***NIH R21 Grant Proposal:*** *Accelerating the Pace of Child Health Research Using Existing Data from the Adolescent Brain Cognitive Development (ABCD) Study (PAR-22-138)*

***Title:*** Investigating the Relationship between Iron Deficiency-Induced Hippocampal Atrophy and BMI: A Conceptual Analysis Using the NIH ABCD Dataset

***Project Summary (30 lines):***

Obesity and iron deficiency (ID) are two widespread yet seemingly distinct public health crises, with global prevalence rates among adolescents rising alarmingly in recent decades. While obesity rates in adolescents have increased from 8% in 1990 to 20% in 2022, ID continuous to remain the most common nutritional deficiency, affecting up to 21% of adolescents. Emerging research suggests a surprising intersection between these conditions, though the mechanisms connecting ID to obesity are not well understood. This gap in knowledge represents a critical opportunity for innovative research.

Given the accumulating evidence suggesting brain-mediated pathways in obesity development, we propose a novel mechanistic link through hippocampal dysfunction. Two well-established lines of evidence support this hypothesis: first, ID consistently induces hippocampal atrophy, leading to documented deficits in memory and cognition; second, preclinical studies have demonstrated that hippocampal impairment directly disrupts appetite regulation, resulting in overeating and increased adiposity. Despite these established relationships, no study to our knowledge has systematically examined whether ID-induced hippocampal atrophy serves as a mechanistic bridge to increased adiposity. Our project aims to investigate this compelling pathway, potentially revealing a novel mechanism linking ID to obesity risk.

To investigate this complex relationship, we will utilize the ABCD dataset through four specific aims:

* **Aim 1:**  Investigate the relationship between iron levels and the volumes of the left and right hippocampus in adolescents.
* **Aim 2:** Analyze how hippocampal atrophy is associated with adiposity, focusing on whether structural brain changes contribute to increased BMI and waist circumference.
* **Aim 3:** Examine the relationship between iron deficiency and adiposity and determine if hippocampal volume mediates the connection between iron status and both BMI and waist circumference.
* **Aim 4:** Assess the long-term effects of iron deficiency-induced hippocampal atrophy on adiposity by tracking changes over time to understand how early hippocampal alterations influence later anthropometric measures.

Due to the scarcity of established frameworks and empirical data to guide our understanding of this relationship, leveraging the comprehensive ABCD dataset for secondary analysis is both strategic and efficient. This approach will allow us to explore an under-researched area while minimizing the resource demands and risks of launching a new clinical trial. The insights gained could significantly advance our understanding of obesity prevention and management, potentially transforming clinical practices and public health strategies for individuals at-risk.

***Project Narrative (3 sentences):***

This research seeks to reveal how iron deficiency in adolescents may impact brain health, potentially leading to overeating and obesity. Insights gained from this study could inform new strategies for preventing and managing obesity, ultimately enhancing the health and well-being of young people and reducing the risk of related diseases in the future.

***Specific Aims (1 page)***

**Background**

Obesity represents a significant global health challenge, with childhood obesity rates in the United States having tripled over the past three decades (Hales et al., 2017). Concurrently, iron deficiency remains the most prevalent nutrient deficiency, affecting millions of young children worldwide (Gedfie et al., 2022). Despite a strong correlation between obesity and iron deficiency, current research has focused primarily on absorption-based mechanisms (Alshwaiyat et al., 2021; Zhao et al., 2015), overlooking potential brain-mediated pathways. Drawing on recent nutritional and neuroscience discoveries, we propose an innovative mechanistic framework linking ID to obesity through hippocampal alterations.

**Hypothesis**

We hypothesize that iron deficiency leads to hippocampal alterations, which in turn mediate an increase in adiposity. This hypothesis emerges from two compelling evidences: (1) ID significantly impairs hippocampal development, affecting neuronal architecture and synaptic plasticity (Bastian et al., 2016; Nelissen et al., 2017), and (2) compromised hippocampal function directly disrupts appetite regulation by impairing meal-related memory and increasing responsiveness to food cues (Kanoski & Grill, 2017; Parent et al., 2014). Using the comprehensive Adolescent Brain Cognitive Development (ABCD) dataset, we will systematically investigate this unexplored pathway through four specific aims:

***Specific aim 1: Characterize the relationship between iron status and hippocampal volume in adolescents***  
Using serum iron biomarkers (hemoglobin, ferritin) and high-resolution structural MRI data, we will analyze how variations in iron status correlate with bilateral hippocampal volumes, controlling for demographic and environmental factors.

