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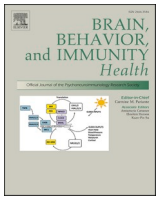

Early life stress and iron metabolism in developmental psychoneuroimmunology

Brie M. Reid [a,b,c,*]

[a] Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, USA
[b] Center for Behavioral and Preventive Medicine, The Miriam Hospital, USA
[c] Department of Psychology, Department of Health Sciences, Northeastern University, USA

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ABSTRACT

An estimated 250 million children face adverse health outcomes from early life exposure to severe or chronic social, economic, and nutritional adversity, highlighting/emphasizing the pressing concern about the link between ELS and long-term implications on mental and physical health. There is significant overlap between populations experiencing high levels of chronic stress and those experiencing iron deficiency, spotlighting the potential role of iron as a key mediator in this association. Iron, an essential micronutrient for brain development and immune function, is often depleted in stress conditions. Iron deficiency among the most common nutrient deficiencies in the world. Fetal and infant iron status may thus serve as a crucial intermediary between early chronic psychological stress and subsequent immune system changes to impact neurodevelopment. The review presents a hypothesized pathway between early life stress (ELS), iron deficiency, and neurodevelopment through the hypothalamic-pituitary-adrenocortical (HPA) axis and the IL-6-hepcidin axis. This hypothesis is derived from (1) evidence that stress impacts iron status (2) long-term neurodevelopmental outcomes that are shared by ELS and iron deficiency exposure, and (3) possible mechanisms for how iron may mediate the relation between ELS and iron deficiency through alterations in the developing immune system. The article concludes by proposing future research directions, emphasizing the need for rigorous studies to elucidate how stress and iron metabolism interact to modify the developing immune system. Understanding these mechanisms could open new avenues for improving human health and neurodevelopment for women and children globally, making it a timely and vital area of study in psychoneuroimmunology research.

1. Introduction

Hundreds of millions of children face increased risk of worse developmental outcomes due to prenatal and early life stress, including exposure to social, economic, and nutritional adversity (Black et al., 2017). The fetal period and the first few years of life are a window of opportunity to support the foundations of rapidly developing immune systems and brains. This window of opportunity also carries risk, especially for fetuses and children exposed to severe or chronic stressors. Early life stress (ELS) is linked to poor mental and physical health outcomes through disruptions to the mammalian stress response and subsequent alterations in the developing immune system (Hughes et al., 2017; Lupien et al., 2009; Nusslock and Miller, 2016; Reid, 2020b). Extensive research across multiple levels of analysis has mapped ELS to neurodevelopmental outcomes through changes on the hypothalamic-pituitary-adrenal (HPA) axis and the immune system. ELS and circulating inflammatory cytokines have been a primary focus of attention (e.g. (Baumeister et al., 2016),). A separate body of work has also mapped the link between nutritional adversity and neurodevelopmental outcomes, with an emerging focus on inflammatory mechanisms (e.g. (Black et al., 2017; Krebs et al., 2017; Suchdev et al., 2017),). Critically, populations with a high prevalence of nutritional inadequacy overlap with populations with a high prevalence of chronic stress exposure (Reid and Georgieff, 2023). I propose that investigating the pathway between ELS, nutrient metabolism, and the developing immune system merits further exploration in psychoneuroimmunology research. This research should aim to encompass global and diverse populations confronting the dual threats of ELS and nutritional adversity.

As nutritional adversities are vast and multifaceted, I propose

* Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, USA
E-mail address: b.reid@northeastern.edu.

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focusing on the micronutrient iron as a model to begin to understand how ELS biologically dovetails with nutritional adversity to impact the immune system and neurodevelopment. Iron is critical for brain development (Georgieff, 2017a), an essential nutrient for the immune system (Beard, 2001), and responsive to conditions of stress (Reid and Georgieff, 2023), making it a candidate to better understand the link between ELS and lifelong well-being. Iron deficiency is prevalent in low, middle, and high-income countries, affecting 30–40% of pregnant women and up to 40% of children under five years of age (Auerbach et al., 2021; Stevens et al., 2013). These are the windows of opportunity and risk for ensuring iron sufficiency during rapid changes in immune and brain development.

Pregnant individuals and young children exposed to chronic financial stress are more susceptible to iron deficiency likely due to food insecurity and diets lacking sufficient iron (Skalicky et al., 2006). Stress can significantly alter eating behavior: individuals experiencing stress may favor foods high in fat and sugar, which are typically lower in iron (Baskin et al., 2015; Monk et al., 2019). However, even with adequate dietary intake, psychological stress may trigger biological changes that may adversely affect iron status (Reid and Georgieff, 2023). In

