0%-8%; see Table 1) were treated within Mplus with the full information maximum likelihood method (FIML), which fits the model being tested directly onto the nonmissing data for each participant. The maximum likelihood estimator (MLR) was used. Mediation was tested using the INDIRECT command within MPlus, which estimates indirect effects with delta method standard errors (Muthén, 2011). The within-time variables were correlated *a priori* for the variables measured during childhood, and rule-breaking and risk-taking were allowed to correlate, as were alcohol use and risky sexual behavior in adolescence. To test whether the strength of relationships within the model differed by child gender, we conducted an omnibus test using multiple-group analyses, which compares a baseline model where all paths are constrained to be equal across gender to a model where all paths are allowed to vary freely. A chi-square difference test, adjusted using a correction factor to account for nonnormality, was then used to assess the equivalence of the fully constrained model to the fully unconstrained model. If significant, it can be concluded that one or more parameters are significantly different for boys and girls.

Prior to conducting this study's main analyses, we computed the main and interaction effects of iron status and iron supplementation on the model's nine (observed) endogenous variables. This was done to rule out the possibility that the effects of iron status are moderated by iron supplementation. There were no statistically significant interactions for any of the endogenous variables. Thus, given that the effects of iron status do not vary across iron supplementation group, we model only the main effects of IDA and ID. We keep iron supplementation in the model as a covariate to control for confounding, as it relates to both our predictors and outcome variables.

Inclusion of covariates—Based on attrition analyses (described above), adolescent age was included as a covariate on all variables assessed at adolescence. Based on correlational results (described below; Table 2), control variables that significantly correlated with a model variable were included as covariates on that variable. For example, child sex, family stressors, mothers' education, and child age were included as covariates on poor emotion regulation. Child sex, family SES, mothers' educational level, whether iron supplementation was given, and whether primarily breastfeeding at 6 months were included as covariates on infant ID status so that comparable controls were included on both IDA and ID. Whether fathers were present in the home was analyzed as a potential covariate but it did not correlate with any of the model variables and, thus, was not considered further. In addition, age at

menarche was included as a covariate on high risk sexual behavior in a model including girls only.

Results

Formation of Latent Variables and Correlations

We constructed latent variables within MPlus for the mediating and endogenous variables. The factor loadings for all latent variables were significant and satisfactory (≥ .41, $p < .001$) and the measurement model had good fit (χ^2 [89] = 150.86, CFI = 0.978, RMSEA = .025, SRMR = .031). When tested separately by gender in a model where all paths were allowed to vary freely, the pattern of loadings was nearly identical for males and females. Table 2 shows the intercorrelations among infant iron status and the model's latent variables, as well as the correlations between the model variables and the child and family characteristics that serve as covariates. The intercorrelations above the diagonal for variables 1- 8 (top of Table 2) are partial correlations controlling for the relevant covariates; the correlations below the diagonal are unadjusted.

Modeling Results

The fit statistics and path coefficients for the model are shown in Figure 2. Model fit was good and modification indices indicated that no additional covariates would improve model fit. Results indicated that, compared to IS, IDA in infancy was related to poorer emotion regulation and more frequent sluggish cognitive tempo symptoms at age 10. Poorer emotion regulation in childhood was related to more frequent rule-breaking in adolescence, and rule-breaking tendencies were strongly related to more excessive-problematic alcohol use and risky sexual behavior in adolescence. More frequent SCT symptoms in childhood were related to more risk-taking in adolescence, and more risk-taking was related to more excessive-problematic alcohol use and risky sexual behavior. When compared to IS, IDA was also directly and positively related to risky sexual behavior. There was no relation between iron deficiency only (without anemia) in infancy (compared to IS) and children's emotion regulation or SCT symptoms ($\beta = .03$ and $\beta = .06$, respectively).

The path coefficient comparing IDA with ID-only to emotion regulation approached significance ($\beta = .19$, $p < .06$), indicating that infants who had iron-deficient anemia had slightly poorer emotion regulation in childhood than infants who had iron-deficiency only. In addition, when compared to an ID status, IDA in infancy was directly related to more excessive-problematic alcohol use in adolescence. The path coefficient comparing IDA with ID-only to SCT symptoms was not significant ($\beta = .05$, *ns*).

