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EXAMINING IRON STATUS, DEVELOPMENT, AND BEHAVIOR IN YOUNG CHILDREN IN THE PENNSYLVANIA FOSTER CARE SYSTEM, AN EXPLORATORY RETROSPECTIVE MEDICAID CLAIMS REVIEW

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Abstract

Children in foster care are classified as a highly vulnerable health population, with nearly 40-90% of children entering foster care with a physical health problem. Nutritional examination of children in foster care is often confined to anthropometric measurements. Knowledge on the micronutrient status of this pediatric population is lacking and requires further exploration. Iron deficiency (ID) is of interest because it is the most common micronutrient deficiency worldwide and contributes to 50% of anemia diagnoses globally. Iron is important for optimal brain development and functioning, which will have downstream effects on a person's developmental and behavioral outcomes. To our knowledge, few studies on children in U.S. Foster Care have quantified the prevalence of anemia, and no studies have examined the association between anemia status and relevant developmental and behavioral outcomes. The aims of the present study are to (1) determine the prevalence of IDA/anemia among children in Pennsylvania (PA) Foster Care, between the ages of six months to ten years and (2) examine if a child's poor iron status is associated with greater odds of relevant developmental and behavioral diagnoses.

The following study was a secondary data analysis, utilizing the *Medicaid Analytic eXtract* database, between 2010-2015 (most recently available data). Children (six months to ten years old) were included in analysis if they were in the PA Foster Care at one point in their life. Children who met the predetermined criterion of IDA/anemia were classified as *diagnosed with IDA/anemia*. The comparison group were children (six months to ten years old) who were in PA Foster Care at one point in their life but did not meet the criterion for IDA/anemia. The comparison group was classified as *not diagnosed with IDA/anemia*. Often hospitals and clinics will utilize hemoglobin to determine anemia, without identifying the etiology. ID is a common driver of anemia, both in the U.S. and globally; however, other etiologies exist. Due to concerns

of low sample size, IDA and anemia diagnoses were combined into one larger group. Developmental and behavioral diagnoses, with well-established or strongly hypothesized relationships with ID and IDA, were extracted for analysis.

50,311 children met the eligibility criteria for the present study, of which 1,365 children were diagnosed with IDA/anemia. Overall, 2.7% of children in the PA Foster Care System were diagnosed with IDA/anemia, between 2010-2015. Children diagnosed with IDA/anemia had greater odds of moderate to profound intellectual disability (Intelligence Quotient < 49), delayed milestones, specific delays in development, and overall intellectual disability, when compared to children not diagnosed with IDA/anemia. Nearly 50% of children diagnosed with IDA/anemia were diagnosed with a specific delay in development, which includes disruptions in reading, arithmetic, and expressive language. Children diagnosed with IDA/anemia had significantly greater odds of adjustment disorder, autism spectrum disorder, restlessness and agitation, disruptive mood dysregulation disorder, and irritability, when compared to children not diagnosed with IDA/anemia.

The prevalence of anemia among children in the PA Foster Care System is within the national rate of U.S. childhood anemia. The odds of developmental and behavioral diagnoses were generally greater among children diagnosed with IDA/anemia than children who were not. Future studies should comprehensively assess iron biomarkers and developmental and behavioral outcomes among children in foster care. If an association between iron status and development and behavior is found, it could reveal an affordable solution, like iron supplementation, which could dismantle at least one burden faced by this vulnerable population.

Table of Contents

Abbreviations vii
List of Tables x
List of Figures xi
Acknowledgements xii
Chapter One: Introduction 1
Chapter Two: Literature Review 7
Rate of physical and mental health issues among children in U.S. Foster Care 7
Studies on children in U.S. Foster Care examining nutrition and development 8
Micronutrient status and cognitive, behavioral, and developmental outcomes in internationally adopted children 12
Prevalence of ID, IDA, and anemia within the U.S. 18
Iron 19
Absorption, storage, and metabolism 20
Heme absorption 20
Non-heme absorption 21
Uptake into peripheral tissues 22
Iron regulation: Hepcidin 22
Iron regulation: Posttranscriptional regulation 22
Location and function of iron in the brain 23
Difference between measuring and diagnosing anemia versus IDA 27
Cognitive, developmental, and behavioral domains (infants and school-aged children) 30
Cognitive domain, developmental domain, and iron 30
Behavioral domain and iron 35
Chapter Three: Methods 39
The Medicaid Analytic eXtract (*MAX*) database 39
Background on ICD-9-CM and ICD-10-CM codes 40
Abbreviations and definitions 41
Eligibility for present study 41
Diagnostic codes extracted for the present study 42
Reasoning for selection of diagnostic codes to extract 49
Well-established relationships: iron deficiency and behavior 49
Strongly hypothesized relationships: iron deficiency and behavior 50
Well-established relationship: iron deficiency and development 51

Iron status diagnostic codes 52
Other codes of interest 53
Data extraction, cleaning, and aggregation 53
Statistics 55
Chapter Four: Results 56
Sample characteristics 57
Group differences by behavioral diagnosis 60
Group differences by developmental diagnosis 62
Chapter Five: Discussion 64
Aim One 64
Aim Two 65
Iron status and the behavioral domain 66
Iron status and the developmental domain 70
Strengths and limitations 75
Overall conclusion and future directions 77
Supplementary Tables and Figures 78
Supplemental Table 1: Definition of diganoses 78
Supplemental Table 2: Sub-diagnosis definitions 101
Supplemental Figure 1: OR for Relevant Behavioral Diagnoses 116
Supplemental Figure 2: OR for Relevant Developmental Diagnoses 116
Bibliography 117

Abbreviations

Abbreviation	Definition
ACT	Alpha-1-Antichymotrypsin
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AFCARS	Adoption and Foster Care Analysis and Reporting System
AFDC	Aid to Families with Dependent Children
AGP	Alpha-1-Acid Glycoprotein
ANT	Attentional Network Task
ASD	Autism Spectrum Disorder
BBB	Blood Brain Barrier
BISD	Bayley Scale of Infant Development
CCT	Central Conduction Time
CRP	C-Reactive Protein
DAT	Dopamine Transporter
DCYTB	Duodenal Cytochrome B
DMT1	Divalent Metal Transporter 1
D_1R	Dopamine Receptor 1
D_2R	Dopamine Receptor 2
EF	Executive Functioning
FEP	Free Erythrocyte Protoporphyrin
FE^{+2}	Ferrous iron
FE^{+3}	Ferric iron

FT	Ferritin
FPN	Ferroportin
GNG	Go-No-Go Task
HAZ	Height-for-Age Z-scores
HB	Hemoglobin
HCP-1	Heme Carrier Protein-1
HX	Hemopexin
ICD-9-CM	International Classification of Diseases, 9th revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th revision, Clinical Modification
ID	Iron Deficiency/Deficient
IDA	Iron Deficiency Anemia/Iron Deficient Anemic
IRE	Iron Regulatory Element
IRP	Iron Regulatory Protein
IS	Iron Sufficiency/Sufficient
IQ	Intelligence Quotient
MPT-1	Metal Protein Transporter-1
MBP	Myelin Basic Protein
NEC	Not Elsewhere Classifiable
NHANES	The National Health and Nutrition Examination Survey
NOS	No Other Symptoms
OFCZ	Occipitofrontal Circumference Z-score

PA	Pennsylvania
PLP	Proteolipid Protein
PND	Post-Natal Day
RBC	Red Blood Cell
RT	Response Time
SRT	Simple Response Time
TBAQ-R	Toddler Behavior Assessment Questionnaire-R
TF	Transferrin
STFR	Soluble Transferrin Receptor
TBI	Total Body Iron
TSAT	Transferrin Saturation
UTR	Untranslated Region
U.S.	United States
WAZ	Weight-for-Age Z-scores
WHZ	Weight-for-Height Z-scores
ZPP	Zinc Protoporphyrin

List of Tables

Table 1: Hemoglobin levels to diagnose anemia at sea level (g/dL) 30
Table 2: Relevant Behavioral and Developmental Diagnoses 44
Table 3: Overall Categories with Sub-diagnoses 47
Table 4: Iron Deficiency Anemia and Anemia Diagnostic Codes 53
Table 5: Descriptive Data (Code) 55
Table 6: IDA/anemia Diagnostic Criterion and Total Frequency 57
Table 7: Demographics by IDA/anemia Diagnosis 59
Table 8: Group Differences and Odds Ratio for Relevant Diagnoses 61
Supplemental Table 1: Definition of diganoses 78
Supplemental Table 2: Sub-diagnosis definitions 101

List of Figures

Supplemental Figure 1: OR for Relevant Behavioral Diagnoses 116
Supplemental Figure 2: OR for Relevant Developmental Diagnoses 116

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Chapter One: Introduction

The total number of children in the U.S. Foster Care System in 2019 was 423,997.[1] The most frequent circumstance for child removal from the home and placement into foster care, in 2019, was neglect (n=158,258). While there has been a decrease in the number of children in the U.S. Foster Care System in recent years, in Pennsylvania (PA), the number of children served in foster care has steadily increased since 2015.[2] In 2019, 24,665 children were served by the PA Foster Care System, of which 63.5% were between 0-11 years of age.[3] The burdens imparted on children in foster care create a clinically challenging picture for clinicians, social workers, and families. Early life adversity and chronic stress, without proper coping or timely intervention, has been physiologically linked to physical and mental health disorders.[4,5]

Often, children who enter child welfare services have undiagnosed chronic or acute medical conditions.[6,7] In one study a striking 92% of children entering Baltimore, Maryland Foster Care had a major or minor physical health abnormality.[6] Another study reported that 86.3% of children, receiving care in a San Diego emergency shelter (type of foster care placement), had at least one physical health abnormality, and 24.2% had three or more abnormalities.[8] A large scale study evaluating laboratory screening data of children in foster care (n = 1,977), reported that 60% had at least one laboratory abnormality.[9] Of the children less than 12 years of age (n = 1,317), 52% had at least one laboratory abnormality. The evidence indicates that children in foster care have a clear risk for physical health abnormalities. Consequently, the American Academy of Pediatrics has classified children in foster care as a special health care needs population.[10]

Children and adolescents in foster care are an understudied pediatric population. Studies evaluating the nutritional status of children in U.S. Foster Care are largely focused on

macronutrient or anthropometric measures (growth trajectory and weight).[11,12] Such studies emphasize the need for early and comprehensive screening to improve overall health, including nutrition-related outcomes. Currently, nutritional evaluations at well-child visits are recommended for both children in foster care[10] and children who have been adopted.[13]

Despite its importance in early childhood development, research on vitamin and nutrient status among children in foster care is limited. This is a clear gap as the evaluation of micronutrient status is critical to understanding the physical and developmental needs of children and to inform comprehensive pediatric evaluations and interventions.[12]

Iron is of particular interest due to the global prevalence of iron deficiency (ID), and the developmental consequences of ID. A large body of evidence indicates ID as the single most common micronutrient deficiency worldwide.[14,15] When ID progresses to its most severe form, it is classified as ID anemia (IDA), which is diagnosed by a reduction in hemoglobin (Hb) in addition to abnormalities in specific iron biomarkers.[16] According to the World Health Organization (WHO), anemia affects approximately 1.62 billion people globally.[15] Worldwide, 47.4% of children < 5 years of age (305 million) and 41.8% of pregnant women (56 million) are predicted to have anemia. Within the United States, the rate of anemia is likely driven by ID. One study, which extracted data from the National Health and Nutrition Examination Survey (NHANES), evaluated children (one to five years old) for ID, IDA, and anemia.[17] From their total sample (n=1,437), 3.2% of children were anemic. It was found that approximately 35% of children who were anemic, had ID. The rate of ID in their total sample was nearly seven times greater than the rate of IDA and two times greater than the rate of anemia. These data suggest that anemia in the U.S. is likely driven by poor iron status. Taken together, several etiologies of

anemia exist, but the most common is ID,[16] contributing to approximately 50% of anemia diagnoses globally.[17]

ID has implications for brain development and behavioral outcomes. Mechanisms of iron's role in the brain continue to be uncovered.[18,19] Animal models support iron's role in myelination, neurogenesis, dendritogenesis, and neurochemical synthesis.[18,19] Globally, the burden of ID is reportedly highest in children < 5 years of age,[15] which is a critical period of growth and development.[20–22] Human studies have demonstrated that ID during infancy and early childhood can increase risk of impaired cognitive, motor, behavioral, and neurological outcomes with both short- and long-term consequences.[23,24]

Adolescents (10-19 years of age) are also vulnerable to ID, especially girls.[25] This is in part due to pubertal growth and physiological demands, which increase nutrient and caloric requirements. Consequently, iron needs show a marked increase from childhood and preadolescence (4-8 years: 10 mg/day iron) to adolescence in both boys (9-13 years: 8 mg/day iron; 14-18 years: 11 mg/day iron and girls (9-13 years: 8 mg/day iron; 14-18 years: 15 mg/day iron).[26] When iron needs are not met one can develop ID and ultimately IDA. ID adolescents, even without anemia, have presented with impaired cognitive outcomes.[27–29]

Consequences of early life ID emphasize the importance of prevention during childhood through monitoring and evaluation. A chart review examining 1,542 children, entering a San Diego emergency shelter, reported anemia among 7.4% of the total sample.[8] For perspective, a previously discussed study utilizing NHANES data indicated that 3.2% of children, aged one to five years, had anemia in the U.S. and 7.1% of children had ID. If a striking 7.4% of children entering an emergency shelter had anemia, there is the potential that ID rates are twice as great; however, evaluation of iron status, specifically, was not conducted within this sample.[8]

Currently, we have limited information on the prevalence and etiology of anemia among children in the U.S. Foster Care System with no studies evaluating ID and IDA, to our knowledge. This gap may be partly driven by lack of awareness on the nutritional needs of children in foster care. Unfortunately, the present study is unable to fully bridge the above gap. Given the available data, we are able to evaluate IDA and anemia, but not ID in the absence of anemia. Additionally, IDA was combined with anemia is our analysis due to concerns about a small sample size.

Given the lack of information on iron status in children in the U.S. Foster Care System, we attempted to find a potential comparison group. We recognize that studies of internationally adopted children are not a direct comparison to children in the U.S. Foster Care System but feel that they provide us with some information on the iron status of children, less than five years of age, who may have experienced similar adverse circumstances early in life. Four such studies have been identified[30–33], of which two[31,32] were part of a larger longitudinal study.[34] Three studies evaluated iron status at baseline (within one month of U.S. entry and adoption) and at a six-month follow-up.[31–33] In these studies, ID was identified in adopted children at baseline, which persisted six-months later (follow-up), despite exposure to a presumably nutritionally replete environment in the adopted home. One publication reported that 26% of the international adoptee sample were found to have ID without anemia at adoption.[32] Interestingly, ten adoptees were ID at the six-month follow-up, of which four were newly diagnosed. The consequences of prolonged ID bare concern for developmental outcomes. For instance, children who were ID at adoption had lower Bayley Scales of Infant Development (BSID-III) motor and cognitive scores at both baseline and the six-month follow-up when compared to iron-sufficient adoptees, despite oral iron intervention for children diagnosed with poor iron status. Notably, motor and cognitive scores were markedly improved at follow-up and were within one standard deviation (SD) of the

mean score (M=100; SD=15) in both groups. Evidence from animal studies examining ID, neurophysiology, and developmental outcomes indicate that ID can have unresolved consequences, if not adequately treated during critical periods of growth and development. This suggests that the timing of ID, and appropriate intervention, are of critical importance.[35–37] Again, internationally adopted children are not an adequate proxy when exploring the needs of children in U.S. Foster Care, but the above findings may shed light on the potential concerns for children in the U.S. Foster Care System. Further research on the nutritional needs of children in U.S. Foster Care is warranted to determine an appropriate clinical picture.

The findings presented above illustrate the nutritional complexities of this pediatric subpopulation. Catch-up growth demands, ID severity upon entering the Foster Care System, timing of ID, poor iron absorption, and other factors can all contribute to prolonged poor iron status; thus, exacerbating risk of suboptimal developmental and behavioral outcomes. Recognizing the inherent risk children in foster care have to physical health issues, the additional burden of poor nutrient status can aggravate suboptimal child development. Despite this evidence, iron status of children in the PA Foster Care System is poorly understood.

The following thesis aims to (1) evaluate the rate of IDA/anemia among children within the PA Foster Care System and (2) determine the odds of developmental and behavioral impairments among children in PA Foster Care System, with and without IDA/anemia. For our first aim, we hypothesize that the rate of IDA/anemia among our sample will be greater than current U.S. rates of childhood anemia. For our second aim, we hypothesize greater odds of developmental and behavioral impairments among children with diagnosed IDA/anemia, relative to children without diagnosed IDA/anemia.

These results will inform future studies exploring iron status in children in foster care, and the effects iron can have on developmental and behavioral outcomes.

Chapter Two: Literature Review

Rate of physical and mental health issues among children in U.S. Foster Care

The total number of children served in the U.S. Foster Care System was 423,997, in 2019.[1] The number of children in foster care has steadily decreased, on a national-level, since 2017. In contrast, the PA Foster Care System has observed an increase in children served, since 2014.[2] In 2019 alone, 24,665 children were served in the PA Foster Care System, a 7.3% increase from 2015. Of the children served in 2019, 63.5% were between 0-11 years of age.[3] Additionally, 10,801 children left the PA Foster Care System in 2019, of which 25.2% were adopted.[3]

The rate of children in foster care with at least one physical health problem (of varying definitions) ranges from approximately 40-90%.[6,8,38–42] Children in foster care are also at risk of poor cognitive, behavioral and developmental outcomes,[41,43–47] warranting clinical evaluation of both physical and mental health for all children in foster care.

Despite the importance of physical, cognitive, behavioral, and developmental evaluations among this population, standardization of health assessments across child welfare services is lacking. One study evaluated 92 primary sampling units (PSU), which reflect a sample of children receiving care at a single U.S. child welfare agency.[48] Of the PSU's assessed, physical health examinations were a policy requirement in 86.4% of comprehensive evaluations.[48] Of importance, the extent of the physical health examinations remains unknown, and many may not include nutritional assessments. Despite the interest in cognitive, behavioral, and developmental outcomes, standardized evaluations of these domains among children in foster care are limited as well. Approximately half of PSUs had a policy requirement to screen all children entering foster

care for mental and developmental health. Further, only 26.8% and 26.4% of all PSUs assessed utilize a specific tool or instrument when assessing a child's mental and developmental health, respectively.[48] Of note, the type of tool used for the assessments is not typically recorded; consequently, the reliability and appropriateness of these mental or developmental screening tools are unknown.

When physical exams are undertaken for children in the foster care system, nutrition and nutrition-related concerns are predominantly focused on a child's growth or weight trajectory.[11,12] Micronutrient status (especially micronutrient deficiency) within children in foster care is understudied, despite its likely pervasiveness.[8,31–33,49,50] Seven studies were identified among children in U.S. Foster Care, which evaluated nutrition related outcomes, such as growth, weight, and/or presence of a nutrient deficiency.[6,8,9,38–40,49,51] Of these studies, six evaluated both nutrition as well as cognitive, developmental, or behavioral outcomes.[6,8,39,40,49,51]

Studies on children in U.S. Foster Care examining nutrition and development

Children in foster care are at increased risk of nutritional problems (i.e., malnutrition, stunting, nutrient deficiencies, etc.),[6,8,9,38–40,49,51] with concerns for worsening health if a child re-enters foster care.[40,52] One study conducted in Maryland reported that 7.7% and 14.6% of children (0-18 years old) entering foster care were below the 5th percentile for weight and height, respectively. In children 0-2 years of age, a striking 15.4%, 27.2%, and 18.8% were below the 5th percentile for weight, height, and head circumference, respectively.[6] The same study reported that an alarming 91.5% of the total sample had at least one abnormality (major or minor), including unspecified neurological abnormalities (2.3%). Furthermore, over half (55.2%) required mental health referrals. Another study reported that 44% of all children, who were taken

into protective custody and screened at a Chicago teaching hospital, had a health problem.[38] Anemia was the most common issue, indicated in 13% of all children. For those children who were diagnosed with failure-to-thrive, 47% had a developmental delay (type of measurement not provided).

