Iron, Lead, and Children's Behavior and Cognition

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Annu. Rev. Nutr. 2010. 30:123–48

First published online as a Review in Advance on April 30, 2010

The *Annual Review of Nutrition* is online at nutr.annualreviews.org

This article's doi: 10.1146/annurev.nutr.012809.104758

0199-9885/10/0821-0123$20.00

Key Words

lead, iron, child, cognition, behavior, interactions

Abstract

Iron deficiency (ID) is the most common micronutrient deficiency in the world, with consequences of ID and ID anemia (IDA) in young children including behavioral and cognitive deficits. In turn, lead exposure is one of the most common environmental toxicants affecting children. Elevated blood lead levels (BLLs) in young children are also associated with behavioral and cognitive deficits. The metabolic and physiological connections between iron and lead, including a common route of entry into the body and similar neural targets, suggest a considerable overlap in their effects on functional outcomes. Very few studies have examined the existence of increased susceptibility to lead neurotoxicity in children with ID, but there is evidence that ID and BLL are independently associated with cognition and behavior. Children's susceptibility to both ID and elevated BLLs will likely depend on the timing and severity of both exposures, something that should be investigated systematically.

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INTRODUCTION

The idea that nutritional and heavy metals may interact in some way, either at the point of absorption or at the point of action on tissues and organs, is not new. Ruff & Bijur (105) proposed an elegant model for how nutritional deficiencies and lead exposure may interact to produce behavioral deficits. Iron and lead in particular have been studied together because both are divalent metals absorbed by the same intestinal mechanism, both lead exposure and iron deficiency occur disproportionately in disadvantaged populations, and both result in potentially irreversible cognitive and behavioral deficits in children. In addition, iron deficiency and elevated blood lead levels often coincide in children with periods of intensive brain development, which act like windows of heightened vulnerability to environmental insults (95). Studies specifically examining the interactive effects of iron deficiency and lead exposure on cognition are limited, leaving open the question of whether iron-deficient individuals, particularly children, are more susceptible to the neurotoxic effects of lead. This review summarizes and discusses the literature connecting iron and lead to cognition and behavior, evaluates the strength of the conclusions that can be reached based on existing studies, and proposes future research directions. In discussing human studies, the focus is mainly on pediatric literature because children are more likely to develop iron deficiency and suffer disproportionately from lead exposure. The prenatal period is also discussed as a time of increased vulnerability to iron deficiency, lead toxicity, and lead-iron interactions.

CO-OCCURRENCE OF IRON DEFICIENCY AND LEAD EXPOSURE: THE EXTENT OF THE PROBLEM

Iron deficiency (ID) is the most common micronutrient deficiency in the world. An estimated 24.8% of the world's population, or 1.62 billion people, suffer from anemia, with 25.7% (1.1 billion) and 42.8% of (367 million) of the affected persons living in medium- and low-income countries, respectively (77). A large proportion of that anemia is due to ID, which in developing countries is ~2.5 times more prevalent than anemia (72). This suggests that in the developing world alone, 1.5 billion people have ID, in particular women of reproductive age and children. But ID is present in industrialized countries as well (19).

Children are also vulnerable to the effects of lead exposure. Although no global

prevalence data exist on environmental lead exposure, individual country reports [for example, (85)] and recent commentaries (97, 123) indicate that it is a common problem, particularly in low- to middle-income countries. There, mining, smelting, battery recycling (123), and electronic waste (138) are important sources of lead. Lead paint and dust are the major determinants of elevated blood lead levels (BLLs) in industrialized countries (109).

In addition to the geographic overlap between ID and lead exposure, several authors have reported on the associations between low iron intake or status and elevated BLLs in children (for review, see 61). Additional recent evidence (50, 81, 86, 92, 94, 99) indicates that anemia or ID is related to higher BLLs. Polymorphisms in the hemochromatosis gene (*HFE*), which are related to increased iron absorption, have also been associated with higher BLLs in young children (46). One study in particular suggests that ID may predispose children to elevated BLLs. Wright et al. (135) examined BLLs in iron-deficient and -replete children at two consecutive lead screening visits and found that children who were ID at first visit were four times more likely to have BLL $\geq$10 μg/dl at second visit than were iron-replete children. It is also noteworthy that higher serum ferritin (SF) concentrations were related to higher urinary lead concentrations in children receiving chelation therapy (75). Thus, whereas poor iron status may result in higher lead absorption, better iron status may promote lead excretion. Further studies should examine the influence of iron status and intake on the body's ability to eliminate lead.

INTESTINAL ABSORPTION OF IRON AND LEAD: COMMON PATHWAYS

One reason children are so vulnerable to lead exposure is that they absorb and retain proportionately more lead than adults. For example, the mean lead absorption in young infants was determined to be ~26% but could reach over 40% at higher levels of dietary lead intake (139). In turn, up to 32% of the absorbed lead could be retained by infants (139). Lead has no biological function in the human body. Therefore, it is unlikely that a specific transporter exists for its absorption. The apical divalent metal transporter-1 (DMT1) is one of the mechanisms thought to participate in the absorption of lead in the small intestine. The DMT1 is also the principal iron transporter, and its expression is increased in the state of iron deficiency and decreased once body iron stores are normalized (34). It is this up-regulation in deficiency that may be responsible for higher lead uptake by intestinal cells (9) and may explain higher lead levels in individuals with ID. In vitro studies show that the DMT1 transports lead (2, 3) but that iron can inhibit this transport (3), possibly because the DMT1 has higher affinity for iron (36). In contrast, lead does not appear to inhibit iron absorption (2). However, some authors question the contribution of the DMT1 to lead toxicity (36). In one study, knocking out the DMT1 in Caco-2 cells did not substantially alter lead uptake, suggesting that other mechanisms, possibly a calcium transporter, may also be involved in intestinal lead absorption (2, 10). On the basolateral side, calcium rather than iron transporters may be lead's preferred exit strategy out of the absorptive cell and into circulation (9).

