Iron as a Model Nutrient for Understanding the Nutritional Origins of Neuropsychiatric Disease

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Abstract

Adequate nutrition during the pre- and early-postnatal periods plays a critical role in programming early neurodevelopment. Disruption of neurodevelopment by nutritional deficiencies can result not only in lasting functional deficits, but increased risk of neuropsychiatric disease in adulthood. Historical periods of famine such as the Dutch Hunger Winter and the Chinese Famine have provided foundational evidence for the long-term effects of developmental malnutrition on neuropsychiatric outcomes. Because neurodevelopment is a complex process that consists of many nutrient- and brain-region specific critical periods, subsequent clinical and pre-clinical studies have aimed to elucidate the specific roles of individual macro- and micronutrient deficiencies in neurodevelopment and neuropsychiatric pathologies. This review will discuss developmental iron deficiency (ID), the most common micronutrient deficiency worldwide, as a paradigm for understanding the role of early-life nutrition in neurodevelopment and risk of neuropsychiatric disease. We will review the epidemiologic data linking ID to neuropsychiatric dysfunction, as well as the underlying structural, cellular, and molecular mechanisms that are thought to underlie these lasting effects. Understanding the mechanisms driving lasting dysfunction and disease risk is critical for development and implementation of nutritional policies aimed at preventing nutritional deficiencies and their long-term sequelae.

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BODY TEXT

Early Life Nutrition and Risk of Neuropsychiatric Disorders

Neurodevelopment is a complex process that involves not only establishment and expansion of neuronal and glial cell populations, but maturation of complex cell morphologies and establishment of appropriate connectivity among cells and among brain regions. The successful construction of these neural circuits during development is critical for the ability of the individual to perform complex behaviors. Increasing evidence supports the hypothesis that disruption of these processes during early development can result in neurocognitive and neuropsychiatric dysfunctions that appear later in life and can last across the lifespan (1). Although much of neurodevelopment proceeds according to a relatively hard-wired, time-locked, experience-independent genetic program, environmental experiences and exposures exert significant influences on neurodevelopment through the complex interplay between genes and the environment.

Nutrition is one of the most important environmental factors in early neurodevelopment. Although almost all nutrients are needed for normal brain development, a subset of nutrients plays a particularly significant role because they support the high rate of brain metabolism during late fetal and early postnatal life (2). These include macronutrients such as protein, long chain polyunsaturated fatty acids (LC-PUFAs), and glucose, as well as select micronutrients such as iron, zinc, and vitamins, which are involved in a variety of critical neurodevelopmental processes across brain regions (Reviewed in detail in 3–5) (Table 1). Moreover, while it has been well established that fetal nutrition plays a role acutely in fetal development and pregnancy outcomes (6), it is increasingly understood that fetal nutrition also exerts long-term effects on offspring health and disease risk – including neurocognitive health and disease – into adulthood and throughout the lifespan. This growing body of both clinical and preclinical literature supports the hypothesis that fetal and early postnatal macro- and micro-nutritional status is linked to the risk of psychopathology later in life (7–9).

Cohort studies of historical periods of famine, such as the Dutch Hunger Winter and the Chinese Famine, have provided foundational evidence for the role of fetal and early postnatal undernutrition in neuropsychiatric disease. These studies demonstrate that inadequate nutrition during fetal development is associated with an increased risk of schizophrenia and affective disorders, among individuals prenatally exposed to famine (10–12). Studies of preclinical models have helped to elucidate the specific roles and mechanisms of individual macro- and micronutrient deficiencies that are particularly associated with the development of neuropsychiatric pathologies.

A comprehensive review of all nutrients is beyond the scope of this article. Thus, the following sections focus on iron deficiency (ID) as a paradigm for the effects of nutritional deficiency on neurodevelopment and neuropsychiatric disease risk, due to its extensive clinical and preclinical literature. ID has been implicated in multiple studies as a risk factor for developmentally-based psychopathologies in humans (13–15) and iron's biology of action has been well-studied. Thus, this review discusses fetal-neonatal ID from the epidemiological evidence linking it to neuropsychiatric disorders, to the structural, cellular,

and molecular mechanisms that underlie its lasting effects. Additionally, the importance and potential application of understanding the underlying mechanisms in shaping therapies is discussed.