A study by Leslie et al.,[8] examining children (three months to five years and 11 months) entering a San Diego emergency shelter, found that 86.7% had a physical problem, with 25% of children diagnosed with at least three physical health problems. Anemia was reported in 7.4% of children. Over half (59.7%) of children in this study were classified as "suspect" for a developmental abnormality, requiring further assessment. Of note, the etiology of anemia was unknown in this population; furthermore, researchers did not stratify developmental outcomes by anemia status.[8]

One cross-sectional study extracted data from medical records among children in the Sacramento County Foster Care System, who were seen at the Foster Care Health Program, and compared them against Medicaid eligible children from the Sacramento County who were not in foster care.[51] At examination, 11.1% and 3.1% of the children sampled (n=224) were below the 5th percentile for height and weight, respectively.[51] Skin abnormalities were indicated in 37.1% of children evaluated. Approximately 30% of children had dental caries, 14.9% of children had a vision abnormality, and 0.7% had a hearing abnormality. When comparing children in foster care to the Medicaid eligible but not in foster care group, physical exam referrals were significantly higher ($p < 0.001$) among children in foster care for medical subspecialties (16.6% vs. 3.4%, $\chi^2 = 78.02$), hearing (12.1% vs. 1.5%, $\chi^2 = 22.76$), vision (16.1% vs. 2.3%, $\chi^2 = 30.87$), and dental (30.9% vs. 9.8%, $\chi^2 = 34.25$). A similar finding was reported among children receiving developmental referrals ($\chi^2 = 65.28$, $p < 0.001$) among foster care (58%) versus Medicaid eligible

non foster care (4%). Mental health referrals were also significantly higher ($\chi^2 = 29.11$, $p < 0.001$) among children in foster care (12.6%) versus Medicaid eligible non foster care (0.8%). These results seem to indicate that children in foster care suffer from greater physical, developmental, and mental health disturbances than low-income children not in foster care.

Children who experience a failed placement (return to foster care after placement)[52] or multiple placements (placed into multiple foster care homes/settings)[53] experience instability, which can exacerbate poor health outcomes. One study, on children re-entering Arkansas foster care, reported significantly greater motor problem rates ($\chi^2 = 31.14$, $p < 0.001$) among children upon re-entry into foster care (14%), when compared to their initial placement (13%).[40] Although statistically significant, the difference is minimal, warranting thought on its clinical significance. However, one could argue that a similar proportion of motor problems from initial placement to re-entry suggests ongoing motor issues, underlining the health vulnerabilities which persist among children who enter foster care. Of note, physicians report that they often defer motor exams until re-entry ($\chi^2 = 23.75$, $p < 0.001$); consequently, an increase in motor problems at re-entry may reflect deferment of motor examination until a child is older. Examinations found a striking difference in abdominal problems from initial placement (9%) to re-entry (15%; $\chi^2 = 12.21$, $p < 0.001$). Nutritionally, no significant differences were identified for mean height z-scores (initial: 0.11 and re-entry: 0.10) but children at re-entry into foster care had significantly greater ($t = -4.27$, $p < 0.001$) mean weight z-scores (0.75) when compared with initial placement (0.58). A trend toward overweight or obesity among re-entry children[40] could be partly related to pharmaceutical use. Antipsychotic polypharmacy is common among children in foster care,[54] especially among adolescents.[55] One study reported greater risk of morbid obesity among adolescents who took either one second-generation antipsychotic (RR 3.05 [2.86-3.27], $p <$

0.05), or at least two second-generation antipsychotics (RR 5.21 [4.21-6.44], $p < 0.05$).[55] Antipsychotics are linked with weight gain, potentially perpetuating poor nutritional outcomes.[56]

A long-term focus on mental health and behavior development is warranted. One study reported that children in Pennsylvania foster care had significantly higher diagnoses ($p < 0.001$) of depression, anxiety, and attention deficit hyperactive disorder (ADHD) when compared with other Medicaid beneficiaries who were not in foster care (Aid to Families with Dependent Children (AFDC)).[57] Children in foster care had expenditures 10 times greater for psychiatric services when compared with children in AFDC ($1,961 vs. $191; $p < 0.001$) as well as greater psychiatric drug expenditures ($110 vs. $14; $p < 0.001$), nonpsychiatric service expenditures ($1,360 vs. $567; $p < 0.001$), and nonpsychiatric drug expenditures ($145 vs. $101; $p < 0.001$). Results illustrate the care management needs of children in foster care and their susceptibility to mental health issues. Of note, Medicaid data were utilized for analysis in this study, which is restricted by the use of coded diagnostic terms. Furthermore, it cannot provide a full clinical picture on services provided to the child. Expanding cognitive and developmental studies to include nutrition assessments may illuminate intervention strategies that are affordable, practical, and potentially effective for both nutrition as well as cognitive and developmental outcomes.

Taken together, these studies, amongst others not detailed,[39,49] underline the health concerns in this pediatric subpopulation. It is clear that nutritional developmental, cognitive and behavioral issues require detailed exploration. Studies presented above illustrate a complex clinical picture involving multisystem abnormalities. Studies which report on nutrition status often limit their focus to anthropometric data.[6,39,40,51] Of the studies which evaluate anemia, they failed to include the etiology of anemia.[8,38,49] Furthermore, relationships between developmental,

cognitive, or behavioral outcomes were not assessed by a child's nutrition status across any of the studies.

Micronutrient status and cognitive, behavioral, and developmental outcomes in internationally adopted children

Four studies were identified, which evaluated micronutrient and/or vitamin status among children in U.S. Foster Care.[8,9,49,50] Only one of these studies evaluated vitamin status (vitamin D) and its association with relevant behavioral outcomes (e.g., anxiety, depression, oppositional defiant disorder, etc.).[50] In this study, children in foster care and non-foster youth from the Minnesota community (control) had similar vitamin D levels (Control: 29.5 ng/mL; Foster: 29.9 ng/mL). The rate of anxiety, oppositional defiant disorder, and ADHD were significantly higher among children in foster care compared to the control group. Two other studies indicated above evaluated anemia (without specificity) and found that approximately 5-8% of children in foster care had an anemia diagnosis.[9,45] One cross-sectional study reviewing the medical charts of California foster youth and dietary information (using a 24-hour recall) of adopted children (n=27) reported that 18.5% of children reported evidence of IDA. However, the biomarkers extracted are unknown. Furthermore, the use of a 24-hour recall, as opposed to a three-day recall for instance, warrants concern for accuracy.[49]

Due to limited domestic research, our literature search expanded to micronutrient status among internationally adopted samples, where five studies were identified.[30–33,58] Of these, four evaluated iron[30–33] and/or zinc[33] status and their relationship to developmental domains. The remaining evaluated the prevalence of vitamin D status only,[50,58] anemia without specificity,[9,45,49] or various micronutrients.[9,33] The following section will focus on studies which evaluated micronutrient status and its association with cognitive, developmental, or behavioral outcomes.

All of these studies of interest[30–33] were conducted among a sample of internationally adopted children. We acknowledge that nutritional, cognitive, behavioral, and developmental outcomes among international children who were adopted and brought to the U.S. cannot be generalized to children in U.S. Foster Care. However, in the absence of other data, these studies serve as proxies, to inform our understanding of iron status and development, as it relates to children who have been displaced from their original home. The following section will focus on studies which evaluated micronutrient status and its association with cognitive, developmental, or behavioral outcomes. All of these studies of interest[30–33] were conducted among a sample of internationally adopted children.

One case-control study[33] recruited internationally adopted children (eight to 18 months) from three regions (China, Ethiopia, Post-Soviet States (Russia and Kazakhstan)), and non-adopted controls (community surrounding the University of Minnesota Adoption Medicine Clinic), to evaluate nutritional, cognitive, and developmental outcomes. Both groups were seen at two timepoints - baseline (within one month of the adoptees arriving in the U.S.) and a six-month follow-up. Only international adoptees received nutritional assessments (conducted at the Adoption Medicine Clinic at both timepoints) and both groups received neurodevelopmental assessments (conducted at the Center for Neurobehavioral Development, University of Minnesota). The Adoption Medicine Clinic required iron intervention if a child was diagnosed with IDA (3-6 mg/kg elemental iron daily for six to eight weeks) or ID (3-6 mg/kg elemental iron daily for four weeks, promotion of iron rich foods, and multivitamin with iron).[33]

Mean height for age z-scores (HAZ) in international adoptees improved from baseline to follow-up (Post-Soviet States: -1.19 vs -0.54, Ethiopia: -1.89 vs -1.09, and China: -0.93 vs -0.58). Similar improvements were found in mean weight-for-age z-scores (WAZ) (Post Soviet

states: -0.31 vs 0.23, Ethiopia: -0.89 vs. 0.26, China: -0.56 vs 0.02), mean weight-for-height z-scores (WHZ) (Post-Soviet states: 0.39 vs. 0.66, Ethiopia: 0.17 vs 1.04, China: -0.37 vs. 0.39), and mean occipitofrontal circumference z-score (OFCZ) by region (Post-Soviet states: 0.05 vs 0.31, Ethiopia: 0.20 vs. 1.23, China: -0.37 vs -0.06).

Some form of micronutrient deficiency was present among 55% of all internationally adopted children at baseline.[33] ID was the third most common micronutrient deficiency across all adoptees at both baseline (15%) and the six-month follow-up (9%). Two children had IDA at baseline and one at follow-up. Vitamin D deficiency (baseline: 21%; follow-up: 28%) and zinc deficiency (baseline: 29%; follow-up: 10%) were the two most common deficiencies, in the entire adoptee sample, at both timepoints. Cognitive and motor development were assessed using the BSID-III. Internationally adopted children had lower BSID-III scores at both baseline and follow-up for cognitive (baseline: $F_{1,92} = 43.76$, $p < 0.001$; follow-up: $F_{1,80} = 10.88$, $p = 0.001$) and motor outcomes (baseline: $F_{1,92} = 48.40$, $p < 0.001$; follow-up: $F_{1,80} = 16.14$, $p < 0.001$), when compared to the non-adopted controls. International adoptees were below average (composite score < 100) for both cognitive and motor scores, during baseline and follow-up; however, only motor scores were less than one SD (score < 85) below the mean at baseline for international adoptees. When stratified by iron status (ID vs. IS adoptees), baseline BSID-III motor and cognitive scores were lower among ID adoptees ($F_{1,45} = 5.23$, $p = 0.027$) compared to IS adoptees. All adoptees had scores below average (composite score < 100) at both timepoints. Of note, children in the ID adoptees group (anemic and non-anemic) had a baseline composite score less than one SD below the mean for both cognitive and motor scores. Marked improvements in mean motor and cognitive scores were observed at follow-up (within one SD of the mean) for both IS and ID adoptees. These observations support further the need to assess iron

status among children in foster care. Additionally, they underline the impact ID (with and without anemia) has on cognitive outcomes.

A separate study focused on ID and its association with cognition and behavior in post-institutionalized (orphanages or hospitals) children (nine to 46 months old) from Eastern Europe and Central Asia, who were adopted in the U.S..[32] Children were assessed at two timepoints: within one month of their arrival into the U.S. (baseline), and at a six-month follow-up. Nutritional assessments were completed as part of the medical evaluation at the International Adoption Clinic. The authors report that 26% (n = 15) of children at baseline were diagnosed with ID, four of which had IDA. Eighteen percent of children were ID at the six-month follow-up, two of which had IDA. Of note, six adoptees presented with ID at baseline and four developed ID from baseline to follow-up. Of importance, the International Adoption Clinic has protocols to treat IDA (2-3 mg/kg oral elemental iron for two months), but not ID. The ID group at follow-up experienced greater mean changes in WAZ (0.73 vs. 1.87, $p = 0.001$), WHZ (0.15 vs 1.74 $p = 0.001$), and OFCZ (0.54 vs. 1.14, $p = 0.05$), when compared with IS adoptees from baseline to follow-up. This may be partly related to increased iron demands for catch-up growth. One study, evaluating international adoptees from Eastern Europe found that growth was negatively associated with serum ferritin at baseline and follow-up ($\beta = -0.34$, $p < 0.05$),[31] with a blunted association, when adjusting for parent-reported iron intake ($\beta = -0.32$, $p = 0.08$).

In the study evaluating adoptees from Eastern Europe and Central Asia, children were observed during a recorded session and evaluated using the Mullen Scales of Early Learning and the Toddler Behavior Assessment Questionnaire-R (TBAQ-R)[59] at baseline and the six-month follow-up.[32] ID adoptees at follow-up had lower scores for expressive language (36.7 vs 43.8, $p = 0.017$), and the early learning composite (79.4 vs 90.6, $p = 0.01$), when compared with IS

adoptees, at follow-up. ID was found to be related to increased odds of scoring below average on the early learning composite (OR = 16.06, 95% CI [2.51,102.67], $p < 0.01$). Of note, confidence intervals are wide, potentially related to the small sample size among ID children. Parents of the adoptees completed the TBAQ-R, to determine if differences existed by iron status. Among parental assessments, ID adoptees scored higher in activity and impulsivity (4.5 vs. 3.9, $p = 0.046$). Examiners observed and rated child behavior independent of the TBAQ-R, with a lower score indicating a poorer outcome. Examiner-rated behavior reported significantly greater scores for the inattention and hyperactivity domain among IS adoptees when compared with ID (3.9 vs. 3.0, $p = 0.016$), suggesting lower cooperation and attention from children with ID. Notably, few TBAQ-R and Mullen scores were found to be significantly different between groups; however, ID children consistently scored poorer than IS children. The lack of significant differences may be related to the small sample size in the ID group (baseline n = 15; follow-up n = 10).

Taken together, these studies indicate persistent ID, even in the presence of oral iron therapy at the clinic, and a presumably nutritionally replete adoptive home. Improvement in growth, with sustained micronutrient deficiencies, indicate a need to acutely observe nutritional outcomes among adopted children, beyond growth parameters.

Of interest, is the presence of poorer developmental outcomes among adoptees with ID, even in the absence of anemia. This outcome is further supported by a study which examined internationally adopted children (adopted 17-36 months old) who had lived in an institution at least four months prior to adoption.[30] Children were adopted from Africa, Asia, Eastern Europe, and Latin America. Duration of institutional care ranged from four to 34 months, with more than half of children spending at least 80% of their lives in institutionalized care. The researchers evaluated IQ with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI; third

edition) and Bayley Mental Developmental Index (second edition). Executive functioning (EF) within various domains, was evaluated using delay of gratification (inhibitory control), the Dimensional Change Card Sort (cognitive flexibility), and split the pots task (working memory). Of importance, ID and anthropometry were assessed at the child's first medical visit (zero to two months post-adoption); however, cognitive and EF assessments were evaluated approximately one year (11-14.6 months; mean age: 37.4 $\pm$ 4.9 months) post-adoption.

In the above study, children were assessed for the following iron indices: Hb, transferrin saturation (TSAT), mean corpuscular volume (MCV), serum ferritin (Ft), and total iron-binding capacity (TIBC). Within their sample, 11 children had ID anemia (IDA), 16 had ID (11 with two abnormal indices; 5 with one abnormal index), and 28 children had normal iron status.[30] Children were coded from 0-3 to classify no ID (0), ID with one abnormality (1), ID with two abnormalities (2), and IDA (3). Longer duration in institutionalized care ($F_{1,49} = -2.74$, $p < 0.01$) and severity of ID ($F_{1,49} = -2.05$, $p < 0.05$), were associated with lower IQ scores among tested children. When controlling for duration of institutional care, ID at adoption was associated with lower EF scores ($\beta = -0.26$, $F_{1,53} = -2.03$, $p < 0.05$). This relationship was blunted when including IQ scores in the augmented model ($F_{1,49} = -0.58$, $p > 0.05$). Poorer IQ and EF scores were observed in children with ID in the absence of anemia and children with ID anemia (IDA). Taken together, ID was associated with poorer IQ and EF outcomes separately. Whether ID mediates the relationship between IQ and EF is not presented in this analysis; however, the study underlines ID as a risk factor for poorer cognitive outcomes among institutionalized children. Of importance, these results support ID's association with cognitive and developmental outcomes among this population.

Prevalence of ID, IDA, and anemia within the U.S.

Iron deficiency is the single most common nutrient deficiency worldwide, with anemia affecting nearly 25% (1.62 billion) of people globally.[15] Anemia can have multiple etiologies, but the most common is ID[14] which is estimated to contribute to 50% of anemia diagnoses globally.[60] One study[61] evaluating National Health and Nutrition Examination Survey (NHANES) data, reported that, of children one to two years old, 9% had ID and 3% had IDA. Among children three to five years old, 3% had ID and < 1% had IDA, and among children six to 11 years old, 2% had ID, and < 1% had IDA. In this study, ID was diagnosed if a child had at least two abnormal iron lab values (FEP, TSAT, and serum Ft). IDA was determined with two of the aforementioned abnormal iron lab values and a low Hb value. Inflammation was accounted for by using a history of infection among children ≤ 3 years old and C-reactive protein (CRP) for older children.[61] The study identified a striking 10% of infants with ID. This proportion is troubling as infancy is a critical period of brain development, requiring optimal iron status.[23]

In recent studies, ID, IDA, and anemia among U.S. children (one to five years old) were determined with 2007-2010 NHANES data.[17] Soluble transferrin receptor (sTfR), serum Ft, and Hb were utilized to determine iron and anemia status. The researchers calculated total body iron (TBI) using the below calculation developed by Cook *et al.*[62], with sTfR/serum Ft:

$$\text{TBI (mg/kg)} = -[\log(\text{sTfR/serum Ft ratio}) - 2.8229]/0.1207]$$

Of note, restrictions to blood collection in highly vulnerable populations hinders the ability to validate the sTfR/serum Ft ratio among children.[62] ID was defined in the 2007-2010 NHANES sample as a TBI < 0 mg/kg, anemia was defined as a hemoglobin (Hb) < 11g/dL,[17] and IDA was a combination of low TBI and Hb. Within their sample, 7.1%, 3.2%, and 1.1% of

children one to five years old had ID, anemia, and IDA respectively.[17] The prevalence of ID (13.5% vs 3.7%, $p < 0.05$) and anemia (5.4% vs 1.9%, $p < 0.05$) was significantly greater among children 1-2 years of age, when compared with children 3-5 years of age.

A separate study analyzed anemia without specificity, using NHANES data from 2003-2012.[63] The study evaluated a sample between 0.5-85 years of age. Among their sample of interest, anemia was classified as a Hb < 11 g/dL and < 11.5 g/dL for children 0.5-4.9 years and 5-11.9 years, respectively. The study classified moderate-severe anemia as < 10 g/dL for children 0.5-4.9 years and < 11 for 5-11.9 years old. Within the sample of those who were 0.5-4.9 years old, 3.4% had anemia and 0.5% had moderate-severe anemia. For children between 5-11.9 years of age, 2% had anemia and 0.5% had moderate-severe anemia.

Among children 0.5-4 years old, a Hb of 10.0-10.9 g/dL, 7.0-9.9 g/dL, and < 7 g/dL classify mild, moderate, and severe anemia, respectively.[64] Children 5-11 years old have Hb cut offs of 11-11.4 g/dL, 8-10.9 g/dL, and < 8 g/dL for mild, moderate, and severe anemia, respectively. In summary, prevalence rates of ID and IDA in the U.S. remain elevated despite supplementation and fortification programs.[65]

Iron

Iron is the second most abundant metal in the Earth's crust.[66] Iron can exist in multiple oxidation states but has two principal states, Fe^{2+} (ferrous iron) and Fe^{3+} (ferric iron).[66,67] Iron's chemical composition makes it readily available for redox reactions, critical to biological processes like cellular respiration and nitrogen fixation.[68] Due to its nature, iron can also serve to exacerbate oxidative stress, by reacting with oxygen metabolites and reactive oxygen species (e.g. superoxide dismutase), producing hydroxyl radicals. These interactions are known as

Haber-Weiss-Fenton reactions (detailed below), and can result in damage to nucleic acids, proteins, and lipids.[67]

$$Fe^{3+} + \cdot O_2^- \rightarrow Fe^{2+} + O_2$$
$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH \text{ (Fenton reaction)}$$
$$\text{Net reaction: } \cdot O_2^- + H_2O_2 \rightarrow OH^- + \cdot OH + O_2 \text{ (Haber-Weiss reaction)}$$

Iron's absorption, storage, and use, under ideal conditions, are tightly controlled for optimal homeostatic regulation. Iron status is controlled at the site of absorption. As such, an understanding of the iron absorptive machinery is critical.

Absorption, storage, and metabolism

Iron is classified as either heme or non-heme iron.[69] Heme iron is found in animal proteins (40% heme and 60% non-heme), where iron is centered in the porphyrin ring of myoglobin and hemoglobin. Non-heme iron is largely found in non-animal or plant-based sources.[70] Non-heme iron is the predominant type that is ingested with foods. Heme iron absorption occurs at a greater rate compared to non-heme iron and undergoes a different form of regulatory absorption. The following description of absorption will be divided into heme and nonheme iron absorption.

