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PREDICTORS AND OUTCOMES OF PICA

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PREDICTORS AND OUTCOMES OF PICA

by

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Dedication

This work is dedicated to my family, my husband Shehzad and our wonderful children, Zohaib and Saniya Sidi. This would not have been possible without their support and understanding. This dissertation is also dedicated to my parents, Abdulaziz and Farida Esani, who taught me to not let anything come in the way of my dreams.

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PREDICTORS AND OUTCOMES OF PICA

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Abstract:
Pica is an eating disorder of chewing non-nutritional substances such as ice, dirt, corn starch, paint etc. for more than one month, as diagnosed based on DSM-V criteria. Pagophagia (consumption of ice) is the predominant type of pica in adults and geophagia (consumption of dirt) is most common in children. Pica is poorly understood, but its association with iron deficiency is well established. The purpose of this study is to identify predictors of pica including iron deficiency, other comorbid conditions, psychiatric disorders, behaviors and laboratory markers in children and adults. We also studied health outcomes of pica including but not limited to hospitalizations in children and adults. This is a case-control study of 7,684 patients aged 2 to 64 years who were enrolled in one of the nation's largest commercial insurance programs between January 1, 2008, and December 31, 2014. Cases were defined as patients who had a diagnosis of pica listed on either inpatient or outpatient claims. Cases were matched with 3 controls based on diagnosis or index date (month and year), age, gender, and region. The predictors of pica were identified in the 12 month look-back period before diagnosis or index date. Cases and controls were also followed for 12 months after diagnosis or index date to study outcomes. The findings of this study suggest that iron deficiency, mood disorders and obesity were significant predictors of pica. In children, autism spectrum disorder (ASD) was the strongest predictor of pica. In adults, additional predictors were anxiety disorder and menstrual bleeding disorders. We also found that decreased hemoglobin and increased red cell distribution width (RDW) were laboratory predictors of pica. Our study identified important outcomes of pica including hospitalization in the first 75 days after diagnosis, gastrointestinal (GI) disorders and infections, and fluid and electrolyte imbalance in both children and adults. Moreover, our findings suggest that lead poisoning was a significant outcome of pica in children. Another major finding of this study was that other eating disorders co-exist with pica in children and adults. These findings enhance our understanding of pica in children and adults.

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DSM	Diagnostic and Statistical Manual of Mental Disorders
ASD	Autism Spectrum Disorder
GI	Gastrointestinal
RLS	Restless leg syndrome
OCD	Obsessive Compulsive Disorder
CBC	Complete Blood Count
RBC	Red Blood Cell Count
WBC	White Blood Cell Count
MCV	Mean Cell Volume
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
RDW	Red Cell Distribution Width
MPV	Mean Platelet Volume
TIBC	Total Iron Binding Capacity

Chapter 1: Background and Significance

HISTORY AND TYPES OF PICA

Pica is an eating disorder characterized by a compulsive appetite for substances that are non-nutritive such as ice, chalk, corn starch, paper, lead paint, soil or clay.[1-3] According to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders) criteria, these actions are considered pica if they persist for longer than one month and are not consistent with cultural or social norms. Moreover, the criteria suggests that presence of pica with another mental condition deserves independent medical attention if the pica is severe in nature.[4] The word "pica" is derived from magpie, which is the Latin name of a bird known for its unusual eating habits.[5] Early writings of Hippocrates and Aristotle describe such behavior, indicating that pica has been around for centuries; it has been classified more recently as an eating disorder.[6,7] Several different types of pica exist including pagophagy (ice consumption), geophagy (consumption of earth) and amylophagy (consumption of raw starch). Pagophagia or ice pica, is the most common type, accounting for 44.4% to 94% of all cases of pica.[1,8-10] In children, geophagia is the most commonly reported type of pica[11-13] and pagophagia seems to be predominant in adults.[1,8-10]

Pica is a poorly understood; however, several etiologies have been proposed. Early British literature attributed pica, particularly pagophagia, to the American cultural habit of ice consumption that was not common in the rest of the world.[6] Other explanations suggested for obsessive consumption of non-nutritive substances include nutritional deficiencies such as iron and zinc deficiency, and cultural and psychological

factors. Micronutrient deficiencies, particularly iron deficiency, have been associated with pica in a number of studies.[1,3,8,9] Pica has been associated with cultural practices or rituals in various regions worldwide.[5] Based on the DSM-V definition, pica can be diagnosed only if this eating behavior has no relationship to normal cultural rituals.

PICA AND DEMOGRAPHIC VARIABLES

The association of demographic factors with pica has not been extensively studied. But pica is suggested to be more common in females than males.[1,10] This is plausible because iron deficiency, which has been associated with pica, is more common in females, who have greater iron needs during their child-bearing years due to monthly menstrual blood loss.[1] Pagophagia is more prevalent in younger than older individuals.[1,3] A study of the Agency for Healthcare Research and Quality (AHRQ) hospital discharge data suggests that a higher proportion of pica hospitalizations occur in females (66.61%), young adults and patients from southern United States (42.62%), as displayed in Table 1.1.[14] To our knowledge, there are no population based studies exploring demographic variables that may be associated with pica in an outpatient setting. Therefore, the true prevalence of pica in the U.S. is unknown.

Table 1.1: Number of hospitalizations in the U.S. due to pica in 2012, stratified by patient demographic (AHRQ – HCUPnet online portal)

		Total number of discharges
All discharges		2,980 (100.00%)
Age group	1-17	515 (17.28%)
	18-44	1,225 (41.11%)
	45-64	950 (31.88%)
	65-84	250 (8.39%)
	85+	*
Sex	Male	995 (33.39%)
	Female	1,985 (66.61%)
Patient residence	Large central metro	890 (29.87%)
	Large fringe metro (suburbs)	525 (17.62%)
	Medium and small metro	1,060 (35.57%)
	Micropolitan and noncore (rural)	495 (16.61%)
	Missing	*
Region	Northeast	575 (19.30%)
	Midwest	790 (26.51%)
	South	1,270 (42.62%)
	West	345 (11.58%)