LEAD IS THOUGHT TO CAUSE ANEMIA

In circulation, some lead is found in plasma (115), but most is associated with red blood cells, bound to cell membrane and proteins (119) or plasma proteins. High lead levels are associated with anemia. At least in adults this anemia may be unaccompanied by ID, suggesting that high lead exposure could cause anemia (66). The etiology of lead-induced anemia is unclear but may be multifactorial. Lead disrupts heme synthesis in the bone marrow. The second step in this process is the condensation of δ-aminolevulinic acid to porphobilinogen by the enzyme δ-aminolevulinic acid dehydratase (ALAD). Lead reversibly inhibits ALAD function, causing δ-aminolevulinic acid to accumulate and be excreted in urine (122). Lower heme production may also result. Lead acts

on additional enzymes in the heme-synthesis pathway: coproporphyrinogen oxidase and ferrochelatase (71). Ferrochelatase inserts iron into the protoporphyrin ring, thus completing the production of heme. As a consequence of inhibiting ferrochelatase, elevated BLLs are associated with increased blood zinc protoporphyrin (ZPP) or free erythrocyte protoporphyrin (FEP) (23, 136). In children with ID, this increase occurred at lower BLLs (17, 74), suggesting that ID may modify the impact of lead toxicity on heme synthesis (90). However, it is difficult to separate the effects of ID and BLL on FEP/ZPP. The observed elevation could be due to ID alone, especially when BLLs are low.

In evaluating the evidence on the relationship between lead and anemia, it is important to consider that most studies on the inhibition of heme synthesis were conducted in adults with occupational exposures that produce BLLs higher than those expected in the general pediatric population. In addition, it appears unlikely that reduced heme synthesis is alone responsible for the lower hemoglobin (Hb) levels observed in lead-exposed individuals (32). Lead has been shown to interfere with transferrin expression (4), which could reduce the supply of iron to tissues (however, there is no evidence of elevated serum transferrin receptor, sTfR, levels). Lead was also associated with reductions in erythropoietin (EPO) levels in adults (43, 108) and children (65) and an impaired EPO response to anemia in adult men (88). In a study of nonanemic children, BLL was positively associated with EPO at younger ages, interpreted as an increased EPO production to maintain a normal Hb level and a sign of red blood cell destruction (32, 42). Finally, lead reduces red blood cell life span (71). All these effects may potentially lead to lower red blood cell regeneration (40).

IRON SUPPLEMENTATION TO LOWER BLOOD LEAD LEVELS

Although iron status is associated with BLL, and ID may predispose children toward elevated BLLs, only a handful of studies have tested the effects of supplemental iron on children's BLLs. One study compared the response to a low-dose (2 mg) or high-dose (200 mg) of iron given daily for four months to 11 pairs of preschool children (1). Of the seven pairs completing the study, children receiving the higher dose experienced more of an increase in BLLs than did children in the low-dose group. Ruff et al. (106) conducted a trial of edetate calcium disodium (EDTA) treatment, in which children with elevated BLLs received iron if they had ID. After 6 months, there was no difference in the amount of decline in BLLs between ID and iron-sufficient children. In another study, 165 Costa Rican infants (13–24 months old) were randomized by anemia status to intramuscular iron, oral iron, or oral placebo for one week (133). Subsequently, iron-sufficient children were given placebo for three months, while all others received oral iron. Nonanemic infants who began the study with depleted iron stores showed the most marked decline in lead levels together with improved iron status. The iron-sufficient group, which received placebo, had an increase in BLLs together with a decrease in SF (133).

Indian schoolchildren (n = 186) with ID but mild or no anemia were randomized to receive an iron-fortified rice meal or a control meal once a day for 16 weeks (140). Iron fortification resulted in a significant decrease in the number of children with BLLs $\geq$10 μg/dl compared to the control group. In another school-based study, 602 Mexican children aged 6–8 years were randomized to receive iron, zinc, both iron and zinc, or a placebo daily for 6 months (100). Although it improved iron status, iron (alone or with zinc) treatment did not produce greater declines in BLLs compared to the placebo (100).

These results suggest that iron supplementation may have limited use in lowering BLLs in children. However, the designs of some studies limit the conclusions that can be drawn: Two were nonrandomized (1, 106), and the third appears to be randomized only in the first phase of treatment (133). The two randomized trials yielded opposite findings, with the study

from India supporting the existence of iron-lead interactions in the intestine. Both enrolled schoolchildren, so age is not the likely explanation for observed differences. The notable difference was the extent of ID, with 10% and ~70% being deficient in Mexico (100) and India (140), respectively. Lead exposure and elevation of BLL will occur in children whether they are iron deficient or not. But if ID predisposes children to elevated BLLs, then it is possible that iron supplementation will be more effective in lowering BLLs in those children who had ID to begin with. This has important implications for the use of nutritional interventions, as well as the functional outcomes in ID lead-exposed children, most notably for their cognition and behavior.

EFFECTS OF IRON DEFICIENCY ON COGNITION AND BEHAVIOR

The effects of iron deficiency on cognitive and behavioral development of children have been reviewed extensively (41, 67, 76). Investigators have documented that in infants and toddlers, ID with anemia (IDA) affects performance on tests of mental, motor, and language development, whereas in schoolchildren, cognitive deficits and lower school achievement are also observed. IDA is associated with slower neural processing, which may explain some of the above findings (67). As discussed by Lozoff (67), the timing, duration, and severity of ID in children is crucial in determining the types of deficits that will be manifested and how easily they can be corrected. In terms of behavior, infants with IDA tend to stay closer to their caregivers, are more irritable, and vocalize less in unfamiliar environments (70). Infants who received iron and zinc supplements scored better on measures of arousal, positive affect, energy, initiative, and social engagement (7). In older children, ID has been associated with behavior problems in some studies (20, 55, 87). Iron supplementation of schoolchildren resulted in a decrease in parental ratings of behavior problems (112). However, more studies are needed to establish a clear link between ID and behavior in older children.

EFFECTS OF LEAD EXPOSURE ON COGNITION AND BEHAVIOR

The effects of lead exposure on children's development and cognition have also been reviewed (16, 64). Most recent work has focused on the effects of low-level lead exposure, showing deficits at BLLs below 10 μg/dl on IQ (15, 54, 63, 120) and measures of attention and visual spatial abilities (56). Higher BLLs or bone lead levels are also associated with a range of externalizing behaviors (59), from hyperactivity, impulsivity, and attention deficit hyperactivity disorder (ADHD) (84), to aggression, delinquency in schoolchildren (82), and higher arrest rates in young adults (134). In tandem with findings on IQ, there is now evidence that BLLs well below 10 μg/dl are associated with behavior problems (8).