The Developmental Origins of Health and Disease (DOHaD) Hypothesis

The Developmental Origins of Health and Disease, or DOHaD, hypothesis posits that the early-life environment, particularly the fetal and early postnatal environment, influences later-life health outcomes and disease risks. The mechanism by which this effect occurs is the subject of considerable research effort. Originally the DOHaD hypothesis was applied to risk for adult cardiovascular disease (16,17). However, it is now understood that a wide range of early life exposures and conditions, including malnutrition, can affect lifetime health and disease risk across multiple organ systems. One of the classic examples with respect to this nutritional deprivation hypothesis comes from cohort studies of individuals who were exposed to gestational malnutrition during the Dutch Famine of 1944–1945. During this 5-month period, daily maternal rations fell to below 1,000 calories. As a result, pregnant women and their fetuses were exposed to famine during early, mid-, or late gestation (18). These cohort studies demonstrated that gestational exposure to famine was associated with a variety of adverse health outcomes in adulthood, including obstructive airway disease (19), impaired glucose tolerance (20), dyslipidemia (21), coronary heart disease (22), and schizophrenia (10,11). Interestingly, famine during different periods of gestation was associated with distinct health risks, suggesting that discrete critical periods exist during the fetal period for different organ systems and health outcomes. These observations also suggested that disruption of nutritional status during critical periods results in permanent compromise of organ systems and related health outcomes.

Nutrition and Critical Periods of Neurodevelopment

A critical period in organ system development is characterized as a window of time in which there is a high degree of plasticity and thus increased malleability in response to environmental exposures, including nutrition (23). With respect to nutrition, critical periods demarcate time windows in which a tissue is most sensitive to the presence or absence of a specific nutrient. Generally, a critical period coincides with the time when a given nutrient is in highest demand - often during a period of rapid tissue growth and development. Because tissue growth and development are highly metabolic processes, and sufficient nutrient supply is critical for energy and metabolism, tissues are most likely to suffer detrimental effects from insufficient supply during this window. Each tissue develops on a different time scale and has different nutritional requirements for appropriate development (23,24), and so an exposure at a given time point may affect one tissue or function but not another. As such, there is no single critical period during development; rather, there are a series of nutrient- and tissue-specific critical periods throughout the broad time-span of development (23).

Relative to other primates, humans have larger and more highly metabolic brains than would be predicted based on average body size. The human brain has a higher energy demand per unit weight than any other tissue, and in the adult, the brain accounts for 20 to 25% of basal energy supply despite comprising only 2% of total body mass (25). The developing fetal and early postnatal brain has an even higher metabolic demand than the adult brain, accounting

for as much as 60% of the total metabolic rate (25). As such, the developing brain is exquisitely sensitive to nutrient supply. The brain does not develop as a uniform tissue. Rather, each region develops on a unique timeline, with unique timing of nutrient demands, resulting in a series of brain region-specific critical periods. Thus, the effects of insufficient nutrient supply on the developing brain vary depending on the nutrient, the duration of the deficiency and the neurodevelopmental timing of the deficiency relative to the various regional critical periods (26). Failure to construct a brain region during its critical period can lead to residual structural and connectivity defects, persistent neurochemical and electrophysiological abnormalities, or permanent dysregulation of gene expression.

Disruption of neurodevelopmental processes by nutritional deficiency can result in irreversible changes to tissue structure, metabolic regulation, physiology and function, which ultimately manifests as functional deficits and increased risk for neuropsychiatric disease, although the specific manifestation of the deficiency is dependent upon the nutrient and the timing of the deficiency (Table 2).

Clinical Studies Linking Early-Life Iron Deficiency and Risk of Psychiatric Diseases

ID is the most common micronutrient deficiency worldwide, affecting an estimated 2 billion people and 40–50% of pregnant women and preschool-aged children (27,28). While ID is most prevalent in developing countries, it is notable among nutrient deficiencies for its prevalence in industrialized countries, including the United States, where 18% of pregnant women and 14% of 1–2 year olds are affected (29,30). Though ID is ubiquitous across age groups, ID in pregnant women and young children is of particular interest due to the well-established relationship between developmental ID and later-life neurologic dysfunction.