*missing data
Age group: age in years

RELATIONSHIP OF IRON DEFICIENCY AND PICA

The relationship of iron deficiency to pica is well established but the mechanism is not well understood.[1,3] Pagophagia is most prevalent in populations prone to iron deficiency, such as pregnant women, blood donors and malnourished individuals.[1,15,16] A few studies of pica report prevalences of iron deficiency ranging from 2% to 76%.[1,3,8,9]

Association of pica with iron deficiency in women and children

The association of pica with iron deficiency in adult females is well reported. Bryant and colleagues found an association between pica and iron deficiency in a cross-sectional study of 1,236 blood donors with iron deficiency anemia (hemoglobin levels of <12.5g/dL) and 400 blood donors without anemia (hemoglobin >12.5g/dL).[1] Pica was

self-reported by study participants and defined by any duration of chewing non-nutritive substances, and not necessarily for one month, as in DSM-V criteria. Iron deficiency was defined as ferritin of <9 ug/L in females and <18 ug/L in males. Iron depletion was defined as ferritin of 9 to 19 ug/L in females and 18 to 29 ug/L in males. The study reported that 11% of iron deficient blood donors and 4% of non-iron deficient controls reported pica ($p<0.0001$). This study found a statistically significant association of iron deficiency or depletion with pica in females but not in males. A number of indicators of iron deficiency such as, low mean red cell volume (MCV), low transferrin saturation and younger age were significantly associated with pica ($p<0.001$). Iron repletion was offered to all donors who were iron deficient or depleted. This resulted in normalization of iron related laboratory parameters. Further confirming the association, all those with pagophagia reported complete disappearance of ice cravings after iron replacement therapy.[1]

In a similar study, Spencer at el. included 1,174 blood donors in a cross-sectional sample from six blood centers. Iron deficiency was defined as serum ferritin of <12 ng/mL and anemia was defined by decreased hemoglobin. Pica was defined as any amount and any duration of chewing or craving of ice or other non-nutritive substances. The study found that pica was associated with iron deficiency in adult females. The prevalence of pica was 13% in iron deficient females (ferritin<12ng/mL) compared to 2% in the iron replete females (ferritin>12ng/mL). The Spencer study also reported that the association of pica with iron deficiency anemia (OR: 7.42, 95% CI: 2.90 -22.96) was stronger than it was with iron deficiency in the absence of anemia (OR: 3.10, 95% CI: 1.07-8.96) but both differences were statistically significant.[3] Neither of the above

discussed studies used DSM-V criteria for diagnosis of pica which may have resulted in overestimation of the association of pica with iron deficiency. Regardless, these studies clearly establish the association of pica with iron deficiency in women.

Pregnant women and children were identified as high risk groups for iron deficiency in a Centers for Disease Control and Prevention (CDC) study.[17] Miao et al. conducted a systematic review and meta-analysis of 43 studies to examine the relationship of iron and zinc deficiency with pica, and found that individuals with pica were 2.35 times more likely to be anemic (95% CI: 1.94 - 2.85, $p<0.001$) and to have lower hemoglobin levels (-0.65 g/dL, 95% CI: -0.83 to -0.48 g/dL, $p<0.001$), lower hematocrits (-1.15%, 95% CI: -1.61 to -0.70%, $p<0.001$) and lower serum zinc concentrations (-34.30 ug/dL, 95% CI: -59.58 to -9.02 ug/dL, $p = 0.008$) than those without pica.[18] They also found children and pregnant women were at risk for pica because of an increased likelihood of being anemic, (OR = 4.23, 95% CI 1.52-11.78 for children, and OR = 1.92, 95% CI 1.68-2.19 for pregnant women). The studies included in their review were inconsistent in defining pica, anemia and children (in terms of age) which made it difficult to draw comparisons.[18] Similar inconsistencies were evident in a cross-sectional study conducted by Simulian et al, of 125 obstetric patients seen by Georgia Health Department. Anemia, defined by a hematocrit of < 32%, was the independent variable.[9] The dependent variable was self-reported pica, defined as the consumption of ice, dirt, laundry starch, corn starch, soap, paint matches, chalk or ashes with a frequency of a few times a week to multiple times a day, the purchase of ice or other substances for the purpose of ingestion or the acquisition of ice from an unusual source such as freezer frost. The prevalence of ice pica was reported to be 14.4% in this

population. Anemia, presumed to be due to iron deficiency, was present in 16.7% of patients with pica and in 17.8% of patients without pica (OR=0.92, p>0.05) which was not a significant difference.[9] This study had several weaknesses or features that differ from other studies. For example, anemia was assumed but not reported to be due to iron deficiency. Pica was not defined based on DSM-V criteria. Moreover, this study was limited to pregnant females and it is well established that this condition can cause multiple food cravings not experienced by non-pregnant women. Therefore, their findings cannot be extended beyond pregnant women. Nonetheless, all of these studies suggest a relationship of pica with iron deficiency that needs to be examined further in future studies.

Association of pica with iron deficiency in men

Most studies suggest that pica is more common in women, but there are also reports of pica in iron deficient men. Barton and Bertoli conducted a case control study utilizing chart reviews of 262 adult outpatients receiving intravenous (IV) iron therapy at a referral hematology and oncology practice between November 1992 and March 2009.[8] Iron deficiency was the independent variable defined as a ferritin of <20.03 ng/mL. The dependent variable was the presence or absence of pica as recorded in the patient's chart. Only 67% of the charts included a note about the presence or absence of pica, with pica reported in 45% of the iron deficient patients. There was no difference in the prevalence of pica between men and women with iron deficiency (p=0.0943), demonstrating that pica related to iron deficiency is not exclusive to women. Those with pica were younger (OR=0.981, 95% CI: 0.965-0.998), had lower MCVs (OR=0.977, 95% CI: 0.962-0.991), higher RDWs (OR=1.11, 95% CI: 1.044 –1.182) and higher platelet counts (OR=1.002,

95% CI: 1.000-1.004) than those without pica, and these observations were statistically significant. Furthermore, treatment with IV iron resolved pica symptoms in all patients in two to three weeks.[8] The limitations of this study were the exclusion of patients that were on oral iron therapy and the inclusion of those individuals who may have been on oral iron therapy previously, which limits generalizability and may possibly introduce confounding. Moreover, 33% of patient charts did not contain appropriate documentation which might have underestimated pica in one or both groups. Nonetheless, this study established that pica occurs in both men and women.