Heme absorption

Heme iron will enter the apical membrane of the enterocyte intact and is thought to either cross the membrane by endocytosis or by heme carrier protein-1 (HCP-1).[71] The primary physiological function of HCP-1 remains in question.[67] Upon entry into the enterocyte, heme oxygenase will act upon the porphyrin ring, releasing biliverdin, carbon monoxide, and iron.[70,71] Upon iron's release it can be stored as Ft (once oxidized) or exist in the labile iron pool. Heme

may also travel across the basolateral membrane intact via the heme exporter, Feline leukemia virus C receptor or the ABCG2 transporter.[71] Heme can then bind to the acute-phase protein, hemopexin (Hx), at the basolateral membrane to prevent heme-induced oxidative stress.[72,73] Endocytosis of the Hx-heme complex, at major peripheral tissue like the hepatocytes, is thought to occur via the LRP/CD91 pathway, with subsequent degradation of Hx and release of heme.[72]

Non-heme absorption

Non-heme iron will enter the intestine as both ferrous or ferric iron; however, if in the form of ferric iron, it will require conversion to ferrous iron, prior to its absorption.[67,71] Ferric iron is reduced to ferrous iron through brush border ferrireductase enzymes, such as duodenal cytochrome b (Dcytb). Ascorbic acid, along with other reducing agents, function to reduce ferric iron for subsequent uptake as well. Once iron is reduced to its ferrous form, it can shuttle into the enterocyte through the Divalent Metal Transporter 1 (DMT1), located on the apical membrane surface. Once iron is in the intracellular space, it may be stored as ferric iron or exported through the basolateral membrane for circulation. Ferrous iron must oxidize to its ferric form before storage in the Ft protein – a hollow sphere which incorporates ferric iron as ferrihydrite. Ft expression is controlled by H and L chain mRNAs and has a positive relationship with the labile iron pool.[74] Ft expression will increase when labile iron is high to reduce risk of iron-mediated oxidative stress. Hormonal and posttranscriptional regulation of iron will be described elsewhere (see *Iron Regulation)*. Iron can also cross the basolateral membrane through iron exporter, Ferroportin (FPN), where it is oxidized by the membrane-bound hephaestin (ceruloplasmin homolog) or ceruloplasmin. Ferric iron is subsequently bound to transferrin (2 ferric iron per protein) for circulation.[70,71]

Uptake into peripheral tissues

Transferrin (Tf) delivers iron to cells by binding to transferrin receptors (TfR1 and TfR2).[71] Once bound, the TfR-Tf complex is internalized into a Clathrin-coated vesicle. Upon endocytosis into the intracellular space, the drop in pH will cause the release of iron, and disassociation of TfR from apo-Tf for subsequent recycling. Within the endosome, iron is reduced from ferric to ferrous iron, via Steap3 ferrireductase.[67] Ferrous iron is then transported out of the endosome by DMT1 so it can be metabolized or stored in Ft.

Iron regulation: Hepcidin

Hepcidin is a 25-amino-acid peptide (bioactive) synthesized in the liver.[70,75] Other forms include 22- and 20-amino-acid peptides; however, their function in regulating iron is markedly reduced when compared to its bioactive form.[75] Hepcidin is a key regulator of iron metabolism and is upregulated in periods of elevated iron concentrations, inflammation, and infection. When upregulated, hepcidin downregulates iron recycling by the macrophages, iron absorption at the intestine, and hepatic release of iron. Importantly, hepcidin can bind to FPN (the only known exporter of ferrous iron), inducing internalization and lysosomal degradation. This action inhibits the export of iron for transport to peripheral tissue. The enterocyte specifically undergoes cell turnover every two to three days; therefore, accumulated iron will be sloughed and excreted.[75]

Hepcidin's role in intestinal absorption continues to be uncovered. Cross-talk between hepcidin and HIF-2alpha (a key regulator in iron absorption) is thought to influence iron absorption, especially during periods of iron overload.[76]

Iron regulation: Posttranscriptional regulation

Ft and TfR expression are controlled post-transcriptionally by iron regulatory proteins (IRP) and iron regulatory elements (IRE).[75,77] TfR and Ft, the H- and L-chains, contain IRE subunits on the 3' and 5' untranslated region (UTR) of TfR and Ft, respectively.[77] When iron concentration is low, IRP1 and IRP2 binds to the five IREs located on the 3' UTR of TfR mRNA and the single IRE located on the 5' UTR of H- and L-Ft mRNA. The IRP-IRE binding functions to stabilize TfR mRNA and represses the translation of H- and L-Ft mRNA. Consequently, TfR expression is upregulated, and Ft expression is downregulated. When iron levels are elevated, IRP1 and IRP2 cannot bind to IREs, thus maintaining TfR mRNA instability and degradation, and supporting ongoing Ft translation.

Location and function of iron in the brain

Iron is transported through the cerebrospinal fluid, attached to Tf.[18] Iron uptake through the blood brain barrier (BBB) is achieved by TfRs expressed on the endothelial cells of the brain.[18] The choroid plexus serves as another barrier between iron and the brain and expresses TfR, albeit to a lesser degree, for iron uptake.[78] Similar to peripheral tissue uptake, the TfR-Tf complex is internalized and iron is released in the intracellular space, with the subsequent recycling of apo-Tf and TfR. Iron transporters DMT-1 and Metal Protein Transporter-1 (MPT-1) function to control the flux of iron in the intracellular space. Lactoferrin has also been indicated as a potential transporter of iron across the BBB; however, its function and presence in the brain remains in question.[78]

Iron is a cofactor in neurotransmitter synthesis as it is critical for enzymes like tyrosine hydroxylase (the rate-limiting step which converts tyrosine to L-DOPA)[79] and tryptophan hydroxylase.[18,78] Regional concentrations of iron are dependent on the stage of brain

development. In animal research, brain iron concentration was found to be approximately two-fold greater in the cortex, relative to the cerebellum-pons and midbrain on postnatal day two.[80] Regional differences in brain iron concentration in adulthood (postnatal day 75 and 730) are markedly blunted, with higher concentrations in the cerebellum-pons, relative to the cortex and midbrain.[80] These findings suggest age dependent requirements for adequate neurophysiological development.

The first years of life encompass a period of significant hippocampal and cortical development, as well as myelinogenesis, dendritogenesis, and synaptogenesis.[23] Iron deficiency during infancy and toddler-hood can in altered development of the hippocampus, with potential downstream effects on spatial learning and memory.[23,36] The function of iron in the brain is predominantly documented in oligodendrocyte metabolism and myelination, monoamine metabolism, and GABA metabolism.[18] Iron's influence on neurological functioning and development is related to brain iron concentration. ID can influence metabolic systems, such as dopaminergic synthesis, GABA metabolism, and oligodendrocyte maturation ,with potentially irreversible impact, if ID occurs during critical periods of growth without amelioration.[18,35,37]

Iron is critical for oligodendrocyte maturation, which is required for adequate myelin composition.[18,78] ID has been found to result in hypomyelination due to lack of iron accumulation in the oligodendrocyte.[81] This is related to decreased cholesterol and fatty acid synthesis, which are key components of myelination. Studies evaluating iron and myelination find that ID during the perinatal period can decrease myelin proteins required for the structural integrity and formation of myelin, myelin basic protein (MBP) and proteolipid protein (PLP).[82–84] Furthermore, the oligodendrocytes have high rates of oxidative metabolism, with high concentration of iron-dependent enzymes like NADH dehydrogenase, succinic dehydrogenase,

and glucose-6-phosphate dehydrogenase.[81] The high energy requirements for myelination supports iron's critical importance in oligodendrocyte function.

Animal studies strongly support the relationship between iron, oligodendrocyte maturation, and myelination,[85] with limited human studies related to ethical and methodological difficulties. Differences in auditory brainstem evoked responses (ABRs) among Chilean children are linked to hypomyelination in the ID brain, despite therapeutic iron treatment (15 mg Ferrous sulfate).[86] Infants were evaluated at six, 12, and 18 months of age for hematological values and ABRs. Infants in the IDA and control group received iron supplementation as a therapeutic or prophylactic measure, during the course of the study, with observed improvements in biomarkers. Despite improvements in iron status, central conduction time (CCT) was longer among IDA children at all time points, with significantly longer CCT at the 12- (4.47 ± 0.03 vs 4.36 ± 0.03, $p < 0.01$) and 18-month (4.37 ± 0.04 vs 4.24 ± 0.04, $p < 0.01$) follow-up.[86]

Longer CCT is indicative of slower nerve conduction and is likely related to hypomyelination. Iron-mediated synthesis of dopamine, serotonin, and γ-amino butyric acid may also contribute to dysfunction in the auditory pathway.[86] Overall, ID induced disruption in the central nervous system auditory pathway was not completely resolved, despite early iron intervention, underlining iron demands for rapid brain development during the first years of life.

The effects of brain ID on dopaminergic activity and receptor density have been well-established.[18,35,37,87] Studies have observed that timing of ID can influence dopaminergic synthesis.[35,37] One rodent study induced ID during the first neonatal period (post-natal day [PND] 4 – 21), with subsequent repletion during the second neonatal period (starting PND 21, for four weeks; denoted as ID to control (IDCN)), found improvements in both hematological and dopaminergic density.[35] However, despite repletion, IDCN rodents maintained reduced

Dopamine receptor 1 (D_1R) concentrations in the striatum, when compared with controls (268 $\pm$ 19 vs. 403 $\pm$ 19, $p < 0.05$).[35] Dopamine transporter (DAT) density in the control group was higher in nearly all regions of interest and was found to be significantly greater in the striatum (8.81 $\pm$ 0.25 vs. 18.10 $\pm$ 0.15, $p < 0.05$). Interestingly, the same study reported higher Dopamine receptor 2 density in previous ID rodents in the striatum (3393 $\pm$ 233 vs 1716 $\pm$ 126, $p < 0.05$) and nucleus accumbens (2806 $\pm$ 462 vs. 1847 $\pm$ 164 $p < 0.05$), when compared to controls. Iron therapy was observed to improve the D_2R density in specific brain regions; however, a similar improvement was not found for D_1R and DAT density.

A separate study induced ID during gestation (gestational day 15 (GD15)), with and without early postnatal repletion, to determine its influence on monoamine function, development, and behavior.[37] Rodents in the ID group (ID during gestation and postnatally), had lower concentrations of DAT, relative to the control group, in nearly all brain regions assessed, with the exception of the nucleus accumbens and substantia nigra on postnatal day 21 (PND 21). Differences in norepinephrine and epinephrine concentration between ID and control rodents were not observed in the prefrontal cortex. ID rodents on postnatal day 15 (PND 15) had significantly lower ($p < 0.05$) concentrations of epinephrine in the striatum, with attenuation by PND 21.

In the same study, rodents who were ID during gestation with early postnatal repletion (IDCN) had improved DA from PND 9 to PND 21 across all brain regions.[37] IDCN rodents had significantly higher DA, relative to the control, in the striatum (20.6 $\pm$ 0.9 vs. 13.9 $\pm$ 0.8, $p < 0.05$), nucleus accumbens (14.0 $\pm$ 0.7 vs. 7.8 $\pm$ 0.9, $p < 0.05$), and olfactory tubercle (11.3 $\pm$ 0.7 vs. 6.4 $\pm$ 0.7, $p < 0.05$) by PND21. Improvements in norepinephrine and epinephrine concentration in the striatum were also observed in the IDCN group. Fur development, eye

opening, and ear development were blunted in the IDCN and ID rodent groups at PND6, with improvements across all groups by PND21. Locomotor activity was assessed using distance traveled over 20 minute periods. ID rodents did not have observed differences in activity level at P15, with significantly lower ($p < 0.05$) distance traveled at PND21, relative to the control.

Taken together these studies emphasize the time-dependent effect of brain iron on neurophysiological and neurochemical development. Importantly, early iron repletion (third trimester to 32 weeks postnatal) could completely ameliorate the long-term consequences of poor brain iron.[37] The findings underline the timing of ID in early life, and the irreversible impact it can have on neurophysiological and neurochemical development, despite iron repletion.

Difference between measuring and diagnosing anemia versus IDA

The gold standard for identifying ID is through bone marrow aspiration to determine hemosiderin concentration.[88] However, the collection of bone marrow is costly and invasive. An alternative method is evaluating Hb levels in response to iron therapy. This method, however, can be confounded by variations in absorption, compliance with therapy, and underlying conditions.[88] ID will initially affect iron storage, followed by transport, and finally erythroid iron concentration.[89] Laboratory methods have been established to evaluate these changes through measurable indices.

Depletion of iron storage is the first indicator of low iron status. Ft provides a measurement of total iron stored. Ft is present in large quantities in the liver and spleen, with minimal amount of Ft found in the serum (12-300 ug/L).[89] Ft is an acute phase protein which will be elevated in the presence of inflammation or infection. If inflammation is present, Ft values may inaccurately determine iron status adequacy. CRP is an acute phase protein which functions

as a non-specific indicator of inflammation.[90] Under normal circumstances, serum CRP levels are < 10 mg/L. CRP can be a beneficial marker for acute inflammation (e.g. infection); however, it is less informative for chronic inflammation (e.g. obesity). Alternative proteins include Alpha-1-antichymotrypsin (ACT) and alpha-1-acid glycoprotein (AGP), and have been indicated as useful acute-phase proteins when determining chronic, long-term inflammation.[90] Adjusting Ft, using a combination of CRP and AGP has been a useful method of determining true iron storage.[91]

Once iron stores have been exhausted, plasma iron will begin to decrease.[89] Plasma iron and TIBC are measured and used to calculate transferrin saturation (TSAT). TSAT will steadily decrease as Tf increases and plasma iron decreases. A reduction to <16% is indicative of ID.[89,92] In a state of ID, heme synthesis is precluded as it lacks the insertion of ferrous iron into protoporphyrin IX (one of the final metabolites in porphyrin synthesis).[93] Consequently, protoporphyrin increases in concentration and can be assessed either as free erythrocyte protoporphyrin (FEP) or as zinc protoporphyrin (ZPP).[94,95] ZPP is the product of protoporphyrin and zinc chelation via ferrochelatase. Both can be used, in a combination with other iron indices, to determine ID.[96] The biomarker sTfR is utilized to determine iron status and is observed to markedly increase in ID erythropoiesis.[97] It was once thought that sTfR does not increase in the presence of inflammation, which made it a useful tool among those facing chronic and acute inflammatory states (e.g. obesity, HIV, infection).[97] However, recent evidence opposes this notion as sTfR is positively correlated with inflammation, which could misdiagnose ID.[98] sTfR concentrations should be adjusted, in the presence of inflammation, however the method of adjustment requires further exploration. Taken together, Ft and sTfR with an inflammatory

marker, measures iron storage, and functional tissue iron, respectively, and Hb will measure reduced erythropoiesis.[97]

Once ID advances to anemia, Hb levels will begin to decrease.[99] Anemia is defined as a reduction in the number of red blood cells in the body, resulting in reduced oxygen delivery to the peripheral tissue.[99] Anemia is determined when Hb levels are two standard deviations below the mean for age and sex. The WHO cut-offs for Hb (at sea level) are provided below (Table 1).[99] The measurement of Hb concentrations requires a blood sample (pooled or individual drops), which could be analyzed with a cynamethohemoglobin, a HemoCue® system (Hb-201 and Hb-301), an automated hematology analyzer (AHA), WHO Colour Scale, paper-based devices, the copper sulfate technique, Masimo Radical®, or a Masimo Pronto®.[100] The WHO Colour Scale, HemoCue, and Masimo Pronto can be used in both a clinical laboratory or in a field setting. One literature review compared the above Hb analysis techniques, using the AHA as a reference, and found acceptable performance across all methods of analysis.[100] The AHA was used as a reference because it is commonly found in clinical laboratories and can test other indices as well. Of the methods mentioned above, AHA is the most expensive piece of equipment ($2,000-15,000) and the most expensive per test ($10/test vs ~$1-2/test). Hemoglobin assessment can only determine anemia status and is not specific to iron. Furthermore, anemia can be related to multiple nutrient deficiencies (e.g. folate, B_{12}, iron),[101] as well as trauma, or injury. Microcytic (small) and hypochromic (pale) red blood cells are a phenotype of ID. Low mean corpuscular hemoglobin concentration (normal limits: 320-360 g/L) and mean corpuscular volume (normal limits: 80-100 fL) indicate pale and small red blood cells, respectively.[101]

Table 1: Hemoglobin levels to diagnose anemia at sea level (g/dL)				
		Anemia		
Population	**Non-Anemia**	**Mild**	**Moderate**	**Severe**
6-59 months	≥ 11.0	10-10.9	7-9.9	< 7.0
5-11 years	≥ 11.5	11-11.4	8-10.9	< 8.0
12-14 years	≥ 12.0	11-11.9	8-10.9	< 8.0
Non pregnant women (≥ 15 years)	≥ 12.0	11-11.9	8-10.9	< 8.0
Pregnant women	≥ 11.0	10-10.9	7-9.9	< 7.0
Men (≥ 15 years)	≥ 13.0	11-12.9	8-10.9	< 8.0
Adapted from the WHO, 2011 Report[99]				

Cognitive, developmental, and behavioral domains (infants and school-aged children)

Cognitive domain, developmental domain, and iron

When a child suffers from ID, brain development can be impacted, with downstream effects on the child's cognitive, developmental, and behavioral outcomes.[23,102] Suboptimal cognitive and developmental outcomes can lead to educational difficulty, reduced working memory, and poorer school performance.[28,29,103] Iron supplementation has been found to improve cognitive function in young children.[104] One study reported that iron supplementation, in combination with trained counseling, improved cognitive outcomes.[105] Interestingly behavioral outcomes worsened, among ID children without at-home counseling, despite iron supplementation.[105]

Another study reported poorer cognitive outcomes in adolescents, who were of normal Hb status in infancy, but received higher iron containing formula (12 mg/L), when compared to the control receiving a lower iron containing formula (2.3 mg/L).[106] For context, iron-fortified formulas in the U.S. have a recommended level of 12 mg/L.[107] Of importance, the same study found that those who were of low Hb status in infancy, receiving higher iron containing formula, had greater cognitive scores, when compared to children with low Hb and receiving lower iron containing formula.[106] The poor cognitive outcomes found in children with normal Hb and higher iron containing formula raise concern for formula-fed infants in the U.S.. Nevertheless, many other studies indicate that children with ID or IDA have improvements in cognitive and developmental outcomes, when provided therapeutic iron.[104,106,108–110]

One study evaluated the association between iron status and cognitive performance using NHANES data from 1988-1994, among children aged six to 16 years old.[28] ID was determined with at least two abnormal values for TSAT, FEP, or serum Ft. Cognitive outcomes were evaluated using the Wechsler Intelligence Scale for Children-Revised and Wide Range Achievement Test-Revised. Children with ID (with and without anemia) had significantly lower math scores (ID only: 87.4 $\pm$ 15.6; IDA: 86.5 $\pm$ 15.9; both $p < 0.05$), when compared to children with normal iron status (93.7 $\pm$ 17.1). Only children in the IDA group had a significantly lower score on block design (8.0 $\pm$ 4, $p < 0.05$), when compared to normal iron status children (9.5 $\pm$ 3.3). The odds of a child scoring below average in math was two times greater among ID children without anemia (AOR: 2.3, $p = 0.02$) and with anemia (AOR: 2.4, $p = 0.03$) compared to children with normal iron status, suggesting poorer school performance. It should be noted that this study utilized NHANES data to obtain a large, nationally representative sample.

Consequently, the cognitive assessments available in NHANES are limited to broad evaluations of overall cognitive performance.

One nested study of a larger randomized controlled trial evaluated the benefit of a home intervention on mental and behavioral scores at three time points.[105] Children enrolled in the larger, parent study, were diagnosed with IDA or non-IDA at either six or 12 months of age, with weekly home visits beginning when the infant was either six or 12 months old. Children were divided into a six- or 12-month cohort, dependent on when they were identified with IDA or anemia and were assessed at three time points (six-month: six, 12, and 18 month follow-up; 12-month: 12, 18, and 24 month follow-up). Of importance, all children in the IDA group were treated with elemental iron for either six months (30 mg/day) or 12 months (15 mg/day). All children received home visits to discuss the importance of iron intake, feeding, and the child's health (basic surveillance). The intervention children received weekly home visits, which consisted of child development support and counseling on the mother-child relationship. The objective was to examine behavioral outcomes by cohort (six- and 12-month), based on the type of home visit a participant received (surveillance vs intervention), and initial iron status (IDA surveillance, IDA intervention, non-anemic surveillance, and non-anemic intervention). The IDA intervention had an improvement in their raw mental scores in both the six-month and 12-month cohort. The IDA surveillance group had a significantly lower rate of change ($p < 0.05$), when compared with all other groups for both the first and second half of the year, in both cohorts. All groups had improvements in raw mental and motor scores over time. The three-way interaction between intervention group, iron status, and change over time was significant for raw mental scores in the six- ($p = 0.03$) and 12-month cohort ($p = 0.04$), with a blunted improvement in IDA

surveillance over time. Raw mental scores in the six- and 12-month cohort were significantly lower ($p < 0.05$) in the IDA surveillance group, when compared to the other groups.

In the same study, all groups had improved scores on the positive social-emotional behavior scale, except for children in the IDA surveillance group in both cohorts.[105] Scores among this group declined at each time point, resulting in significantly lower ($p < 0.05$) scores, relative to the control and IDA intervention group. Of note, despite improvements in the IDA intervention group, they did not catch-up to the non-anemic group in social-emotional behavior scores, in either cohort. The findings above underline prolonged poor cognitive and behavioral outcomes, despite early iron therapy and tailored at-home visits, which could be related to onset of IDA. Regardless, the study emphasizes the importance of iron supplementation, in combination with tailored counseling, for improved cognitive and behavioral outcomes. The worsening of behavioral outcomes among IDA children, despite iron therapy and home-clinic interventions, suggests ongoing exploration into potential confounders – such as type of intervention, dosage of iron, and timing of intervention.