Longitudinal cohort studies of formerly ID (FID) individuals who experienced iron deficiency during infancy have provided detailed information about the specific cognitive and socioemotional functions that are impaired by developmental iron deficiency. At 5 years of age, FID children exhibited slower perceptual speed and poorer understanding of quantitative concepts (31) and impaired language abilities (32). In early adolescence, FID individuals were characterized as having slower perceptual speed, poorer spatial memory, and developmental delays in a selective attention task (31). These impairments may contribute to the lower scores of FID adolescents on tests of reading and arithmetic as well as the increased likelihood to repeat a grade or receive referrals for tutoring (33). As young adults, FID individuals performed worse on measures of recognition memory and strategy shifting (34). Finally, outcome measures of employment and education at 25 years suggested that the cognitive deficits experienced throughout infancy, childhood, and adolescence had a significant impact on the lives of FID adults (35). Compared with non-ID individuals, a larger proportion of FID adults did not complete secondary school and were not actively pursuing further training or education (35).

Likewise, ID infants and FID children and adults exhibit long-lasting socioemotional and affective deficits. At ages 4 to 5, FID children exhibited reduced positive affect during an interactive task with their mother (36) or a stranger (37) and were found to be more passive and unengaged than iron sufficient children (37,38). FID children also displayed poorer self-control on a delayed-gratification task (37). As early adolescents, FID individuals received

higher ratings from parents or teachers on measures of anxiety and depression, social problems, delinquent behavior, and aggression (33). Finally, FID adults self-reported more feelings of detachment and negative emotions and had lower ratings for emotional health (35).

Separate cohort studies have used measures of maternal iron intake and maternal iron deficiency during pregnancy to assess the effects of iron deficiency during fetal development on long-term neurodevelopmental outcomes of offspring. These studies have found a significant association between maternal iron deficiency and increased risk of schizophrenia spectrum disorders in adulthood (13,15), as well as an association between low maternal iron intake and increased risk of autism spectrum disorders (14).

Collectively, these human cohort studies point to a specific set of neurocognitive and neuropsychiatric deficits that arise from fetal and early postnatal iron deficiency, implicating a critical role for iron in the normal development of these functions.

Biological Bases for the Long-term Neuropsychiatric Effects of Early-life Nutritional Perturbations

Understanding the potential mechanisms by which early-life nutritional perturbations influence neurodevelopment and subsequent risk for neuropsychiatric disease is critical for developing effective prevention and treatment strategies. The two central hypotheses for these effects are residual structural defects and dysregulation of genes involved in neural function. In the residual structural defects hypothesis, an early-life nutritional exposure, such as malnutrition, during a critical period of development results in aberrant structural development ranging from gross structural abnormalities to fine ultrastructural changes (23,39,40). In the gene dysregulation hypothesis, the early-life nutritional environment aberrantly programs gene expression, which in turn stably alters the subsequent phenotype (41–45). Though these can be posed as two separate hypotheses, in fact, it is likely a combination of both that drives aberrant neurodevelopment and lifetime risk for neuropsychiatric dysfunction.

Residual Structural Defects—Rodent and porcine models of fetal-neonatal ID have both demonstrated gross morphological changes to both grey and white matter in the brains of developmentally iron deficient individuals. In a porcine model, developmental ID during the first 30 days of life (approximately equivalent to the first 4 months of human postnatal development) results in a decreased total brain volume, with specific decreases in several brain regions including cortex and hippocampus (46). This is accompanied by decreased total white matter volume and integrity (47). Rodent models of early life ID corroborate these effects on both hippocampal volume (48,49) and white matter volume/integrity (50). Importantly, these changes are partially reversible: iron restoration starting at 30 days of life is sufficient to normalize gross brain volume after only 30 days of iron repletion in the porcine model. However, disorganization of brain structure persists despite normalization of total brain volume, with remaining deficits in hippocampal volume and white matter organization/integrity (46). Together, these results indicate that while iron repletion may

correct gross morphological measures such as total brain volume, ultrastructural changes to grey and white matter may persist beyond the period of iron deficiency and into adulthood.