***Specific aim 2: Determine the association between hippocampal volume and adiposity measures***  
We will examine how structural variations in hippocampal volumes relate to BMI and waist circumference, establishing the potential link between brain structure and body composition.

***Specific aim 3: Test the mediating role of hippocampal volume***  
Through mediation analyses, we will evaluate whether hippocampal volume serves as a mechanistic bridge between iron status and adiposity measures.

***Specific aim 4: Assess longitudinal relationships between early hippocampal alterations and BMI trajectories***  
Using sophisticated machine learning approaches, we will analyze how early hippocampal changes predict long-term BMI outcomes, providing insights into developmental trajectories. This will inform the optimal timing for interventions to prevent or reduce obesity.

**Impact**  
Our multidisciplinary team combines expertise in iron deficiency and nutrient metabolism (Dr. Laura Murray-Kolb), iron-associated hippocampal development (Dr. Micheal Georgieff), ingestive behavior and appetite regulation (Dr. Richard Mattes), childhood obesity and developmental trajectories (Dr. Kameron Moding), and obesity and metabolic regulation (Dr. Gregory Henderson). This innovative investigation will establish whether ID-induced hippocampal changes represent a novel mechanism contributing to obesity risk. Success will provide the first human evidence linking iron status to obesity through hippocampal alterations, potentially revolutionizing prevention strategies for vulnerable populations.

***Research Strategy****(6 pages)*

***Significance:***

**1.1: Childhood Obesity**: Childhood obesity is a critical public health crisis, impacting the well-being of children and adolescents, particularly in the United States. The alarming prevalence of obesity, affecting approximately 14.7 million individuals aged 2-19 years in 2017-2020, underscores the magnitude of this issue (Key et al., 2023). Beyond its immediate consequences, childhood obesity significantly amplifies the risk of numerous non-communicable diseases, including cardiovascular disorders, hypertension, high cholesterol, type 2 diabetes, asthma, sleep apnea, and joint problems (Pulgarón, 2013). The multifaceted origins of childhood obesity involve environmental factors, genetics, lifestyle choices, and cultural influences. At its core, excessive caloric intake combined with reduced physical activity contributes to this crisis. Understanding the underlying causes of overeating is essential for developing innovative prevention and intervention strategies.

**1.2: Iron Deficiency during Childhood**: ID, on the other hand, emerges as the most prevalent single nutrient deficiency globally, acknowledged by the WHO as a paramount global health concern. Anemia affects over 2 billion individuals worldwide, with a staggering number twice that suffering from ID, indicating a substantial global burden (Miller, 2013). The impact of ID extends far beyond hematological manifestations, profoundly affecting cognitive, emotional, and behavioral development. Iron-deficient children exhibit reduced mental and motor development, alongside behavioral alterations including heightened wariness and clinginess (Lozoff, 1988; Lozoff et al., 2007). The hippocampus, a critical brain region involved in learning and memory, is particularly vulnerable to the effects of iron deficiency. Even in the absence of anemia, hippocampal ID can lead to structural and functional impairments, with potentially irreversible consequences. (Bastian et al., 2016). This fact emphasizes the alarming nature of this deficiency.

**1.3: Sensitivity of Hippocampal Neurons to Iron Deficiency:**  The hippocampus demonstrates unique sensitivity to iron status, with implications for neural development and function. Iron plays a crucial role in:

* Neuronal maturation, including axon and dendrite growth
* Synapse formation and maintenance
* Mitochondrial energy production essential for dendritic arborization
* Neurotransmitter balance and synaptic protein expression

When deprived of iron, neurons face an energy crisis, impairing their ability to form dendritic arbors (Figure 1). This reduction in dendritic complexity signifies compromised neuronal architecture, potentially leading to long-term impairments in synaptic function and efficacy, severely affecting learning and memory. In addition to morphology, ID affects the delicate balance of neurotransmitters, neurotrophins, and synaptic proteins, crucial for information processing, impacting cognitive abilities and potentially affect the quality of life of affected individuals, if not treated timely.