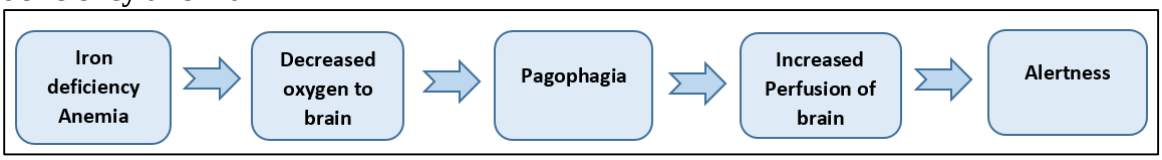
Proposed mechanism of the association of iron deficiency with Pagophagia

The studies discussed above provide ample evidence that iron deficiency is associated with pica, at the very least pagophagia, and that iron replacement may relieve pica symptoms. However, pica behavior due to iron deficiency is difficult to rationalize. There is no iron in ice, so pagophagia is not beneficial for iron deficiency itself. The relationship is not obligatory because not all iron deficient patients have pica and not all patients with pica have iron deficiency. Yet, iron replacement results in complete cessation of pica symptoms and behaviors.[1,8] Iron deficiency is associated with a burning sensation of the oral mucosa, dry mouth and trophic glossitis (inflammation of tongue).[19] Perhaps ice relieves these symptoms which encourages iron deficient individuals to consume ice. In a study conducted by Woods and Weisinger, albino rats with iron deficiency consumed 96% of their water in the form of ice compared to only 45% for the control group, even though amounts of water consumption were the same.[20] They also reported a direct relationship between severity of iron deficiency anemia and the amount of ice consumed. Similar to the findings in the human study by Bryant, iron repletion

resulted in disappearance of pagophagia.[20] This study provides further strong evidence that pagophagia results from iron deficiency.

Pagophagia clearly does not ameliorate anemia, but may make anemic individuals feel more alert. Hunt and colleagues attempted to explain the correlation between a craving for coldness of water or ice with anemia. In their study, pagophagia occurred in those with iron deficiency anemia but not in those without anemia. They found that anemic adults who chewed ice performed significantly better on neuropsychological test but this did not occur in healthy controls.[2] Hunt et al. explained this phenomenon by citing another study in which pagophagia, found to be a result of iron deficiency anemia, was associated with activation of the dive reflex. This autonomic nervous system response allows divers to stay alive in cold water without oxygen by maintaining perfusion of essential organs such as the brain and heart. [21] It is possible that the supply of oxygen to the brain is deficient in iron deficiency anemia, and that ice consumption increases blood flow and oxygen supply to the brain, which helps anemic individuals feel more alert. The stepwise process that explains the mechanism of pagophagia in anemic individuals is illustrated in Figure 1.1.

Figure 1.1: Mechanism of pagophagia leading to increased alertness in iron deficiency anemia

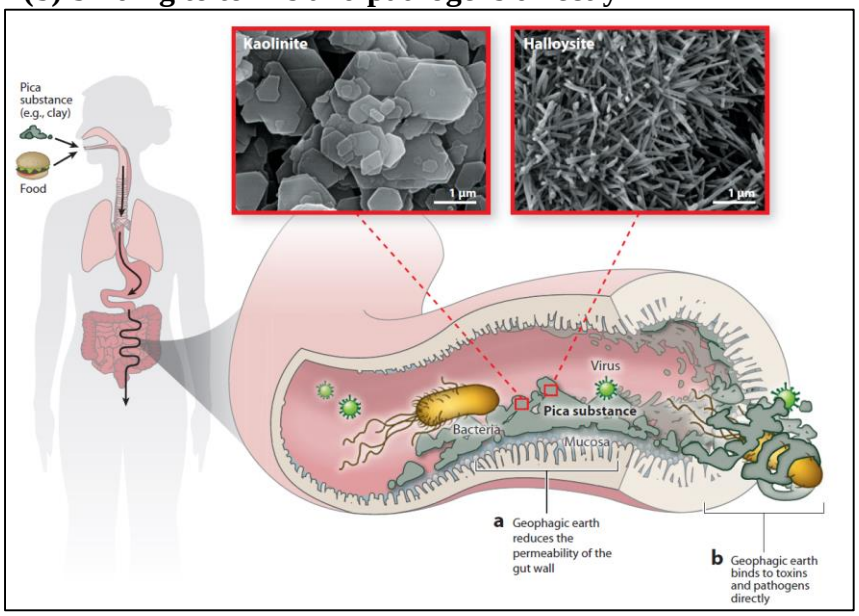


Proposed mechanism of association of iron deficiency with geophagia

The mechanism of geophagy is as much of a mystery as pagophagy. The association of iron deficiency and geophagy has mostly been studied in pregnant women

and children.[5,22] It was suggested that geophagy is a response to micronutrient deficiency such as iron deficiency.[23] However, it is unlikely that geophagia can supply needed iron, because iron requires an extremely low pH to be absorbed. Paradoxically, dirt and clay increase intestinal pH to an alkaline level, and presumably has a similar effect in the duodenum where iron absorption occurs.[24] This may explain why geophagy makes the iron deficiency worse rather than better.[25] Dirt binds to nutrients like iron, copper and zinc, as well as microbes, and prevents them from being absorbed, [26-29] (Figure 1.2). This is purportedly a protective effect of geophagy preventing microbes and toxins from being absorbed from the gut.[5] Thus, there is no clear explanation for geophagy as a response to iron deficiency anemia. Craving special foods, especially by pregnant women and children, might supply needed nutrients such as iron, but obsessive craving for non-nutritious substances remains unexplained.

Figure 1.2: Geophagy provides protection by (a) reducing permeability of gut wall (b) binding to toxins and pathogens directly[5]



In our non-mechanistic study we have attempted to more completely understand the association of iron deficiency anemia with pica in both children and adults of both

genders. We also explored possible associations of pica with other clinical factors such as gastrointestinal (GI) disorders and infections and menstrual bleeding disorders, as they can contribute to development of iron deficiency.