The amount of variance explained in the endogenous variables is shown in Figure 2. The amount of variance explained net of control variables was: emotion control, $R^2 = .02$; SCT symptoms, $R^2 = .02$; rule-breaking, $R^2 = .07$; risk-taking, $R^2 = .05$; alcohol use, $R^2 = .33$, and; risky sexual behavior, $R^2 = .10$.

Tests of indirect effects—The significant indirect effects are listed in Table 3. All significant indirect effects derived from an IDA status in infancy when compared to an IS status. Results indicated that IDA was related to both adolescent alcohol use and risky sexual

behavior through poor emotion regulation at age 10 and rule-breaking tendencies in adolescence. The three 3-variable pathways that comprise this sequence were also significant. Additionally, the pathway linking childhood SCT symptoms to adolescent alcohol use as mediated by risk-taking tendencies approached significance.

Gender differences in model paths—The results of multiple group analysis testing whether the model paths differed for males and females was not significant (χ^2 [44] = 59.34, *ns*).

Including age at menarche as a control—The analytic model was re-computed for girls using age at menarche as an additional covariate on risky sexual behavior. All covariates controlled in previous models were also included. Model fit was good (χ^2 [146] = 269.96, CFI = 0.946, RMSEA = .040, SRMR = .039, N = 511). Younger age at menarche was significantly related to girls' riskier sexual behaviors (β = -.11, p < .05), however including age at menarche as a covariate did not change any of the significant associations to risky sexual behavior.

Test of an Alternate Ordering of Effects

To potentially strengthen our interpretation about the ordering of effects within the hypothesized model, we tested an alternate model wherein excessive-problematic alcohol use and risky sexual behavior served as mediators and rule-breaking and risk taking were the endogenous variables. All covariates controlled in the original model were included. Results showed that model fit was good (χ^2 [142] = 401.78, CFI = 0.946, RMSEA = .040, SRMR = .031). Path coefficients stemming from the three iron status comparisons were identical to those in the original model (as shown in Fig. 2). However, there were no significant associations from poor emotion control to either alcohol use or risky sexual behavior, or from SCT symptoms to alcohol use or risky sexual behavior. Poor emotion control, though, was associated with rule-breaking (β = .25, p < .001). Additionally, alcohol use was significantly related to both rule-breaking and risk-taking (β = .50 and β = .45, respectively, p < .001), and risky sex was related to rule-breaking (β = .08, p < .05), but risky sex was not related to risk-taking (β = .05, *ns*). One significant indirect effect was found, with poor emotion control in childhood mediating the relation between infant IDA and adolescent rule-breaking. Given that this particular indirect effect was found and that the alternate model did not support alcohol use and risky sexual behavior as mediators, we can conclude that the hypothesized model provides a more accurate representation about the ordering of associations among the study variables.

Discussion

The findings of this study provide an understanding of the mechanisms through which iron deficiency and iron-deficiency anemia in infancy affect “downstream” problem behaviors in adolescence. The results suggest four general findings. First, results showed that, compared to an iron-sufficient status, iron-deficiency anemia in infancy was related to excessive-problematic alcohol use and high-risk sexual behavior in adolescence through poorer emotion regulation in childhood and more frequent rule-breaking in adolescence. IDA in

infancy was also directly related to risky sexual behavior in adolescence. These findings are important because iron-deficiency anemia in infancy has been linked to poorer regulatory abilities in children (Lozoff, 2011), but little is known about how these early deficits might compromise later development. This study is one of the first to outline a series of associations by which early iron-deficiency anemia affects later development by way of earlier deficits. The role of poor emotion regulation in subsequent rule-breaking behavior is consistent with findings observed by others (Eisenberg et al., 2000, 2001), and was expected given that the rule-breaking behaviors studied here (lying, stealing) reflect deficits in control. We propose that the neurological and executive function impairments related to early iron-deficiency anemia, (i.e., altered dopamine-dependent pathways), might set the stage for deficits in emotion control (Lewis & Stieben, 2004), which can lead to greater engagement in rule-breaking and consequent problem behaviors. This has important ramifications given that the behaviors studied here, that is, becoming heavily intoxicated and having unprotected sex, can have serious consequences.