A collage of images of neurons

Description automatically generated

*Figure 1: ID impairs the dendritic arbor complexity of cultured hippocampal neurons. Representative stage 1 (A) and stage 2(B) images of neurons and tracings [primary dendrite (red/black), secondary branch (blue/dark gray), tertiary branch (green/light gray)] of control (Aa, Ac, Ba, Bc) and ID (Ab, Ad, Bb, Bd) neurons. {Figure extracted from Carlson et al. (2009)}*

**1.4: Hippocampal Regulation of Eating Behavior:** The ventral hippocampus (vHP) serves as a critical integrator of feeding-related signals, processing (i) meal-related memories, (ii) food-associated cues, (iii) sensory information, and (iv) metabolic signals (leptin, insulin, ghrelin).

This integration occurs through complex neural circuits, with the dorsal hippocampus (dHP) processing visuospatial cues while the vHP manages olfactory inputs. Disruption of hippocampal function can lead to impaired meal memory and heightened responsiveness to food cues, creating a cycle that promotes overconsumption (Figure 2).

A diagram of obesity

Description automatically generated

*Figure 2: Memory influences* [*(Nelissen et al., 2017)*](https://www.sciencedirect.com/topics/medicine-and-dentistry/eating-behavior) *in a cyclical manner. Decreased hippocampal mnemonic functioning leads to decreased memory of meals and increased response to food cues. This leads to increased caloric consumption and obesity, which in turn leads to increased inflammation and cardiometabolic dysfunction which in turn decreases hippocampal function. {Figure extracted from Farr et al. (2016)}*

**1.5: Novel Perspective on ID-Obesity Relationship:** While traditional research has established that obesity can induce iron deficiency through obesity-induced chronic inflammation, which increases hepcidin production and disrupts iron absorption (González-Domínguez et al., 2020), our study proposes a novel reverse pathway. We suggest that ID might serve as an initiating factor in obesity development through its effects on hippocampal structure and function (Figure 3). This hypothesis is supported by the timing of ID occurrence during critical developmental periods and the crucial role of hippocampal integrity in memory-dependent appetite regulation. This perspective represents a paradigm shift in understanding the relationship between nutritional deficiency and obesity, potentially opening new avenues for intervention and prevention strategies.

A diagram of a diagram

Description automatically generated

Figure 3: Conceptual framework for the relationship between ID and obesity

***Innovation***:

Our study takes a different approach from traditional research in a few key ways:

1. **Paradigm-Shifting Perspective**We challenge the traditional unidirectional view of the ID-obesity relationship by proposing an innovative reverse-causation hypothesis. While existing research focuses primarily on how obesity affects iron absorption and metabolism, our study is the first to systematically investigate how ID-induced hippocampal changes might contribute to obesity development. This novel perspective could fundamentally reshape our understanding of the relationship between nutritional deficiencies and obesity.
2. **Multidisciplinary Integration**  
   The strength of our approach lies in its unique integration of diverse scientific expertise to address a complex public health challenge. Our team brings together Dr. Laura Murray-Kolb's extensive experience in iron deficiency and nutrient metabolism, Dr. Michael Georgieff's pioneering work in iron-associated hippocampal development, Dr. Richard Mattes' expertise in ingestive behavior and appetite regulation, Dr. Kameron Moding's insights into childhood obesity and developmental trajectories, and Dr. Gregory Henderson's significant contributions to obesity research and metabolic regulation. This collaborative synthesis enables a comprehensive investigation of the intricate relationships between nutritional status, brain development, and eating behaviors, offering a novel perspective on the mechanisms linking ID to obesity risk.
3. **Translational Impact**  
   Our study has the potential to revolutionize both clinical practice and public health strategies by providing the first human evidence linking ID to obesity through hippocampal alterations. This work could lead to animal studies to confirm the pathway, and randomized controlled trials to see the effect of timely interventions. This could lead to innovative screening approaches that combine iron status and brain structure measurements, potentially identifying at-risk individuals during critical developmental periods. By challenging existing paradigms and proposing novel mechanistic pathways, our study has the potential to significantly advance our understanding of how nutritional deficiencies contribute to obesity risk through brain-mediated mechanisms.