RELATIONSHIP OF PICA WITH OTHER MEDICAL CONDITIONS

Eating disorders can coexist with a number of other medical conditions. An AHRQ report described several of these disorders: eating disorders other than pica, including anorexia nervosa, bulimia nervosa, rumination disorder and psychogenic vomiting; malnutrition; GI disorders and infections; lead poisoning; parasitic infections; menstrual disorders; restless leg syndrome (RLS); GI bleeding; and psychiatric disorders such as autism, mood disorders, schizophrenia, anxiety disorders and obsessive compulsive disorder (OCD). These are described as common findings in patients with a secondary diagnosis of an eating disorder.[30]

These disorders have not yet previously been studied in patients with pica, to our knowledge. In the current study we explored their association with pica as predictors and outcomes. Disorders that may coexist with pica, including eating disorders, malnutrition, GI disorders and infections, lead poisoning and parasitic infections, were grouped together and were designated as Medical Conditions I in our study and were studied as both predictors and outcomes of pica. Those conditions that may clinically occur prior to diagnosis of pica, such as menstrual bleeding disorders, RLS, GI and non-GI bleeding, were grouped together as Medical Conditions II and were studied only as predictors of pica. Finally, disorders that have been reported as consequences of pica, such as dental complications, intestinal obstructions, fluid and electrolyte imbalance and cardiac dysrhythmias, were only studied as outcomes of pica.

Eating disorders and pica

Coexistence of more than one eating disorder is well known. Eating and feeding disorders are examples of psychiatric conditions that impact a person's well-being and physical, social, emotional and cognitive development.[31] These disorders include anorexia nervosa (intentional avoidance of food leading to decreased body weight and other complications), bulimia nervosa (binge eating followed by self-induced removal of food via vomiting or diarrhea), rumination disorder (regurgitation of food), feeding disorder of infancy and childhood, binge eating disorder (BED), pica as well as other unspecified disorders.[30-32] Anorexia nervosa is the most common eating disorder and has the highest mortality rate.[30] Other eating disorders, can co-exist with pica and have been reported mostly in adolescent females who try to control their weight or suppress their hunger by eating substances that do not contribute to calories.[7,33] A study conducted in pregnant women reported that pica in pregnancy was associated with an increased risk of developing either anorexia or bulimia.[34] Another study suggested that obsessive ice consumption was common in patients with other eating disorder seven though the associated pica did not always fit the DSM-V criteria of being at least one month duration.[35] Consequently, the presence of one eating disorder may predict another.

Currently, feeding problems of childhood are not classified by DSM-Vas eating disorders. Marchi and Cohen followed children with eating and feeding problems, including picky eating behavior, avoiding food, too much and too little eating, eating too slowly, and those with pica into adolescence. Their study found that mealtime struggles and pica in childhood were predictive of bulimia in adolescence.[36] Therefore, it is important to study the relationship between different eating disorders and also their

association in adults with previous childhood feeding problems. To this end, one of our objectives was to examine the relationships of childhood feeding problems and eating disorders with later occurrence of pica.

Malnutrition and pica

Malnutrition has been associated with eating disorders, including pica, in a number of studies.[11,13,18] However, the etiology and direction of this association is unknown.[18] It has been suggested that micronutrient deficiency may cause the body to seek the deficient nutrients in non-nutritional substances like dirt or chalk.[37] On the other hand, as discussed earlier, pica and particularly geophagia may contribute to malnutrition by decreasing absorption of nutrients.[26-29,37] A meta-analysis conducted by Miao et al. found that zinc levels were generally lower in patients with pica, although the difference was not statistically significant ($p = 0.178$). But a Turkish study found significant decreases in zinc, iron and selenium levels in patients with pica compared to controls ($p = 0.001$, all three nutrients). We evaluated the association of malnutrition with pica, both as a predictor and outcome.

Gastrointestinal disorders and infections and parasitic infections with pica

Many gastrointestinal disorders and infections as well as parasitic infections can lead to iron deficiency and other types of malnutrition. These are linked with pica[1,8,11,18] but can also be outcomes of pica, particularly with regard to geophagia[38]. These disorders can also lead to iron deficiency that may mediate pica. A Jamaican study of 108 patients with pica (mostly geophagia) and 50 controls, found that 46% of cases and 12% of controls had poor nutritional status ($p<0.05$). Also a significant number of those

with diarrhea had anemia which was likely due to iron deficiency, although this was not specifically examined. Controls were not evaluated for parasitic infections, but 70.3% of cases had intestinal infections from parasites that include *Giardia lamblia, Ascaris lumbricoides* and *Trichuris* species.[11] Bay at el. associated pica with GI infections, particularly *Helicobacter* (*H)-pylori* ($p<0.05$). They reported that the prevalence of celiac disease in patients with pica and iron deficiency anemia was 8.5% compared to 4.5% in patient with iron deficiency anemia alone but analysis of significance was not performed due to the very small number of study participants.[39] These findings suggest that GI infections and disorders such as celiac disease can cause pica at least in part by causing iron deficiency.[40]

Enteric infections, particularly with pathogenic *Escherichia coli* bacteria, were also reported in young children in Zimbabwe with geophagy (mean age 1.56 years ±0.8).[12,13] Moreover, a longitudinal study from Bangladesh of 10 to 18 year old children reported that the prevalence of geophagy was 77% in those noted to have poor growth and that geophagia was associated with intestinal parasitic infections.[41] Similarly, George and colleagues reported that infections associated with geophagy, as observed by caregivers in children under the age of 5 years in rural Bangladesh, resulted in impaired growth (OR: 2.27, 95% CI: 1.14, 4.41).[42] These studies provide evidence that pica, particularly geophagia, can be a source of GI bacterial infections, parasitic infections and GI disorders that may lead to further complications such as iron deficiency and other nutrient deficiencies that may exacerbate or prolong pica.

It is unclear whether GI disorders and infections lead to pica or are a consequence of this disorder. Therefore, it was reasonable in our study to explore these as not only predictors but also as outcomes of pica.

Lead poisoning and pica

Lead is a toxic heavy metal with no beneficial function in the human body. Excess lead can cause anemia, GI disturbances, behavior problems, growth and development problems and cognitive impairment in children.[43] Lead exposure in pregnant women may cause anemia, gestational hypertension, low infant birth weight, developmental delays and birth defects.[44] Although children may chew on or consume odd items such as toys, dirt from sandboxes, etc., the amounts consumed are generally not high enough to cause lead toxicity. However, with pica behavior, lead absorption may be high enough to cause toxicity, including anemia.[45] In this study, we explored an independent association between lead exposure and pica as well as one mediated by iron deficiency.