Rodent models, as well as *in vitro* primary culture models of ID have been critical in determining the ultrastructural effects of developmental iron deficiency, particularly on neurons. The neuronal ultrastructural effects of developmental ID were first characterized using a rat model of fetal-neonatal ID in which animals experience iron deficiency throughout gestation and early postnatal life. At postnatal day (P) 15 – the peak of hippocampal dendritogenesis – ID rats had truncated apical dendrites in hippocampal area CA1 (39). Additionally, branches in the dendritic arbor of hippocampal neurons occurred more proximally to the soma and dendritic spine heads were smaller (51). These hippocampal neuronal findings have been corroborated using mouse models of non-anemic ID (40,52) and primary neuronal culture models of ID (53). In the rat model of ID, these hippocampal neuronal ultrastructural deficits persisted into adulthood despite early-life iron repletion (39,51). Further refinement of iron repletion experiments determined that there was a critical period for iron in hippocampal neurodevelopment. If iron was restored within the critical period, than adult hippocampal neuronal structure was normalized; however, if iron repletion occurred outside of the critical period, then hippocampal neuronal structure remained permanently altered (40).

Increasing evidence shows that cortical neurons are also affected by developmental ID. Ultrastructural changes to both apical and basal dendritic arbors have been characterized in cortical neurons in rodent models of ID, primarily manifesting as decreased branching of dendrites proximal to the cell body (54). Correspondingly, in a study of infants of mothers with low iron intake during pregnancy, cortical grey matter fractional anisotropy (FA) was increased in infants with low maternal iron intake (55). In cortical tissue, FA decreases as neurodevelopment progresses and dendritic arborization increases (56,57). Thus, the increased FA seen in infants of ID mothers supports the preclinical model findings of compromised cortical neuron structure.

Notably, neuronal development is a highly metabolically demanding process that is dependent on adequate availability of energy substrates for development of complex cell morphology (58,59). Production of the metabolic substrate ATP by mitochondria is irondependent, as several key enzymes in the electron transport chain are mechanistically dependent on iron for their enzymatic activity (60). Preliminary evidence suggests that mitochondrial function may thus be compromised by developmental iron deficiency (53), contributing to the above-described neuronal ultrastructural defects associated with developmental ID.

Rodent models have also been critical in determining the ultrastructural effects of developmental ID on white matter. Oligodendrocytes, the myelinating cells of the central nervous system, stain more densely for intracellular iron than other cell types in the central nervous system (61), and the peak of iron uptake in the developing brain corresponds to the peak period of myelination (50,62), suggesting that adequate iron supply is important for their development and function. In both *in vitro* and *in vivo* models, oligodendrocyte precursor cell (OPC) differentiation to oligodendrocytes is impaired when iron uptake in

impaired (63,64). Additionally, the diameter of myelinated axons is significantly decreased in developmentally ID rats, even in adulthood, suggesting that iron is critical for establishment of myelination (54). This has been noted to correspond functionally with decreased conduction velocity (65).

In order to understand the relationship between developmental ID and complex psychopathologies, it is important to understand not only its effects on individual brain regions and cell types, but also its effects of the developmentally driven interconnection of multiple brain regions and cell types. Because each brain area develops on a different time scale, critical periods differ between and even within brain areas (24,26), and an exposure at a given time point in development may affect one brain region or physiologic function but not another. This nonuniform effect on the developing brain can disrupt the connectivity among brain regions that work together in complex circuits that are critical for higher-order behaviors in adulthood.

For example, proper functional control of the ventral tegmental area (VTA) loop depends on the balance between tonic hippocampal input and intermittent frontal lobe input. Disruption of this balance is postulated to result in schizophrenia (66), a psychopathology that presents later in life but that has distinct developmental origins. Within the loop, the hippocampus develops earlier and more rapidly than the frontal cortex during late fetal/early neonatal life, and thus is far more vulnerable to the adverse effects of fetal deficiencies of nutrients such as iron that support rapid growth. This selective vulnerability of the hippocampus (relative to frontal cortex) to developmental iron deficiency has the potential to disrupt VTA circuit structure and function by unbalancing the inputs. Further contributing to the unbalance of VTA loop connectivity, the dopaminergic system, a key neurotransmitter system in VTA loop, is disrupted by ID due to the iron-dependence of enzymes in the dopamine synthesis pathway (67). Pre-clinical models of fetal/neonatal iron deficiency support this hypothesis (68,69).