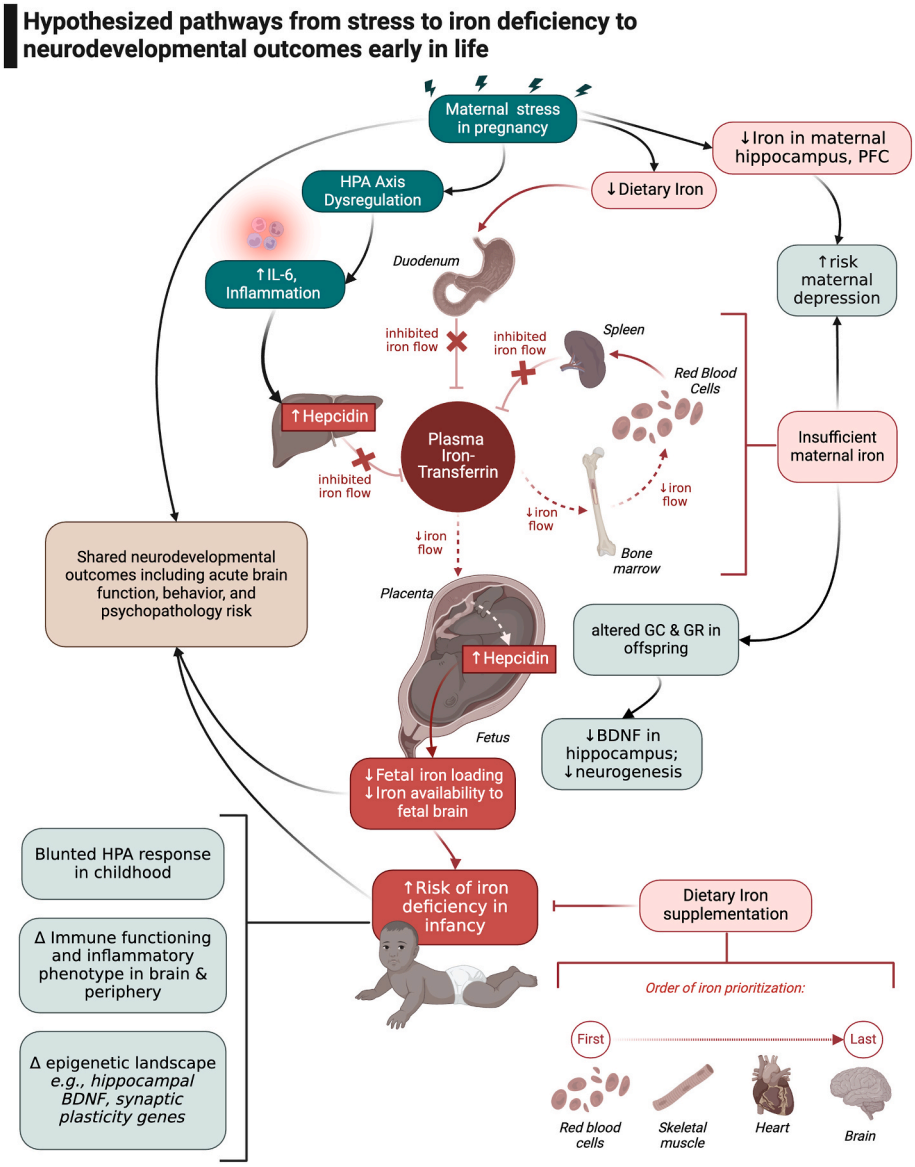

Fig. 1. Hypothesized pathways from stress to iron deficiency to neurodevelopmental outcomes early in life. Following chronic or severe maternal stress during pregnancy, HPA axis dysregulation and subsequent increases in inflammation are hypothesized to trigger the IL-6-hepcidin axis, which alters or inhibits iron flow throughout the maternal milieu and subsequently reduces iron availability to fetal iron endowment and the fetal brain. This in turn increases the risk for iron deficiency in the infant, which is associated with changes to the developing HPA axis, immune system, and epigenetic landscape in the infant which are hypothesized to result in shared neurodevelopmental outcomes between stress and iron deficiency early in life. Even in the context of iron supplementation to the iron deficient infant, iron is prioritized to other tissues and prioritized to the brain last, which puts the infant at risk of the adverse impacts of iron deficiency for neurodevelopment even if the infant is clinically iron replete. It is also possible that stress in infancy carries similar ramifications to iron metabolism through the HPA-IL-6-hepcidin axis that is shown in the maternal side, posing risks of iron deficiency even if the infant was born iron replete. Additional pathways between maternal stress, iron metabolism, and offspring neurodevelopment include (A) stress-induced changes to maternal eating behaviors in pregnancy favoring lower dietary iron consumption, and (B) risks to increased maternal depression. For instance, iron deficiency is a risk factor for maternal depression and reduced iron in the maternal hippocampus and PFC may increase the likelihood of maternal depression and impact offspring neurodevelopment through multiple routes. HPA = hypothalamic-pituitary-adrenocortical axis; PFC = prefrontal cortex; IL6 = interleukin 6; GC = glucocorticoids; GR = glucocorticoid receptors; BDNF = brain derived neurotrophic factor. Figure created using Biorender.

experimental rodent models, stress led to lower blood iron levels (Teng et al., 2008) and resulted in decreased serum iron, increased liver iron, and altered iron transporter levels, including lower ferroportin in the duodenum and liver (Li et al., 2012; Teng et al., 2008; Wei et al., 2008; Zhao et al., 2008). Stressed rodents also had reduced serum iron, hemoglobin, ferritin, and erythropoietin, along with impaired iron absorption and transporter expression in the small intestine (Chen et al., 2009). In humans, military trainees undergoing weeks of psychological stress exhibited disrupted iron levels (Singh et al., 1991). In the brain, stress in rodents has been linked to decreased iron levels in the hippocampus and prefrontal cortex (Zhang et al., 2023). Stress hormones may disrupt iron metabolism in the brain: corticosterone application in vitro was found to dysregulate iron metabolism in hippocampal neurons (Wang et al., 2010). Thus, there is growing concern that increasing dietary iron intake and oral iron supplementation might not be enough to adequately address the risks of iron deficiency in the context of systemic inflammation, including inflammation produced by chronic psychosocial stress (Reid and Georgieff, 2023).

In this review, I will first present a hypothesized pathway between maternal stress during pregnancy and ELS in infancy, iron deficiency, and neurodevelopment through the HPA axis and the IL-6-hepcidin axis. I then will review the current literature that shows how iron metabolism is altered in stress conditions and focus on how this might occur in the prenatal and early infancy period, reflected in Fig. 1. I will outline possible mechanisms for how iron may mediate the relation between ELS and neurodevelopment through emerging research that focuses on the developing immune system as one of particular interest for PNI research.

1.1. Stress and iron deficiency: a hypothesized relationship between the HPA axis and the IL-6-hepcidin axis

In conditions of acute, time-limited stress, the mammalian body releases glucocorticoids through the activation of the HPA-axis. As glucocorticoids bind to receptors in monocytes, macrophages, and other immune cells, the cells subsequently reduce the release of pro-inflammatory cytokines and dampen the immune response (Irwin and Cole, 2011). If stress is chronic or severe, the HPA-axis remains activated for prolonged periods of time and does not return to baseline, potentially leading to glucocorticoid receptors (GR) in immune cells becoming resistant to glucocorticoids (Cohen et al., 2012). Consequently, the body fails to effectively down-regulate inflammatory responses with glucocorticoids released by the HPA axis. This results in higher levels of chronic inflammation, leading to higher levels of proinflammatory cytokines such as IL-6 and C-reactive protein (CRP) (Hantsoo et al., 2019; Lopresti, 2020).

Iron is tightly regulated by inflammation, as both the mammalian immune system and microbial pathogens require iron to grow and function. For this reason, iron plays a key role in infection susceptibility through the hypoferremic response which is an essential facet of the innate immune system that limits iron availability to invading pathogens by sequestering iron within cells and tissues (Cassat and Skaar, 2013). Hepcidin, along with its receptor and the iron transporter ferroportin, regulates iron absorption, storage, and distribution. Inflammatory responses, especially IL-6, increase hepcidin levels, reducing iron availability (Ganz and Nemeth, 2009). IL-6, crucial for hepcidin synthesis, increases with acute and chronic stress (Bower and Kuhlman, 2023; Marsland et al., 2017; Nemeth et al., 2004). This process helps control infections and adjusts iron supply to red blood cell precursors, contributing to the anemia often seen in infections and inflammatory conditions (Ganz and Nemeth, 2009). Consequently, iron is withheld from pathogens with the tradeoff of limiting iron for erythropoiesis and contributing to anemia (Nemeth and Ganz, 2023). Research in adult rats supports the hypothesis suggesting that inflammatory and hepcidin pathways connect stress and iron deficiency: IL-6 and hepcidin expression increased under stress and normalized following IL-6 monoclonal antibody treatment (Zhao et al., 2008). In a study of adolescent Indian boys, self-reported stress was positively associated with IL-6 and hepcidin concentrations (Augustine et al., 2014). Therefore, early life stress may not only sustain inflammation but may also disrupt iron homeostasis, compounding the body's vulnerability to infections and contributing to conditions that impact neurodevelopment such as iron deficiency anemia.