GI bleeding and pica

Blood loss results in loss of iron which can lead to iron deficiency and eventually to iron deficiency anemia. Patients with GI bleeding are at risk for pica because iron deficiency is associated with and is an apparent cause of pica.[1,8,18] Chronic GI bleeding due to malignancy and many other disorders can gradually lead to iron deficiency. A retrospective study consisting of 55 patients with iron deficiency associated with chronic gastrointestinal bleeding reported a pica prevalence of over 50%.[10] Although there was no control group, such a high prevalence of pica has not been described in normal

population samples. To our knowledge, no other published studies have examined this association with pica. Therefore, we explored the relationship of pica with gastrointestinal bleeding as well as non-GI bleeding.

Menstrual bleeding disorders and pica

Menstrual bleeding is an important cause of iron deficiency in women. In a four-year French study of 17 adolescents (16 females and 1 male) with iron deficiency anemia (mean serum ferritin 7.17 ng/mL, mean hemoglobin 8.7 g/dL), 13 subjects had raw rice pica, 11 had pagophagia, and 10 had both raw rice pica and pagophagia. Eight of the 16 girls reported excessive menstrual bleeding. Interestingly, pica symptoms disappeared with iron repletion therapy within a few weeks even in cases where iron deficiency persisted.[46] Therefore menstrual bleeding may be associated with pica in women most likely because it contributes to iron deficiency, as it is well known that chronic iron deficiency anemia is often a consequence, at least in part, of heavy or excessive menstrual bleeding in women of child bearing age. Studies show that women often do not seek treatment for excess menstrual bleeding, and this can result in severe iron deficiency anemia with fatigue and shortness of breath.[47,48] In this study we examined menstrual bleeding disorders as a possible association with pica as well as with iron deficiency.

Restless Leg Syndrome and pica

RLS is a disorder characterized by the urgency in moving legs during sleep.[49] The association of RLS with iron deficiency has been described in multiple studies,[49,50] particularly in women.[1] However, no studies have compared RLS with pica. Bryant found that in blood donors, pica and RLS often coexisted and were even associated with

shared risk factors such as iron deficiency, female gender and younger age, but the associations did not reach statistical significance. However, RLS as well as pica can occur in the absence of iron deficiency.[3] Because of these suggested relationships, we also examined RLS as possibly associated with pica in this study.

Intestinal obstruction and pica

Intestinal obstructions can result from ingesting substances that cannot be digested and absorbed by the intestinal tract. For example, this was the case in a 40 year old mentally retarded man who ingested clothing leading to intestinal obstruction and perforation.[51] In another study, intestinal obstruction was a complication of pica in 43 cases, where the ingested materials had to be surgically removed, usually from the ileum. The majority of these patients had geophagia but some also ingested other materials such as cloth, foil, plastic and starch.[52] Our study is the first, to our knowledge, to look for an association between pica and intestinal obstruction.

Dental complications of pica

Dental complications, including abrasions, cracked teeth and tooth decay, have been reported in cases of pica, particularly with pagophagia. The majority of these cases occurred during pregnancy.[53-55] There are currently no studies, to our knowledge, that have reported measures of dental complications as outcomes of pica. Our study examined dental complications as independent outcomes of pica.

Fluid and electrolyte imbalances and pica

Fluid and electrolyte imbalances are possible consequences in patients with eating disorders. The AHRQ report listed fluid and electrolyte imbalances as one of the top 10

consequences of eating disorders,[30] specifically in anorexia nervosa and bulimia nervosa.[56] Fluid, electrolyte and other abnormalities in anorexia nervosa may include hypokalemia, metabolic alkalosis, hyponatremia, hypoalbuminemia, hypoglycemia, liver and kidney disorders, and decreased hormone functions. These complications may be acute and life threatening. Whether fluid and electrolyte imbalances can be a consequence of pica is unknown.[57] Our study is the first, to the best of our knowledge, to explore this association.

Cardiac dysrhythmias and pica

Cardiac dysrhythmias may co-exist with eating disorders, and are sometimes due to electrolyte abnormalities such as hypokalemia. The AHRQ report suggested that cardiac dysrhythmias co-exist with eating disorders in hospitalized patients.[30] This association has never been thoroughly studied with reference to pica. However, a case report involving geophagia suggested that hyperkalemia due to increased ingestion of clay resulted in cardiac complications in a patient.[58] Thus, cardiac dysrhythmias were explored as an outcome of pica in our study.

PICA AND OTHER PSYCHOLOGICAL DISORDERS

The neural pathways and neurobiological mechanisms involved in pica have not been elucidated. Obsessive consumption of ice and other non-nutritive substances suggests involvement of addiction centers in the brain, perhaps affected by cerebral iron deficiency. Autism spectrum disorder has been linked to pica behavior in some studies.[59,60] The AHRQ data suggests that 31% of children hospitalized with pica in 2009 also had autism spectrum disorders. Moreover, in persons with a secondarily diagnosed

eating disorder, the top 10 principally diagnosed disorders included psychologic disorders such as mood disorder, anxiety disorder, OCD and schizophrenia.[30] It has been suggested that pica co-exists with OCD and depression and its symptoms are relieved by treatment of compulsive behaviors using selective serotonin reuptake inhibitors (SSRIs).[61,62] These studies indicate that psychological disorders may be predictive of pica behavior. Because the association of pica with psychological disorders needs to be further explored, we measured the predictability of these disorders for pica.

BEHAVIOR DISORDERS AND PICA

Eating disorders, especially pica, involve obsessive behaviors and may be related to other behavioral disorders such as excessive food intake, smoking and alcoholism. Consumption of non-nutritive substance such as ice has been reported in patients, females in particular, who are obese and are interested in weight reduction.[35] Obesity is a risk factor for eating disorders.[31] It is partly related to lifestyle and unhealthy eating behavior. Likewise, smoking and alcoholism are also unhealthy addictive behaviors. Due to the obsessive nature of pica behavior, we investigated obesity, as a proxy for obsessive consumption of food, as well as smoking and alcoholism as predictors of pica.