IRON AND LEAD IN THE BRAIN: UPTAKE AND POTENTIAL OVERLAP IN MECHANISMS

The cognitive and behavioral deficits of ID and lead exposure have their bases in the effects of these two insults on brain structure and function. To arrive in the brain, iron is initially taken up by capillary endothelial cells through transferrin receptors (TfRs) (80). It is transported to astrocytes and neurons through various mechanisms, including DMT1 (80), and to oligodendrocytes via ferritin and transferrin (121). In turn, lead may cross the blood brain barrier (BBB) in several ways, including calcium channels and nonenergy-dependent passage of lead-ion complexes (137). There is also evidence of increased BBB permeability to lead (118), possibly through decreased expression of tight junction proteins (129). In developing animals, this resulted in increased lead and lower iron levels in brain tissues (129). Thus, maturing BBB in young children could be particularly permeable as a result of lead exposure. However, iron

supplementation appears to protect the BBB against lead-induced damage (129).

The DMT1 specifically has been shown to transport lead in astrocytes, but another, unidentified, mechanism has a higher affinity for lead in these cells (18). In addition, at a neutral pH likely found in the brain, iron did not block lead uptake by astrocytes, and the upregulation of DMT1 did not enhance lead uptake. This suggests that the DMT1 may not be biologically relevant to lead neurotoxicity. Furthermore, a competitive interaction between iron and lead transport into neural cells, or at least the astrocytes, may be limited. Although iron supplementation has been shown to reduce brain tissue lead levels, the antagonism could be occurring at the level of intestinal absorption (129). One implication of these findings is that whereas ID is associated with increased intestinal lead absorption, it may not increase lead transport to neural tissues. Nevertheless, the possibility of interactions at the level of uptake into brain tissues should be investigated further.

Numerous studies have examined the effects of ID and lead on neural anatomy and physiology, but an exhaustive review is beyond the scope of this article. Instead, the evidence is briefly summarized, with a focus on myelination and dopamine neurotransmission because considerable work has been done in these domains for both metals. Iron maintains oligodendrocyte function and participates in myelin production, with the time of highest iron uptake coinciding with peak myelination (see 121 for review). ID is associated with a reduction in myelin components including proteins, lipids, and cholesterol (121). In turn, glial cells are thought to protect neurons by sequestering lead and thus become targets for lead-related injury (26). Lead affects the development of oligodendrocytes from precursor cells (26) and disrupts myelin morphology, resulting in irregular and loose sheaths, and membrane fluidity (25). Myelin proteins and phosopholipids are generally unaffected (25), but glycoprotein levels are reduced (24) in mature oligodendrocytes. In humans, childhood lead exposure was associated with increased disorganization of white matter fibers and lower levels of myelination in adulthood (12). Both ID and lead exposure have been associated with altered nerve conduction, which may at least partly be explained by disrupted myelination (98, 103).

Iron deficiency and lead exposure are also associated with impaired neurotransmission. One example is the dopaminergic system. Changes in the function of dopamine neurons are relevant to cognition and behavior because dopamine is involved in regulating several central nervous system processes including motor activity, mood, motivation, reward, and attention (53). ID affects dopamine neurotransmission (5) through reduced number and function of receptors, particularly the D_2 (31, 33), and transporters (30) in ways that may be irreversible. Depending on the timing of ID, dopamine metabolism and dependent behaviors may not be completely restored by iron supplementation (5). The D_2 is also vulnerable to the effects of lead in a region-specific and developmentally specific manner (37), while dopamine synthesis and release may be impaired as well (21). There is evidence that lead disrupts the mesocorticolimbic dopaminergic system (37), implicating it in reinforcement and reward processes and impulsivity (11, 22). Lead-induced changes in dopamine levels have also been related to hyperactivity (73).

ID and lead exposure are associated with other alterations in neural physiology (for review, see 5, 64, 69, 109, and 124). But the examples of disruptions in myelination and dopamine neurotransmission demonstrate considerable anatomic and physiological overlap in the effects of two apparently unrelated insults. The effects of combined ID and lead exposure on neural cell morphology or physiology have not been studied in animal models or in vitro. Such studies are critical to the understanding of the consequences of combined ID and lead exposure because both conditions produce differential effects on neural function depending on the stage of development when exposure occurs. Nevertheless, the findings of individual insults in myelination and dopamine

neurotransmission suggest that effect modification is plausible if ID and lead exposure occur in the same individual. Thus, acknowledging that the link between neural insults and behavioral alterations is not direct and may be influenced by myriad factors, especially in humans, it is reasonable to expect some interactions between ID and elevated BLLs at the level of behavior and cognition in children exposed to both conditions.

IRON, LEAD, AND COGNITION/BEHAVIOR

In thinking about the cognitive and behavioral effects of combined ID and elevated BLLs, it is important to outline the types of studies that have been conducted. They generally fall into two categories: (*a*) studies of environmentally exposed children in whom iron status was determined as a potential confounder/effect modifier and (*b*) studies of iron-deficient children in whom lead status was determined as a potential confounder/effect modifier. Most available evidence on ID, lead, and cognition is derived from the former, although a recent review recommends that environmental exposures, including lead, be considered in studies investigating the effects of nutritional deficiencies on child development (128). To date, few authors have specifically attempted to answer the question of whether children with ID are more susceptible to the neurotoxic effects of lead or whether the provision of iron to lead-exposed children could successfully improve their cognition or behavior.

The following is a review of the available evidence on the combined effects of iron status and lead exposure on child cognition and behavior based on 26 publications from 19 different studies (**Table 1**). These include cross-sectional (8, 14, 44, 48, 49, 52, 57, 58, 62, 78, 89, 104, 116, 125) and longitudinal (15, 54, 59, 91, 96, 106, 107, 113, 130–132) evaluations of children of varying ages.

Only five publications specifically discussed ID by BLL interactions, with two reporting some effect modifications (57, 107) and three not finding any (106, 130, 132). Ruff et al. (107) examined the six-month change in BLL and the Bayley Scales of Infant Development mental development index (MDI) in 18- to 30-month-olds who were treated with (*a*) EDTA, (*b*) 6 mg/kg/d iron, or (*c*) both EDTA and iron, or who were not treated at all. Treatment was not randomized, EDTA was given based on a lead mobilization test (MLT), and iron was given only to children with ID (48%). BLL and SF were not associated with mental development; there was no BLL x ID interaction. However, a six-month change in BLL was associated with better MDI scores in children who were iron replete but not iron deficient at the study outset, possibly because early ID may be associated with cognitive deficits that are not easily corrected (107). In another study, Kordas et al. (57) studied sleep patterns ($n = 550$) and classroom behavior ($n = 168$) of 6- to 7-year-old Mexican children. Those children who had both BLLs $\geq$10 μg/dl and mild anemia had a later bedtime but experienced fewer episodes of night waking. Additional tests for interactions revealed that children with anemia spent less time on-task and more time actively off-task in the classroom than did children with elevated BLL or with combined anemia and elevated BLL. Finally, BLL but not anemia was associated with shorter sleep duration and more passive off-task behaviors.