Emerging evidence in human cohorts also supports the hypothesis that functional connectivity of brain regions is disrupted by ID. A functional magnetic resonance imaging (fMRI) study of developmentally ID individuals in adulthood found significant changes in connectivity of the Default Mode Network (DMN), a major network of interconnected regions in the brain (70). Connectivity of the posterior cingulate cortex within the DMN was particularly affected by ID (70). Similar disruptions to the DMN are seen in a variety of neurocognitive and neuropsychiatric disorders (71).

Gene Dysregulation—Widespread hippocampal gene dysregulation has been shown in both rodent and porcine models of developmental ID, both acutely (72,73) and in adulthood after complete resolution of ID (44,45). The dysregulated genes map to functions critical for neurodevelopment as well as neuropsychiatric disorders including mood disorders, pervasive developmental disorders, autism, and schizophrenia (44,45,72,73). These widespread and stable long-term alterations to gene expression implicate an underlying transcriptional regulatory mechanism that functions on a genome-wide scale, such as epigenetic modification.

Epigenetics is the study of how supragenomic modifications to DNA and chromatin can alter gene expression and resultant phenotype, independent of alterations to the genome itself. Two major classes of epigenetic modification include cytosine modifications (DNA methylation and DNA hydroxymethylation) and histone modifications. Each of these classes of epigenetic modifications is associated with distinct effects on transcriptional regulation. Additionally, all have been demonstrated to be environmentally labile, meaning that their prevalence and distribution in the genome can be altered, sometimes permanently, in response to environmental conditions and exposures such as stress (74,75), toxicants (76–78), and nutrition (41–43,79,80). Thus, epigenetic modification presents a plausible mechanism by which the environment, including nutritional status, can exert an effect on central nervous system gene expression and subsequent neurodevelopmental and neuropsychiatric outcomes.

DNA methylation is an epigenetic modification generated by covalent addition of a methyl group to cytosine nucleotides, primarily at CpG dinucleotides. On a genome-wide scale, the hippocampal DNA methylation pattern is significantly altered by developmental ID in a porcine model, with 853 differentially methylated CpG sites identified in the developmentally iron deficient hippocampus compared to controls (73). However, relatively few of these differentially methylated CpG sites map to differentially expressed genes (73), leaving open the question of the functional significance of these changes. DNA methylation has also been assessed at the gene-specific level at the brain derived neurotrophic factor (*Bdnf*) promoter. *Bdnf*, a gene critical for neuronal development, synaptic formation and plasticity, learning, and memory is downregulated in the hippocampus both acutely during the period of developmental ID (81), and in adulthood after complete resolution of ID (82). In adult, formerly iron deficient rats, total *Bdnf*-IV promoter methylation rate is significantly decreased, with 2 of 7 specific CpG sites significantly hypomethylated (80). Given that promoter hypomethylation is canonically associated with transcriptional activation (83), the functional significance of these changes at the downregulated *Bdnf*-IV promoter is again uncertain.

Despite the evidence that developmental ID alters DNA methylation, there is no clear biological mechanism through which iron directly influences the establishment of DNA methylation. In contrast, active DNA demethylation relies on the iron-dependent family of TET methylcysosine dioxygenases which require iron for their enzymatic conversion of methylcytosine to hydroxymethylcytosine and its derivatives (Figure 1) (84). Hydroxymethylcytosine, or DNA hydroxymethylation, itself is a stable epigenetic modification that may alter gene expression (85,86). However, it has not yet been assessed in the context of developmental iron deficiency.