HOSPITALIZATIONS DUE TO PICA

Pica can lead to serious complications such as GI disorders and infections, as discussed earlier, which may require hospitalization. National statistics reported by the Healthcare Utilization Project (HCUP) suggest that hospitalizations due to eating disorders has declined in the last decade, except for pica which has increased by 93%. The data also suggested that 6% of patients hospitalized for eating disorders were

diagnosed with pica in 2008 and 2009. However, data on non-hospitalized patients with pica were not collected. [30,63] Figures 1.3 and 1.4 display the increasing trend in hospitalizations with a diagnosis of pica (ICD-9 code: 307.52) from 1993 to 2013 in all patients and children respectively. These hospitalizations suggest the serious nature of this disorder and require further investigation regarding the risk factors that contribute to pica behavior.

Figure 1.3: Total number of hospital discharges with diagnosis of pica in U.S. from 1993 to 2013 (AHRQ HCUPnet online portal)[14]

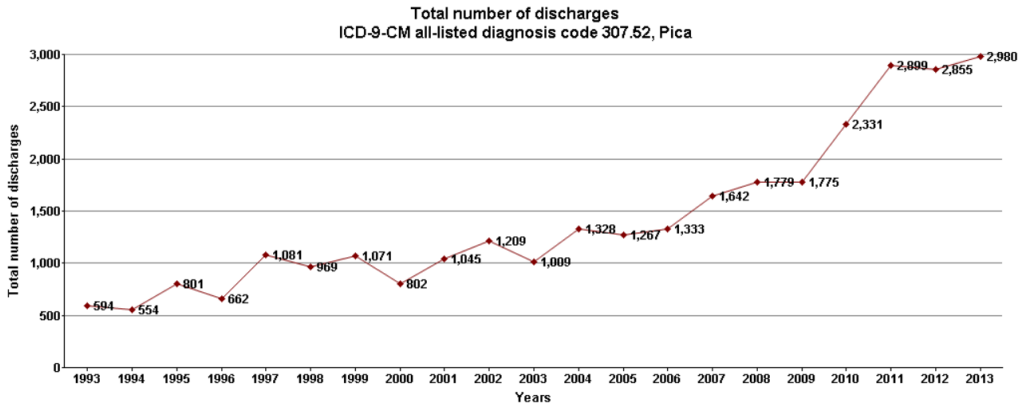
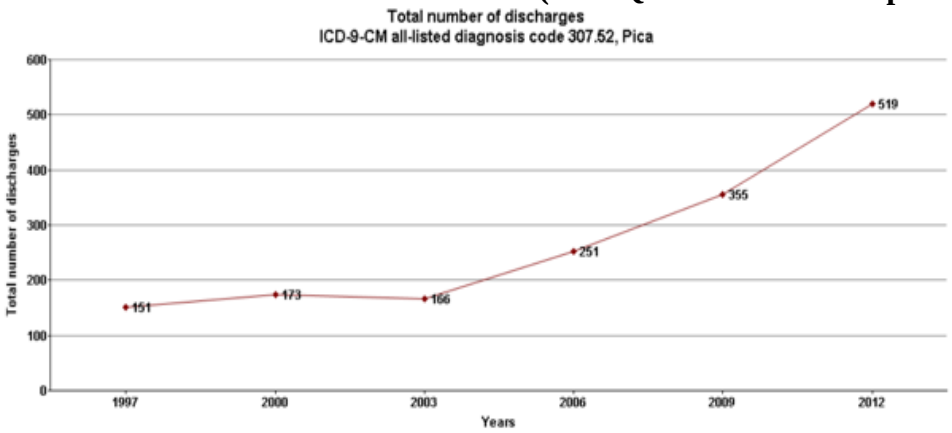


Figure 1.4: Total number of hospital discharges with a diagnosis of pica in children in the U.S. from 1997 to 2012 (AHRQ HCUPnet online portal)[14]



LABORATORY PREDICTORS OF PICA

There are no biomarkers currently available to predict or assess pica directly or indirectly. However, markers that predict the different stages of iron deficiency have been suggested for screening purposes, particularly for pagophagia.[64] Ferritin and serum iron are decreased beginning in the initial stages of iron deficiency and can prove to be a risk factor for pica. Depleted iron stores indicated by ferritin levels of <30 mcg/dL occur well before development of iron deficiency anemia, at which time hemoglobin levels decrease to less than 13 g/dL in males and less than 12 g/dL in menstruating females. Studies show that pica is significantly associated with low hemoglobin. Moreover, geophagic individuals are twice as likely to be anemic than those without geophagia.[18] Some studies suggest that an individual must be very anemic, with a hemoglobin of <6 g/dL, before the manifestation of symptoms of pica occur.[20,65] However, Barton's study suggested that patients with pica had an average hemoglobin of 108 ±16 g/L and that reoccurrence of pica occurred in persons with an average hemoglobin of 122 ±18 g/L suggesting that pica can occur in iron deficient individuals with or without anemia.[8]

These studies suggest that decreased hemoglobin may serve as a predictor of pica in anemia, since it is often due to iron deficiency. However, it is also important to measure earlier markers of iron deficiency and thereby establish the cause of anemia in anemic patients with pica. Other laboratory tests used to evaluate iron deficiency and its associated anemia include serum iron, transferrin saturation (% sat), total iron binding capacity (TIBC), red cell count (RBC), red cell distribution width (RDW), and mean corpuscular volume (MCV).[1,66] Although the serum ferritin concentration is considered the most definitive indicator, it is not always obtained, so our study explored the

association of these additional biomarkers of iron deficiency with pica and their predictability for this disorder.

CLOSING REMARKS

Pica is a complex and intriguing but poorly understood disorder. The studies reviewed above provide strong evidence that pica is associated with iron deficiency. However, most of this work involved select groups such as pregnant women or blood donors and it is unclear whether are generalizable to the larger U.S. population. Moreover, some studies report associations of pica with other disorders such as ASD and malnutrition, and with eating disorders with pica and it is unclear whether these are predictors or outcomes of pica and whether their association to pica is due to iron deficiency.