Frequency of iron dosing may also influence developmental outcomes. One study on school-aged children in Thailand evaluated change in cognitive performance by dosing frequency (daily iron supplementation, weekly iron supplementation, placebo).[111] Children in the iron intervention group received 300 mg ferrous sulfate orally for two school semesters (1998-1999). Children in the weekly group had a greater positive point difference (indicating an improvement) from pre- to post-intervention, when compared with children receiving daily iron supplementation (6 ± 12 vs. 3 ± 12, $p < 0.05$). Changes in test assessment for mathematics and language were not different by group, suggesting no change in overall school performance. Importantly, iron status was determined with Hb and serum Ft only. No other iron-specific

biomarkers were collected. CRP, or another inflammatory biomarker, was not reported in the study, potentially underestimating the prevalence of IDA in the sample.[111] Furthermore, supplementation compliance and timing of supplement consumption are not reported with the sample. The differences found between the daily and weekly group may also be driven by bioavailability.

The benefits of iron supplementation versus multiple micronutrients on cognitive function should be considered as well. One study, conducted in Peru, randomly assigned infants (six to 17 months) to receive 12.5 mg iron (control), or a multiple micronutrient power (MMN), which contained iron, zinc, folic acid, vitamin C, and vitamin A.[110] Both supplements lasted for six months and were sprinkled on food provided in the home. The study included multiple cognitive and socio-emotional exams such as WPPSI (overall cognitive development), Day-Night Stroop test (cognitive flexibility and processing), Nine Boxes test (working memory), Theory of Mind (reasoning), and the parent-reported Brief Infant-Toddler Social Emotional assessment (BITSEA). Within-group differences by gender were found for the Day-Night Stroop test with boys performing more poorly than girls in both the control and MMN groups ($p = 0.01$). No differences by supplemental group were found on the executive, verbal, and total IQ on the WPPSI. Group differences were reported in vocabulary, with greater scores in the MMN female group, relative to the control female group (5.78 ± 1.59 vs. 6.83 ± 2.05, $p < 0.05$). However, overall scores by supplemental group, remained relatively similar.

The above studies report varied findings, possibly attributable to heterogeneity of design, sample age, and supplementation. Timing, frequency, and length of supplementation all warrant exploration. Importantly, early iron intervention can ameliorate potential cognitive impairments, which can influence later cognitive outcomes.[35–37] Therefore, inconsistencies in findings may be

related to the timing of ID among the children assessed, and when iron supplementation was provided.

Behavioral domain and iron

ID can result in neurodevelopmental impairments, such as monoamine disruption and poor myelination.[112–116] Such impacts not only influence cognitive outcomes, but also behavioral and socio-emotional outcomes as well.[115] ID can influence temperament (alertness, distress, and soothability), reduce interaction with novel objects, alter affect, and reduce tendency for exploration, in children and infants.[117–120] ID and IDA during infancy can have downstream effects on childhood emotional regulation, which can further influence adolescent behavior.[121,122]

One study, nested within a larger longitudinal complementary feeding trial, evaluated complementary food interventions among Chinese infants, between 2001-2003.[120] Infants were enrolled between four to 12 months of age, and those in the experimental group received micronutrient sachets, which contained iron, zinc, calcium, B_2, vitamin D, and protein, as part of their complementary food consumption. Children in the control group received rice flour with vegetable oil to match the macronutrient composition of the intervention supplement. All children received vitamin A supplements every six months. Anthropometrics were evaluated every three months, and hematological measures every six months. The nested study evaluated behavioral and developmental outcomes at a four-year follow-up.[120] Children were divided into three groups: chronic anemia (anemic at 12- and 24-month assessment and nonanemic at the 4-year follow-up), corrected anemia (anemic at 12-month assessment and nonanemic at the 24-month assessment, and 4-year follow-up), or nonanemic (nonanemic at all timepoints). Of importance, the researchers assigned their groups as chronic IDA, corrected IDA, and

nonanemic; however, only Hb levels were assessed at each timepoint. The etiology of anemia is unconfirmed. As such children in this sample should not be identified as having IDA. Children were assessed for affect, interactions with the mother, passiveness, gratification, and self-soothing.

When presented with a snack, children in the chronic anemia group had lower latency for delayed-gratification (chronic anemia: 7.8 $\pm$ 11.4; nonanemic: 24.8 $\pm$ 7.9; $p < 0.05$), and greater self-soothing behavior (chronic anemia: 7.2 $\pm$ 1.6; nonanemic: 1.5 $\pm$ 2.3; $p < 0.05$), when compared with nonanemic children. Passive behavior when approached by a stranger was greater among chronic anemia children (23.0 $\pm$ 6.6), when compared with non-anemic children (14.8 $\pm$ 4.3, $p < 0.05$) as well. Positive affect during delay of gratification, when presented with a snack, was lower among children with chronic anemia when compared with nonanemic children (chronic anemia: 4.7 $\pm$ 5.2; nonanemic: 11.0 $\pm$ 3.4, $p < 0.05$). No significant differences were found between the corrected anemia and chronic anemia, or corrected anemia and nonanemic children.

This study follows a similar theme, discussed in previous studies. Early correction of anemia resulted in affect and behavioral scores comparable to children within the nonanemic group.[120] Timing of ID itself can have long-term consequences, especially without early intervention. Of note, recruitment into the original study were of children between 4-12 months, which may result in late correction of ID with potentially irreversible consequences. However, children recruited at the four-year follow-up were relatively similar in age, without significant between-group differences. Importantly, children in this sample were only evaluated for Hb status; consequently, rate of group ID and IDA is unknown, and could be confounding results.

Overall, this study supports early MMN containing iron intervention to improve behavioral and developmental outcomes.

One study evaluated Costa Rican infants (12-23 months) diagnosed with IDA and non-IDA (comparison), to determine differences in infant behavior with caregiver (functional isolation).[118] Children were assessed at baseline and three months after iron therapy (ferrous sulfate twice/day at 5 mg/kg (first week) then 3 mg/kg (following 12 weeks))[123] to determine if iron intervention would reverse any differences noted at the baseline visit. Behavioral observations were conducted at two time points: before treatment and after three months of treatment. Infants were videotaped free-playing in a controlled environment with their caregiver and were assessed using the BSID. The Infant Behavior Record (part of BSID) was used to rate the child's affect and orientation to tasks. Caregiver participation during the free-play was assessed using a Likert scale. Observations at home were also conducted briefly during the daily check-in to monitor child's compliance to the iron therapy. Children were denoted as having a *suspect* rating if their behavior was seen as non-adaptive to their environment or if the child reacts in a way that is different from a 'normal' (or healthy) child.

The IDA group had a greater proportion of infants remaining at arm's length of their caregiver when playing (23%) compared to the comparison group (10%; $\chi^2 = 5.25$, $p < 0.05$). During the Bayley Scales (first edition) mental test, infants in the ID group showed less delight and laughter (3.2 ± 3.6) when compared to infants in the comparison group (4.6 ± 5.6) ($t(1, 144) = 2.09$, $p < 0.05$). The proportion of wariness and hesitation was significantly greater ($\chi^2 = 7.53$, $p < 0.01$) among infants in the IDA group (25%) when compared to the comparison (10%). The proportion of infants with suspect affect (hesitant, less engaged, less expressed delight) was greater among infants with IDA, when compared to non-IDA infants, across all scales.

Significant differences were observed for suspect endurance (easy fatiguability) between infants with IDA (42%) versus infants in the comparison group (19%, $\chi^2 = 10.39$, $p < 0.001$). Attempts at test-taking was lower among infants with IDA for both mental tasks ($p < 0.01$) and motor tasks ($p < 0.001$), when compared to the comparison group. These results support the role ID has on isolation. This study is supported by rodent studies which found decreased exploration and activity, and increased anxiety among rodents who were ID.[124]

Behavioral differences in early life may result in poor behavior regulation in later childhood and adolescence. One study reported that ID during infancy impacted childhood emotional regulations, which had downstream consequences on adolescent rule breaking and risk taking, like alcohol use and risky sexual behavior.[121] A similar finding was reported in a study[122] nested within a randomized-controlled, community-based intervention study.[123] Children in this study were grouped as having chronic ID (infancy IDA with continued evidence of ID after three months of oral iron therapy) or as IS (IS at infancy or resolved their ID after three months of oral iron therapy). Compared to IS children, greater parent-reported externalizing (e.g. aggression) and internalizing (e.g. depression) behavior was reported, among children with chronic ID, at both five years of age and 11-14 years of age.[122] Children with IDA and low physical activity during infancy, had reduced improvement in externalizing problems, from ages five to 11-14 years. While physical activity may be driven by parental/guardian interactions, it suggests environmental burdens which further exacerbate behavioral impairments.

Chapter Three: Methods

The current study is a retrospective, cross-sectional, Medicaid claims review, utilizing the Medicaid Analytic eXtract (*MAX*) database. We extracted data from children between six months to ten years of age who were in PA Foster Care between January 1, 2010 to December 31, 2015 (the most recently available data). Data on IDA, anemia, behavioral, and developmental impairments were all extracted using diagnostic codes, as detailed below. Our sample is identified as children in PA Foster Care. However, Medicaid criterion for identifying children in foster care is a rough approximate and may not reflect a child's current foster care status (review Eligibility for Present Study below).

The Medicaid Analytic eXtract (*MAX*) database

The *MAX* database contains national files with enrollment and claims data, available from 1999 to 2015.[126] It is a collection of both Medicaid and Children's Health Insurance Program (CHIP) data. Every state has a Medicaid program tailored to its needs, and data of those enrolled in Medicaid or CHIP are collected at the state-level in the Medicaid Management Information System (MMIS). The MMIS is state-specific, therefore it must be standardized on a national level, for submission to the Medicaid and CHIP Statistical Information System (MSIS).[127] MSIS data contain both enrollment and claims data which are reported to the Centers for Medicare and Medicaid Services (CMS) quarterly. CMS developed the *MAX* database in order to translate complex MSIS data into files which can be used for research purposes. All claims in *MAX* include the services provided and service expenditures.

MAX files contain protected and personally identifiable information. As such, they are protected under the Privacy Act and are available for research by approval only.[127] Our lead

healthcare data analyst (XX) was the sole researcher licensed to view, de-identify, aggregate, and analyze all *MAX* claims.

Background on ICD-9-CM and ICD-10-CM codes

Healthcare codes are critical for documenting and classifying diseases, procedures, morbidity, and the overall healthcare process.[3] Furthermore, they are used to collect and present mortality statistics.[129] The international classification of diseases, 9th revision (ICD-9) was developed by the WHO in the 1970s. ICD-9 was a globally utilized resource for categorizing and classifying diseases; however, it lacked applicability in U.S. healthcare settings. Revisions were made by the National Center for Health Statistics and the Council on Clinical Classifications, to develop the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). In the United States, the ICD-9-CM was utilized as the official language to classify death from 1979 to 1998, at which point mortality classifications transitioned to ICD-10 (1999 to present).[5]

In May of 1990, the ICD-10 code set were introduced and endorsed by the WHO.[131] ICD-10, Clinical Modification (ICD-10-CM), is a global code set that utilizes a structurally different coding format. The structural changes allow for greater flexibility in classifying diseases, and it expands on the number of available codes and categories.[131] ICD-9-CM contains approximately 17,000 codes, whereas the ICD-10-CM contains upwards of 155,000 codes. Its expansion allowed for more specificity when coding for a patient's diagnosis as well as more detailed descriptions on the care process. Although the ICD-10 code set were endorsed by the WHO in 1990, the U.S. maintained use of ICD-9 codes, with delays in official transition.[132] Due to the advantages of ICD-10 codes, the US Department of Health and Human Services required that

ICD-10-CM replace ICD-9-CM at all Health Insurance Portability and Accountability Act (HIPAA)-serving institutions by October 1, 2015.[3]

Abbreviations and definitions

Among the diagnoses, there are abbreviations and terms including: "not elsewhere classifiable" (NEC), "no other symptoms" (NOS), "unspecified", and "other".

NEC represents "other specified" and is utilized when a specific code to describe a condition is not available.[133,134] NOS is synonymous with unspecified. Codes that include "other" or "other specified" are utilized when a specific disease entity does not exist. This could be related to lack of necessary detail to code a disease under another coded term. "Unspecified" is also utilized when the diagnoses listed do not contain the information needed to assign it to another specific code. Taken together, the above terms and abbreviations are relatively similar to one another and are utilized when other coded terms do not sufficiently encompass a person's disease state.

Eligibility for present study

As previously mentioned, the current study extracted data from children served in the PA Foster Care System, between January 1, 2010 to December 31, 2015. Children had to be between six months to ten years of age to be included in the analyses. Children in foster care are identified with a IV-E Medicaid eligibility marker.[135] All children who receive IV-E eligibility were in foster care at one point in their life. Of note, children in foster care and children receiving adoption assistance (after having been in foster care) receive the same Medicaid eligibility. A child who has been adopted could retain the IV-E marker, which cannot be differentiated in *MAX*. Data extracted for this study represents children who were in foster care at

some point in their life; however, a child could have been adopted from the foster care system and maintained within the sample, due to their Medicaid eligibility marker.

Adoption and Foster Care Analysis and Reporting System (AFCARS) data were utilized as a proxy, to understand our sample.[136–141] The AFCARS data provide a complete census of all children in foster care in PA, during the years of the study. Although they cannot be linked to the *MAX* data, they can be used to provide a baseline estimate of the number of IV-E eligible children in foster care during the study period. According to AFCARS data, 20,591 unduplicated children (six months to ten years old) were maintained in PA Foster Care, from 2010-2015. The total sample size for the present study is 50,311. We approximate that 29,720, or 59%, of children in our sample were likely adopted out of foster care during our years of interest. To determine these values, we only included PA children who retained the IV-E marker in AFCARS datasets. Age was calculated as the difference between the child's date of birth and the first day of the fiscal year (October 1), for each year.

Diagnostic codes extracted for the present study

Diagnostic codes were determined using the ICD-9-CM and ICD-10-CM, since our data span from 2010 to 2015. All ICD codes were collected from ICD-9-CM[7] and ICD-10-CM[8] websites. All diagnoses required an ICD-9-CM code, and nearly all diagnoses had an ICD-10-CM equivalent. If a diagnosis did not have an exact ICD-10-CM equivalent, we determined an *ICD-10-CM approximate* (Table 2). Diagnostic coding cannot definitively determine whether a disease is present, therefore, all children were identified as diagnosed or not diagnosed/non-diagnosed for any given disease state. If an ICD-9-CM code did not contain an ICD-10-CM equivalent or approximate, its diagnosis was not captured after October 1, 2015, which was when ICD-10-CM codes were exclusively utilized (example *developmental reading disorder*; Table 3).

Table 2: Relevant Behavioral and Developmental Diagnoses[144,145]				
Behavioral Diagnoses				
Diagnosis	**ICD-9-CM**	**ICD-10-CM**	**ICD-10-CM Approximate**	**ICD-10-CM Approximate Description**
Anxiety, dissociative and somatoform disorders	300	N/A	F41.9	ICD-10 code for anxiety disorder, unspecified
Generalized anxiety disorder	300.02	F41.1	N/A	N/A
Depressive disorder, NEC	311	F32.9	N/A	N/A
Adjustment Disorder (overall)	309	F43.2	N/A	N/A
Prolonged Depressive Reaction	309.1	N/A	F43.21	ICD-10 code for adjustment disorder with depressed mood
Specific delays in development (overall)	315	R62.50	N/A	N/A
ADHD, inattentive	314.00	F90.0	N/A	N/A
ADD with hyperactivity	314.00	F90.9	N/A	N/A
ADHD, combined	314.01	F90.2	N/A	N/A
Autism spectrum disorder	299.0	F84.0	F84.0	N/A
Disruptive mood dysregulation disorder	296.99	F34.81	N/A	N/A
Impulse control disorder	312.3	F63.9	N/A	N/A
Other and unspecified special symptoms or syndromes, NEC	307.9	N/A	R45.1	ICD-10 code for restlessness and agitation
Emotions specific to childhood or adolescence with misery and unhappiness	313.1	N/A	R45.2	ICD-10 code for unhappiness
Irritability	799.22	N/A	R45.4	ICD-10 code for irritability and anger
Other signs and symptoms involving emotional state	799.29	R45.8	N/A	N/A

Developmental Diagnoses				
Diagnosis	**ICD-9-CM**	**ICD-10-CM**	**ICD-10-CM Approximate**	**ICD-10-CM Approximate Description**
Educational Problem	V62.3	N/A	Z55.9	ICD-10 code for problem (with/related to) education or literacy
Other psychological or physical stress, NEC	307.9	N/A	R41.83	ICD-10 code for borderline intellectual functioning
Disability, intellectual	319	F79	N/A	N/A
Mild intellectual disability (IQ 50-70)	317	F70	N/A	N/A
Moderate intellectual disability (IQ 35-49)	318	F71	N/A	N/A
Severe intellectual disability (IQ 20-34)	318.1	F72	N/A	N/A
Profound intellectual disability (IQ under 20)	318.2	F73	N/A	N/A
Delayed Milestones	783.42	R62.0	N/A	N/A
Signs and symptoms involving cognition (overall)	799.5	R41.89	N/A	ICD-10 code for other symptoms and signs involving cognitive functions and awareness
Other signs and symptoms involving cognition	799.59	N/A	R41.84	ICD-10 code for other specified cognitive deficits
NOS: No other symptoms NEC: Not elsewhere classifiable ADHD: Attention Deficit Hyperactivity Disorder ADD: Attention Deficit Disorder				

Three extracted diagnoses had several sub-diagnoses (*specific delays in development* [ICD-9-CM: 315; ICD-10-CM: R625.0], *adjustment reaction* [ICD-9-CM: 309; ICD-10-CM: F43.2], and *signs and symptoms involving cognition* [ICD-9-CM: 799.5; ICD-10-CM: R418.9]; Table 4)). All sub-diagnoses, within these three terms, were relevant and are hypothesized to be associated with poor iron status from prior literature (Table 3).[23] Therefore, each of these three

diagnoses were extracted as an overall category; the number of children in each sub-diagnosis were not extracted for analysis. Extraction by sub-diagnosis did not occur due to concerns of small sample sizes, limiting the ability to make group comparisons. Since all sub-diagnoses were relevant, grouping as an overall category would improve the sample size for our analysis.

Table 3: Overall Categories with Sub-diagnoses[144,145]			
Diagnosis	**ICD-9-CM**	**ICD-10-CM**	**ICD-10-CM Approximate**
Specific delays in development (ICD-9-CM: 315; ICD-10-CM: R62.50)			
Developmental reading disorder	315.0	N/A	N/A
Developmental reading disorder, unspecified	315.00	F81.0	N/A
Alexia	315.01	R48.0	N/A
Developmental dyslexia	315.02	F81.0	N/A
Other specific developmental reading disorder	315.09	F81.81	N/A
Mathematics disorder	315.1	F81.2	N/A
Other specific developmental learning difficulties	315.2	F81.81 or F81.89	N/A
Developmental speech or language disorder	315.3	N/A	F80.9
Expressive language disorder	315.31	F80.1	N/A
Mixed receptive-expressive language disorder	315.32	F80.2 or H93.25	N/A
Speech and language developmental delay due to hearing loss	315.34	F80.4	N/A
Childhood onset fluency disorder	315.35	F80.81	N/A
Other developmental speech or language disorder	315.39	F80.0 or F80.82 or F80.89	N/A
Developmental coordination disorder	315.4	F82	N/A
Mixed development disorder	315.5	F82	N/A
Other specified delays in development	315.8	F88	N/A
Unspecified delay in development	315.9	F81.9 or F89	N/A
Adjustment Reaction (ICD-9-CM: 309; ICD-10-CM: F43.2)			
Adjustment disorder with depressed mood	309.0	F43.21	N/A
Prolonged depressive reaction	309.1	F43.21	N/A
Adjustment reaction with predominant disturbance of other emotions	309.2	N/A	F43.25
Separation anxiety disorder	309.21	F93.0	N/A
Emancipation disorder of adolescence and early adult life	309.22	F94.8	N/A

Specific academic or work inhibition	309.23	F94.8	N/A
Adjustment disorder with anxiety	309.24	F43.22	N/A
Adjustment disorder with mixed anxiety and depressed mood	309.28	F43.23	N/A
Other adjustment reaction with predominant disturbance of other emotions	309.29	N/A	N/A
Adjustment disorder with disturbance of conduct	309.3	F43.24	N/A
Adjustment disorder with mixed disturbance of emotions and conduct	309.4	F43.25	N/A
Other specified adjustment reactions	309.8	N/A	N/A
Posttraumatic stress disorder	309.81	F43.10 or F43.12	N/A
Adjustment reaction with physical symptoms	309.82	F43.8	N/A
Adjustment reaction with withdrawal	309.83	F43.8	N/A
Other specified adjustment reactions	309.89	F43.8	N/A
Unspecified adjustment reaction	309.9	F43.20	N/A
Signs and Symptoms Involving Cognition (ICD-9-CM: 799.5; ICD-10-CM: R41.89)			
Attention or concentration deficit	799.51	R41.840	N/A
Cognitive communication deficit	799.52	R41.841	N/A
Visuospatial deficit	799.53	R41.842	N/A
Psychomotor deficit	799.54	R41.843	N/A
Frontal lobe and executive function deficit	799.55	R41.844	N/A
Other signs and symptoms involving cognition	799.59	R41.89	N/A
N/A: Not Applicable			

Reasoning for selection of diagnostic codes to extract

The present study extracted specific development and behavioral diagnoses that either have a well-established relationship with ID/IDA or a strongly hypothesized relationship with ID/IDA. The following sub-section provides a brief overview on the literature used to support our diagnostic extraction. A detailed discussion of the evidence is available in the *Literature Review* chapter. Supplemental Table 1 provides a detailed description and/or synonyms for all diagnoses discussed below.