Of the three studies that found no interactions, Wasserman et al. (130) assessed the MDI of 24-month-old children in relation to BLLs and Hb that were measured prospectively from birth. There were no BLL-by-anemia interactions, but the 24-month BLL and the 18-month Hb were independently associated with MDI. Wolf et al. (132) also used the Bayley Scales of Infant Development to assess 184 infants ages 12 to 23 months and found that whereas IDA was clearly associated with poorer outcomes, BLL was not. There was no interaction between BLL and IDA. The same children were retested at 5 years of age with similar results. Finally, Ruff et al. (106) gave EDTA, iron, both, or neither to 13- to 87-month-old children ($n = 154$) and tested their cognitive outcomes

Table 1 Evidence from studies on iron, lead, and cognition

Author	Setting	N	Ages	Iron measures	Lead measure	Outcome measure	Results
Studies examining iron-by-lead interactions							
Wasserman et al. 1992 (130)	Former Yugoslavia; Pristina & Mitrovica	392	Longitudinal; assessed every 6 mo from birth to 24 mo	Geometric mean SF ~40 ng/ml at 6 mo and ~17 ng/ml at 24 mo; geometric mean Hb ~11.5 g/dl at 6 mo and ~11 g/dl at 24 mo	Geometric mean BLL <10 μg/dl in Pristina, ~20 μg/dl at 6 mo and ~35 μg/dl at 24 mo in Mitrovica	BSID	BLL levels not different by Hb level. 24-mo BLL negatively associated with 24-mo BSID MDI when adjusted for Hb. 18-mo Hb associated with MDI even when adjusted for BLL; no association with Hb at other ages. BLL by Hb interaction ns, but limited by small sample size. SF not a significant predictor of MDI.
Ruff et al. 1993 (106)	Bronx, NY	154	Longitudinal with EDTA treatment; 13–87 mo at enrollment	SF baseline range: 2–49 ng/ml; kids with ID (SF<16 ng/ml, 39%) given Fe for 6 mo	BLL baseline range: 13–46 μg/dl	BSID & Stanford Binet IV	Baseline SF but not BLL associated with CI. SF by BLL interaction ns. No effect of EDTA on CI in 6 months. EDTA by Fe supplementation interaction ns. Change in BLL (ΔBLL) associated with increased CI, adjusted for ΔSF. ΔSF not independently associated with improved CI. ΔSF by ΔBLL interaction ns.
Wolf et al. 1994 (132)	Costa Rica	184	Longitudinal; 12–23 mo; followed up at 5 years	27.7% had IDA	11.0 ± 3.8 μg/dl	BSID Stanford Binet	BLL not associated with biomarkers of iron status; BLL not associated with BSID; BLL by IDA interaction tested and found to be ns. BLL measured at infancy not associated with any of the 5-yr measures; BLL by IDA interaction tested and found to be ns.

Ruff et al. 1996 (107)	Bronx, NY	42	Longitudinal with EDTA treatment; 18–30 mo at enrollment	SF baseline: 10.0 ± 3.2 in ID; 26.5 ± 8.7 ng/ml in non-ID; when ID (SF <16 ng/ml, 48%) given Fe for 6 mo	BLL baseline 28.3 ± 6.0 in ID; 30.4 ± 6.1 μg/dl in non-ID	BSID	BLL or SF not associated with MDI at baseline (overall sample). Chelation treatment also given. BLL by baseline ID interaction ns. ΔBLL by ID interaction ($p < .01$): ID kids no change in MDI; non-ID 1.2 pt↑ in MDI for 1 μg/dl↓ in BLL.
Kordas et al. 2007 (57)	Torreón, Mexico	550; 168	Cross-sectional; 6–7 years	Hb 13.3 ± 0.8 g/dl; SF 27.2 ± 16.1 μg/L; 10% anemia, 10% ID	11.5 ± 6.1	Sleep questionnaire; observations of child behavior in class; activity level during recess	BLL associated with later wake-up time but shorter sleep duration; also with more passive off-task behaviors in class. Anemia associated with earlier bedtime and shorter sleep latency; less time spent on task, more time spent actively off-task; less activity at recess. BLL by anemia interactions: with anemia & elevated BLL, (*a*) less night waking, (*b*) later bedtime. But anemic children spent less time on-task than elevated BLL and more time off-task.
Studies not testing interactions but reporting independent associations of iron and lead with cognition/behavior							
Padich et al. 1985 (89)	Cincinnati, OH	?	Longitudinal study with an assessment of behavior at 18 mo	Hematocrit (Hct), serum iron, total iron-binding capacity assessed but not reported	BLL at 18 mo: 16.8 ± 1.6 μg/dl	Three problem-solving tasks in which infant behavior was observed: on task; room movement; active exploration of task materials	BLL not associated with on-task or active exploration behaviors. Cumulative Pb exposure up to 18 mo was associated with less movement about the room. Hematocrit, serum iron, total iron-binding capacity not related to movement (association with other outcomes not assessed). BLL by iron status interaction not assessed.

(*Continued*)

Table 1 (*Continued*)