1.2. Evidence of stress and iron connections in the context of pregnancy and early life

Pregnancy poses a significant risk for developing iron deficiency due to increased iron demands of the fetoplacental unit and maternal blood volume expansion (Sangkhae et al., 2023). Low-income and racially- and ethnically-minoritized women are at especially high risk of iron deficiency in pregnancy (Brannon and Taylor, 2017). Maternal iron deficiency in pregnancy compromises fetal and neonatal iron levels and is linked to fetal iron deficiency (for review, see (Sangkhae et al., 2023)). Maternal iron deficiency in pregnancy also increases risks for cognitive deficits and impaired immune function in offspring (Arija et al., 2019; Coe et al., 2007; Georgieff, 2011). In the context of stress, our preliminary analyses in a pregnant cohort of Black women found an association between heightened cortisol response to a laboratory stressor and reduced serum ferritin levels in the third trimester (Reid and Keenan, 2023).

Iron transport to the fetus hinges on its transfer across the placenta. Maternal, placental, and fetal signals regulate placental and fetal iron homeostasis (Sangkhae et al., 2023). In iron-deficient pregnancies, the placenta adapts to sustain its iron content during iron scarcity, potentially compromising fetal iron, to sustain placental metabolic functions that indirectly support fetal development (Sangkhae et al., 2023). In healthy pregnancies, hepcidin is suppressed, which is crucial for ensuring adequate iron supply to the fetus through placental iron transport (Sangkhae et al., 2023). In conditions that result in inflammation and heightened hepcidin levels, maternal iron transfer to the placenta is reduced (Young et al., 2012). Thus, chronic stress may override pregnancy's suppression of maternal hepcidin.

Accordingly, we can look to the large literature on maternal immune activation to generate hypotheses on how stress and inflammation together may impact offspring iron endowment and ultimately neurodevelopment. Maternal immune activation in pregnancy is implicated in the pathogenesis of multiple psychopathologies and insults to neurodevelopment (Estes and McAllister, 2016), and may operate along iron metabolism pathways. For example, in mice, using lipopolysaccharide (LPS) injection to induce acute systemic inflammation resulted in increased hepcidin and iron deficiency in the dam and fetus (Fisher et al., 2020; Sangkhae et al., 2020). Similarly, in human pregnancies complicated by infection or inflammation, fetuses exhibit elevated cord blood plasma hepcidin levels and iron deficiency (Sangkhae et al., 2023). Perhaps more relevant to stress and its association with inflammation, chronic maternal inflammation due to excess adipose tissue and obesity heightens the risk of infant anemia (Yin et al., 2020). This is thought to be due to prolonged elevation of hepcidin levels in obese women, which ultimately lead to iron restriction (Sangkhae et al., 2023). More research is needed into the mechanisms of how stress leads to worse iron status in the neonate. Nevertheless, as prenatal maternal stress is associated with increased and chronic maternal inflammation (Coussons-Read et al., 2007), it as a potential pathway connecting stress to iron insufficiency for the maternal and fetal side alike.

Maternal stress exposure in pregnancy has now been associated with offspring iron status across multiple studies, possibly due to stress's impact on fetal iron endowment through inflammation and hepcidin. One study demonstrated that mothers in an area subjected to rocket attacks during pregnancy had offspring with lower cord blood ferritin levels compared to those living outside of rocket attack areas (Armony-Sivan et al., 2013). The association between maternal stress

and reduced offspring iron status was replicated in a study of 493 mother-infant pairs, where higher maternal stress, violence exposure, and anxiety were linked to lower cord blood ferritin in infants (Campbell et al., 2020). Pregnant women with elevated stress levels had one-year-old infants who were at greater risk for low plasma ferritin (Rendina et al., 2018). This is especially important in the third trimester of pregnancy, when the human fetus accumulates most of its iron endowment (Sangkhae et al., 2023). Reduced iron endowment in the fetus leads to increased risk of iron deficiency in infancy, as the rapidly growing neonate and infant places large demands on iron in the first few years of life (Cusick et al., 2018). This risk was observed in an animal model of prenatal stress: pregnant rhesus macaques exposed to stress gave birth to infant monkeys with lower iron levels as they grew (Coe et al., 2007).

Unfortunately, the risk to the iron deficient infant remains even with dietary iron supplementation. Elegant research shows that in an iron deficient state, iron is prioritized to red blood cells first and the brain (see (Cusick et al., 2018) for review). Thus, even when clinical markers of iron deficiency normalize, the infant brain can remain functionally iron deficient (Cusick et al., 2018). Even in the context of iron replete neonates, our work in a cohort of healthy, iron-replete infants found that infants with accumulated family stressors during the first year of life had poorer iron status and were at higher risk of being classified as either having iron deficiency or iron deficiency anemia (Reid et al., 2022). Thus, reduced iron endowment either through maternal stress leading to reduced fetal iron loading or through stress in infancy may carry ramifications for reduced iron availability to the rapidly growing brain. Taken together, the intricate relationship between maternal stress, inflammation, and iron regulation highlights the critical need for targeted PNI research that seeks to understands how maternal stress can significantly impact fetal iron endowment and subsequent infant iron status, ultimately affecting neurodevelopmental outcomes and long-term health.

1.3. Long term outcomes of stress and iron deficiency

1.3.1. Iron's impacts on the immune system

The immune system and its development in contexts of stress has been a key area of focus for PNI research on ELS and neurodevelopmental outcomes (O'Connor et al., 2014; Slopen et al., 2015; Yirmiya and Goshen, 2011; Yuan et al., 2019). In addition to iron acting as a direct mediator between ELS and the brain, iron deficiency that arises from contexts of stress may carry long-lasting implications for development through its impact on the immune system. Adequate iron is required for a wide range of immune and metabolic processes that include the proper functioning of physical barriers and immune cells, immune cell differentiation, and immune cell growth (Gombart et al., 2020; Haryanto et al., 2015). In the innate immune system, iron influences the reactive oxygen species that kill pathogens, cytokine production and action, cellular iron homeostasis, immune cell proliferation, monocyte and macrophage differentiation, and lymphocyte malnutrition (Gombart et al., 2020; Haryanto et al., 2015; Maggini et al., 2018). Iron also affects cytokines secretion and transcription factor activities involved in the immune response (Brittenham, 2012; Nairz et al., 2014). In the adaptive immune response, iron is important in T lymphocyte differentiation and proliferation (Maggini et al., 2018). Iron may influence the adaptive immune responses by its impact on immune cell differentiation and function as cofactors for epigenetic enzymes involved in histone and DNA demethylation (Chen et al., 2022).