Histone modifications are covalent modifications to the amino acid residues of histone tails, and include histone acetylation, methylation, phosphorylation, and ubiquitination. The histone code is complex and has not been studied in depth in the context of developmental ID. However, one family of histone modifications, lysine methylation, has been of particular interest due to its mechanistic dependence on iron. Removal of methyl groups from lysine residues is catalyzed by the JmjC ARID-domain containing histone demethylase (JARID) family proteins, which have an absolute requirement for iron for their enzymatic activity

(Figure 1) (87,88). Accordingly, in the adult, formerly iron deficient rat hippocampus, enrichment of histone methylation is significantly altered at the dysregulated *Bdnf*-IV promoter (80). K27me3 and K4me3, histone modifications associated with silenced genes, were found to be enriched at the *Bdnf*-IV promoter, while K4me3, a modification associated with active gene expression, was significantly depleted (80). Interestingly, properly timed dietary supplementation with the methyl donor choline mitigates the effects of ID on histone methylation in the hippocampus of preclinical models (80). This finding underscores the potential for dietary epigenetic "workarounds" in humans in the near future.

Clinical Implications

Emerging literature suggests that early life folate, LC-PUFA, Vitamin A and Vitamin D status may also influence the risk of later psychopathology (8,9,89). Folic acid (folate) is of particular interest because it fits into a more general category of one-carbon metabolites along with its dietary counterparts choline, betaine, methionine and their co-factors vitamins B12 and B6.These nutrients are found in methyl diets, which have been shown to promote epigenetic modifications in the developing brain. A meta-analysis identified low maternal folate and high homocysteine levels as risk factors for schizophrenia in the offspring (90). Low maternal periconceptional folic acid intake, especially in the context of a pesticide exposure as a "second hit" increases the risk of autism in the offspring by up to 2.5-fold (91). It will be important to consider the proper timing, dose and duration of dietary methyl donors with respect to brain development in light of the finding that these diets have potential for epigenetic modification of brain genes (42,92). Clinical trials of choline for vulnerable pediatric populations, such as children with fetal alcohol syndrome, have already begun and show positive effects on learning and memory behavior (93).

Due to the high worldwide prevalence of malnutrition, particularly among pregnant women and young children, understanding the effects of nutrient deficiencies on long-term neurocognitive outcomes and risk for neuropsychiatric disorders is critical because sound nutritional policy and practice can potentially mitigate risk. Prevention of nutrient perturbations during fetal and early postnatal life is an accomplishable goal with long-term societal implications. Women of child-bearing age should be in optimal nutritional health entering into pregnancy, particularly with respect to critical nutrients such as those listed in Tables 1 and 2. Prevention strategies to optimize fetal brain nutritional status throughout pregnancy include not only maintaining maternal nutritional sufficiency but also reducing conditions in nutritionally sufficient women that nevertheless alter fetal nutritional status. These conditions include maternal hypertension, the most common cause of intrauterine growth restriction (IUGR) in developed countries (94), gestational diabetes mellitus (95), maternal smoking (96), obesity/excessive gestational weight gain (97,98), and maternal stress (99). Postnatally, provision of human milk and maintenance of the status of nutrients listed in Table 1 are key prevention strategies. While the promising pre-clinical data on the role of nutrient-mediated epigenetic modification of brain development suggests a potential for therapeutic intervention in humans, it is too soon to propose methyl diets as routine therapeutic interventions until more is known about the optimal timing, dose and duration of these agents (100).