Author	Setting	N	Ages	Iron measures	Lead measure	Outcome measure	Results
Johnson et al. 1992 (52)	Los Angeles, CA	236	Cross-sectional; 2–5 years	Mean Hb not provided; 16%–23% anemic (Hb <11.5 g/dl) girls at 2–3 years; 0%–8% anemic at 4–5 years	BLL 5.3 ± 2.6 μg/dl at 2 years; 8.8 ± 3.9 μg/dl at 5 years; measured on a subsample of 82 children	Modified version of the Child Behavior Checklist	Lower Hb associated with higher frequency of internalizing & externalizing behavior problems in girls. Higher BLL associated with increased aggression in girls. Anemia by BLL interaction not tested.
Wasserman et al. 1994 (131)	Former Yugoslavia; Pristina & Mitrovica	332	Longitudinal; assessed every 6 mo up to 48 mo	Same as above; SF ~30 ng/ml at 48 mo; Hb ~12 at 48 mo	Same as above; BLL <10 μg/dl at 48 mo, ~40 μg/dl at 48 mo	MSCA	Iron given to all children at one point in the study (kids ages 18–38 mo). Unclear how long Fe given. Infancy and childhood BLL negatively associated with General Cognitive Index & all scale scores. Hb was not consistently associated with MSCA scores. BLL by Hb interactions not tested.
Mendelsohn et al. 1998 (78)	New York City	72	Cross-sectional; 1–3 years	ID is Hct <32 or MCV <72 fL in capillary blood; 13.9%	BLL 10.4 ± 5.0 μg/dl; 56.9% ≥10 μg/dl	BSID Behavior Rating Scale	ID not associated with BLL. Higher BLL associated with lower scores on emotion regulation and orientation-engagement factors. ID reportedly not associated with behavior ratings. ID by BLL interaction not tested.
Lanphear et al. 2000 (62)	U.S. national sample	4853	Cross-sectional; 6–16 years	SF measured; mean not provided	Geometric mean BLL 1.9 μg/dl; 2.1% with BLL ≥10 μg/dl	Arithmetic & reading from WRAT-R; block design & digit span from WISC-R	SF associated with BLL. BLL negatively associated with all outcome measures after adjusting for covariates, including SF. SF not associated with cognitive/achievement outcomes in unadjusted regressions. SF by BLL interaction not tested.

Calderón et al. 2001 (14)	Morales & Martínez, Mexico	41 & 39	Cross-sectional; mean age 7.4–7.6 in the two towns	Tf saturation: 29.1 ± 9.0% Morales; 24.8 ± 9.0% Martínez	BLL: 8.98 ± 0.03 Morales; 9.73 ± 0.02 Martínez	WISC-R	Neither BLL nor Tf saturation correlated with IQ from WISC-R. BLL negatively correlated with sequential subtest (arithmetic, digit span, coding) when adjusted for covariates including Tf saturation. Tf saturation not correlated with any WISC-R subtests.
Rahman et al. 2002 (93)	Karachi, Pakistan	138	Cross-sectional; 6–10 years	13.2 ± 1.2 g/dl; 10% with Hb <11.5 g/dl	BLL 16.1 ± 6.3 μg/dl; 88% with ≥10 μg/dl	Raven's SPM	Hb negatively associated with BLL. Both Hb and BLL were negatively associated with IQ. Hb by BLL interaction not tested.
Kordas et al. 2004 (58)	Torreón, Mexico	595	Cross-sectional; 6–7 years	Hb 13.3 ± 0.8 g/dl; SF 27.2 ± 16.1 μg/L; 10% anemia, 10% ID	11.5 ± 6.1	PPVT; WISC-R Mexican Version; coding, digit span, arithmetic; number and letter sequencing	BLL negatively associated PPVT, coding, number and letter sequencing. BLL & anemia independently associated with PPVT and number sequencing. BLL by anemia interaction not tested.
Kordas et al. 2005 (59)	Torreón, Mexico	515	Longitudinal; 6–7 years	Hb at baseline 13.3 ± 0.8 g/dl; SF 27.2 ± 16.1 μg/L; 10% anemia, 10% ID	11.5 ± 6.1	Conners Behavior Rating Scales for Teachers and Parents	BLL negatively associated with teacher ratings of oppositional, hyperactive, cognitive problems, and ADHD behavior ratings. SF not associated with teacher ratings. Anemic children more likely rated by parents as oppositional or having cognitive problems (did not reach statistical significance). Iron supplementation did not improve behavior ratings overall. But in children with BLL ≥10 μg/dl, children receiving Fe had a 2-pt decline in cognitive problem ratings by parents and a 3-pt decline in oppositional ratings by teachers.

(*Continued*)

Table 1 (*Continued*)

Author	Setting	N	Ages	Iron measures	Lead measure	Outcome measure	Results
Braun et al. 2006 (8)	U.S. national sample	4704	Cross-sectional; 4–15 years	SF measured; value for study sample not reported	Mean BLL not reported; 75.5% with BLL <2 μg/dl	Parent-reported ADHD	BLL >2.0 μg/dl associated with higher likelihood of ADHD reports (adjusted for SF and other covariates). Higher SF marginally associated with higher likelihood of ADHD. SF by BLL interaction not tested.
Rico et al. 2006 (96)	Torreón, Mexico	515	Longitudinal; 6–7 years	Hb at baseline 13.3 ± 0.8 g/dl; SF 27.2 ± 16.1 μg/L; 10% anemia, 10% ID	11.5 ± 6.1	Same as Kordas et al. 2004 (58) plus math achievement test, Sternberg memory, figure matching, stimulus discrimination, visual memory span, visual search, figure design	BLL associated with 7 of 11 outcomes tested. No consistent short- or long-term effects of iron supplementation.
Vega-Dienstmaier et al. 2006 (125)	Callao, Peru	134	Cross-sectional; 6–8 years	Hb, Hct, SF, RBC measured; 10.8% with Hb <12 g/dl; 25.2% with SF <16 ng/ml in boys (<12 in girls)	44.6% with BLL ≥10 μg/dl	GTR; KBDT	BLL negatively correlated with Hb, Hct, RBC. BLL negatively correlated with KBDT, and numeric problems, inferences, similarities on GTR. Hct, Hb, RBC correlated with numeric problems & relationships. In combined models, both BLL & RBC associated with GTR in whole group, particularly boys. BLL but not RBC associated with KBDT. RBC by BLL interaction not tested. Other iron status markers not tested.