Iron deficiency can dampen the innate and adaptive arms of antiviral immunity (Gombart et al., 2020) and is associated with immune system deficiencies (Drakesmith et al., 2021; Ganz and Nemeth, 2015; Stoffel et al., 2020). Iron deficiency impairs an organism's immune response, leading to decreased mitogen response, lowered natural killer cell activity, reduced lymphocyte ability to kill bacteria, and diminished interleukin-6 production (Calder, 2013). Individuals with iron deficiency have weaker antibody responses to vaccinations (Jiang et al., 2019; Stoffel et al., 2020). Children with anemia exhibit diminished inflammatory and immune responses (Ekiz et al., 2005). Randomized controlled trials in infants show that iron supplementation in the context of iron deficiency enhances infants' antibody response to vaccines (Stoffel et al., 2020). Iron supplementation may play a role in reducing the risk of childhood respiratory tract infections (Chen et al., 2013), and iron supplementation is associated with modulating immune function and reducing the severity of infections (Muñoz et al., 2007).

In recent years, a growing area of research has begun to shed light on how ELS and iron deficiency may have long-lasting effects on the developing immune system. A seminal study in nonhuman primates demonstrated that maternal stress during fetal development could lead to reduced iron levels in the offspring (Coe et al., 2007). More importantly, these lower iron levels were associated with subsequent changes in the offspring's innate immune system, specifically affecting NK cells (Coe et al., 2007). This finding establishes a direct link between early-life iron insufficiency and long-term alterations to the immune system. In my previous study conducted with a Chilean cohort, infants randomly assigned to receive iron supplementation showed reduced levels of peripheral CRP during adolescence, even after the supplementation trial had concluded (Reid et al., 2020). Additionally, I found that early iron status correlated with adolescent monocyte counts (Reid, 2020a). Higher serum ferritin levels at 6 months of age and randomization to receive iron supplementation between 6 and 12 months of age were both associated with lower monocyte counts (Reid, 2020a). Serum ferritin in infancy statistically mediated the relationship between family-level stressors in the first year of life and adolescent monocyte count (Reid, 2020a). This research indicates that early-life stress can lead to poor iron status, which may later be linked to increased inflammation and higher monocyte counts. As these are the first human studies supporting the association between stress, iron, and the immune system, they are preliminary but intriguing paths to follow for future research. Iron deficiency resulting from early-life stress may significantly impair both innate and adaptive immune responses, leading to long-term developmental consequences.

1.3.2. Shared neurodevelopmental impacts

Insufficient iron and ELS impact the foundation of the developing brain, affecting brain function, behavior, and psychopathology risk (Reid and Georgieff, 2023). Insufficient iron during gestation is associated with worse recognition memory, slower neural processing speed, poor offspring-mother bonding, and poor maternal interaction (Amin et al., 2010; Geng et al., 2015; Siddappa et al., 2004; Wachs et al., 2005). Pre- and postnatally, insufficient iron is associated with alterations in the hippocampus, dendritic structure, brain metabolism, myelination, and neurotransmitter function (Barks et al., 2018; Beard, 2001; Black et al., 2011; Lozoff et al., 2006). Similarly, stress exposure pre- and postnatally is associated with cortical thinning and decreased cognitive functioning, alterations in synaptic signaling, and changes in gene expression in the hippocampus and amygdala that are associated with anxious and depressive phenotypes (Sandman et al., 2018; Turecki and Meaney, 2016; Ishikawa et al., 2015). Other outcomes of early stress include reduced dendritic arborization in the prefrontal cortex and hippocampus, changes in hippocampal synaptic plasticity, and diminished spatial memory learning (Bagot et al., 2009; Monroy et al., 2010; Smith and Pollak, 2022; Turecki and Meaney, 2016).

Behavior is also affected by early iron deficiency, including motor dysfunction, altered social and affective behavior, and reduced memory performance (Jabès et al., 2015; Lozoff et al., 2008; Riggins et al., 2009). In parallel, fetal and early life stress are associated with impaired learning, worse attention regulation, impaired executive function, increased anxiety, increased depressive behaviors, and increased emotional reactivity (Gunnar and Reid, 2019; Swales et al., 2018; Vallée et al., 1999). Both exposures also carry an increased risk for long-term psychopathology, including autism spectrum disorder, schizophrenia,

and increased risk of anxiety, depression, and attention deficit hyperactivity disorder (Chan et al., 2018; Doom et al., 2018; Insel et al., 2008; Lukowski et al., 2010; O'Donnell et al., 2014; Schmidt et al., 2014; Van den Bergh et al., 2020). Whether these neurodevelopmental outcomes arise from parallel impacts or interplay between insufficient iron and ELS exposure is a nascent area of research.

There are likely multiple potential mechanisms that may mediate the lasting effects of iron status on immune function, behavior, and neuronal function. HPA axis development may play a role, as children who were iron deficient in infancy exhibited blunted HPA response to stressors (Felt et al., 2012). Insufficient maternal iron in pregnancy has been associated in rodent models with altered glucocorticoid levels and glucocorticoid receptors (GR) in offspring, which subsequently lead to reduced BDNF in the hippocampus and reduced neurogenesis (Ranade et al., 2013). Rodent models have also found evidence of changes to the epigenetic landscape after early iron deficiency, including expression changes in synaptic plasticity genes and BDNF in the hippocampus (Georgieff, 2017b; Tran et al., 2015). The relationship between iron metabolism and long-term changes to brain and immune functioning has been further elaborated in murine models. Emerging evidence suggests that iron deficiency in neonatal mice leads to an increased expression of proinflammatory cytokine gene pathways in the adult brain, even after iron levels are normalized (Personal communication, Phu Tran, 2023). Early life stress and iron deficiency may also contribute to the development of Alzheimer's disease later in life by promoting neuroinflammation, oxidative stress, and altering the expression of genes linked to Alzheimer's disease pathogenesis (Hoeijmakers et al., 2017, 2018; Carlson et al., 2008; Pappolla et al., 1992). Though more work is needed, these studies highlight possible cellular and molecular impacts of early stress and iron deficiency. Both insufficient iron and ELS profoundly impact development, affecting brain structure, function, behavior, and increasing the risk of psychopathology. These findings highlight the importance of understanding the potential parallel and interactive mechanisms within PNI research through which iron deficiency and ELS shape long-term neurodevelopmental outcomes.