Associations between ID/IDA and poor developmental and behavioral outcomes have been well-established in research. This is related to iron's role in the brain, especially during the first years of life, which is defined by a period of rapid hippocampal and cortical development.[23,36] Iron-mediated neurophysiological development (synaptogenesis, myelinogenesis, and dendritogenesis), along with iron-requiring neurochemical synthesis (monoamine and GABA metabolism) are rapidly occurring during childhood, underlining the importance of iron during this period.[37,80,81,146] ID during infancy and childhood can lead to altered cognitive development, which can impact spatial learning and memory.[23] Furthermore, studies have found reduced school performance among children with ID when compared with IS children.[28] Behavioral outcomes, including increased anxiety, depressive symptoms, functional isolation, dull affect, and poor emotional regulation have been cited as well.[102,121,147]

Well-established relationships: iron deficiency and behavior

ID/IDA has a known association with anxiety, reduced affect (less engaged/expressive) and depressive symptoms.[118,124,148,149] Depressive symptoms and ID/IDA have been studied in child development, as it relates to maternal depression and/or maternal ID/IDA.[150,151] ID/IDA

during infancy or childhood, and depressive symptoms, focus on the long-term effects of functional isolation, internalization, and externalization, which can be linked with anxiety and depressive symptoms.[30,122,147] One recent nested study has shown ID and psychological stress can impact emotion and cognitive development later in life.[152] As such, *anxiety, dissociative and somatoform disorders* (ICD-9-CM: 300; ICD-10-CM: F41.9), *generalized anxiety disorder* (ICD-9-CM: 300.02; ICD-10-CM: F41.1), *depressive disorder* (ICD-9-CM: 311; ICD-10-CM: F43.2), *emotions specific to childhood or adolescence with misery and unhappiness* (ICD-9-CM: 313.1; ICD-10-CM approximate: R45.2), *prolonged depressive reaction* (ICD-9-CM: 309.1; ICD-10-CM: F43.21), and *other psychological or physical stress, not elsewhere classifiable* (ICD-9-CM: V62.89; ICD-10-CM: R41.83), were included in our extraction.

Poor emotional regulation and impulse control have also been indicated in children and infants with ID and IDA.[119,121,122,153] As mentioned above, children with ID/IDA present with both internalizing (e.g., depression) and externalizing (e.g., aggression) behavior.[122,148] As a result, *adjustment disorder* (ICD-9-CM: 309; ICD-10-CM: F43.2), *irritability* (ICD-9-CM: 799.22; ICD-10-CM: R45.4), *disruptive mood dysregulation disorder* (ICD-9-CM: 296.99; ICD-10-CM: F34.81), *impulse control disorder* (ICD-9-CM: 312.3; ICD-10-CM: F63.9), and *other and unspecified special symptoms or syndromes, not elsewhere classifiable* (ICD-9-CM: 307.9; ICD-10-CM: R45.1) were included.

Strongly hypothesized relationships: iron deficiency and behavior

Iron is critical for dopaminergic activity with previous studies reporting reduced dopamine receptor density in ID rodents.[35,37] Although not fully understood, an association between dopamine dysfunction and ADHD has been hypothesized in previous research.[154] A

relationship between poor iron status and Attention Deficit Disorder (ADD) and/or ADHD symptomology have been hypothesized as well.[155–157] Taken together, the relationship between IDA/anemia, and *ADHD, inattentive* (ICD-9-CM: 314.00; ICD-10-CM: F90.0), *ADD with hyperactivity* (ICD-9-CM: 314.00; ICD-10-CM: F90.9), and *ADHD, combined* (ICD-9-CM: 314.01; ICD-10-CM: F90.2) were included in our analysis for exploration.

Autism is another diagnosis, with a hypothesized relationship with iron status. Children with Autism Spectrum Disorder (ASD) are often characterized with food selectivity, which could limit their intake of iron-rich foods.[158,159] Consequently, ID and IDA are a concern among children with ASD. Developmental and behavioral impairments present among children with ASD could be compounded by ID/IDA, which can further exacerbate ASD symptomology;[158] however, the association between ID and ASD remains inconclusive.[160–162] We included *Autism Spectrum Disorder* (ICD-9-CM: 299.0; ICD-10-CM: F84.0) in our diagnoses of interest to explore this relationship among children in foster care.

Well-established relationship: iron deficiency and development

The relationship between ID/IDA and poor cognitive outcomes has been well-established in the literature,[28,163–165] with noted improvements in cognitive measures when iron fortification is provided.[29] As such, we included *disability, intellectual* (ICD-9-CM: 319; ICD-10-CM: F79), *mild intellectual disability (IQ: 50-70)* (ICD-9-CM: 317; ICD-10-CM: F71), *moderate intellectual disability (IQ: 35-49)* (ICD-9-CM: 318; ICD-10-CM: F71), *severe intellectual disability (IQ: 20-34)* (ICD-9-CM: 318.1; ICD-10-CM: F72), *profound intellectual disability (IQ under 20)* (ICD-9-CM: 318.2; ICD-10-CM: F73); and *educational circumstances* (ICD-9-CM:

V62.3; ICD-10-CM: Z55.9). Of note, educational circumstances include synonyms such as underachievement in school, school problems, and academic problems.[166]

As discussed in previous chapters, ID/IDA has been strongly linked with neurophysiological and neurochemical development, which has downstream effects on cognitive and global developmental outcomes.[102] To capture this relationship, we extracted data from codes indicating *signs and symptoms involving cognition* (ICD-9-CM: 799.5; ICD-10-CM: R41.89), *other signs and symptoms involving cognition* (ICD-9-CM: 799.59; ICD-10-CM: R41.84), and *delayed milestones* (ICD-9-CM: 783.42; ICD-10-CM: R62.0). Delayed milestones is synonymous with those who are classified as "late talker" and/or "late walker".[167]

Iron status diagnostic codes

Children diagnosed with IDA/anemia, were included in the group "diagnosed IDA/anemia". Several diagnostic terms (Table 4) were used to determine if a child was identified with poor iron status and/or anemia. No codes were identified which determine ID without anemia exclusively; consequently, analysis only represents children with a diagnosis of IDA and/or anemia. The current codes for IDA were chosen because they were related to a dietary deficiency, rather than a deficiency related to trauma, injury, or autoimmune condition. We recognize that hospitals and clinics often evaluate hematological status using Hb and hematocrit concentrations as the only laboratory values. Although these biochemical indices indicate anemia, they are not specific to ID. Anemia, and anemia-related diagnoses were included in order to capture this. Children who were not diagnosed with IDA/anemia comprised our "non-diagnosed IDA/anemia" group. One diagnosis (*iron deficiency anemia, no other symptoms* [ICD-

9-CM: 280.9]) did not contain an appropriate ICD-10-CM equivalent or approximate. As such, it was not provided an ICD-10 code for inclusion in analysis beyond October 1, 2015.

Table 4: Iron Deficiency Anemia and Anemia Diagnostic Codes[144,145]

Diagnosis	ICD-9-CM	ICD-10-CM	ICD-10-CM Approximate
Chronic blood loss anemia	280.0	D50.0	N/A
Iron deficiency anemia, dietary	280.1	D50.9	N/A
Iron deficiency anemia, NEC	280.8	D50.8	N/A
Iron deficiency anemia, NOS	280.9	N/A	N/A
Anemia, unspecified	285.9	D64.9	N/A
Hematocrit, low	285.9	D64.9	N/A
Hemoglobin, low	285.9	D64.9	N/A

NEC: Not elsewhere classifiable
NOS: No other symptoms

Other codes of interest

Relevant codes for body mass index (BMI) were extracted and children were classified as follows: *Less than 5th percentile for age* (ICD-9-CM: V85.51; ICD-10-CM: Z68.51); *5th percentile to less than 85th percentile for age* (ICD-9-CM: V85.52; ICD-10-CM: Z68.52); *85th percentile to less than 95th percentile for age* (ICD-9-CM: V85.53; ICD-10-CM: Z68.53); *Greater than or equal to 95th percentile for age* (ICD-9-CM: V85.54; ICD-10-CM: Z68.54). The above codes were extracted because the *MAX* database does not provide data regarding anthropometrics. ICD-9-CM and ICD-10-CM codes uniquely addressing height or weight status were not available for extraction.

Data extraction, cleaning, and aggregation

Data were extracted by the healthcare data analyst (XX), utilizing the above diagnoses and eligibility criteria.

Children in PA Foster Care were captured by *MAX* uniform eligibility code "48", then were labeled into two major groups: diagnosed with IDA/anemia and not diagnosed with IDA/anemia using the ICD-9-CM and ICD-10-CM codes indicated in Table 4. Children with each type of sub-diagnosis were identified by correspondent diagnostic codes. Only unique instances of children with an IDA/anemia sub-diagnosis were utilized in group comparison.

Descriptive data (Table 5: Descriptive Data (Code)) were extracted for race and sex with codes from the *Centers for Medicare and Medicaid Services Chronic Conditions Data Warehouse Data Dictionary*.[168,169] To evaluate age, children were categorized into three major groups: 6 months – 1.99 years, 2 – 4.99 years, and 5 – 10 years of age. For children in the IDA/anemia group, age was calculated as the difference between the first instance of an IDA/anemia diagnosis and the child's birth date. For children in the not diagnosed with IDA/anemia group, the difference between the first day of each calendar year and the child's birth date was utilized.

Table 5: Descriptive Data (Code)	
Code	**Category**
Race and Ethnicity (Race-Ethnicity-Code)	
1	White, not of Hispanic origin (changed to "white" beginning 10/98)
2	Black, not of Hispanic origin (changed to "Black or African American" beginning 10/98)
3	American Indian or Alaskan native
4	Asian or pacific islander (changed to "Asian" beginning 10/98)
5	Hispanic (changed to "Hispanic or Latino - no race information available" beginning 10/98)
6	Native Hawaiian or other pacific islander (new code beginning 10/98)
7	Hispanic or Latino and one or more races (new code beginning 10/98)
8	More than one race (Hispanic or Latino not indicated) (new code beginning 10/98)
9	Unknown
Sex (EL_SEX_CD)	
F	Female
M	Male

Statistics

All statistical analyses were run in SAS 9.4, SAS Enterprise Guide 7.15, and RStudio, version 1.2.5033 (*epitools* package) software.[170–172] The total number of children in PA Foster Care diagnosed with IDA/anemia were quantified and divided by the total number of children in PA Foster Care, to determine the percent prevalence of diagnosed IDA/anemia among children (6 months – 10 years) in PA Foster Care, between 2010 to 2015.

Children in the diagnosed IDA/anemia group were compared against children in foster care without diagnosed IDA/anemia for relevant behavioral and developmental diagnoses. All variables in the second aim are categorical; therefore, chi-squared test of independence was conducted to determine group differences.[173,174] When cell values were small (less than five), a Fisher's exact test was utilized in place of a chi-squared test. All statistical tests were two-sided,

and an alpha level of 0.05 was set to determine significance. All *p*-values below the cut-off were bolded in the Results. Due to the design of the study and the research question, no variables were controlled for. Due to licensing restrictions on the *MAX* database, the lead healthcare data analyst (XX) conducted all cleaning, aggregation, and analysis. The first author (AA) checked statistical output using RStudio, version 1.2.5033, and conducted chi-squared tests on demographic data.

Chapter Four: Results

Sample characteristics

A total of 50,311 children met eligibility criteria for the present study. Accounting for unique instances, 1,365 children (2.71%) were diagnosed with IDA/anemia. Of importance, diagnostic terms are not mutually exclusive; therefore, there are 1,483 total instances in Table 6.

Table 6: IDA/anemia Diagnostic Criterion and Total Frequency

Diagnosis	Diagnosed with IDA/anemia (total = 1,483)
Chronic blood loss anemia	8 (0.54%)
Iron deficiency anemia, dietary	37 (2.49%)
Iron deficiency anemia, NEC	16 (1.08%)
Iron deficiency anemia, NOS	290 (19.55%)
Anemia, unspecified[ł]	1132 (76.33%)
Hematocrit, low[ł]	1132 (76.33%)
Hemoglobin, low[ł]	1132 (76.33%)

ł Indicated diagnoses have the same diagnostic code and are included in the total sample once.
NEC: Not elsewhere classifiable
NOS: No other symptoms

There was an even distribution of male and females in both groups (Table 7). In the IDA/anemia group, the greatest proportion of children were between 2 to 4.99 years of age (44.69%), followed by children 6 months to 1.99 years of age (30.11%), and 5 to 10 years of age (25.20%) at ID/anemia diagnosis. A majority of children in the not diagnosed with IDA/anemia group were between 5 to 10 years of age (42.98%), followed by 2 to 4.99 years of age (30.64%), and 6 months to 1.99 years of age (26.38%). As discussed in the methods, IDA/anemia was determined by a child's first instance with a diagnosis within the IDA/anemia diagnostic criterion. Their age was the difference between the first instance of an IDA/anemia diagnosis and the child's birth date. In contrast, children not diagnosed with IDA/anemia were determined by

the difference between the first day of each calendar year and the child's birth date. Age comparisons by iron status group were not feasible since different methods were utilized.

Group differences by race and ethnicity were present (Table 7). The majority of children were Non-Hispanic (NH) White in both groups (IDA/anemia: 44.82%; not diagnosed with IDA/anemia: 53.87%), followed by NH Black (IDA/anemia: 41.78%; not diagnosed with IDA/anemia: 33.14%), Hispanic/Latino (IDA/anemia: 7.08%; not diagnosed with IDA/anemia: 6.07%) and Unknown race and ethnicity (IDA/anemia: 3.12%; not diagnosed with IDA/anemia: 3.62%). All other race and ethnic groups made up < 1% of the current sample. NH White and NH Black participants were significantly different by iron status group ($p < 0.001$).

A limited number of children in the total sample received a BMI-for-age diagnosis (Table 7; 3.75% of total sample). Of this proportion, 87 children were diagnosed with IDA/anemia. A majority of children were within the 5^{th} to 85^{th} percentile-for-age (IDA/anemia: 56.32%; not diagnosed with IDA/anemia: 60.42%). In both groups, nearly 20% of children were classified with a BMI-for-age $\geq 95^{th}$ percentile for age. Ten percent (10.34%) of children had a BMI-for-age below the 5^{th} percentile in the diagnosed with IDA/anemia group. No BMI-for-age categories were significantly different by iron status group.

Table 7: Demographics by IDA/anemia Diagnosis

Category	Diagnosed with IDA/anemia	Not Diagnosed with IDA/anemia	*p* Value[a]
N	1,365 (2.71)	48,946 (97.29)	
Sex			
Male	718 (52.60)	25,214 (51.51)	0.44
Age[b]			
6 months to 1.99 years	411 (30.11)	12,912 (26.38)	N/A
2 to 4.99 years	610 (44.69)	14,997 (30.64)	N/A
5 to 10 years	344 (25.20)	21,037 (42.98)	N/A
Race and Ethnicity[ł]			
NH White	589 (44.82)	26,367 (53.87)	**< 0.001**
NH Black	549 (41.78)	16,219 (33.14)	**< 0.001**
Hispanic/Latino	93 (7.08)	2,973 (6.07)	0.15
Hispanic or Latino and $\geq$ 1 or more race	26 (1.98)	1,204 (2.46)	0.31
Unknown	41 (3.12)	1,770 (3.62)	0.38
Other [§]	16 (1.22)	413 (0.82)	0.19
BMI Classifications[ł]			
Less than 5th percentile-for-age	9 (10.34)	98 (5.45)	0.09[c]
5th percentile to less than 85th percentile-for-age	49 (56.32)	1,087 (60.42)	0.51
85th percentile to less than 95th percentile-for-age	12 (13.79)	262 (14.56)	0.97
Greater than or equal to 95th percentile-for-age	17 (19.54)	352 (19.57)	1.00

Values are N(%)
Any *p value* < 0.05 is bolded to denote significance
a. χ^2 test for independence, with Yates' correction, of all factors, unless otherwise indicated.
b. Unable to determine variation because method of extraction was different between groups.
c. Fisher test for small, expected frequencies (< 5) between iron status group
ł Total diagnosed with IDA/anemia = 1,314; total not diagnosed with IDA/anemia = 48,946
ł Total diagnosed with IDA/anemia = 87; total not diagnosed with IDA/anemia = 1,799
§"Other" includes Asian or Pacific Islander, Native American or Alaskan Native, Native Hawaiian or Other Pacific Islander, and More than one race (NH or non-Latino). The above groups made up < 1% of their total sample.

Group differences by behavioral diagnosis

Nearly 20% (18.90%) of children in the diagnosed with IDA/anemia group were diagnosed with an adjustment disorder, overall category (Table 8). A child diagnosed with IDA/anemia had greater odds of an adjustment disorder diagnosis ($p < 0.001$; OR: 1.49 [1.30, 1.71]), when compared to children not diagnosed with IDA/anemia. None of the diagnoses related to anxiety and depression/depressive symptoms were significantly different by group ($p \geq 0.05$). Despite a non-significant difference, more children in the diagnosed with IDA/anemia group had a diagnosis of anxiety than the not diagnosed with IDA/anemia group.

Autism spectrum disorder (ASD) was diagnosed to a significantly greater extent among children with diagnosed IDA/anemia (4.03%), when compared to children in the not diagnosed with IDA/anemia group (2.60%; $p < 0.001$; OR: 1.58 [1.20, 2.09]). Disruptive mood dysregulation disorder (synonymous with mood swings, mood disorder, disruptions in affect, etc.) was significantly higher among children in the IDA/anemia group (0.88%), when compared to children in the not diagnosed with IDA/anemia group (0.50%; $p = 0.026$; OR: 1.92 [1.07, 3.44]). Irritability was significantly higher among children in the IDA/anemia group (0.88%), when compared with children in the not diagnosed with IDA/anemia group (0.11%; $p < 0.001$; OR: 8.03 [4.29, 15.05]). No significant differences were noted between groups for ADHD, inattentive (2.19% vs. 2.76%, $p = 0.21$), ADD with hyperactivity (13.77% vs. 13.56%, $p = 0.82$), or ADHD combined (14.10% vs. 13.82%, $p = 0.80$).