Hubbs-Tait et al. 2007 (49)	Rural Oklahoma	42	Cross-sectional; 3–5 years	SF 24.4 (19.1 – 30.6) μg/L; 74% ID	1.86 (1.2 – 2.9) μg/dL^2, 9% with BLL >5 μg/dl	MSCA; California Preschool Social Competency Scale; Preschool Behavior Questionnaire	When entered together as a block of variables, BLL, SF, and SZn were associated with McCarthy Verbal Ability scores and anxiety in boys, together explaining 24% and 46% of variability in these outcomes, respectively. When analyzed as separate variables, SF and SZn were individually associated with McCarthy scores but lead was not. BLL by SF interaction not assessed.
Plusquellec et al. 2007 (91)	East Hudson Bay, Quebec	169	Longitudinal; assessed at 11 mo	Hb at 6 mo: 10.8 ± 1.2 g/dl; 10.3% anemia	Maternal BLL at birth 5.95 ± 3.6 μg/dl; cord BLL 4.8 ± 3.6 μg/dl	BSID Behavior Rating Scale; behavioral observation coding of off-task duration and latency (how quickly child looks away from object)	Prenatal BLL negatively associated with frenetic movement and off-task duration. Hb positively associated with adaptation to change in test materials and attention to tasks. BLL & Hb negatively associated with off-task latency. BLL by Hb interaction not assessed.
Solon et al. 2008 (116)	Visayas region, Philippines	877	Cross-sectional; 6–59 mo	Hb 11.8 ± 1.5 g/dl; 23.7% anemic (<11 g/dl)	BLL: 7.1 ± 7.7 μg/dl	BSID-II for 6–35 mo olds; WIPPSI-III	Hb and BLL inversely associated. BLL negatively associated with MDI and verbal IQ. Anemia reported to be associated with IQ (reference to this found in discussion) but relationship not specifically presented in the results. Anemia by BLL interaction not reported.

(*Continued*)

Table 1 (*Continued*)

Author	Setting	N	Ages	Iron measures	Lead measure	Outcome measure	Results
Hubbs-Tait 2009 (48)	Rural Oklahoma	112	Cross-sectional; 4.1 ± 0.5 years	sTfR 8.71 ± 1.71 μg/dl; Hb 9.1–14.3 g/dl; 10% anemia	2.1 ± 1.2 μg/dl	MSCA; (PPVT-III)	BLL not significantly correlated with sTfR. Higher sTfR but not BLL negatively associated with lower MSCA-Verbal and PPVT-III scores. Higher BLL but not sTfR negatively associated with lower MSCA-Perceptual scores. BLL by sTfR interaction not reported.
Studies measuring iron and lead status but not reporting on association of both with cognition/behavior							
Shen et al. 1998 (113)	Shanghai	133	Longitudinal; BLL assessed in cord blood; outcomes at 3, 6, & 12 mo	Maternal Hb in midpregnancy measured, not reported	Geometric mean & range BLL 9.2 (1.6 – 17.5) μg/dl; 40.8% ≥10	BSID	Cord BLL associated with 3-mo MDI & PDI, 6-mo MDI, and 12-mo MDI after adjusting for covariates. Mid-pregnancy Hb included as covariate in 12-mo model; coefficient not reported. Hb by BLL interaction not tested.
Halterman et al. 2001 (41)	U.S. national sample	5398	Cross-sectional; 6–16 years	3% with ID overall	BLL measured; not presented	Math & reading from WRAT-R; Digit span & block design from WISC-R	Children with ID and IDA had lower math scores than did iron-replete children after adjusting for lead and other covariates. Children with IDA scored lower on block design than did iron-replete children. Coefficient for lead not given. BLL by ID interaction not tested.

Canfield et al. 2003 (15)	Rochester, NY	172	Longitudinal; 6–60 mo	Tf saturation at 5 years of age: 22.5 ± 9.4%; Tf saturation <20% in 39% of children	Lifetime average: 7.4 ± 4.3 μg/dl At 5 years: 5.8 ± 4.1 μg/dl	Stanford Binet IV	Tf saturation not associated with lifetime average Pb or IQ at 5 years; Tf saturation used as covariate but coefficient not reported. Tf by Pb interactions not assessed.
Jusko et al. 2008 (54)	Rochester, NY	174	Longitudinal; 6–72 mo	Tf saturation at 6 years of age: 20.7 ± 8.6%	Lifetime average: 7.2 ± 4.1 μg/dl; at 6 years: 5.0 ± 3.3 μg/dl	WIPPSI-R	Association between Tf saturation and Pb or IQ not shown; Tf saturation used as covariate but coefficient not reported. Tf by Pb interactions not assessed.
Roy et al. 2009 (104)	Chennai, India	756	Cross-sectional; 3–7 years	Hb assessed; not reported	11.4 ± 5.3 μg/dl	Conners ADHD/ DSM-IV Scales; Conners Behavior Rating Scale for Teachers; Behavior Rating Inventory of Executive Function	BLL associated with higher anxiety, ADHD, and composite executive function scores; all indicative of deficit. Hb used as a covariate for adjustment; β coefficient not reported. BLL by Hb interaction not assessed.

Abbreviations: BLL, blood lead level; BSID, Bayley Scales of Infant Development; CI, cognitive index; DMT1, divalent metal transporter-1; GTR, Graphic Test of Reasoning; ID, iron deficiency; IDA, iron deficiency anemia; KBDT, Kohs Block Design Test; MDI, Mental Development Index; MSCA, McCarthy Scales of Children's Abilities; PPVT, Peabody Picture Vocabulary Test; SF, serum ferritin; SPM, Standard Progressive Matrices; sTfR, serum transferrin receptor; Tf, transferrin; WIPPSI-III, Wechsler Preschool and Primary Scales of Intelligence, Revised; WISC-R, Wechsler Intelligence Scale for Children, Revised; WRAT-R, Wide Range Achievement Test, Revised; ZPP, zinc protoporphyrin.

at baseline and after six months of treatment. EDTA treatment was based on results of an MLT, whereas iron was given to children with ID. Baseline SF but not BLL was positively correlated with cognitive scores, and there were no interactions. A reduction in BLL was associated with higher cognitive scores, but there was no interaction with change in SF levels.

Nineteen publications did not test BLL–iron status interactions, but 14 did discuss the independent contributions of BLL and iron status to cognitive performance or behavior, as described below. Certain studies found significant relationships with lead but not iron. Padich et al. (89) found that cumulative lead exposure (but not iron status) was associated with less movement in 18-month-olds but not with on-task or active exploration of toys during cognitive testing. In 332 Yugoslavian children, BLL was negatively associated with the General Cognitive Index of the McCarthy Scales of Children's Abilities (MSCA) but Hb was not consistently related to any MSCA scores (131). Similarly, ID was not associated with behavior ratings of 72 young children exposed to lead (78). Lanphear et al. (62) and Calderón et al. (14) also did not find a relationship between iron status and cognitive outcomes in lead-exposed children.