2. Conclusion

This review seeks to initiate the exploration of the complex relationship/connection between prenatal and early life stress, disruptions in iron metabolism, and consequent alterations in brain and immune system development. Non-infectious, chronic psychological stress, mediated by glucocorticoid regulation and the hypothalamic-pituitary-adrenocortical (HPA) axis, could result in iron sequestration and reduced maternal iron absorption, even with adequate intake (Monk et al., 2013; Suchdev et al., 2017). Chronic, severe stress affects how the HPA axis functions (Lupien et al., 2009). HPA axis functioning may affect iron metabolism through increased inflammation and its effect on hepcidin, an essential iron regulator (Reid and Georgieff, 2023).

There are far more questions than answers in this domain. Can the impact of early life stress on the developing brain and immune system be modulated through iron metabolism? How does developmental timing of stress affect its impact on iron metabolism and immune development? Is there a degree of stress and HPA axis dysregulation that triggers the IL-6-hepcidin axis? How does this vary across developmental stages? How do ELS and iron deficiency create lasting effects on the developing immune system and contribute to neurodevelopment? Addressing these questions will not only expand our understanding but also guide interventions to mitigate the long-term impacts of ELS and nutritional deficiencies.

Research going forward across human and pre-clinical animal models is required to rigorously explore how stress affects iron metabolism and immune function in early life, and how these interactions shape long-term health. This research is interesting not just for applications in higher-income countries, but also could have the potential to redefine PNI within a global context, addressing health disparities arising from iron deficiency and ELS in various populations. As young children, infants, and pregnant people in the global majority experience the dual burdens of stress and iron deficiency, the recognition of iron's pivotal role in modulating the effects of ELS on the immune system and brain development underscores the urgency – and potential utility – of this research. PNI research is uniquely positioned to investigate the intersection of stress and iron metabolism in the developing immune system, offering opportunities improvement in health and neurodevelopmental outcomes globally.

AI statement

During the preparation of this work the author used ChatGPT and Grammarly to improve grammar and readability of the manuscript. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

CRediT authorship contribution statement

Brie M. Reid: Writing – review & editing, Writing – original draft, Visualization, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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References

Amin, S.B., Orlando, M., Eddins, A., MacDonald, M., Monczynski, C., Wang, H., 2010. In utero iron status and auditory neural maturation in premature infants as evaluated by auditory brainstem response. J. Pediatr. Urol. 156, 377–381.

Arija, V., Hernández-Martínez, C., Tous, M., Canals, J., Guxens, M., Fernández-Barrés, S., Ibarluzea, J., Babarro, I., Soler-Blasco, R., Llop, S., Vioque, J., Sunyer, J., Julvez, J., 2019. Association of iron status and intake during pregnancy with neuropsychological outcomes in children aged 7 Years: the prospective birth cohort infancia y medio ambiente (INMA) study. Nutrients 11.

Armony-Sivan, R., Aviner, S., Cojocaru, L., Fyttovitch, S., Ben-Alon, D., Etiassy, A., Babkoff, H., Lozoff, B., Anteby, E., 2013. Prenatal maternal stress predicts cord-blood ferritin concentration. J. Perinat. Med. 41, 259–265.

Auerbach, M., Abernathy, J., Juul, S., Short, V., Derman, R., 2021. Prevalence of iron deficiency in first trimester, nonanemic pregnant women. J. Matern. Fetal Neonatal Med. 34, 1002–1005.

Augustine, L.F., Nair, K.M., Rao, S.F., Rao, M.V., Ravinder, P., Balakrishna, N., Laxmaiah, A., Vazir, S., 2014. Adolescent life-event stress in boys is associated with elevated IL-6 and hepcidin but not hypoferremia. J. Am. Coll. Nutr. 33, 354–362.

Bagot, R.C., van Hasselt, F.N., Champagne, D.L., Meaney, M.J., Krugers, H.J., Joels, M., 2009. Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. Neurobiol. Learn. Mem. 92, 292–300.