Compulsive consumption of clay, lead paint, dirt and other non-nutritive substances in pica is a significant public health concern and can result in malnutrition, GI disorders and infections, parasitic infections hospitalizations and other health concerns. Even a seemingly harmless substance like ice can have adverse side effects, including damage to teeth and gums. Whether the different types of pica share predictors and outcomes is unknown.

Pica is the only eating disorder that is increasing, as suggested by increased hospitalizations.[30] It is important to study this disorder so that high risk groups can be identified, treated and monitored, if necessary. Currently, there are no identified biomarkers or tools that can be utilized for diagnosis of pica. Moreover, outcomes of pica such as GI disorders and hospitalizations are both of concern from a clinical and public health standpoint.

PURPOSE AND SIGNIFICANCE

Studies have suggested that hospitalizations due to eating disorders have decreased from 2007 to 2009; whereas, admissions for pica have increased during this same time period.[30] Studies also suggest that iron deficiency is associated with pica. However, the majority of these studies were conducted in pregnant women and children, reporting a prevalence of pica ranging from 11% to 76.5%.[1,2, 9,15,30] Moreover, the definition of pica was not consistent across studies and only inpatient data was used in most of the studies. There have been no population based studies that explored predictors and outcomes of pica. Our study examined a wide range of predictors of pica in the general population using both inpatient and outpatient claims data, including but not limited to iron deficiency. Moreover, clinical outcomes of pica, including hospitalizations were studied.

SPECIFIC AIMS

Based on the findings of previous studies and the identified needs for further exploration, the following specific aims and Hypothesis were be examined in this study:

Specific Aim 1

Assess predictors associated with pica including iron deficiency, laboratory markers and health behaviors/conditions.

Hypothesis 1: Patients with pica are more likely to be iron deficient than those without pica.

Hypothesis 2: Children with pica are more likely to have gastrointestinal disorders and infections than those without pica.

Hypothesis 3: The association of menstrual bleeding disorders with pica in females is mediated by iron deficiency.

Specific Aim 2

Evaluate the clinical outcomes of pica.

Hypothesis 4: Patients with pica are more likely to be hospitalized than those without pica.

Hypothesis 5: Patients with pica are more likely to have intestinal obstructions than those without pica.

This study examined the associations between pica and other disorders and explore whether these disorders are predictors, outcomes, or both of pica that have not been extensively studied. Moreover, it is expected that our study will help to explain the role of iron deficiency as a mediator of pica. From a public health perspective, this project will measure the impact of pica on the health of the population, identify high risk groups that may warrant screening efforts and will further educate the healthcare community about adverse consequences of this debilitating disorder.

Chapter 2: Methods

APPROACH

The purpose of this study was to examine the association of pica with a number of predictors and outcomes. A conceptual model was created to visually illustrate the design and analysis for this study as displayed in Figure 2.1. We conducted a case-control study using commercial insurance claims data from Clinformatics Data Mart (CDM). A major variable of interest was the presence or absence of pica. To accomplish aim 1, we studied the association of predictors including medical conditions, psychiatric disorders, health behaviors and laboratory results with pica. Disorders that were to be studied as both predictors and outcomes of pica— including eating disorders, malnutrition, GI disorders and infections, lead poisoning and parasitic infections— were grouped together and labeled Medical Conditions I. However, those that were to be examined only as predictors of pica, including menstrual bleeding disorders, restless leg syndrome (RLS), GI bleeding and non-GI bleeding, were grouped together and labeled Medical Conditions II. The association of Medical Conditions I and II, as mediated by iron deficiency, with pica was also explored. Finally, hospitalizations as well as health outcomes including dental complications, intestinal obstruction, fluid and electrolyte abnormalities and cardiac dysrhythmias were evaluated as outcomes of pica.

DATA SOURCE

This study was reviewed and granted exemption status by the Institutional Review Board (IRB) at the University of Texas Medical Branch at Galveston (IRB#: 16-0057). We utilized Clinformatics Data Mart (CDM; OptumInsight), a claims database of one of the

nation's largest commercial health insurance programs. This database is de-identified and is a longitudinal source containing over 14 years of data from over 56 million unique members with 12.4 to 14 million unique members each year.[67] It includes medical claims (hospital and ambulatory care), pharmacy claims, laboratory results and member enrollment data. CDM data has been the primary data source for numerous NIH-funded studies and over 75 peer-reviewed journal articles.[68,69] Table 2.1 provides a brief description of the CDM files that were utilized for data extraction in this study. Data were retrieved for pica and all predictor and outcome variables to be analyzed in this study. A list of these variables is provided in Table 2.2 with the corresponding ICD9 and CPT4 codes shown in Appendix A.