Several studies found independent associations of BLL and iron status with children's cognition and behavior. Hb levels in 236 Hispanic preschool girls were inversely associated with internalizing and externalizing behavior ratings, including aggression and hyperactivity, whereas higher BLLs were associated with increased aggression (52). In contrast, Braun et al. (8) found that higher BLLs and higher SF were associated with parent-reported ADHD in a representative sample of U.S. children. This was also true for BLL and Hb in 138 Karachi schoolchildren (93). In 595 Mexican schoolchildren, elevated BLL and low Hb were independently associated with measures of receptive vocabulary (58). Hubbs-Tait et al. (49) found that SF, serum zinc, and BLL together were associated with several cognitive and behavioral outcomes in 42 preschoolers enrolled in Head Start, but when analyzed separately, SF was significantly associated with some of the outcomes (verbal ability, anxiety in boys), whereas BLL was associated with others (social competency, sociability in girls). This group reported similar patterns of findings for sTfR and BLL (48). Plusquellec et al. (91) also found separate associations of BLL and Hb with different cognitive and behavioral measures, but in the case of off-task latency (a measure of how quickly a child looks away from a toy), both elevated BLL and higher Hb were associated with shorter latency. In a sample of Peruvian schoolchildren ($n = 134$) with a high prevalence of elevated BLLs and moderate prevalence of iron deficiency, BLLs (negatively) and several iron status indicators (positively) were correlated with children's performance on general cognitive function tests. When modeled together, both BLLs and red blood cell counts were associated with test scores (125). Finally, Solon et al. (116) reported an association among BLL, Hb, and cognitive outcomes, particularly IQ, in 6- to 59-month-old children ($n = 877$).

One study examining the association between ID and cognition in children and adolescents adjusted for BLLs but did not report the relationship between lead status and cognition (44). Conversely, Shen et al. (113), Canfield et al. (15), Jusko et al. (54), and Roy et al. (104) used iron status indicators as covariates in their statistical models but did not report on whether iron status was associated with outcomes. In a reanalysis of the data from the Rochester cohort, serum transferrin (Tf) saturation was not a significant predictor of any of the cognitive measures originally reported by Canfield or Jusko and colleagues (T. Jusko, personal communication). Finally, some studies assessed iron status in lead-exposed children (or their mothers in pregnancy) but did not include it in the final regression models, indicating that it was unassociated with BLL, specific outcomes, or both (6, 29, 45, 79, 117).

The interaction between iron and lead was also tested in iron supplementation studies. In one, Mexican schoolchildren were given 30 mg ferrous fumarate, either alone or with 30 mg

zinc oxide for six months. A placebo-control group was also included. At baseline, BLL was negatively associated with teacher ratings of oppositional, hyperactive, and ADHD-like behaviors as well as cognitive problems (59). Iron supplementation did not improve behavioral ratings overall but benefited those children who had BLLs $\geq$10 μg/dl in terms of parental ratings of cognitive problems and teacher ratings of oppositional behaviors (59). However, there were no consistent benefits of iron on children's cognitive outcomes (96). Three other studies provided iron to children, but because in one study all participants received iron at one time point but different ages (131), and in the others only ID children received iron (106, 107), it is difficult to systematically evaluate the effects of supplementation on cognition in those children.

Based on the above evidence, it would be difficult to conclude that ID or IDA increases the susceptibility of children to the neurotoxic effects of lead, mostly because there is such scarcity of studies addressing this issue. In a few cases, lead-exposed children with ID or anemia were worse off in terms of cognitive or behavioral outcomes than were non-ID or nonanemic children. Another pattern of findings is worth considering because it suggests that elevated BLLs and ID may be independently associated with poorer cognitive performance and behavior of children. The independent associations are indicative of additive effects, with children who are both iron deficient and lead exposed likely experiencing worse outcomes than children who are iron deficient only or lead exposed only. Moreover, in several studies, ID (or anemia) and BLL were associated with different cognitive and behavioral domains, suggesting that insults may be more extensive in children who are both lead exposed and iron deficient. However, because ID and lead exposure occur together and each is associated with cognitive outcomes, it is possible that the above results are due to confounding and incomplete covariate-adjustment, rather than the independent effects of ID and BLL on cognition. Also, because several studies found an association with BLL but not iron status (or the reverse), these relationships should be investigated further in large, well-designed studies.

One of the most interesting results suggesting interactions comes from a study that did not assess interactions directly. Plusquellec et al. (91) reported that the look-away latency (time to look away from a toy presented during cognitive testing) was shorter in infants with higher Hb and higher BLLs. This finding appears paradoxical if look-away latency is thought of as a measure of inattention. But if good iron status is associated with faster information processing (shorter looking time), whereas higher BLLs are related to inattention (shorter looking time) (91), then this finding makes sense and is noteworthy because it suggests that iron and lead do act on similar neural processes. Such results also suggest that interactions are possible and should be investigated further in large, well-designed studies.

IRON, LEAD, AND COGNITION: ISSUES OF INTERPRETATION

In weighing the above evidence, it is essential to consider the types of iron-status indicators used in studies of iron, lead, and cognition because they directly affect study findings and interpretation. Iron status in the above studies was measured with a variety of indicators, including Hb, serum ferritin, serum transferrin saturation, and serum transferrin receptors. Additional studies have been identified where the relationship between lead, ZPP, and cognition was evaluated, but these are not discussed because ZPP is an indicator of both elevated BLL and ID, which limits the ability to separate the contributions of each condition to elevated ZPP levels.

Iron biology is complex, and several indicators exist to describe iron status, from repletion to severe deficiency resulting in anemia. ID occurs in stages, with depletion of stores occurring earliest, as indicated by low serum ferritin levels (38). The second stage of ID is the reduction in the supply of iron for erythropoiesis (38), which can be measured in serum by

declining Tf saturation and rising sTfR levels. Finally, more severe or prolonged ID results in anemia (low Hb). Some studies also use red cell indices, including mean cell volume, to diagnose and distinguish between types of anemia (38). Hb is the most commonly used iron status indicator because it is relatively easy to measure in field situations. But because it drops in late stages of ID, it is not a sensitive marker. It is also nonspecific: Other factors, such as vitamin B12 and folic acid deficiency or helminth infections, may cause anemia (38).

In general, the use of a single indicator of iron status is not recommended because without measuring at least two indicators, it is impossible to tell whether the individual has ID only, anemia only, or both. This problem was found in several studies investigating the relationship between iron status, lead, and cognition. Another difficulty in using single indicators of iron status is that they may be affected by inflammation, infection, and other factors (38). To limit the possibility of misclassification due to extraneous factors, fasting blood should be collected (which may be a problem in young children) or the timing of blood collection standardized across all participants. In addition, a measure of an acute-phase protein such as C-reactive protein is recommended to account for inflammation or infection.