Barks, A., Hall, A.M., Tran, P.V., Georgieff, M.K., 2018. Iron as a model nutrient for understanding the nutritional origins of neuropsychiatric disease. Pediatr. Res. 85, 176–182.
Baskin, R., Hill, B., Jacka, F.N., O'Neil, A., Skouteris, H., 2015. The association between diet quality and mental health during the perinatal period. A systematic review. Appetite 91, 41–47.
Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. Mol. Psychiatr. 21, 642–649.
Beard, J.L., 2001. Iron biology in immune function, muscle metabolism and neuronal functioning. J. Nutr. 131, 568S–579S. ; discussion 580S.
Black, M.M., Quigg, A.M., Hurley, K.M., Pepper, M.R., 2011. Iron deficiency and iron-deficiency anemia in the first two years of life: strategies to prevent loss of developmental potential. Nutr. Rev. 69 (Suppl. 1), S64–S70.
Black, M.M., Walker, S.P., Fernald, L.C.H., Andersen, C.T., DiGirolamo, A.M., Lu, C., McCoy, D.C., Fink, G., Shawar, Y.R., Shiffman, J., Devercelli, A.E., Wodon, Q.T., Vargas-Barón, E., Grantham-McGregor, S., 2017. Early childhood development coming of age: science through the life course. Lancet 389, 77–90.
Bower, J.E., Kuhlman, K.R., 2023. Psychoneuroimmunology: an introduction to immune-to-brain communication and its implications for clinical psychology. Annu. Rev. Clin. Psychol. 19, 331–359.
Brannon, P.M., Taylor, C.L., 2017. Iron supplementation during pregnancy and infancy: uncertainties and implications for research and policy. Nutrients 9, 1327.
Brittenham, G.M., 2012. Safety of iron fortification and supplementation in malaria-endemic areas. Nestlé Nutrition Inst Work Ser 117–127.
Calder, P.C., 2013. Feeding the immune system. Proc. Nutr. Soc. 72, 299–309.
Campbell, R.K., Tamayo-Ortiz, M., Cantoral, A., Schnaas, L., Osorio-Valencia, E., Wright, R.J., Tellez-Rojo, M.M., Wright, R.O., 2020. Maternal prenatal psychosocial stress and prepregnancy BMI associations with fetal iron status. Curr. Dev. Nutr. 4.
Carlson, E.S., Magid, R., Petryk, A., Georgieff, M.K., 2008. Iron deficiency alters expression of genes implicated in Alzheimer disease pathogenesis. Brain Res. 1237, 75–83.
Cassat, J.E., Skaar, E.P., 2013. Iron in infection and immunity. Cell Host Microbe 13, 509–519.
Chan, J.C., Nugent, B.M., Bale, T.L., 2018. Parental advisory: maternal and paternal stress can impact offspring neurodevelopment. Biol. Psychiatr. 83, 886–894.
Chen, H.Y., Hsu, M., Lio, C.W.J., 2022. Micro but mighty-Micronutrients in the epigenetic regulation of adaptive immune responses. Immunol. Rev. 305, 152–164.
Chen, J.B., Shen, H., Chen, C.J., Wang, W.Y., Yu, S.Y., Zhao, M., Li, M., 2009. The effect of psychological stress on iron absorption in rats. BMC Gastroenterol. 9.
Chen, K., Chen, X.R., Zhang, L., Luo, H.Y., Gao, N., Wang, J., Fu, G.Y., Mao, M., 2013. Effect of simultaneous supplementation of vitamin A and iron on diarrheal and respiratory tract infection in preschool children in Chengdu City, China. Nutrition 29, 1197–1203.
Coe, C.L., Lubach, G.R., Shirtcliff, E.A., 2007. Maternal stress during pregnancy predisposes for iron deficiency in infant monkeys impacting innate immunity. Pediatr. Res. 61, 520–524.
Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., Turner, R. B., 2012. Chronic Stress, Glucocorticoid Receptor Resistance, Inflammation, and Disease Risk, vol. 109. Proceedings of the National Academy of Sciences, pp. 5995–5999.
Coussons-Read, M.E., Okun, M.L., Nettles, C.D., 2007. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain Behav. Immun. 21, 343–350.
Cusick, S., Georgieff, M., Rao, R., 2018. Approaches for reducing the risk of early-life iron deficiency-induced brain dysfunction in children. Nutrients 10, 227.
Doom, J.R., Richards, B., Caballero, G., Delva, J., Gahagan, S., Lozoff, B., 2018. Infant iron deficiency and iron supplementation predict adolescent internalizing, externalizing, and social problems. J. Pediatr. 195, 199–205.
Drakesmith, H., Pasricha, S.R., Cabantchik, I., Hershko, C., Weiss, G., Girelli, D., Stoffel, N., Muckenthaler, M.U., Nemeth, E., Camaschella, C., Klenerman, P., Zimmermann, M.B., 2021. Vaccine efficacy and iron deficiency: an intertwined pair? Lancet Haematology 8, E666–E669.
Ekiz, C., Agaoglu, L., Karakas, Z., Gurel, N., Yalcin, I., 2005. The effect of iron deficiency anemia on the function of the immune system. Hematol J 5, 579–583.
Estes, M.L., McAllister, A.K., 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353 (6301), 772–777.
Felt, B.T., Peirano, P., Algarín, C., Chamorro, R., Sir, T., Kaciroti, N., Lozoff, B., 2012. Long-term neuroendocrine effects of iron-deficiency anemia in infancy. Pediatr. Res. 71, 707–712.
Fisher, A.L., Sangkhae, V., Presicce, P., Chougnet, C.A., Jobe, A.H., Kallapur, S.G., Tabbah, S., Buhimschi, C.S., Buhimschi, I.A., Ganz, T., Nemeth, E., 2020. Fetal and amniotic fluid iron homeostasis in healthy and complicated murine, macaque, and human pregnancy. Jci Insight 5.
Ganz, T., Nemeth, E., 2009. Iron sequestration and anemia of inflammation. Semin. Hematol. 46, 387–393.
Ganz, T., Nemeth, E., 2015. Iron homeostasis in host defence and inflammation. Nat. Rev. Immunol. 15, 500–510.
Geng, F., Mai, X., Zhan, J., Xu, L., Zhao, Z., Georgieff, M., Shao, J., Lozoff, B., 2015. Impact of fetal-neonatal iron deficiency on recognition memory at 2 Months of age. J. Pediatr. 167, 1226–1232.
Georgieff, M.K., 2011. Long-term brain and behavioral consequences of early iron deficiency. Nutr. Rev. 69, S43–S48.
Georgieff, M.K., 2017a. Iron assessment to protect the developing brain. Am. J. Clin. Nutr. 106, 1588S–1593S.