***Research Approach****:*

***Aim 1****: Investigate Iron Status and Hippocampal Volume in Children*

***Rationale:*** Data from past studies strongly suggest that there are profound alterations in brain structure and function observed during and after iron deficiency. Historically, the neurological consequences of iron deficiency were attributed primarily to anemia. However, pioneering studies by Dallman et al. challenged this notion by demonstrating the primary effects of iron deficiency within the brain tissue, independent of anemia (Dallman, 1986). Specifically, reductions in brain cytochrome c concentrations indicated altered cerebral energy metabolism, leading to inefficient ATP generation and electron transport. These alterations, particularly in the hippocampus and frontal cortex, set the stage for our investigation into hippocampal volume and its relationship with iron status. Furthermore, Georgieff et al, established through experiments that disruptions in energy metabolism, neurotransmitter systems, and myelination are particularly significant within the hippocampus, thereby affecting memory and learning capabilities (Georgieff, 2008). These effects are not only acute but persist into adulthood, suggesting a critical window during development when iron deficiency permanently alters brain regions' physical trajectories.

***Experimental Approach:***

* *Data Selection and Quality Control*
  + Extract iron biomarkers (hemoglobin, serum ferritin) and bilateral hippocampal volumes from ABCD dataset
  + Classify participants into ID and iron-sufficient groups using clinical cutoffs (Hb < 12 g/dL, Ft < 15 ng/mL)
  + Apply quality control measures to neuroimaging data
* *Statistical Analysis*
  + Conduct multiple regression analyses examining associations between iron status and hippocampal volumes
  + Control for relevant covariates (e.g. age, sex, socioeconomic status, pubertal status, etc.)
  + Test for potential non-linear relationships using generalized additive models, if needed
  + Conduct sensitivity test for outliers

***Expected results:*** We hypothesize that iron-deficient children will have smaller hippocampal volumes compared to those who are iron-sufficient.

***Aim 2:*** *Analyze the Association Between Hippocampal Atrophy and Adiposity*

***Rationale:***The hippocampus plays a crucial role in regulating eating behavior through memory-dependent mechanisms and integration of metabolic signals. Animal studies demonstrate that hippocampal dysfunction leads to increased meal frequency and altered satiety signaling (Kanoski & Grill, 2017). The ventral hippocampus particularly integrates metabolic hormone signals with environmental food cues (Parent et al., 2014).

***Experimental Approach:***

* *Data Preparation*
  + Extract anthropometric measurements (BMI z-scores, waist circumference)
  + Obtain quality-controlled hippocampal volumes
  + Adjust for site-specific variability
* *Data Analysis*
  + Implement linear mixed-effects models to examine relationships
  + Investigate potential sex-specific effects through stratified analyses
  + Adjust for covariates like total intracranial volume, physical activity, socioeconomic factors, etc.
  + Test interaction effects

***Expected results:*** We hypothesize that reduced hippocampal volumes will be associated with higher BMI and waist circumference, suggesting a link between brain atrophy and adiposity.

***Aim 3:*** *Examine the Mediating Role of Hippocampal Volume in the Relationship Between Iron Deficiency and Adiposity*

***Rationale:*** The relationship between iron status and adiposity may be mediated through hippocampal alterations. Understanding this mediating pathway is crucial as it could reveal a mechanistic link between nutritional deficiency and obesity risk. While previous research has established independent relationships between iron status and hippocampal structure, and between hippocampal function and eating behavior, no study has systematically examined whether hippocampal volume serves as a mediating factor. This knowledge could inform the development of targeted interventions that address both nutritional status and brain-mediated eating behaviors.