Second, findings indicated that, when compared to children who were iron sufficient in infancy, those who were iron-deficient anemic had more frequent sluggish cognitive tempo symptoms at age 10, or higher levels of mental fogginess and daydreaming. This substantiates results of earlier studies that found attention problems among children and young adults who were iron deficient as infants (Akman et al., 2004; Lukowski et al., 2010). The relation between iron deficiency anemia and inattentiveness found here appears to fit with an effect of iron-deficiency anemia on altered prefrontal-striatal and hippocampal systems functioning, which can contribute to an inability to sustain attention (Lozoff, 2011). Both iron deficiency and attention deficient disorder-inattentive type have been linked to alterations in the neural circuitry in the frontal-parietal region (Diamond, 2005; Georgieff, 2011), indicating a possible structural link for this relation. Indeed, the behavioral characteristics of sluggish cognitive tempo are similar morphologically to those used to describe iron-deficiency anemia, or “slow moving,” “low energy,” and “less physically active” (Lozoff et al., 1998). Sluggish cognitive tempo has emerged relatively recently as a distinct attention deficit subtype, and there is limited understanding of possible neurobiological markers associated with this unique symptom pattern (Bauermeister et al., 2012). Further research on the possible structural and functional links between iron-deficiency anemia and sluggish cognitive tempo symptoms might prove fruitful.

A third finding of this study is that iron-deficiency anemia (IDA) was associated with slightly greater deficits in emotion control and more excessive and problematic alcohol use than iron-deficiency without anemia (ID only). Although some studies have found linear trends of functional impairment associated with increasing levels of iron deficiency (Lozoff et al., 2008), significant differences in cognitive or self-regulatory abilities between children having IDA or ID-only have not been found (Doom et al., 2014). We speculate that the slightly higher levels of childhood emotion dysregulation and problematic adolescent behaviors associated with IDA (relative to ID only) is a function of more severe alterations in the striatal-frontal dopaminergic system connections which are responsible for, among other functions, impulse control. Dopamine plays a major role not only in systems of behavioral activation and inhibition, but also in positive affect. Thus, intense and volatile negativity would be consistent with altered dopaminergic neurotransmission (Lozoff, 2011).

Rarely have the long-term effects of iron deficiency-only been compared to those of iron-deficiency anemia; thus, replication is needed to firmly establish these associations.

Finally, results revealed an indirect effect approaching significance from sluggish cognitive tempo symptoms in childhood to adolescent alcohol use as mediated by more frequent risk-taking. This finding supports assertions by Diamond (2005) that engaging in thrill-seeking, "high octane" behaviors serve to remedy the low arousal level that accompanies inattentiveness. Other explanatory models of risk-taking that emphasize deliberate decision-making of risks versus benefits associated with certain behaviors would also explain the inattentive child's vulnerability to risk-taking, given the primary symptoms of difficulty focusing and mental confusion (Reyna & Farley, 2006). Children with sluggish cognitive tempo symptoms have a deficit in speed of information processes, generally, and in focused or selective attention, specifically (Bauermeister et al., 2012). Adults with these deficits have been found to engage in risky decision making (Matthies, Phillipsen, & Svaldi, 2012), thus this explanation might also hold for children. Other variables possibly mediating the link between SCT symptoms and later problem behaviors are poor learning and a tendency to associate with deviant peers. We encourage further research that addresses these variables, as well as heightened risk-taking, in the association between early inattentiveness and subsequent problem behaviors.

Limitations and Strengths

Certain study limitations are important for interpreting the findings. For instance, ID and ID-anemia are known to be disproportionately present within disadvantaged circumstances (Alaimo et al., 2001). Although we statistically controlled for many home, family, and child and adolescent characteristics in attempts to adjust for these factors, unmeasured features in the environments of formerly iron-deficient children could account for their poorer outcomes. In addition, the current sample was low- to middle-income. Thus, we caution that the results found here may not be generalizable to children from either affluent or very impoverished backgrounds. As stated earlier, because testing and treatment of IDA occurred at 6-, 12-, and 18-months of age, the longest a child could have been iron-deficient anemic was typically 6 months. However, a child could have been iron deficient at any time between 6 and 18 months. There was fluctuation across the various time points with regard to iron status. Thus, although the current operationalization of iron status as *ever* ID or IDA in infancy captures well the fluid clinical picture of children up to 18 months, it precludes an understanding of effects related to the timing and duration of iron deficiency. Animal studies where the timing and dose of iron intake can be controlled can best address timing and duration effects and are discussed elsewhere (Beard, 2007; McCann & Ames, 2007).