Georgieff, M.K., 2017b. Iron assessment to protect the developing brain. Am. J. Clin. Nutr. 106, 1588S–1593S.
Gombart, A.F., Pierre, A., Maggini, S., 2020. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. Nutrients 12.
Gunnar, M., Reid, B.M., 2019. Early deprivation revisited: contemporary studies of the impact on young children of institutional care. Annual Rev.Develop. Psychology 1, 93–118.
Hantsoo, L., Kornfield, S., Anguera, M.C., Epperson, C.N., 2019. Inflammation: a proposed intermediary between maternal stress and offspring neuropsychiatric risk. Biol. Psychiatr. 85, 97–106.
Haryanto, B., Suksmasari, T., Wintergerst, E., Maggini, S., 2015. Multivitamin supplementation supports immune function and ameliorates conditions triggered by reduced air quality. Vitam. Miner 4, 2376, 1318.1000128.
Hoeijmakers, L., Lesuis, S.L., Krugers, H., Lucassen, P.J., Korosi, A., 2018. A preclinical perspective on the enhanced vulnerability to Alzheimer's disease after early-life stress. Neurobiology of Stress 8, 172–185.
Hoeijmakers, L., Ruigrok, S.R., Amelianchik, A., Ivan, D., van Dam, A.M., Lucassen, P.J., Korosi, A., 2017. Early-life stress lastingly alters the neuroinflammatory response to amyloid pathology in an Alzheimer's disease mouse model. Brain Behav. Immun. 63, 160–175.
Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Jones, L., Dunne, M.P., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health 2, e356–e366.
Insel, B.J., Schaefer, C.A., McKeague, I.W., Susser, E.S., Brown, A.S., 2008. Maternal iron deficiency and the risk of schizophrenia in offspring. Arch Gen Psychiatry 65, 1136–1144.
Irwin, M.R., Cole, S.W., 2011. Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11, 625–632.
Ishikawa, J., Nishimura, R., Ishikawa, A., 2015. Early-life stress induces anxiety-like behaviors and activity imbalances in the medial prefrontal cortex and amygdala in adult rats. Eur. J. Neurosci. 41, 442–453.
Jabès, A., Thomas, K.M., Langworthy, S., Georgieff, M.K., Nelson, C.A., 2015. Functional and anatomic consequences of diabetic pregnancy on memory in ten-year-old children. J. Dev. Behav. Pediatr. 36, 529–535.
Jiang, Y.H., Li, C.F., Wu, Q., An, P., Huang, L.Q., Wang, J., Chen, C., Chen, X., Zhang, F., Ma, L., Liu, S.H., He, H.Q., Xie, S.Y., Sun, Y.B., Liu, H.S., Zhan, Y., Tao, Y., Liu, Z., Sun, X.H., Hu, Y.M., Wang, Q., Ye, D.J., Zhang, J., Zou, S.H., Wang, Y., Wei, G., Liu, Y.Z., Shi, Y.F., Chin, Y.E., Hao, Y.Q., Wang, F.D., Zhang, X.R., 2019. Iron-dependent histone 3 lysine 9 demethylation controls B cell proliferation and humoral immune responses. Nat. Commun. 10.
Krebs, N.F., Lozoff, B., Georgieff, M.K., 2017. Neurodevelopment: the impact of nutrition and inflammation during infancy in low-resource settings. Pediatrics 139, S50–S58.
Li, Y.J., Zheng, Y.Y., Qian, J.X., Chen, X.M., Shen, Z.L., Tao, L.P., Li, H.X., Qin, H.H., Li, M., Shen, H., 2012. Preventive effects of zinc against psychological stress-induced iron dyshomeostasis, erythropoiesis inhibition, and oxidative stress status in rats. Biol. Trace Elem. Res. 147, 285–291.
Lopresti, A.L., 2020. The effects of psychological and environmental stress on micronutrient concentrations in the body: a review of the evidence. Adv. Nutr. 11, 103–112.
Lozoff, B., Beard, J., Connor, J., Barbara, F., Georgieff, M., Schallert, T., 2006. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr. Rev. 64, S34–S43 discussion S72-91.
Lozoff, B., Clark, K.M., Jing, Y., Armony-Sivan, R., Angelilli, M.L., Jacobson, S.W., 2008. Dose-response relationships between iron deficiency with or without anemia and infant social-emotional behavior. J. Pediatr. Urol. 152, 696–702.
Lukowski, A.F., Koss, M., Burden, M.J., Jonides, J., Nelson, C.A., Kaciroti, N., Jimenez, E., Lozoff, B., 2010. Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory. Nutr. Neurosci. 13, 54–70.
Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445.
Maggini, S., Pierre, A., Calder, P.C., 2018. Immune function and micronutrient requirements change over the life course. Nutrients 10.
Marsland, A.L., Walsh, C., Lockwood, K., John-Henderson, N.A., 2017. The effects of acute psychological stress on circulating and stimulated inflammatory markers: a systematic review and meta-analysis. Brain Behav. Immun. 64, 208–219.
Monk, C., Georgieff, M.K., Osterholm, E.A., 2013. Research Review: maternal prenatal distress and poor nutrition - mutually influencing risk factors affecting infant neurocognitive development. JCPP (J. Child Psychol. Psychiatry) 54, 115–130.
Monk, C., Lugo-Candelas, C., Trumpff, C., 2019. Prenatal developmental origins of future psychopathology: mechanisms and pathways. Annu. Rev. Clin. Psychol. 15, 317–344.
Monroy, E., Hernandez-Torres, E., Flores, G., 2010. Maternal separation disrupts dendritic morphology of neurons in prefrontal cortex, hippocampus, and nucleus accumbens in male rat offspring. J. Chem. Neuroanat. 40, 93–101.
Muñoz, C., Rios, E., Olivos, J., Brunser, O., Olivares, M., 2007. Iron, copper and immunocompetence. Br. J. Nutr. 98, S24–S28.
Nairz, M., Haschka, D., Demetz, E., Weiss, G., 2014. Iron at the interface of immunity and infection. Front. Pharmacol. 5, 152.
Nemeth, E., Ganz, T., 2023. Hepcidin and iron in health and disease. Annu. Rev. Med. 74, 261–277.
Nemeth, E., Rivera, S., Gabayan, V., Keller, C., Taudorf, S., Pedersen, B.K., Ganz, T., 2004. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J. Clin. Invest. 113, 1271–1276.
Nusslock, R., Miller, G.E., 2016. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol. Psychiatr. 80, 23–32.