***Experimental Approach:***

* *Data Preparation*
  + Extract iron biomarkers (hemoglobin, ferritin)
  + Obtain quality-controlled bilateral hippocampal volumes
  + Include anthropometric measurements (BMI z-scores, waist circumference)
  + Apply quality control procedures to ensure reliable data.
* *Statistical Analysis*
  + Use mediation analysis to test hippocampal volume as a mediator between iron status and adiposity
  + Apply bootstrapping for confidence intervals
  + Assess model fit using standard indices and test for moderated mediation as necessary.

***Expected results:*** Based on existing literature, we hypothesize that hippocampal volume mediates the relationship between iron status and eating behavior.

***Aim 4:*** *Assess the Long-term Effects of ID-induced Hippocampal Atrophy on BMI*

***Rationale:*** Understanding the temporal relationship between early iron deficiency, hippocampal alterations, and subsequent weight trajectories is crucial for several reasons. First, early developmental periods represent critical windows when nutritional deficiencies can have lasting impacts on brain structure and function (Georgieff, 2008). Second, animal studies suggest that early hippocampal alterations can lead to persistent changes in eating behavior patterns that extend into later life (Kanoski & Grill, 2017). By leveraging the longitudinal nature of the ABCD dataset, we can uniquely examine whether early ID-related hippocampal changes predict future weight trajectories in human adolescents. This knowledge is essential for developing targeted early interventions and identifying critical periods when nutritional supplementation might be most effective in preventing obesity risk.

***Experimental Approach:***

* *Data Organization*
  + Structure longitudinal measurements of iron biomarkers, hippocampal volumes, and BMI
  + Create time-based variables to track developmental trajectories
  + Prepare data for predictive modeling by creating training and testing sets
* *Analysis Strategy*
  + Begin with mixed-effects models to establish baseline temporal relationships
  + Use linear regression to examine predictive associations between iron status, hippocampal volume, and BMI.
  + Follow with decision trees to identify thresholds of iron status and hippocampal volume that correlate with BMI changes over time.
  + Apply K-Nearest Neighbors (KNN) to assess pattern similarity and classify BMI outcomes based on historical data.

***Expected Results:*** We anticipate identifying specific developmental windows when iron deficiency most strongly predicts future BMI trajectories, potentially informing the timing of preventive interventions.

**Potential Challenges and Mitigation Strategies:**

We acknowledge potential challenges and will adopt strategies to ensure scientific rigor and ethical integrity:

1. **Data Quality and Missing Values**: The ABCD dataset may contain missing or incomplete data, which can hinder the accuracy of our analyses. To mitigate this, we will employ robust data imputation techniques, such as maximum likelihood estimation, ensuring that our analyses are based on the most comprehensive dataset possible. Additionally, we will conduct sensitivity analyses to evaluate the potential impact of missing data on our findings, allowing us to assess the robustness of our conclusions.
2. **Causality Inference:** The longitudinal nature of our study presents challenges related to temporal relationships and causality inference. We will address these through careful consideration of temporal precedence in our analyses, implementation of robust mediation techniques, and appropriate acknowledgment of limitations in causal inference. Throughout the study, we will maintain detailed documentation of all analytical decisions and create comprehensive analysis protocols to ensure reproducibility of our findings.

**Timeline:**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Research activities** | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** |
| IRB preparation and approval |  |  |  |  |  |  |  |  |
| ABCD data acquisition from the NIH |  |  |  |  |  |  |  |  |
| Data cleaning and preprocessing |  |  |  |  |  |  |  |  |
| Primary analysis of iron biomarkers, hippocampal volumes and BMI relationships |  |  |  |  |  |  |  |  |
| Application of machine learning techniques for data analysis |  |  |  |  |  |  |  |  |
| Interpretation of results and manuscript writing |  |  |  |  |  |  |  |  |
| Submission of manuscript to a peer-reviewed journal |  |  |  |  |  |  |  |  |

**References:**

Alshwaiyat, N. M., Ahmad, A., Wan Hassan, W. M. R., & Al-Jamal, H. A. N. (2021). Association between obesity and iron deficiency (Review). *Experimental and Therapeutic Medicine*, *22*(5), 1268. https://doi.org/10.3892/etm.2021.10703