There is also a need to distinguish between the types of questions that may be asked in relation to iron status. The question of whether ID makes children more susceptible to the neurotoxic effects of lead is different from the question of whether IDA increases such susceptibility. This distinction is clearly drawn in the iron-deficiency literature and should be made when studying iron-lead interactions in young children. The preponderance of evidence on ID and cognition suggests that it is ID with anemia that results in cognitive and behavioral deficits in infants and toddlers (67; but see 68). In older children, ID alone appears sufficient to affect cognitive performance and achievement (13, 44). There are various implications of this differential effect of ID and IDA on cognitive outcomes in lead-exposed children. One is that the age of exposure to combined ID and lead is crucial and may determine the types of outcomes that can be observed. Another implication is that in studying the combined insults among young children, if only ID is assessed, no interactions may be apparent. Thus, biomarkers of both early and late stages of iron deficiency should be included.

A corollary question is, how extensive does ID or IDA need to be in a population to find statistical interactions or independent effects of ID/IDA and BLL at any age group? Studies included here ranged widely in the prevalence of ID. Those studies that reported interactions or independent associations of ID and BLL on cognition/behavior had low-moderate prevalence of anemia (48, 52, 57, 58, 78, 91, 93, 116, 125) or high prevalence of ID/anemia (49, 106, 107). Of the studies that did not find interactions or independent effects, one reported moderate ID (132), whereas others did not report the extent of ID (14, 62, 131). It appears that even at low prevalence of anemia (~10%), statistical interactions or independent effects of iron status and BLL are observable, albeit not guaranteed. This suggests that combined ID and lead exposure pose an important problem not only in developing country populations but also in middle-income and developed countries, where ID may be prevalent in young children.

PREGNANCY: A PERIOD OF HEIGHTENED VULNERABILITY TO IRON DEFICIENCY AND LEAD EXPOSURE

Because early ID and lead exposure appear to produce lasting behavioral and cognitive deficits, there is now considerable focus on the prenatal period and the critical window it represents in brain development. There are no reports on the effects of combined prenatal ID and lead exposure on child development, although ongoing prospective cohort studies are poised to provide the lacking evidence. It is nevertheless worthwhile to briefly address the importance of the prenatal period as a time of heightened vulnerability to the two insults.

The placenta does not filter out lead (60, 101). Consequently, cord BLLs correlate highly with maternal BLLs (102). Maternal iron status may impact not only the mother's absorption of lead but also the placental transfer of lead. Schell et al. (110) and Janjua et al. (51) found an inverse association between maternal iron intake during pregnancy and cord BLLs. There is also evidence that the DMT1 expression is higher in the placentas of iron-deficient animals (35).

Prenatal ID and lead exposure are each associated with poorer developmental outcomes. Human neonates with lower iron status show more negative emotionality and lower levels of alertness and soothability (127), whereas higher iron levels predict positive scores on infant emotional reactivity and social attention (126). Young infants of diabetic women have impaired recognition memory (83, 114), which is thought to result from prenatal ID (114). Rhesus monkeys exposed to iron-deficient diets during the prenatal period show higher incidence of exploratory behaviors and are less fearful than controls (39). Gestational ID in animal models results in alterations in monoamine neurotransmitter metabolism and myelination, among other effects (69). In turn, cord or maternal BLLs are associated with higher intervals in brainstem auditory-evoked responses (103), more frenetic movements, and higher off-task duration in infants (91). Stage of pregnancy when lead exposure occurs may produce differential effects on infant development (47, 111). In terms of neural effects, prenatal exposure may delay oligodendroglial development, resulting in impaired myelin formation (27). Early exposure may also be more detrimental to the function of the dopaminergic system than postnatal exposure (28). This evidence clearly indicates the need to investigate the combined short and long-term effects of maternal ID and lead exposure on child development.

SUMMARY POINTS

1. There is considerable geographic overlap between iron deficiency and lead exposure in children. Among other mechanisms, lead uses the intestinal iron transporter, divalent metal transporter-1 (DMT1), to gain entrance into the human body. Several studies have shown an inverse association between iron status and blood lead levels. The increase in DMT1 expression that occurs in ID contributes to increased lead absorption.
2. Although no studies examine the combined effects of elevated blood lead levels and iron deficiency on neural targets, the existing evidence suggests that lead exposure and ID affect related neural tissues or neurotransmitter systems. Such overlap would make interactions between ID and lead exposure on functional outcomes more plausible.
3. Very few studies have investigated whether children with ID are more susceptible to the neurotoxic effects of lead exposure. Most evidence looks at independent associations of ID and BLLs on child cognition and behavior. There is some indication that both conditions are negatively and independently related to functional outcomes.
4. The existing pool of studies has not systematically addressed interactions or independent effects of lead exposure and ID on child cognition or behavior. This is in part due to the differences in ages at which exposure to lead, biomarkers of iron status, and outcome measures are assessed. Some of the few studies that tested for statistical interactions were either not designed adequately or underpowered to find interactions.

FUTURE ISSUES

1. Future studies need to address several mechanistic aspects of the interactions between iron and lead, including any involvement of iron or iron transporters in shuttling lead into neural tissues, the effects of combined ID and BLLs on neural anatomy and physiology, as well as mechanisms and interactions at the level of placental transfer.
2. Well-designed, large studies are needed to systematically examine the independent and combined effects of ID and lead exposure on child cognition and behavior. These studies need to take into account the age of children at the time of exposure to both insults, the duration of exposure, as well as the prevalence and severity of iron deficiency in the population. Thus, studies should consistently measure at least two markers of iron status so that the extent of ID can be compared among different populations.
3. The prenatal period is a time of heightened susceptibility to ID and lead exposure, and each condition is associated with cognitive and behavioral deficits that appear to last into the preschool or even school age. The effects of combined ID and lead exposure during the prenatal period need to be studied together. Furthermore, at least for ID, there is evidence that prenatal and postnatal ID produces differential behavioral effects. Thus, future studies need to carefully document both conditions throughout the exposure period to attempt to identify possible differential effects on functional outcomes. This might require large longitudinal birth cohorts.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENT

The author was supported by the 2009 American Association of University Women Summer/Short-Term Publication Fellowship. Many thanks to Dr. Todd Jusko for conducting additional analyses on data from the Rochester cohort study for inclusion in this article.

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Volume 30, 2010

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Errata

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