O'Connor, T.G., Moynihan, J.A., Caserta, M.T., 2014. Annual research review: the neuroinflammation hypothesis for stress and psychopathology in children–developmental psychoneuroimmunology. JCPP (J. Child Psychol. Psychiatry) 55, 615–631.
O'Donnell, K.J., Glover, V., Barker, E.D., O'Connor, T.G., 2014. The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev. Psychopathol. 26, 393–403.
Pappolla, M.A., Omar, R.A., Kim, K.S., Robakis, N.K., 1992. Immunohistochemical evidence of oxidative [corrected] stress in Alzheimer's disease. Am. J. Pathol. 140 (3), 621.
Ranade, S.C., Nawaz, S., Chakrabarti, A., Gressens, P., Mani, S., 2013. Spatial memory deficits in maternal iron deficiency paradigms are associated with altered glucocorticoid levels. Horm. Behav. 64, 26–36.
Reid, B.M., 2020a. Pathways to Depressive Symptoms and Inflammation from Early Psychosocial and Nutritional Adversity: A Longitudinal Study of Chilean Youth. University of Minnesota, United States – Minnesota, p. 65.
Reid, B.M., Doom, J.R., Argote, R.B., Correa-Burrows, P., Lozoff, B., Blanco, E., Gahagan, S., 2020. Pathways to inflammation in adolescence through early adversity, childhood depressive symptoms, and body mass index: a prospective longitudinal study of Chilean infants. Brain Behav. Immun. 86, 4–13.
Reid, B.M., East, P., Blanco, E., Doom, J.R., Burrows, R.A., Correa-Burrows, P., Lozoff, B., Gahagan, S., 2022. Early-life adversity is associated with poor iron status in infancy. Dev. Psychopathol. 1–12.
Reid, B.M., Georgieff, M.K., 2023. The interaction between psychological stress and iron status on early-life neurodevelopmental outcomes. Nutrients 15, 3798.
Reid, B.M.D.A., 2020b. Challenges in researching the immune pathways between early life adversity and psychopathology. Dev. Psychopathol. 32 (5), 1597–1624.
Reid, B.M.G., Keenan, K., 2023. Association between cortisol stress response and iron status in pregnancy: insights from a study of pregnant Black women with medicaid insurance. In: Proceedings of the International Society of Psychoneuroendocrinology Annual Conference.. London, UK.
Rendina, D.N., Blohowiak, S.E., Coe, C.L., Kling, P.J., 2018. Maternal perceived stress during pregnancy increases risk for low neonatal iron at delivery and depletion of storage iron at one year. J. Pediatr. Urol. 200, 166.
Riggins, T., Miller, N.C., Bauer, P.J., Georgieff, M.K., Nelson, C.A., 2009. Consequences of low neonatal iron status due to maternal diabetes mellitus on explicit memory performance in childhood. Dev. Neuropsychol. 34, 762–779.
Sandman, C.A., Curran, M.M., Davis, E.P., Glynn, L.M., Head, K., Baram, T.Z., 2018. Cortical thinning and neuropsychiatric outcomes in children exposed to prenatal adversity: a role for placental crh? Am. J. Psychiatr. 175, 471–479.
Sangkhae, V., Fisher, A.L., Ganz, T., Nemeth, E., 2023. Iron homeostasis during pregnancy: maternal, placental, and fetal regulatory mechanisms. Annu. Rev. Nutr. 43, 279–300.
Sangkhae, V., Fisher, A.L., Wong, S., Koenig, M.D., Tussing-Humphreys, L., Chu, A., Lelic, M., Ganz, T., Nemeth, E., 2020. Effects of maternal iron status on placental and fetal iron homeostasis. J. Clin. Invest. 130, 625–640.
Schmidt, R.J., Tancredi, D.J., Krakowiak, P., Hansen, R.L., Ozonoff, S., 2014. Maternal intake of supplemental iron and risk of autism spectrum disorder. Am. J. Epidemiol. 890–900.
Siddappa, A.M., Georgieff, M.K., Wewerka, S., Worwa, C., Nelson, C.A., DeRegnier, R.A., 2004. Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. Pediatr. Res. 55, 1034–1041.
Singh, A., Smoak, B.L., Patterson, K.Y., LeMay, L.G., Veillon, C., Deuster, P.A., 1991. Biochemical indices of selected trace minerals in men: effect of stress. Am. J. Clin. Nutr. 53, 126–131.
Skalicky, A., Meyers, A.F., Adams, W.G., Yang, Z., Cook, J.T., Frank, D.A., 2006. Child food insecurity and iron deficiency anemia in low-income infants and toddlers in the United States. Matern. Child Health J. 10, 177–185.
Slopen, N., Loucks, E.B., Appleton, A.A., Kawachi, I., Kubzansky, L.D., Non, A.L., Buka, S., Gilman, S.E., 2015. Early origins of inflammation: an examination of prenatal and childhood social adversity in a prospective cohort study. Psychoneuroendocrinology 51, 403–413.
Smith, K.E., Pollak, S.D., 2022. Early life stress and neural development: implications for understanding the developmental effects of COVID-19. Cognit. Affect Behav. Neurosci. 22, 643–654.
Stevens, G.A., Finucane, M.M., De-Regil, L.M., Paciorek, C.J., Flaxman, S.R., Branca, F., Peña-Rosas, J.P., Bhutta, Z.A., Ezzati, M., 2013. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. Lancet Global Health 1, e16–e25.
Stoffel, N.U., Uyoga, M.A., Mutuku, F.M., Frost, J.N., Mwasi, E., Paganini, D., van Der Klis, F.R.M., Malhotra, I.J., LaBeaud, A.D., Ricci, C., Karanja, S., Drakesmith, H., King, C.H., Zimmermann, M.B., 2020. Iron deficiency anemia at time of vaccination predicts decreased vaccine response and iron supplementation at time of vaccination increases humoral vaccine response: a birth cohort study and a randomized trial follow-up study in Kenyan infants. Front. Immunol. 11.
Suchdev, P.S., Boivin, M.J., Forsyth, B.W., Georgieff, M.K., Guerrant, R.L., Nelson, C.A., 2017. Assessment of neurodevelopment, nutrition, and inflammation from fetal life to adolescence in low-resource settings. Pediatrics 139.
Swales, D.A., Winiarski, D.A., Smith, A.K., Stowe, Z.N., Newport, D.J., Brennan, P.A., 2018. Maternal depression and cortisol in pregnancy predict offspring emotional reactivity in the preschool period. Dev. Psychobiol. 60, 557–566.
Teng, W.F., Sun, W.M., Shi, L.F., Hou, D.D., Liu, H., 2008. Effects of restraint stress on iron, zinc, calcium, and magnesium whole blood levels in mice. Biol. Trace Elem. Res. 121, 243–248.
Tran, P.V., Kennedy, B.C., Lien, Y.C., Simmons, R.A., Georgieff, M.K., 2015. Fetal iron deficiency induces chromatin remodeling at the *Bdnf* locus in adult rat hippocampus. Am. J. Physiol. Regul. Integr. Comp. Physiol. 308, R276–R282.
Turecki, G., Meaney, M.J., 2016. Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. Biol. Psychiatr. 79, 87–96.
Vallée, M., Maccari, S., Dellu, F., Simon, H., Le Moal, M., Mayo, W., 1999. Long-term effects of prenatal stress and postnatal handling on age-related glucocorticoid secretion and cognitive performance: a longitudinal study in the rat. Eur. J. Neurosci. 11, 2906–2916.
Van den Bergh, B.R.H., van den Heuvel, M.I., Lahti, M., Braeken, M., de Rooij, S.R., Entringer, S., Hoyer, D., Roseboom, T., Raikkonen, K., King, S., Schwab, M., 2020. Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. Neurosci. Biobehav. Rev. 117, 26–64.
Wachs, T.D., Pollitt, E., Cueto, S., Jacoby, E., 2005. Relation of neonatal iron status to individual variability in neonatal temperament. Dev. Psychobiol. 46, 141–153.
Wang, L., Wang, H., Li, L., Li, W., Dong, X., Li, M., Lv, L., 2010. Corticosterone induces dysregulation of iron metabolism in hippocampal neurons in vitro. Biol. Trace Elem. Res. 137, 88–95.
Wei, C.L., Zhou, J., Huang, X.Q., Li, M., 2008. Effects of psychological stress on serum iron and erythropoiesis. Int. J. Hematol. 88, 52–56.
Yin, S.H., Zhou, Y.B., Li, H.T., Cheng, Z.H., Zhang, Y.L., Zhang, L., Liu, J.F., Liu, J.M., 2020. Association of maternal BMI during early pregnancy with infant anemia: a large Chinese birth cohort. Nutr. Metabol. 17.
Yirmiya, R., Goshen, I., 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav. Immun. 25, 181–213.
Young, M.E., Griffin, I., Pressman, E., McIntyre, A.W., Cooper, E., McNanley, T., Harris, Z.L., Westerman, M., O'Brien, K.O., 2012. Maternal hepcidin is associated with placental transfer of iron derived from dietary heme and nonheme sources. J. Nutr. 142, 33–39.
Yuan, N., Chen, Y., Xia, Y., Dai, J., Liu, C., 2019. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. Transl. Psychiatry 9, 233.
Zhang, H., He, L., Li, S.F., Zhai, M.H.Y., Ma, S.M., Jin, G., Li, M.Y., Zhou, F., Tian, H., Nuerkaman, T., Sun, Q.R., Zhang, Y., Hou, J.C., Sun, G.X., Yin, S.L., 2023. Cerebral iron deficiency may induce depression through downregulation of the hippocampal glucocorticoid-glucocorticoid receptor signaling pathway. J. Affect. Disord. 332, 125–135.
Zhao, M., Chen, J.B., Wang, W.Y., Wang, L., Ma, L., Shen, H., Li, M., 2008. Psychological stress induces hypoferremia through the IL-6-hepcidin axis in rats. Biochem. Biophys. Res. Commun. 373, 90–93.