ID and ID-anemia are also known to adversely affect children's socio-emotional development, including their social interactions with others (Lozoff et al., 2000, 2008). Indirect effects through these mechanisms could also be at work in producing problematic outcomes at adolescence and should be considered in future work. Although we were able to control for pubertal status in tests of the model for girls, an adequate pubertal development measure was not available within the current study for boys. Given that the types of sexual

risk behaviors studied here are known to relate to youths' pubertal development, it would seem important to control for boys' pubertal development in future research of this kind.

Important strengths of the current study are its use of multiple-wave longitudinal data, the specificity with which iron deficiency and iron-deficiency anemia were assessed, the use of tester-, parent-, and youth-reports in the assessment of study variables, the large sample, good follow-up rates, and the inclusion of multiple covariates in the modeling analyses. It is also noteworthy that all children had good iron status levels in childhood and adolescence, allowing us to discount chronic iron deficiency and anemia as possibly contributing to adolescent outcomes. In addition, all study children were exceptionally healthy as newborns. Thus, there were no neonatal health problems confounding infants' health status. Finally, tests of an alternate ordering of effects lacked key mediational pathways, strengthening our interpretation that poor emotion control and SCT symptoms do not lead directly to alcohol use or risky sexual behavior in adolescence but, rather, contribute to alcohol use and risky sex by their association with rule-breaking and risk-taking tendencies.

Conclusion

Findings indicate problematic outcomes of infant iron-deficiency anemia that emerge at adolescence. Youth with a known history of IDA would benefit from monitoring for emotional volatility and inattention, both during childhood and at adolescence, as they become more independent and have the potential to engage in serious risk behaviors. The persistence of problem behaviors derived from infant iron-deficiency anemia highlights the need for primary prevention to reduce its prevalence, and secondary prevention to lessen the long-term effects of this pervasive nutrient disorder.

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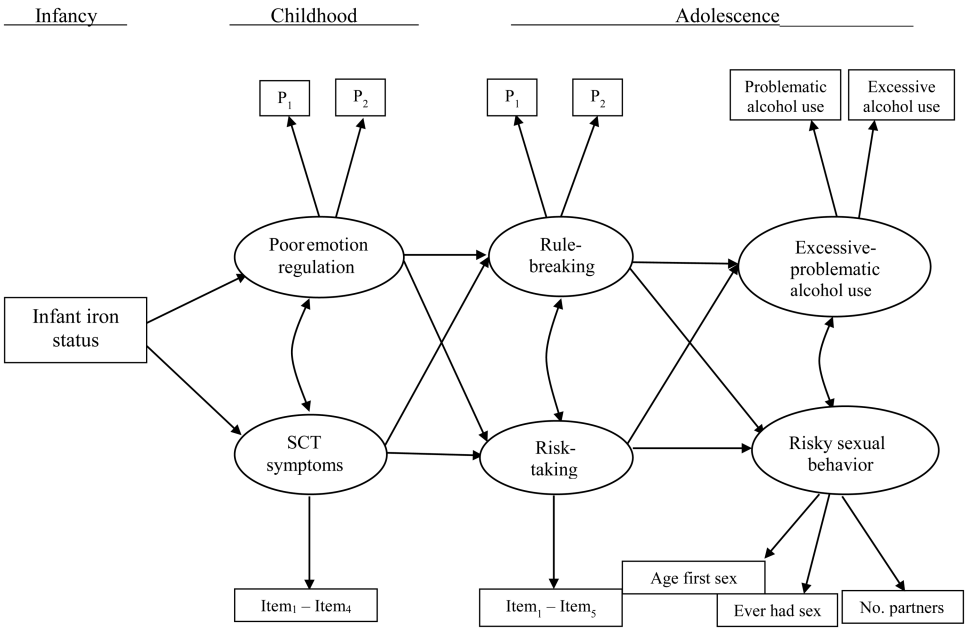

Figure 1.