Table 8: Group Differences and Odds Ratio for Relevant Diagnoses

Relevant Behavioral Diagnoses				
Diagnosis	**Diagnosed with IDA/anemia (total = 1,365)**	**Not diagnosed with IDA/anemia (total = 48,946)**	***p* Value**	**OR (95% CI)** [ł]
Anxiety, dissociative and somatoform disorders	45 (3.29)	1277 (2.61)	0.12	1.27 (0.94, 1.72)
Generalized anxiety disorder	8 (0.59)	274 (0.56)	0.90	1.05 (0.52, 2.12)
Depressive disorder, NEC	14 (1.03)	533 (1.10)	0.82	0.94 (0.55, 1.61)
Adjustment disorder (overall)	258 (18.90)	6627 (13.54)	**< 0.001**	**1.49 (1.30, 1.71)**
Prolonged depressive reaction	2 (0.15)	31 (0.06)	0.24	2.32 (0.55, 9.68)
ADHD, inattentive	30 (2.19)	1351 (2.76)	0.21	0.79 (0.55, 1.14)
ADD with hyperactivity	188 (13.77)	6636 (13.56)	0.82	1.02 (0.87, 1.19)
ADHD, combined	192 (14.10)	6765 (13.82)	0.80	1.02 (0.87, 1.19)
Autism spectrum disorder	55 (4.03)	1264 (2.60)	**< 0.001**	**1.58 (1.20, 2.09)**
Disruptive mood dysregulation disorder	12 (0.88)	225 (0.50)	**0.026**	**1.92 (1.07, 3.44)**
Impulse control disorder	18 (1.31)	577 (1.18)	0.64	1.12 (0.70, 1.80)
Other and unspecified special symptoms or syndromes, NEC	10 (0.73)	145 (0.29)	**0.004**	**2.48 (1.31, 4.73)**
Other psychological or physical stress, NEC	3 (0.22)	42 (0.09)	0.10	2.56 (0.79, 8.29)
Emotions specific to childhood or adolescence with misery and unhappiness	0 (0.00)	2 (0.00)	0.81	N/A
Irritability	12 (0.88)	54 (0.11)	**< 0.001**	**8.03 (4.29, 15.05)**
Other signs and symptoms involving emotional state	3 (0.22)	52 (0.11)	0.21	2.07 (0.65, 6.64)
Relevant Developmental Diagnoses				
Educational Circumstances	0 (0.00)	40 (0.08)	0.29	N/A
Disability, intellectual	23 (1.69)	280 (0.57)	**< 0.001**	**2.98 (1.94, 4.57)**

Mild intellectual disability (IQ 50-70)	7 (0.51)	194 (0.40)	0.50	1.30 (0.61, 2.76)
Moderate intellectual disability (IQ 35-49)	7 (0.51)	78 (0.16)	**0.002**	**3.23 (1.49, 7.01)**
Severe intellectual disability (IQ 20-34)	7 (0.51)	50 (0.10)	**< 0.001**	**5.04 (2.28, 11.14)**
Profound intellectual disability (IQ under 20)	7 (0.51)	40 (0.08)	**< 0.001**	**6.30 (2.82, 14.09)**
Delayed Milestones	134 (9.82)	1483 (3.03)	**< 0.001**	**3.48 (2.89, 4.19)**
Signs and symptoms involving cognition (overall)	6 (0.44)	124 (0.25)	0.18	1.74 (0.76, 3.95)
Other signs and symptoms involving cognition	2 (0.15)	25 (0.05)	0.13	2.87 (0.68, 12.14)
Specific delays in development (overall)	655 (48.0)	9457 (19.32)	**< 0.001**	**3.85 (3.46, 4.29)**

Values are N(%)
ł The reference group were children not diagnosed with IDA/anemia
NOS: No other symptoms
NEC: Not elsewhere classifiable
ADHD: Attention Deficit Hyperactivity Disorder
ADD: Attention Deficit Disorder
N/A: Not applicable related to a null cell value
Overall signifies an overall category with several subcategories

Group differences by developmental diagnosis

No child in the IDA/anemia group was diagnosed with an educational circumstance (Table 7), which is synonymous with educational problem or academic underachievement (Supplemental Table 1). Intellectual disabilities were reported in 1.69% of children in the IDA/anemia group, which was a significantly greater proportion than children in the not diagnosed with IDA/anemia group (0.57%; $p < 0.001$; OR: 2.98 [1.94, 4.57]). Mild intellectual disability was not significantly different by group (0.51% vs. 0.40%, $p = 0.50$). Moderate, severe,

and profound intellectual disability (IQ ≤ 49) were significantly higher among children in the diagnosed with IDA/anemia group, when compared to children in the not diagnosed with IDA/anemia group (0.51% vs. 0.16%, $p = 0.002$, OR: 3.23 [1.49, 7.01]; 0.51% vs. 0.10%, $p < 0.001$, OR: 5.04 [2.28, 11.14]; 0.51% vs. 0.08%, $p < 0.001$, OR: 6.30 [2.82, 14.09], respectively). Delayed milestones (applies to "late talker" and "late walker") were significantly higher among children in the diagnosed with IDA/anemia group (9.82%), when compared to children in the not diagnosed with IDA/anemia group (3.03%; $p < 0.001$; OR: 3.48 [2.89, 4.19]). A small proportion of children were diagnosed with signs and symptoms involving cognition, overall category, for both groups (0.44% vs. 0.25%, $p = 0.180$). Forty-eight percent of children diagnosed with IDA/anemia were diagnosed with a specific delay in development. Specific delays in development include disruptions in reading, arithmetic, coordination, etc. (Supplemental Table 2). A child diagnosed with IDA/anemia had a nearly four times greater odds of a specific delay in development diagnosis, when compared to children not diagnosed with IDA/anemia (OR: 3.85 [3.46, 4.29]).

Chapter Five: Discussion

Aim One

To our knowledge, this is the first study which evaluates IDA and anemia among children in the PA Foster Care System. Children were eligible for the study if they were in foster care (or adopted out of foster care) and were between six months to ten years of age, in 2010 to 2015. We hypothesized that the rate of IDA/anemia among children in the PA Foster Care System would be greater than current U.S. rates of childhood anemia. Of our sample, 2.7% (n = 1,365) of children were diagnosed with IDA/anemia. Analysis of NHANES data from 1988 to 1994 indicated a 9.0% prevalence of ID and 3.0% prevalence of IDA among toddlers, aged one to two years.[61] A more recent NHANES analysis (2007 to 2010),[17] examined prevalence rates of ID, anemia, and IDA in children aged one to five years and found 7.1%, 3.2%, and 1.1% rates, respectively. Since our study sample includes children up to ten years of age, we examined an additional NHANES study, which extracted data from 2003 to 2012.[175] The study found that 3.4% of children aged six months to four years, and 2.0% of children aged five to 11 years, had anemia, without specificity. Taken together, the U.S. prevalence of anemia among children between six months and ten years of age, is approximately 2.0– 3.4%. Our sample proportion is within the above approximate as opposed to being higher, which was our hypothesis.

Children in foster care and recently adopted children receive frequent medical visits as they are a highly vulnerable health population.[10,13] Therefore, one could speculate that the examination and identification of anemia (low Hb) is more likely to occur among children in foster care, relative to children in the general population. However, the rates of ID and IDA, specifically, are likely underreported in both groups, due to lack of assessing iron-specific biomarkers (e.g., serum Ft, TSAT, TfR) at the clinic visits. ICD-9 and ICD-10 codes do not

include a diagnosis of ID, as such we were limited to evaluating IDA and anemia only. Poor iron status occurs in a stepwise manner, starting with depletion of iron storage (ID), reduction in functional tissue iron (IDA), and finally reduced erythropoiesis (anemia).[89] As such, we speculate that ID among children in foster care occurs to a greater degree than the rate of IDA/anemia. This is supported by the findings of Gupta *et al.* who examined children between one to five years of age in the U.S. and reported that the rate of ID was two times greater than the rate of anemia, and seven times greater than the rate of IDA.[17]

Aim Two

Our second hypothesis was that a higher prevalence of developmental and behavioral impairments would be present among children with diagnosed IDA/anemia, when compared to children not diagnosed with IDA/anemia. Of the 16 relevant behavioral diagnoses which were extracted, four were significantly greater among children diagnosed with IDA/anemia, when compared to children not diagnosed with IDA/anemia. Of the nine relevant developmental diagnoses which were extracted, five were significantly greater among children diagnosed with IDA/anemia, when compared to children not diagnosed with IDA/anemia. The lack of differences between some of the diagnoses could be related to small sample sizes. Children in foster care are also a vulnerable pediatric group to mental health issues.[44,45,176] Other drivers of behavioral and developmental issues, such as an unstable home, reason for child displacement, number of foster care entries, and timing of foster care entries were not able to be addressed by this study and are likely confounding the results.[46] One previous nested case-control study found that the age at placement was positively related to executive functioning, while neglect or emotional abuse was negatively correlated with visuospatial processing and memory. [46] The number of foster care entries was not related to cognitive or developmental outcomes but,

unexpectedly, the number of maltreatment types was positively correlated with visuospatial processing, language, and executive functioning. This study identified relationships between various environmental measures and development and cognitive outcomes. Such relationships warrant examination in a future study, to determine if they mediate the association between iron status and developmental and behavioral outcomes.

Iron status and the behavioral domain

Despite the suggestions of a relationship between anxiety, depression, and ID,[30,122,147] there were no significant differences between groups for these diagnoses. Interestingly, no children in the IDA/anemia group were diagnosed with an educational circumstance (i.e., educational problem). This is worth noting as ID and educational problems have a well-established relationship.[28] It is important to remember, however, that our diagnosed group was composed mostly of individuals who were categorized as anemic and not necessarily as ID or IDA. As mentioned above, the rate of ID and IDA is likely greater than the rate of anemia. This is supported by Gupta *et al*., who reported that 3.2% of children (one to five years old) are anemic in the U.S..[17] Of this proportion, approximately 35% of children were reported to have ID. We anticipate that if we could properly identify ID in our sample, the overall proportion of children with poor iron status would be greater. A more robust sample size would improve our analysis and could identify a difference between groups for various behavioral and developmental diagnoses. Of note, nearly half of children (48%) in the IDA/anemia group had a delay in development. This is of importance, as iron and developmental outcomes have been previously linked [28,146,163,177] and requires further exploration in this population.

Three studies were identified which evaluated micronutrient status and development, among an internationally adopted sample.[32,33,178] Of importance, an internationally adopted sample cannot be generalized to U.S. children in foster care, but it is informative when exploring IDA and development. One study had a case-control design[33], and two[31,32] were nested within a larger longitudinal study.[34] All three studies evaluated children at two time points: once approximately between one to two months upon arrival to the U.S. (baseline), and at six or 12 months later (follow-up). The studies varied in age requirements, but generally children had to be approximately four years old or younger at baseline for inclusion, across all three studies. Developmental and behavioral outcomes were examined with well-established assessments. Across all studies, the assessments included TBAQ-R (temperament), Mullen Scales of Early Learning (IQ), the Delay of Gratification Task (inhibitory control), the Dimensional Change Card Sort (cognitive flexibility), the Spin the Pots Task (working memory), and BSID-III (cognitive and motor development). Finally, across all studies, children received comprehensive medical assessments, including iron specific biomarkers like serum Ft, TSAT, TIBC, Hb, and MCV. These studies support the relationship between ID/IDA and poor developmental and behavioral outcomes among a highly vulnerable pediatric population. Of note, ID/IDA was present even at the follow-up visit for all studies, suggesting that nutritional deficiencies can persist even when a person's environment improves.

One of the nested studies indicated above evaluated development and behavior at the six-month follow-up, among post-institutionalized children, stratified by iron status (ID vs IS).[32] Children with poor iron status had poorer scores on fine motor function, visual reception, language, early learning, activity and impulsivity, and inattention/hyperactivity when compared to IS adopted children. This is worth noting as children assessed were in a presumably stable and

nutritionally replete environment. Despite such assumption, ID persisted, and developmental and behavioral scores remained significantly lower than in IS children within the same pediatric population. The studies above contrast greatly to our own. All three studies recruited and evaluated internationally adopted children and their ages only partly overlap with our study sample age. Our study is a retrospective, cross-sectional design whereas the above studies conducted prospective cohort studies, with follow-up within a year of the initial assessment. Comprehensive medical assessments included iron-specific biomarkers to diagnose ID and IDA, whereas our study was unable to distinguish IDA from anemia. Lastly, the above studies recruited children who recently entered the U.S. for adoption, whereas our study evaluated children who entered the PA Foster Care System at one point in their life. Sample contamination is likely in our study, with a mixture of both children who have been adopted out of foster care and children in foster care. Despite these differences, the above studies suggest that IDA/anemia further exacerbates poor developmental and behavioral outcomes among a population already at high risk of physical and mental health problems. Such conclusions are supported by the high rate of behavioral and developmental impairments present among children with IDA/anemia in our sample. The above studies also indicate potential confounders that should be addressed in future studies, such as duration of institutionalization, presence of infections, dietary intake, and iron supplementation.

Adjustment disorder was indicated in nearly 20% of children in the IDA/anemia group. This was significantly greater than in children not diagnosed with IDA/anemia. Adjustment disorder applies to children who feel sorrow or develop emotional or behavioral symptoms related to a stressor (Supplemental Table 2). In our study, irritability was also significantly greater among children diagnosed with IDA/anemia. Animal studies have indicated that ID is

linked with disruption in brain myelination and monoamine synthesis and metabolism.[112] Human studies have found that disruption in these processes can lead to emotional behavior and psychological issues, such as mood dysregulation, and anxiety-like behavior.[118,148,149] Of the studies listed, two were part of the same longitudinal study, based in Costa-Rica.[118,148] ID was evaluated at infancy and infants diagnosed with IDA received subsequent iron therapy. One study evaluated the behavior of IDA infants at 12-23 months of age[117] and the other was a follow-up which evaluated the behavior of children at 11-14 years of age, who were ID in infancy.[148] The two human-subject studies support the relationship between IDA and poor behavioral outcomes, like functional isolation. One study supports that IDA in infancy is related to increased wariness, and withdrawal from stimulating environments.[118] The nested follow-up, among children 11-14 years of age, found that those who had IDA in infancy had greater parent reported signs of social problems, anxiety/depressive symptoms, internalizing, and externalizing behaviors. Ultimately, ID can have a downstream influence on long-term emotional regulation, with one study reporting increased risky behavior, rule-breaking, and excessive alcohol consumption among adolescents with ID during infancy.[179]

Autism spectrum disorder (ASD) and ID/IDA are hypothesized to be linked, and children with ASD are often found to be ID, which may be related to picky-eating behaviors.[159] One retrospective study, in South Wales, UK, identified 52 children (aged 19 months to eight years and five months) who had autism.[180] Hb, MCV, MCH, MCHC, and Ft were measured, of which Ft values were available in only four children diagnosed with autism. Six children diagnosed with autism were also diagnosed with anemia, of which three had low Ft (< 5 ug/L) and low MCV for age (MCV < 65 fL in all three children).[181] The study defined ID as low Ft only and IDA as low Ft and low Hb. Best practice indicates that the classification of ID should be

determined by abnormalities in two or more iron specific biomarkers, not just one.[101] Also, inflammation was not accounted for, when evaluating Ft. A separate retrospective study in Australia evaluated 122 children (one to 12 years of age) from a community pediatric clinic, with a formal diagnosis of autism or Asperger Syndrome (now recognized as ASD) and/or a global developmental delay.[182] Among their sample, 6.6% of children had ID and 4.1% had IDA, which was significantly higher ($p < 0.05$) than the national prevalence statistics extracted from Sydney (1992-1994; 2-5 years old; ID: 1.8% and IDA: 1.0%), the U.S. (1988-1994; 3-11 years old; ID: 2.4% and IDA: < 1.0%), and New Zealand (2002; 5-14 years old; ID: 1.40% and IDA: 0.30%). Univariate analysis identified three potential risk factors for ID and IDA among their sample, which were problems with sucking, swallowing, or chewing, poor eating behavior, and poor intake of animal-based proteins. Although the above studies are not based in the U.S., and do not focus on a foster care population, they support the hypothesized relationship between ID/IDA and autism. Children with ASD are more likely to have picky-eating behavior which can drive ID and IDA, which may then lead to behavioral issues, further exacerbating ASD symptomology.[159] Within our sample, children had a 58% greater odds of ASD if they were diagnosed with IDA/anemia versus not (OR: 1.58, $p < 0.001$).

Iron status and the developmental domain

Moderate to profound intellectual disability was significantly higher among children with IDA/anemia than children not diagnosed with IDA/anemia in our sample. Similarly, delayed milestones (synonymous with "late talker" and "later walker") and specific delays in development (overall) were significantly higher among children with IDA/anemia. This is in agreement with previous findings indicating a relationship between ID and cognition and development.[28,29,102,103,148] Disruption in these processes can lead to emotional behavior and

psychological issues, such as mood dysregulation, and anxiety-like behavior.[118,148,149] A previous study[149] evaluated children in Taiwan utilizing the National Health Insurance Database, with data collected from 1996-2008. The study was similar to our own as it was cross-sectional, retrospectively evaluating data on children (< 18 years), across a number of years. Chen *et al.* utilized ICD-9-CM codes to extract IDA diagnoses and a number of psychiatric disorders. Multiple diagnoses, including anxiety, depressive disorder, and delayed development were significantly higher in proportion among children with IDA, when compared to the control (age and gender matched with no major physical illness). Unlike our study, Chen *et al.* utilized an international sample; however, their results are relevant and should be explored due to the differences in our findings. In our study, anxiety and depressive disorder diagnoses were not significantly different by group. Notably, in our study the adjustment reaction (overall) diagnosis was significantly higher among the IDA/anemia group, and it contains multiple sub-diagnoses that pertain to anxiety and depressive symptoms (Supplemental Table 2). Chen *et al.* had a larger sample size of 2,957 children in the IDA group, and a control group that matched each IDA participant 4:1. Our study contained 1,365 children diagnosed with IDA/anemia, representing ~3.0% of the total sample. The differences in sample sizes between groups may explain why we found no significant differences for anxiety and depression. Furthermore, Chen *et al.* largely utilized overall categories for ICD-9-CM diagnoses, which will capture multiple sub-diagnoses, creating a more robust sub-sample between the IDA and control groups.

One cross-sectional study which evaluated NHANES data from 1988-1994 cycles reported cognitive test scores among children and adolescents (6-16 years), stratified by iron status.[28] Of the 5,398 children included in the study, 3% of children were diagnosed with ID. The study found that mean math test scores were significantly lower in children with ID and IDA,

when compared to children with normal iron status. Mean block design tests were significantly lower among children with IDA when compared to children with normal iron status as well. Demographically, the above study was largely comprised of children aged 6-11 years of age (n = 3,309). Children in their sample were predominantly Black (n=1,875), Mexican American (n=1874), White (n=1,402), and Other (n=247). ID and IDA were diagnosed using iron-specific diagnostic criterion, such as TSAT, serum Ft, and FEP. Furthermore, they utilized general cognitive tests – Wechsler Intelligence Scale for Children – Revised (digit span and block design) and the Wide Range Achievement Test – Revised (math and reading). Similar to our study, the Halterman *et al.* study discussed above was cross-sectional in design.[28] There are clear differences in our study, compared to Halterman *et al.*, especially when evaluating the demographic breakdown. First, our sample utilizes children who were in the PA Foster Care System at one point in their life, whereas Halterman *et al.*, utilizes NHANES data, which is a large-scale, nationally representative survey. Our sample extracts data from an age range (6 months – 10 years) that only partially overlaps with Halterman *et al.* (6 – 16 years). Additionally, our demographic sample is largely comprised of White children in both the diagnosed with IDA/anemia and not diagnosed with IDA/anemia groups. We were unable to definitively determine the etiology of anemia within the sample as no ICD-9-CM or ICD-10-CM codes described abnormalities in iron-specific lab values. Lastly, diagnostic codes such as specific delays in development, include sub-diagnoses like reading and math dysfunction; however, the form of assessment utilized to determine a developmental delay within our sample is unknown. Despite these differences, both Halterman *et al.* and our study link developmental delays with poor iron status, further supporting the need for continued examination of this relationship among children in foster care.

The timing of ID can result in persistent cognitive impairment and disruptions in scholastic achievement. One nested study within a larger, longitudinal study evaluated 11-14 year old children who either had ID or IS during infancy, in San Jose, Costa Rica.[148] Children who were iron deficient in infancy had significantly lower scores in reading, writing, and arithmetic when compared to children with good iron status during infancy. A greater proportion of children who were iron deficient during infancy had to repeat a grade (26%) when compared to children with good iron status during infancy (12%; $\chi^2 = 4.33$, $p = 0.04$). The above study was longitudinal and evaluated the developmental and behavioral outcomes of children that have been followed since infancy. Children assessed in this study were older than our study population (11-14 years) and received comprehensive cognitive and developmental assessments. Although the study design and sample population are different from our study, their findings warrant thought. The above results support our concerns that ID during childhood can result in prolonged poor cognitive outcomes, which can persist into adolescence and beyond. If we extend these associations to children in foster care, a population already at risk for poor physical and cognitive/developmental outcomes,[40,41,44–46] we can see how poor nutritional status may be especially detrimental for such a population.

Notably, cognitive performance among ID adolescents can largely improve in the presence of iron biofortification.[29] One double-blind randomized control trial, evaluated 140 Indian adolescents (aged 12-16 years) who received either iron biofortified (86 parts per million (ppm) iron) or control (21-52 ppm iron) pearl millet.[29] A treatment effect was present for response time (RT) on the simple response time (SRT), Go-No-Go task (GNG), and certain tasks in the Attentional Network Task (ANT). These computerized assessments evaluate simple processing and reaction, attention, spatial orienting, and alertness. Improvements in cognitive

outcomes suggest that iron biofortification of a locally consumed crop is a viable option for improving iron status. Importantly, this study supports that poor cognitive performance extends to adolescents with poor iron status; furthermore, improvements – but not total amelioration – of poor cognitive performance is present with iron intervention. The study by Scott *et al.,* [29] differs greatly from the present study. Scott *et al.* conducted a randomized controlled trial, which included assessment of iron specific biomarkers, computerized cognitive tasks, and an iron intervention. Their study also utilizes an international sample of Indian, school-going adolescents (aged 12-16 years) whose age range does not overlap with our sample. Despite these differences, the findings from Scott *et al.* support that biofortification can improve both iron status and cognition in adolescents. While our study utilizes an infant to preadolescent sample, it warrants thought on possible intervention strategies to improve cognition among a population that is vulnerable to poor nutritional status.

Our study adds to the literature as few studies have evaluated developmental and behavioral outcomes, stratified by anemia status, among children in U.S. Foster Care. Anemia without specificity has been explored in previous studies.[6,8,9,49] One study, which evaluated laboratory screening results of children entering an Ohio Foster Care, found that 4.2% of children < 12 years old, and 5.9% of children $\geq$ 12 years old had anemia.[9] A separate study found that 1.75% of children entering a Baltimore Foster Care System, were diagnosed with anemia (Hematocrit $\leq$ 32%).[6] That said, no previous study has explored the specific relationship between anemia and developmental and/or behavioral diagnoses in the Foster Care System. As such, our current study adds to the limited literature on this topic and our findings highlight the need for more studies on children in foster care, specifically studies that are able to distinguish between ID, IDA, and anemia.