Bastian, T. W., von Hohenberg, W. C., Mickelson, D. J., Lanier, L. M., & Georgieff, M. K. (2016). Iron Deficiency Impairs Developing Hippocampal Neuron Gene Expression, Energy Metabolism, and Dendrite Complexity. *Developmental Neuroscience*, *38*(4), 264–276. https://doi.org/10.1159/000448514

Bourdier, L., Fatseas, M., Maria, A.-S., Carre, A., & Berthoz, S. (2020). The Psycho-Affective Roots of Obesity: Results from a French Study in the General Population. *Nutrients*, *12*(10). https://doi.org/10.3390/nu12102962

Dallman, P. R. (1986). Biochemical basis for the manifestations of iron deficiency. *Annual Review of Nutrition*, *6*, 13–40. https://doi.org/10.1146/annurev.nu.06.070186.000305

Fisher, J. O., & Birch, L. L. (2002). Eating in the absence of hunger and overweight in girls from 5 to 7 y of age. *The American Journal of Clinical Nutrition*, *76*(1), 226–231. https://doi.org/10.1093/ajcn/76.1.226

Fretham, S. J. B., Carlson, E. S., & Georgieff, M. K. (2011). The Role of Iron in Learning and Memory12. *Advances in Nutrition*, *2*(2), 112–121. https://doi.org/10.3945/an.110.000190

Gedfie, S., Getawa, S., & Melku, M. (2022). Prevalence and Associated Factors of Iron Deficiency and Iron Deficiency Anemia Among Under-5 Children: A Systematic Review and Meta-Analysis. *Global Pediatric Health*, *9*, 2333794X221110860. https://doi.org/10.1177/2333794X221110860

Georgieff, M. K. (2008). The Role of Iron in Neurodevelopment: Fetal Iron Deficiency and the Developing Hippocampus. *Biochemical Society Transactions*, *36*(Pt 6), 1267–1271. https://doi.org/10.1042/BST0361267

González-Domínguez, Á., Visiedo-García, F. M., Domínguez-Riscart, J., González-Domínguez, R., Mateos, R. M., & Lechuga-Sancho, A. M. (2020). Iron Metabolism in Obesity and Metabolic Syndrome. *International Journal of Molecular Sciences*, *21*(15), 5529. https://doi.org/10.3390/ijms21155529

Hales, C. M., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2017). Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. *NCHS Data Brief*, *288*, 1–8.

Zhao, L., Zhang, X., Shen, Y., Fang, X., Wang, Y., & Wang, F. (2015). Obesity and iron deficiency: a quantitative meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity*, *16*(12), 1081–1093. https://doi.org/10.1111/obr.12323

Kanoski, S. E., & Grill, H. J. (2017). Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms. *Biological Psychiatry*, *81*(9), 748–756. https://doi.org/10.1016/j.biopsych.2015.09.011

Key, J., Burnett, D., Babu, J. R., & Geetha, T. (2023). The Effects of Food Environment on Obesity in Children: A Systematic Review. *Children*, *10*(1), 98. https://doi.org/10.3390/children10010098

Lozoff, B. (1988). Behavioral alterations in iron deficiency. *Advances in Pediatrics*, *35*, 331–359.

Lozoff, B., Corapci, F., Burden, M. J., Kaciroti, N., Angulo-Barroso, R., Sazawal, S., & Black, M. (2007). Preschool-Aged Children with Iron Deficiency Anemia Show Altered Affect and Behavior,. *The Journal of Nutrition*, *137*(3), 683–689.