Conceptual model of the long-term effects of infant iron status on excessive-problematic alcohol use and risky sexual behavior in adolescence. Direct effects between distal variables (e.g., poor emotion control → risky sexual behavior) were tested but are not shown for ease of presentation. SCT = sluggish cognitive tempo symptoms. P_1 = parcel 1, etc.

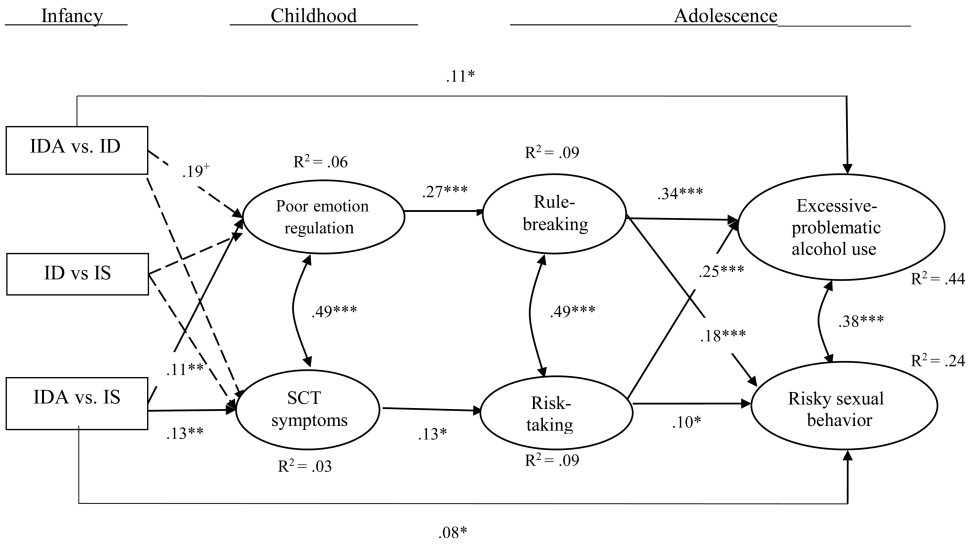

Figure 2.

IDA = iron-deficient anemic. ID = iron deficient (only). IS = iron sufficient. Standardized coefficients are shown. SCT = sluggish cognitive tempo symptoms. Dashed lines indicate a nonsignificant path. All direct effects between distal variables (e.g., poor emotion control → risky sexual behavior) were tested; only significant direct distal paths are shown. The model had good fit: χ^2 [142] = 298.43, CFI = 0.953, RMSEA = .031, SRMR = .030, N = 1116. +p < .06. *p < .05. **p < .01. ***p < .001.

Table 1

Descriptive Statistics of Sample and Study Measures

	N	Min	Max	Mean or %	Standard deviation
Infant assessment					
Iron sufficient	621	--	--	55.6%	--
Iron deficient without anemia (ID)[a]	310	0	1	27.8%	--
Iron-deficient with anemia (IDA)[a]	185	0	1	16.6%	--
Child sex (1=male)	1116	0	1	54.0%	--
Family socioeconomic status[b]	1116	13	78	38.34	8.14
Family stressors	1116	0	30	4.67	2.67
HOME score	1116	0	45	30.30	4.75
Mothers' educational level	1116	0	17	9.45	2.71
Father present	1116	0	1	85.0%	--
Iron supplementation	1024	0	1	65.01%	--
Breastfeeding at 6 months	1116	0	1	60.0%	--
10-year assessment					
Child age	1116	10	11	10.0	0.03
Mothers' educational level	1111	1	19	9.74	2.78
Poor emotion regulation	1116	0	22	7.48	4.37
Sluggish cognitive tempo symp	1116	0	8	1.93	1.63
Adolescent assessment					
Adolescent age	1116	11.9	17.8	14.61	1.54
Girls' age at menarche[d]	424	8.1	15.1	12.0	1.14
Rule-breaking	1046	0	28	4.86	3.13
Risk-taking	1057	0	7	1.64	1.41
Excessive alcohol use	1112	0	3	0.31	0.76
Problematic alcohol use	1112	0	15	1.07	1.93
Ever had sex	1112	0	1	0.17	0.38
Age at first sex[e]	1112	12	20	18.10	2.17
Number of sex partners	1112	0	6	0.30	0.75

Note. See Measures for description of coding.