Strengths and limitations

The study has several strengths, including that it is the first study which evaluates IDA and anemia among children in the PA Foster Care System. Children in foster care are a highly vulnerable population, making recruitment of this pediatric population challenging. Utilizing a Medicaid database highlights a methodological option to understand this population, in the presence of these limitations. To our knowledge, this is the only study which evaluates developmental and behavioral outcomes by IDA/anemia status, among children in U.S. Foster Care. Finally, the present study highlights the need for comprehensive clinical evaluations of ID and IDA, for children in U.S. Foster Care. ID in the absence of anemia may have an irreversible impact on brain development,[35,37] especially when ID is present during critical periods of growth (e.g., the perinatal period). Therefore, early iron screening and prevention is preferred to attenuate risk of cognitive impairment.

Our study must be interpreted with caution due to its limitations. The present study was unable to discern between ID, IDA, and anemia. Our study evaluates Medicaid claims only; therefore, we are unable to confirm if the child was correctly diagnosed with IDA and/or anemia. The *MAX* database does not differentiate between a child presently in foster care and a child who has been adopted from the Foster Care System. As such, we cannot confidently report that children in our sample were in foster care during the selected study period. This is of concern because a child who is in foster care and a child who is adopted represents two different pediatric groups. We can, however, speculate as to the representation of children in the Foster Care System versus children who have been adopted, in our database. Data from AFCARS suggests that 29,720 children were likely adopted out of foster care during our study period. This roughly suggests that 60% of our sample are children who have been adopted out of foster care, and the

remaining 40% were in foster care, during our study period. The length of time a child was in foster care, prior to our data extraction, is also unknown. Consequently, the clinical picture of a child who has recently entered foster care is not captured in our analysis. Another limitation was the small sample size in various diagnoses. As mentioned above, we were unable to determine ID and we suspect that the rate of IDA was not adequately captured in our analysis. Since the rate of ID and IDA is likely higher than the rate of anemia, we would suspect a more robust sample if these diagnoses were appropriately identified. Four of the six behavior diagnoses with significant differences had a small sample size ($n < 20$) in the IDA/anemia group. These diagnoses were *disruptive mood dysregulation disorder, other and unspecified special symptoms or syndromes, NEC* (synonymous with restlessness and agitation; Supplemental Table 1*), other psychological or physical stress, NEC* (synonymous with borderline intellectual functioning; Supplemental Table 1), and *irritability*. Similarly, three of the six developmental diagnoses, with significant differences by iron status group, had small sample sizes. These included *moderate, severe, and profound intellectual disability*. Cumulatively, these seven diagnoses should be interpreted with caution due to their small sample sizes. Future studies could extract for overall diagnoses rather than specific sub-diagnoses, to improve sample size.

Finally, the present study was not designed to control for important covariates, such as age, BMI status, race and ethnicity, reason for foster care placement, months spent in foster care, or other potentially relevant variables. As such, it is possible that our findings would differ, if we controlled for these important variables. However, we can postulate that iron is a driver and should be examined in future samples.

Overall conclusion and future directions

The present study identified the prevalence of IDA and anemia among children in PA Foster Care, a rate that was not previously known. In this sample, children with IDA/anemia had a higher rate of several developmental and behavioral impairments, when compared to children not diagnosed with IDA/anemia.

There are few previous studies which evaluated the micronutrient/vitamin status of children in foster care[8,9,49,50] and none which looked at the associations between micronutrient status and developmental and behavioral impairments. Future studies on ID and IDA, among children in U.S. Foster Care, are needed to better understand this population. A prospective cohort study on children recently entering foster care, with the collection of iron specific biomarkers and developmental outcomes, would inform early ID screening and timely interventions, to potentially dismantle one burden faced by this vulnerable pediatric population.

Supplementary Tables and Figures

Supplemental Table 1: Definition of diganoses[144,145]			
Diagnosis	**ICD-9-CM Definitions**	**ICD-10-CM Diagnosis**	**ICD-10-CM Definitions**
Anxiety, dissociative and somatoform disorders	See ICD-10-CM definition	*Anxiety disorder, unspecified*	**Clinical Information** • A category of psychiatric disorders which are characterized by anxious feelings or fear often accompanied by physical symptoms associated with anxiety.
Generalized anxiety disorder	See ICD-10-CM definition	Generalized anxiety disorder	**Clinical Information** • A condition marked by excessive worry and feelings of fear, dread, and uneasiness that last six months or longer. Other symptoms of generalized anxiety disorder include being restless, being tired or irritable, muscle tension, not being able to concentrate or sleep well, shortness of breath, fast heartbeat, sweating, and dizziness.
Depressive disorder, NEC	**Clinical Information** • A mental state of depressed mood characterized by feelings of	Depressive disorder	**Clinical Information** • A disorder characterized by melancholic feelings

	sadness, despair and discouragement		of grief or unhappiness. • A melancholy feeling of sadness and despair. • A mental condition marked by ongoing feelings of sadness, despair, loss of energy, and difficulty dealing with normal daily life. Other symptoms of depression include feelings of worthlessness and hopelessness, loss of pleasure in activities, changes in eating or sleeping habits, and thoughts of death or suicide. Depression can affect anyone, and can be successfully treated
Adjustment Disorder (overall)	**Approximate Synonyms** • Feeling of great sorrow • Sorrowful response to an immediate cause; self-limiting and gradually subsides within a reasonable time • Suffering and distress associated with loss	Adjustment disorder (overall)	**Clinical Information** • A category of psychiatric disorders which are characterized by emotional or behavioral symptoms that develop within 3 months of a stressor and do not persist for more than an additional 6 months after the stressor is no longer present. • A category of psychiatric disorders which are characterized by

	Overall category, see Supplemental Table 2: Sub-diagnosis definitions		emotional or behavioral symptoms that develop within 3 months of a stressor and do not persist for more than an additional 6 months after the stressor is no longer present. **Overall category, see Supplemental Table 2: Sub-diagnosis definitions**
Prolonged Depressive Reaction	See ICD-10-CM definition	*Adjustment disorder with depressed mood*	**Approximate Synonyms** • Adjustment reaction, depressive, brief • Adjustment reaction, depressive, prolonged • Bereavement, complicated • Brief depressive adjustment reaction • Complicated bereavement • Complicated grieving • Prolonged depressive adjustment reaction
Specific delays in development (overall)	See ICD-10-CM synonyms	Delayed, development	**Approximate Synonyms** • Developmental delay • Developmental delay, mild-moderate • Developmental delay, severe • Growth retardation • Lack of expected normal physiological development • Mild to moderate developmental delay • Mild-moderate developmental delay

			• Physiological development failure • Severe developmental delay
ADHD, inattentive	See ICD-10-CM	ADHD inattentive (presentation and type)	**Approximate Synonyms** • ADHD, inattentive • ADHD, inattentive • Attention deficit disorder • Attention deficit hyperactivity disorder, predominantly inattentive type
ADD with hyperactivity	See ICD-10-CM	Attention Deficit (child) with hyperactivity	**Clinical Information** • A behavior disorder in which the essential features are signs of developmentally inappropriate inattention, impulsivity, and hyperactivity. • A behavior disorder originating in childhood in which the essential features are signs of developmentally inappropriate inattention, impulsivity, and hyperactivity. Although most individuals have symptoms of both inattention and

			hyperactivity-impulsivity, one or the other pattern may be predominant. The disorder is more frequent in males than females. Onset is in childhood. Symptoms often attenuate during late adolescence although a minority experience the full complement of symptoms into mid-adulthood. (from DSM-IV)
ADHD, combined	**Approximate Synonyms** • ADHD • ADHD, adult residual • ADHD, combined • ADHD, hyperactive impulsive • Attention deficit hyperactivity disorder • Attention deficit hyperactivity disorder adult effect • Attention deficit hyperactivity disorder combined • Attention deficit hyperactivity disorder combined type • Attention deficit hyperactivity	ADHD combined (presentation and type)	**Approximate Synonyms** • ADHD, combined • ADHD, combined presentation • Attention deficit hyperactivity disorder combined • Attention deficit hyperactivity disorder, combined type

	disorder, combined type • Attention deficit hyperactivity disorder, hyperactive impulsive type • Attention deficit hyperactivity disorder, predominantly hyperactive impulsive type • Long term ADHD medication therapy • Long term current use of medication for ADD and or ADHD • Long term current use of medication for attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) • Residual adult attention deficit hyperactivity disorder		
Autism spectrum disorder	**Clinical Information** • Disorder beginning in childhood marked by the presence of markedly	Autism, autistic (childhood and infantile) spectrum disorder	**Clinical Information** • A disorder beginning in childhood. It is marked by the presence of markedly abnormal or impaired development in social

	abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interest; manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual • Type of autism characterized by very early detection (< 30 months), social coldness, grossly impaired communication, and bizarre motor responses		interaction and communication and a markedly restricted repertoire of activity and interest. Manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual. (DSM-IV) • A disorder characterized by marked impairments in social interaction and communication accompanied by a pattern of repetitive, stereotyped behaviors and activities. Developmental delays in social interaction and language surface prior to age 3 years.
Disruptive mood dysregulation disorder	**Approximate Synonyms** • Agonistic behavior • Appropriate affect • Blunted affect • Blunting of mood • Complaining of feeling unhappy	Disruptive mood dysregulation disorder	See synonyms for ICD-9-CM

	• Crying associated with mood • Cyclic mood swings • Dispiritment • Disturbance in mood • Diurnal variation of mood • Ecstasy • Elevated mood • Emotionally cold • Emotionally distant • Euphoria • Euthymic mood • Faddy behavior • Feeling a failure • Feeling abandoned • Feeling angry • Feeling emotionally hurt • Feeling mixed emotions • Feeling of discouragement • Flat affect • Hyperirritability • Hypomanic mood • Incongruity of mood • Indifference • Mood anorexia • Mood disorder • Mood disorder in full remission • Mood disorder with manic features due to general medical condition • Mood swing • Mood swings		

	• Moody • Non-delusional perplexed mood • Overoptimism • Physiological disturbance associated with mood • Pleasurable affect • Rebound mood swings • Restricted affect • Right hemispheric organic affective disorder • Seasonal affective disorder • Seasonal variation of mood • Sensitivity • Severe mood disorder with psychotic features, mood-incongruent • Sublimation - mental defense mechanism • Temperamental • Unpleasurable affect • Unpredictable in mood • Variability of mood • Volatile Mood		
Impulse control disorder	See definition from ICD-10-CM	Disorder (of) impulse (control)	**Clinical Information** • A category of psychiatric disorders

			whose essential features are the failure to resist an impulse to perform an act that is harmful to the individual or to others. Individuals typically experience an increased sense of tension prior to the act and then pleasure, gratification or release of tension at the time of committing the act.
Other and unspecified special symptoms or syndromes, NEC	**Approximate Synonyms** • Abnormal affect • Abnormal craving for drugs • Actions not completed • Adult habitual masturbation • Agitated wandering • Agitation • Aimless overactivity • Alternately sitting and standing • Ambulatory automatism • Arms not swung when walking • Attachment avoidant • Automanipulatory vulvoclitoral habituation • Auto-masturbation	*Restlessness and agitation*	See ICD-9-CM

	• Bad trips • Behavior showing reduced motor activity • Biting own fingers • Biting own toes • Bizarre dreams • Callosity due to biting and/or chewing • Catatonic reaction • Chewing hair • Communication disorder • Communication disorder, nonorganic • Communication disorder, psychogenic • Complex mannerisms - behavior • Compulsive drug taking • Compulsive uncontrollable drug taking • Conscientious • Demoralization • Denial - mental defense mechanism • Digit sucking • Disorientated in place • Disorientation as to self • Disorientation for person • Dyskinesia, psychogenic • Dysphoric mood		

	• Excessive chewing • Excessive craving for drugs • Excessive masturbation • Excessive spitting • Eye poking • Feeling agitated • Feeling hatred • Fidgeting • Finger-flicking • Flashbacks have stopped • Foreign body chewing • Gesticulation • Habit • Habitual finger biting • Habitual hair twisting • Habitual hand biting • Habitual nocturnal eating of own hair • Habitual pulling own hair • Hand sucking • High-pitched crowing • Impaired psychomotor development • Implement sucking • Inappropriate elimination • Inappropriate movement of face • Incomplete masturbation		

	• Insecure attachment • Insecure avoidant attachment • Inserting foreign bodies into own orifices • Juvenile masturbation • Lisping • Loss of interest in previously enjoyable activity • Markedly diminished pleasure • Masturbation • Mentally dull • Misery and unhappiness reaction of childhood • Mutual masturbation • Nail biting • Nail dystrophy due to nail picking • Nipping self • Non-organic communication disorder • Nose-picking • On examination - agitated • On examination - fearful mood • On examination - impulsive behavior • On examination - irreverent behavior		

	• On examination - irritable • On examination - suspicious • Onychotillomania • Pacing up and down • Pen sucking • Physical aggression • Poking fingers into wound • Powerlessness, moderate • Pseudomasturbation • Psychogenic dyskinesia • Public masturbation • Pulling out sutures • Pulling own teeth out • Rambling speech • Reinforced aggression • Removing own nails • Repetitive finger tapping • Repetitive flapping movements • Repetitive flicking movements • Repetitive hand wringing • Repetitive spinning movements • Repetitive tail chasing		

	• Repetitive tapping movements • Restlessness and agitation • Scalp rubbing • Screws up eyes • Screws up face • Self-asphyxiation during masturbation • Sexual harassment • Shooting self • Slapping self • Sleep state misperception • Squirming • Stillness • Structure of associations • Substance misuse behavior • Substance misuse decreased • Substance misuse increased • Thumb sucking • Tongue chewing • Tongue sucking • Tongue sucking or chewing • Twirling • Unpleasant dreams • Vocal abuse in children		
Other psychological or physical stress, NEC	**Clinical Information** • A disorder characterized by an individual's	*Borderline intellectual functioning*	See ICD-9-CM

	inability to comprehend or share ideas or feelings because of an impairment in language, speech, or hearing • Any of various disorders characterized by impaired verbal or nonverbal exchange or impaired transmission of thoughts, messages, or information • Detection of diminished ability to exchange thoughts, opinions, information, or other forms of communication such as disorders of language, reading, speech and hearing • Diminished ability to exchange thoughts, opinions, or information • Excessive pulling of one's own hair • Impaired ability to communicate usually, due to speech,		

	language, or hearing disorders		
Emotions specific to childhood or adolescence with misery and unhappiness	**Approximate Synonyms** • Misery and unhappiness reaction of childhood • Reaction of childhood, misery and unhappiness	*Unhappiness*	**Approximate Synonyms** • Feeling unhappy
Irritability	**Clinical Information** • Abnormal or excessive excitability with easily triggered anger, annoyance, or impatience • An abnormal responsiveness or morbid excitability of an organ, its part, or entire organism or its part to stimuli • Used for human or animal populations	*Irritability and anger*	See definition for ICD-10-CM
Other signs and symptoms involving emotional state	Within the subcategory of Nervousness (ICD-9-CM: 799.2)	Other symptoms and signs involving emotional state	See ICD-9-CM
Developmental Diagnoses			
ICD-9-CM Diagnosis	**ICD-9-CM Definitions**	**ICD-10-CM Diagnosis**	**ICD-10-CM Definitions**

Educational Circumstances	**Approximate Synonyms** • academic underachievement • Counseling for educational problems done • Educational problems counseling • Encounter for school problem • Encounter for school problem done • Underachievement in school	*Problem (with/related to) education or literacy*	**Approximate Synonyms** • Counseling for educational problems done • Educational problems counseling • Encounter for school problem • Encounter for school problem done
Disability, intellectual	**Clinical Information** • Impaired intellectual (IQ below 70) and adaptive functioning manifested during the developmental period. Use a more specific term if possible. Use for both the concept of the disorder itself and for populations of mentally retarded persons • Subnormal intellectual functioning which originates during the developmental	Disability, intellectual	**Clinical Information** • A broad category of disorders characterized by an impairment to the intelligence an individual possesses. These impairments can result from trauma, birth or disease and are not restricted to any particular age group. • A developmental disorder characterized by less than average intelligence and significant limitations in adaptive behavior with onset before the age of 18. • Impaired intellectual (IQ below 70) and adaptive functioning

	period; multiple potential etiologies, including genetic defects and perinatal insults; intelligence quotient (IQ) scores are commonly used to determine whether an individual is mentally retarded; IQ scores between 70 and 79 are in the borderline mentally retarded range and scores below 67 are in the retarded range		manifested during the developmental period. Use a more specific term if possible. Use for both the concept of the disorder itself and for populations of mentally retarded persons.
Mild intellectual disability (IQ 50-70)	**Approximate Synonyms** • Intellectual disability, mild • Mild intellectual disability • Mild mental retardation (I.Q. 50-70)	Mild intellectual disability (IQ 50-70)	See synonyms from ICD-9-CM
Moderate intellectual disability (IQ 35-49)	**Approximate Synonyms** • Intellectual disability, moderate • Moderate intellectual disability	Moderate intellectual disability (IQ 35-49)	See synonyms from ICD-9-CM

	• Moderate mental retardation (I.Q. 35-49)		
Severe intellectual disability (IQ 20-34)	**Approximate Synonyms** • Intellectual disability, severe • Severe intellectual disability • Severe mental retardation (I.Q. 20-34)	Severe intellectual disability (IQ 20-34)	See synonyms from ICD-9-CM
Profound intellectual disability (IQ under 20)	**Approximate Synonyms** • Intellectual disability, profound • Profound intellectual disability • Profound mental retardation (I.Q. below 20)	Profound intellectual disability (IQ under 20)	See synonyms from ICD-9-CM
Delayed Milestones	**Approximate Synonyms** • Delayed developmental milestones • Delayed milestone • Delayed speech milestone • Delayed speech milestones • Not yet speaking	Delayed milestone in childhood	See ICD-9-CM

Signs and symptoms involving cognition (overall)	Overall category, see Supplemental Table 2: Sub-diagnosis definitions	Other symptoms and signs involving cognitive functions and awareness	Overall category, see Supplemental Table 2: Sub-diagnosis definitions
Other signs and symptoms involving cognition	Overall category, see Supplemental Table 2: Sub-diagnosis definitions	*Other specified cognitive deficits*	Overall category, see Supplemental Table 2: Sub-diagnosis definitions
Iron Deficiency Anemia/Anemia Diagnoses			
ICD-9-CM Diagnosis	**ICD-9-CM Definitions**	**ICD-10-CM Diagnosis**	**ICD-10-CM Definitions**
Chronic Blood Loss Anemia	**Approximate Synonyms** • Anemia due to blood loss • Anemia due to chronic blood loss • Anemia, blood loss • Anemia, chronic blood loss	Chronic Blood Loss Anemia	See ICD-9-CM
Iron deficiency anemia, dietary	See ICD-10-CM	Iron deficiency anemia, dietary	**Clinical Information** • Anemia caused by low iron intake, inefficient iron absorption in the gastrointestinal tract, or chronic blood loss. • Anemia characterized by decreased or absent iron stores, low serum iron concentration, low transferrin saturation, and low hemoglobin concentration or hematocrit value. The erythrocytes are hypochromic and

			microcytic, and the iron binding capacity is increased.
Iron deficiency anemia, NEC	See ICD-10-CM	Iron deficiency anemia, NEC	**Clinical Information** • Anemia caused by low iron intake, inefficient iron absorption in the gastrointestinal tract, or chronic blood loss. • Anemia characterized by decreased or absent iron stores, low serum iron concentration, low transferrin saturation, and low hemoglobin concentration or hematocrit value. The erythrocytes are hypochromic and microcytic, and the iron binding capacity is increased.
Iron deficiency anemia, NOS	See synonyms for ICD-10-CM	Iron deficiency anemia, NOS	**Approximate Synonyms** • Anemia, dietary iron deficiency • Iron deficiency anemia due to dietary causes • Iron deficiency anemia due to erythropoietin deficiency • Iron deficiency anemia, erythropoietin deficiency
Anemia, unspecified	**Approximate Synonyms** • Anemia • Anemia chronic	Anemia, unspecified	**Clinical Information** • A condition in which the number of red blood cells is below normal.

	• Anemia due to lead paint exposure • Anemia due to medication • Anemia due to radiation • Anemia during pregnancy - baby not yet delivered • Anemia, chronic kidney disease erythropoietin protocol • Anemia, due to another condition • Anemia, due to lead paint exposure • Anemia, due to medications • Anemia, normocytic, normochromic • Anemia, pre ESRD erythropoietin protocol • Anemia, pre-ESRD erythropoietin protocol • Anemia, radiation • Anemia, secondary • Chronic anemia • Drug induced anemia • Maternal anemia in pregnancy, antepartum		• A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.