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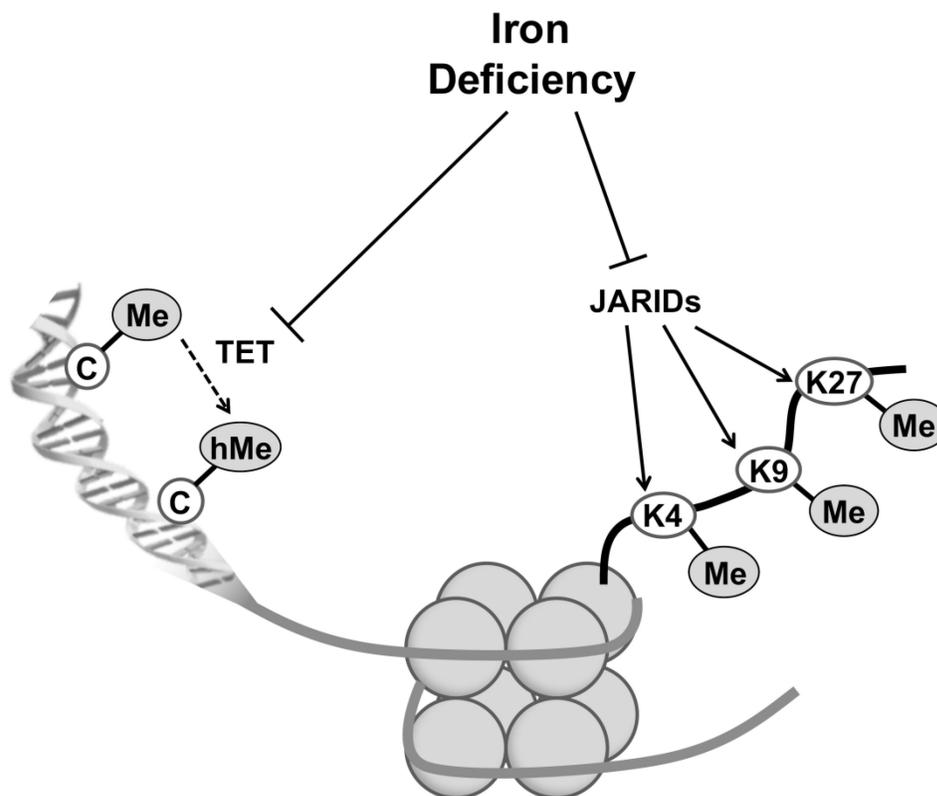
Figure 1. Epigenetic modifications of DNA and chromatin are sensitive to nutritional status.
Two major categories of epigenetic modification, DNA methylation (left) and histone
modification, specifically histone methylation (right), are both modified by iron deficiency.
DNA methylation consists of cytosine bases with a covalently added methyl group. Active
DNA demethylation is performed by TET methylcytosine dioxygenases, which require iron
for their enzymatic conversion of methylcytosine to hydroxymethylcytosine and its
derivatives. Lysine residues of histone tails can undergo mono-, di-, or trimethylation.
JARID histone demethylases enzymatically remove methyl groups from di- or trimethylated
lysine residues, and also require iron for their enzymatic activity. C: Cytosine; hME:
Hydroxymethyl; K: Lysine; Me: Methyl.

Table 1:

Select Nutrients that affect neural processes during development

Nutrients	Neurodevelopmental Processes	Affected Brain Regions
Macronutrients: protein, fatty acids, glucose	Cell proliferation, cell differentiation, synaptogenesis, growth factor expression, myelination	Global, cortex, eye, hippocampus
Micronutrients: zinc, copper, iron	Myelination, dopamine synthesis, energy metabolism, migration	White matter, striatalfrontal connectivity, hippocampus-frontal connectivity
Vitamins/Cofactors: vitamin A, vitamin B (6, 12), vitamin B_9/folate, choline	Growth factor expression, myelination, synaptogenesis, proliferation, differentiation	Eye, motor cortex, cortex, hippocampus

Table 2:

Specific deficits and increased disease risks associated with nutritional deficiencies during development

Nutrient	Age	Risk of Deficiency	Critical Period	Long-Term Impact after Resolution of Nutrient Deficit
Protein	Fetus	IUGR (Maternal malnutrition, maternal hypertension, etc.)	3rd trimester	Lower IQ at 7 yr of age (101)
	Child	Malnutrition	6 mo–10 yr	Impaired cognition (102); Increased risk of depression (103)
Long chain polyunsaturated fatty acids	Fetus and toddler	Maternal insufficiency during gestation and lactation	3rd trimester–24 mo postnatal	Lower Bayley Scales at 18 mo; Slower information processing; Lower visual acuity; Lower motor skill (104,105)
Vitamin B$_9$/folate	Fetus	Maternal insufficiency	1st trimester	Increased risk of neural tube defects (104)
Iron	Fetus	Maternal iron status; maternal diabetes	3rd trimester	Increased risk of schizophrenia (13,15) and autism spectrum disorders (14)
	Infant and toddler	Rapid growth, dietary insufficiency, intestinal blood loss; intestinal parasites	6–24 mo	Impaired cognition (31); Increased risk of behavioral and emotional problems (33); Increased risk of anxiety and depression (33,35)
Zinc	Fetus	Maternal deficiency	1st trimester	Increased risk of neural tube defects (106)
	Infant and toddler	Dietary insufficiency	8–18 mo	Decreased working memory function (107)