[a] Measured as ever present at 6, 12, or 18 months.

[b] Higher scores reflect higher socioeconomic status.

[c] Iron supplementation as part of the preventive trial; coded as 0 = no, 1 = yes.

[d] Eighty-nine girls had not yet reached menarche at the adolescent assessment.

[e] To avoid a large number of missing values, age 20 was imputed for those who had not yet had sex.

Table 2

Intercorrelations among Model Variables and Correlations between Model Variables and Controls

Model variables	1	2	3	4	5	6	7	8
1. Iron deficient (ID) only[a]	–	–	.00	.02	-.01	-.06	-.09*	-.01
2. Iron-deficient anemic (IDA)[b]	–	–	.10**	.10**	-.01	.09*	.06	.09*
3. Poor emotion regulation - 10 yrs	.04	.14***	–	.49***	.31***	.28***	.09*	.05
4. Sluggish cognitive tempo sym - 10 yrs	.06	.11**	.49***	–	.19***	.30***	.12**	.08
5. Rule-breaking - adolescence	-.01	-.01	.35***	.21***	–	.49***	.48***	.22***
6. Risk-taking - adolescence	-.05	.02	.30***	.30***	.49***	–	.49***	.31***
7. Excessive-problematic alcohol use – adolescence	-.08*	-.02	.10*	.12**	.50***	.51***	–	.38***
8. Risky sexual behavior - adolescence	.01	.03	.06	.09*	.27***	.37***	.48***	–
Controls								
Child sex (1=male)	.05	.17***	.11**	.04	.13**	.13**	.08*	.02
Family socioeconomic - infancy	-.04	-.11**	.01	.01	.04	.06	.03	.01
Family stressors – 1 yr	.02	.04	.11**	.08*	.08	.03	.07	.04
HOME environment – 1yr	-.04	-.03	-.05	-.06	-.08*	-.05	-.07	-.05
Mothers' education - 1 yr	-.02	-.09*	-.13**	-.05	-.04	-.03	-.02	.02
Iron supplementation[c]	-.15***	-.40***	-.00	.06	.07	.13**	.22***	.20***
Child age – 10 yrs	-.02	-.02	.08*	-.01	-.01	.04	.00	.04
Age at adolescent follow-up	-.02	-.13**	-.01	-.01	.07	.23***	.40***	.40***

Note. The intercorrelations above the diagonal for variables 1-8 control for the relevant control variables; the coefficients below the diagonal include no controls. Variables 3 – 8 are latent variables. Father present in the household at 1 year, whether breastfeeding was the sole source of milk at 6 months, and girls' age at menarche did not correlate significantly with any of the model variables and are not shown.

[a] 0 = iron sufficient, 1 = iron deficient without anemia at 6, 12 or 18 months; excludes those diagnosed as ID-anemic. *N*s ranged from 885-931.

[b] 0 = iron sufficient, 1 = iron-deficient with anemia at 6, 12, or 18 months; excludes those who were iron deficient only. *N*s ranged from 763-806.

[c] 0 = no iron supplementation in infancy, 1 = some form of iron supplementation as part of the preventive trial.

* $p < .05$.

** $p < .01$.

***$p < .001$.

Table 3
Summary of Significant Indirect Effects

	B	(SE)
IDA → poor emo reg → rule-breaking → alcohol use	.010*	(.004)
IDA → poor emo reg → rule-breaking→ risky sex	.005*	(.002)
IDA → poor emo reg → rule-breaking	.029*	(.012)
Poor emo reg → rule-breaking → alcohol use	.091**	(.029)
Poor emo reg → rule-breaking → risky sex	.049**	(.016)
SCT → risk-taking → alcohol use	.033+	(.020)

Note. IDA coded as 1 = iron-deficient anemic, 0 = iron sufficient. Poor emo reg = poor emotion regulation. SCT = sluggish cognitive tempo symptoms.

+ $p < .10$.

* $p < .05$.

** $p < .01$.