Miller, J. L. (2013). Iron Deficiency Anemia: A Common and Curable Disease. *Cold Spring Harbor Perspectives in Medicine*, *3*(7), a011866. https://doi.org/10.1101/cshperspect.a011866

Nelissen, E., De Vry, J., Antonides, A., Paes, D., Schepers, M., van der Staay, F. J., Prickaerts, J., & Vanmierlo, T. (2017). Early-postnatal iron deficiency impacts plasticity in the dorsal and ventral hippocampus in piglets. *International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience*, *59*, 47–51. https://doi.org/10.1016/j.ijdevneu.2017.03.006

Parent, M. B., Darling, J. N., & Henderson, Y. O. (2014). Remembering to eat: Hippocampal regulation of meal onset. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *306*(10), R701–R713. https://doi.org/10.1152/ajpregu.00496.2013

Pulgarón, E. R. (2013). Childhood Obesity: A Review of Increased Risk for Physical and Psychological Co-morbidities. *Clinical Therapeutics*, *35*(1), A18–A32. https://doi.org/10.1016/j.clinthera.2012.12.014

Georgieff M. K. (2008). The role of iron in neurodevelopment: fetal iron deficiency and the developing hippocampus. *Biochemical Society transactions*, *36*(Pt 6), 1267–1271. [Alshwaiyat, N. M., Ahmad, A., Wan Hassan, W. M. R., & Al-Jamal, H. A. N. (2021). Association between obesity and iron deficiency (Review).](https://doi.org/10.1042/BST0361267" \t "_blank) *[Experimental and Therapeutic Medicine](https://doi.org/10.1042/BST0361267" \t "_blank)*[,](https://doi.org/10.1042/BST0361267" \t "_blank) *[22](https://doi.org/10.1042/BST0361267" \t "_blank)*[(5), 1268. https://doi.org/10.3892/etm.2021.10703](https://doi.org/10.1042/BST0361267" \t "_blank)

[Bastian, T. W., von Hohenberg, W. C., Mickelson, D. J., Lanier, L. M., & Georgieff, M. K. (2016). Iron Deficiency Impairs Developing Hippocampal Neuron Gene Expression, Energy Metabolism, and Dendrite Complexity.](https://doi.org/10.1042/BST0361267" \t "_blank) *[Developmental Neuroscience](https://doi.org/10.1042/BST0361267" \t "_blank)*[,](https://doi.org/10.1042/BST0361267" \t "_blank) *[38](https://doi.org/10.1042/BST0361267" \t "_blank)*[(4), 264–276. https://doi.org/10.1159/000448514](https://doi.org/10.1042/BST0361267" \t "_blank)

[Gedfie, S., Getawa, S., & Melku, M. (2022). Prevalence and Associated Factors of Iron Deficiency and Iron Deficiency Anemia Among Under-5 Children: A Systematic Review and Meta-Analysis.](https://doi.org/10.1042/BST0361267" \t "_blank) *[Global Pediatric Health](https://doi.org/10.1042/BST0361267" \t "_blank)*[,](https://doi.org/10.1042/BST0361267" \t "_blank) *[9](https://doi.org/10.1042/BST0361267" \t "_blank)*[, 2333794X221110860. https://doi.org/10.1177/2333794X221110860](https://doi.org/10.1042/BST0361267" \t "_blank)

[Hales, C. M., Carroll, M. D., Fryar, C. D., & Ogden, C. L. (2017). Prevalence of Obesity Among Adults and Youth: United States, 2015-2016.](https://doi.org/10.1042/BST0361267" \t "_blank) *[NCHS Data Brief](https://doi.org/10.1042/BST0361267" \t "_blank)*[,](https://doi.org/10.1042/BST0361267" \t "_blank) *[288](https://doi.org/10.1042/BST0361267" \t "_blank)*[, 1–8.](https://doi.org/10.1042/BST0361267" \t "_blank)

[Nelissen, E., De Vry, J., Antonides, A., Paes, D., Schepers, M., van der Staay, F. J., Prickaerts, J., & Vanmierlo, T. (2017). Early-postnatal iron deficiency impacts plasticity in the dorsal and ventral hippocampus in piglets.](https://doi.org/10.1042/BST0361267" \t "_blank) *[International Journal of Developmental Neuroscience: The Official Journal of the International Society for Developmental Neuroscience](https://doi.org/10.1042/BST0361267" \t "_blank)*[,](https://doi.org/10.1042/BST0361267" \t "_blank) *[59](https://doi.org/10.1042/BST0361267" \t "_blank)*[, 47–51. https://doi.org/10.1016/j.ijdevneu.2017.03.006](https://doi.org/10.1042/BST0361267" \t "_blank)