	• Maternal anemia in pregnancy, before birth • Normocytic normochromic anemia • Secondary anemia		
Hematocrit, low	Review anemia, unspecified	Hematocrit, low	Review anemia, unspecified
Hemoglobin, low	Review anemia, unspecified	Hemoglobin, low	Review anemia, unspecified
NOS: No other symptoms NEC: Not elsewhere classifiable ADHD: Attention Deficit Hyperactivity Disorder ADD: Attention Deficit Disorder Italicized definitions denote definitions which are ICD-10-CM Approximates.			

Supplemental Table 2: Sub-diagnosis definitions[144,145]		
Diagnosis	**ICD-9-CM**	**ICD-10-CM**
Specific delays in development (ICD-9-CM: 315; ICD-10-CM: R62.50)		
Developmental reading disorder	See *developmental reading disorder, unspecified, alexia, developmental dyslexia, and other specific developmental reading disorder*	See *developmental reading disorder, unspecified, alexia, developmental dyslexia, and other specific developmental reading disorder*
Developmental reading disorder, unspecified	**Approximate Synonyms** • Developmental disorder in reading	**Clinical Information** • A cognitive disorder characterized by an impaired ability to comprehend written and printed words or phrases despite intact vision. This condition may be developmental or acquired. • Developmental dyslexia is marked by reading achievement that falls substantially below that

		expected given the individual's chronological age, measured intelligence, and age-appropriate education. • The disturbance in reading significantly interferes with academic achievement or with activities of daily living that require reading skills. (from DSM-IV)
Alexia	**Clinical Information** • Inability to read which may be the result of neurological impairment. • In a less severe form, often referred to as dyslexia	See ICD-9-CM
Developmental dyslexia	See ICD-10-CM	**Clinical Information** • A cognitive disorder characterized by an impaired ability to comprehend written and printed words or phrases despite intact vision. This condition may be developmental or acquired. • Developmental dyslexia is marked by reading achievement that falls substantially below that expected given the individual's chronological age, measured intelligence, and age-appropriate education. • The disturbance in reading significantly interferes with academic achievement or with activities of daily living

		that require reading skills. (from DSM-IV)
Other specific developmental reading disorder	See ICD-10-CM	**Approximate Synonyms** • Developmental disorder in expressive writing • Developmental disorder, expressive writing • Developmental expressive writing disorder • Specific learning disorder w impairment in written expression
Mathematics disorder	**Approximate Synonyms** • Developmental arithmetic disorder • Developmental disorder in mathematics • Developmental disorder, mathematics	See ICD-9-CM
Other specific developmental learning difficulties	**Approximate Synonyms** • Basic learning problem in writing • Developmental academic disorder • Developmental disorder in expressive writing • Difficulty solving problems • Difficulty writing • Disturbance of cognitive learning • Impaired ability to learn new material • Information conversion problem • Learning difficulties • Slow learner	**Approximate Synonyms** • Developmental disorder in expressive writing • Other developmental disorders of scholastic skills (ICD-10-CM: F81.89)
Developmental speech or language disorder	See expressive language disorder and mixed receptive-expressive language disorder	See expressive language disorder and mixed receptive-expressive language disorder

Expressive language disorder	**Clinical Information** • A disorder characterized by an impairment in the development of an individual's expressive language which is in contrast to his/her nonverbal intellect and receptive language development. The impairment may be acquired (i.e., due to a brain lesion or head trauma) or developmental (i.e., no known neurological insult)	See ICD-9-CM
Mixed receptive-expressive language disorder	**Clinical Information** • A disorder characterized by an impairment in the development of an individual's expressive and receptive language capabilities which is in contrast to his/her nonverbal intellect. The impairment may be acquired (i.e., due to a brain lesion or head trauma) or developmental (i.e., no known neurological insult)	**Clinical Information (F80.2: Mixed receptive-expressive language disorder)** • A disorder characterized by an impairment in the development of an individual's expressive and receptive language capabilities which is in contrast to his/her nonverbal intellect. The impairment may be acquired (i.e., due to a brain lesion or head trauma) or developmental (i.e., no known neurological insult). **Clinical Information (H93.25: Central auditory processing disorder)** • A disorder characterized by impairment of the auditory processing, resulting in deficiencies in the recognition and interpretation of sounds by the brain. Causes include brain maturation

		delays and brain traumas or tumors.
Speech and language developmental delay due to hearing loss	**Approximate Synonyms** • Speech, language developmental delay from hearing loss	**Approximate Synonyms** • Speech and language developmental delay due to hearing loss • Speech, language developmental delay from hearing loss
Childhood onset fluency disorder	**Approximate Synonyms** • Childhood onset stuttering • Childhood onset stuttering and stammering • Fluency disorder, childhood onset	**Clinical Information** • A disturbance in the normal fluency and time patterning of speech that is inappropriate for the individual's age. This disturbance is characterized by frequent repetitions or prolongations of sounds or syllables. Various other types of speech dysfluencies may also be involved including interjections, broken words, audible or silent blocking, circumlocutions, words produced with an excess of physical tension, and monosyllabic whole word repetitions. Stuttering may occur as a developmental condition in childhood or as an acquired disorder which may be associated with brain infarctions and other brain diseases. (from DSM-IV, 1994)
Other developmental speech or language disorder	**Clinical Information** • Speech disorders involving the substitution, omission,	**Clinical Information (F80.0: phonological disorder)**

	distortion, or addition of phonemes	• A disorder characterized by the failure to use developmentally expected speech sounds that are appropriate for the individual's age (i.e., the individual makes errors in sound production or use or omits sounds such as final consonants). • Disorders of the quality of speech characterized by the substitution, omission, distortion, and addition of phonemes. • Speech disorders involving the substitution, omission, distortion, or addition of phonemes. **Approximate Synonyms (F80.89: Other developmental disorders of speech and language)** • Semantic-pragmatic impairment • Social (pragmatic) communication disorder **Clinical Information (F80.82: Social pragmatic communication disorder)** • See ICD-9-CM and other related ICD-10-CM diagnoses listed above.

Developmental coordination disorder	**Clinical Information** • A disorder characterized by an impairment in the development of an individual's motor coordination skills; this impairment in motor development is not due to a medical condition • Inability to execute complex coordinated movements resulting from lesions in the motor area of the cortex but involving no sensory impairment or paralysis • Loss of ability to perform familiar, purposeful movements in the absence of paralysis or other neural sensorimotor impairment	**Clinical Information** • A disorder characterized by an impairment in the development of an individual's motor coordination skills; this impairment in motor development is not due to a medical condition. • Marked impairments in the development of motor coordination such that the impairment interferes with activities of daily living. (from DSM-IV, 1994)
Mixed development disorder	**Approximate Synonyms** • Developmental disorder, mixed • Mixed developmental disorder • Sensory integration disorder	**Clinical Information** • A disorder characterized by an impairment in the development of an individual's motor coordination skills; this impairment in motor development is not due to a medical condition. • Marked impairments in the development of motor coordination such that the impairment interferes with activities of daily living. (from DSM-IV, 1994)

Other specified delays in development	**Approximate Synonyms** • Borderline cognitive developmental delay • Cognitive development, borderline • Cognitive developmental delay • Developmental agnosia • Developmental delay in feeding • Developmental delay, cognitive • Developmental delay, cognitive, borderline • Developmental delay, feeding • Developmental disorder, specific • Developmental mental disorder • Disorder of psychological development • Feeding delay, developmental • Ideomotor dyspraxia • Learning disorder, nonverbal • Nonverbal learning disorder • Persistent developmental avoidance • Savant syndrome • Specific developmental disorder	See ICD-9-CM
Unspecified delay in development	**Clinical Information** • According to United States Federal legislation, learning problems that are due to visual, hearing, or motor handicaps, mental retardation, emotional disturbance or environmental, cultural, or economic disadvantage. Compare learning disabilities	**Clinical Information (F81.9: Developmental disorder of scholastic skills, unspecified)** • A group of disorders that affect a person's ability to learn or process specific types of information which is in contrast to his/her apparent level of intellect.

		Clinical Information (F89: Unspecified disorder of psychological development) • A disorder diagnosed in childhood that is marked by either physical or mental impairment or both, which in turn affects the child from achieving age related developmental milestones.
Adjustment Reaction (ICD-9-CM: 309; ICD-10-CM: F43.2)		
Adjustment disorder with depressed mood	**Clinical Information** • Feeling of great sorrow • Sorrowful response to an immediate cause; self-limiting and gradually subsides within a reasonable time • Suffering and distress associated with loss	**Approximate Synonyms** • Adjustment reaction, depressive, brief • Adjustment reaction, depressive, prolonged • Bereavement, complicated • Brief depressive adjustment reaction • Complicated bereavement • Complicated grieving • Prolonged depressive adjustment reaction
Prolonged depressive reaction	**Approximate Synonyms** • Adjustment disorder w depressed mood, prolonged • Adjustment reaction, depressive, prolonged • Prolonged depressive adjustment reaction	**Approximate Synonyms** • Adjustment reaction, depressive, brief • Adjustment reaction, depressive, prolonged • Bereavement, complicated • Brief depressive adjustment reaction • Complicated bereavement • Complicated grieving • Prolonged depressive adjustment reaction

Adjustment reaction with predominant disturbance of other emotions	See ICD-10-CM	**Approximate Synonyms** • Adjustment disorder w mixed disturbance of emotion and conduct • Adjustment disorder with mixed disturbance of emotion
Separation anxiety disorder	**Clinical Information** • An anxiety disorder characterized by recurrent excessive distress due to fear of separation from the home or from major attachment figures; the distress is developmentally inappropriate and causes impairment in social, academic, or other areas of functioning	**Clinical Information** • Anxiety experienced by an individual upon separation from a person or object of particular significance to him
Emancipation disorder of adolescence and early adult life	No description or synonyms provided	No description or synonyms provided
Specific academic or work inhibition	**Approximate Synonyms** • Adjustment disorder with academic inhibition • Adjustment disorder with work inhibition • Adjustment disorder with academic inhibition • Specific work inhibition • Work inhibition, specific	See ICD-9-CM
Adjustment disorder with anxiety	**Approximate Synonyms** • Adjustment disorder w anxiety • Adjustment disorder with anxious mood	See ICD-9-CM
Adjustment disorder with mixed anxiety and depressed mood	See ICD-10-CM	**Approximate Synonyms** • Adjustment disorder with mixed anxiety and depressed

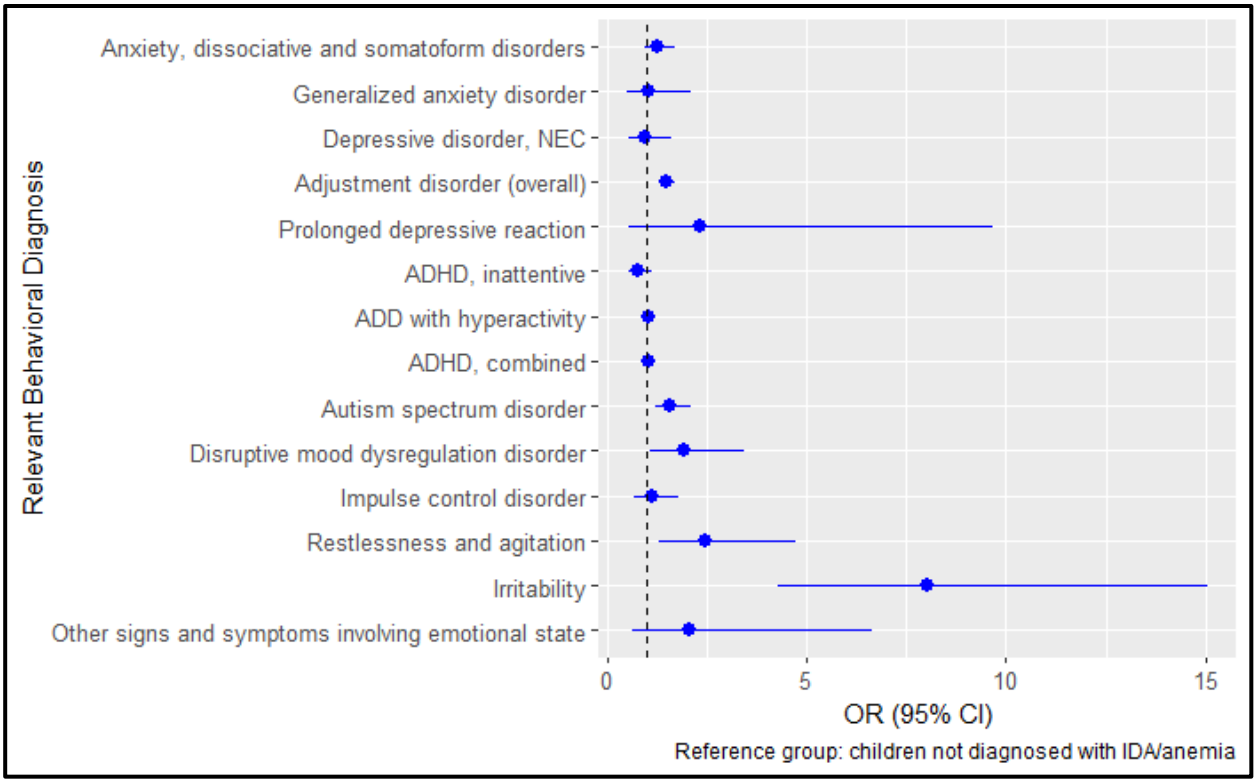
		• Adjustment disorder with mixed emotional features
Other adjustment reaction with predominant disturbance of other emotions	**Clinical Information** • Social, psychological, or emotional difficulties in adapting to a new culture or similar difficulties in adapting to one's own culture as the result of rapid social or cultural changes	See ICD-9-CM
Adjustment disorder with disturbance of conduct	**Approximate Synonyms** • Adjustment disorder with disturbance of conduct	See ICD-9-CM
Adjustment disorder with mixed disturbance of emotions and conduct	**Approximate Synonyms** • Adjustment disorder with mixed disturbance of emotion and conduct • Adjustment disorder with mixed disturbance of emotion	See ICD-9-CM
Other specified adjustment reactions	See post-traumatic stress disorder and adjustment reaction with physical symptoms	See post-traumatic stress disorder and adjustment reaction with physical symptoms

Posttraumatic stress disorder	**Clinical Information** • A class of traumatic stress disorders with symptoms that last more than one month. There are various forms of post-traumatic stress disorder, depending on the time of onset and the duration of these stress symptoms. In the acute form, the duration of the symptoms is between 1 to 3 months. In the chronic form, symptoms last more than 3 months. With delayed onset, symptoms develop more than 6 months after the traumatic event	**Clinical Information (F43.10: post-traumatic stress disorder, unspecified)** • A class of traumatic stress disorders with symptoms that last more than one month. There are various forms of post-traumatic stress disorder, depending on the time of onset and the duration of these stress symptoms. In the acute form, the duration of the symptoms is between 1 to 3 months. In the chronic form, symptoms last more than 3 months. With delayed onset, symptoms develop more than 6 months after the traumatic event. **Approximate Synonyms (F43.12: post-traumatic stress disorder, chronic)** • Chronic post-traumatic stress disorder • Chronic posttraumatic stress disorder • Posttraumatic stress disorder, chronic

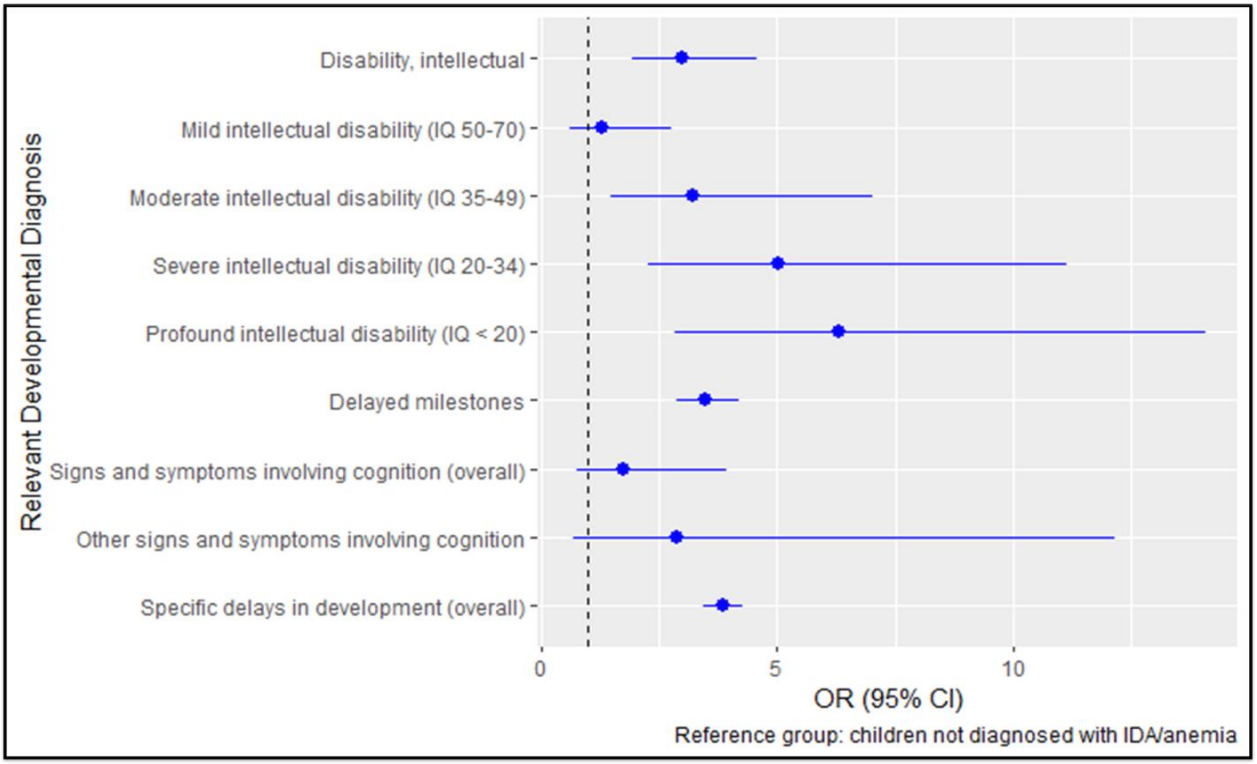
Adjustment reaction with physical symptoms	See ICD-10-CM	**Approximate Synonyms** • Emotional stress • Emotional stress reaction • Muscle tension, stress related • Persistent complex bereavement disorder • Stress reaction causing mixed disturbance • Stress reaction causing mixed disturbance of emotion and conduct • Stress reaction with psychomotor agitation • Stress reaction, emotional • Stress-induced muscle tension • Tension, muscle, stress related
Adjustment reaction with withdrawal	See ICD-10-CM	**Approximate Synonyms** • Emotional stress • Emotional stress reaction • Muscle tension, stress related • Persistent complex bereavement disorder • Stress reaction causing mixed disturbance • Stress reaction causing mixed disturbance of emotion and conduct • Stress reaction with psychomotor agitation • Stress reaction, emotional • Stress-induced muscle tension • Tension, muscle, stress related

Other specified adjustment reactions	See ICD-10-CM	**Approximate Synonyms** • Emotional stress • Emotional stress reaction • Muscle tension, stress related • Persistent complex bereavement disorder • Stress reaction causing mixed disturbance • Stress reaction causing mixed disturbance of emotion and conduct • Stress reaction with psychomotor agitation • Stress reaction, emotional • Stress-induced muscle tension • Tension, muscle, stress related
Unspecified adjustment reaction	**Approximate Synonyms** • Adjustment disorder • Adjustment disorder to medical therapy	**Clinical Information** • A category of psychiatric disorders which are characterized by emotional or behavioral symptoms that develop within 3 months of a stressor and do not persist for more than an additional 6 months after the stressor is no longer present.
Signs and Symptoms Involving Cognition (ICD-9-CM: 799.5; ICD-10-CM: R41.89)		
Attention or concentration deficit	**Approximate Synonyms** • Cognitive deficit in attention or concentration	See ICD-9-CM
Cognitive communication deficit	See ICD-10-CM	**Approximate Synonyms** • Cognitive deficit in communication skills

		• Cognitive linguistic dysfunction • Language-related cognitive disorder
Visuospatial deficit	**Approximate Synonyms** • Cognitive deficit in visuospatial function	**Approximate Synonyms** • Cognitive deficit in visuospatial function
Psychomotor deficit	**Approximate Synonyms** • Cognitive deficit in psychomotor function	See ICD-9-CM
Frontal lobe and executive function deficit	**Approximate Synonyms** • Cognitive deficit in executive function • Cognitive deficit in frontal lobe or executive function	See ICD-9-CM
Other signs and symptoms involving cognition	See ICD-10-CM	**Clinical Information** • Lack of awareness of, or refusal or failure to deal with or recognize that one has a mental or physical disorder.



Supplemental Figure 2: OR for Relevant Behavioral Diagnoses



Supplemental Figure 1: OR for Relevant Developmental Diagnoses

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