Figure 2.1: Conceptual model for the study

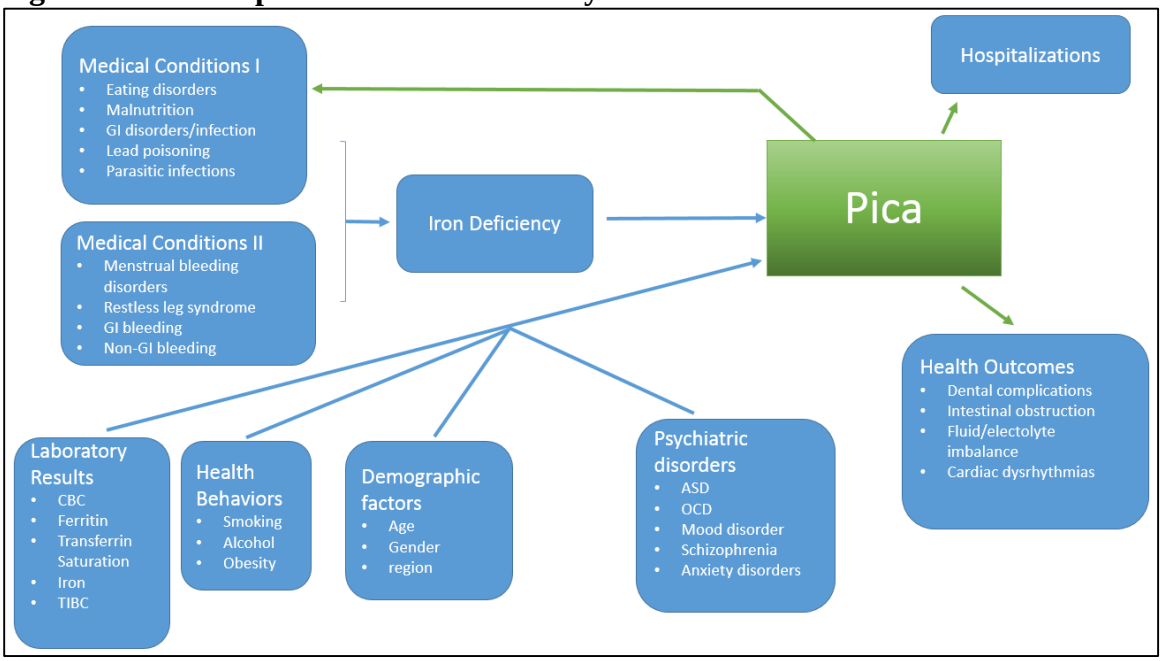


Table 2.1: Summary of data elements and files utilized from the Clinformatics Data Mart

File	Description of data
Member	Member identifier, month and year of birth, enrollment start date, enrollment end date, state of residence, insurance plan type, Gender
Medical claims	Member identifier, hospital admission date, hospital discharge date, physician identifier, facility identifier, dates and place of service, diagnostic codes (ICD-9-CM code, DRG code), procedure codes (CPT-4, HCPCS, ICD-9-CM code, revenue codes)
Inpatient Confinement	Admit and discharge dates and diagnoses, Length of stay, diagnosis and procedures (ICD9-CM, DRG), standard pricing
Laboratory	Member identifier, test description, test code, test name, test date, laboratory test value, test unit of measure, Logical Observation Identifiers Names and Codes (LOINC).

Table 2.2: Definition and data source for each predictor and outcome variable included in the study

Variable Name	Data Source	Definition	Title	Use of variable
Pica	Medical	Eating disorder		Outcome aim 1, Predictor aim 2
Age	Member	Between 2-64 years	Demographic factors	Matching
Region	Member	Midwest, Northeast, South, West	Demographic factors	Matching
Gender	Member	Male vs. female	Demographic factors	Matching
Year of diagnosis	Member	2009-2013	Demographic factors	Matching
Pregnancy	Medical	Live birth, spontaneous abortion, therapeutic abortion, ectopic pregnancy, trophoblastic disease, still birth, other outcomes (using pregnancy algorithm)[70]	Demographic factors	Descriptive analysis
Iron deficiency	Medical	Iron deficiency, iron deficiency anemia		Predictor aim 1, Mediator aim 1
Other eating disorders	Medical	Anorexia nervosa, Unspecified eating disorder, Bulimia	Medical Conditions I	Predictor aim 1 Outcome aim 2

		nervosa, Rumination disorder, Psychogenic vomiting, Other disorders of eating, feeding problems, polyphagia		
Menstrual bleeding disorders	Medical	Excessive menstruation, ovulation bleeding, menorrhagia, disorders of menstruation, premenopausal menorrhagia	Medical Conditions II	Predictor aim 1
RLS	Medical	Restless leg syndrome	Medical Conditions II	Predictor aim 1
GI bleeding	Medical	Gastrointestinal bleeding	Medical Conditions II	Predictor aim 1
Non-GI bleeding	Medical	Non-gastrointestinal bleeding	Medical Conditions II	Predictor aim 1
Malnutrition	Medical		Medical Conditions I	Predictor aim 1 Outcome aim 2
GI disorders and infections	Medical	Gastrointestinal functions disorders (anal fissures, hemorrhoids, impaction of intestine, specified intestinal obstruction, unspecified intestinal obstruction, mega colon, other specified and unspecified functional disorders of intestine, perforation, Crohn's disease, ulcers of rectum, anus and intestine, ulcerative colitis and volvulus, intestinal infectious diseases	Medical Conditions I	Predictor aim 1 Outcome aim 2
Lead poisoning	Medical	Lead toxicity	Medical Conditions I	Predictor aim 1 Outcome aim 2
Parasitic Infections	Medical		Medical Conditions I	Predictor aim 1 Outcome aim 2

Smoking	Medical		Health Behaviors	Predictor aim 1
Alcoholism	Medical		Health Behaviors	Predictor aim 1
Obesity	Medical	Unspecified obesity, morbid obesity, overweight	Health Behaviors	Predictor aim 1
Autism Spectrum Disorders	Medical		Psychiatric disorders	Predictor aim 1
Obsessive Compulsive Disorder	Medical		Psychiatric disorders	Predictor aim1
Mood disorder	Medical	Includes depression and bipolar disorder	Psychiatric disorders	Predictor aim 1
Schizophrenia	Medical		Psychiatric disorders	Predictor aim 1
Anxiety disorders	Medical		Psychiatric disorders	Predictor aim 1
Dental complications	Medical	Broken & cracked teeth	Health Outcomes	Outcome aim 2
Intestinal obstruction	Medical		Health Outcomes	Outcome aim 2
Fluid and electrolyte imbalance	Medical		Health Outcomes	Outcome aim 2
Cardiac dysrhythmias	Medical		Health Outcomes	Outcome aim 2
Complete blood count (hemogram) and platelets without differential	Laboratory	RBC, WBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, Platelets, MPV	Laboratory results	Predictor aim 1
Iron and Iron binding capacity panel	Laboratory	Serum/plasma iron, TIBC, % saturation	Laboratory results	Predictor aim 1
Ferritin	Laboratory		Laboratory results	Predictor aim 1
Hospitalizations	Confinement	All causes hospitalizations		Outcome aim 2
Otitis Media	Medical	Ear infection		Control Outcome
Orbital Cellulitis	Medical	Acute infection behind the orbital septum		Control Outcome

AMI	Medical	Acute Myocardial Infarction, Heart Attack		Control Outcome
Fractures	Medical			Control Outcome

Abbreviations: GI: Gastrointestinal, RLS: restless Leg Syndrome, RBC: red blood cell count, WBC: white blood cell count, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean cell hemoglobin concentration, RDW: red cell distribution width, MPV: mean platelet volume, TIBC: total iron binding capacity

STUDY DESIGN

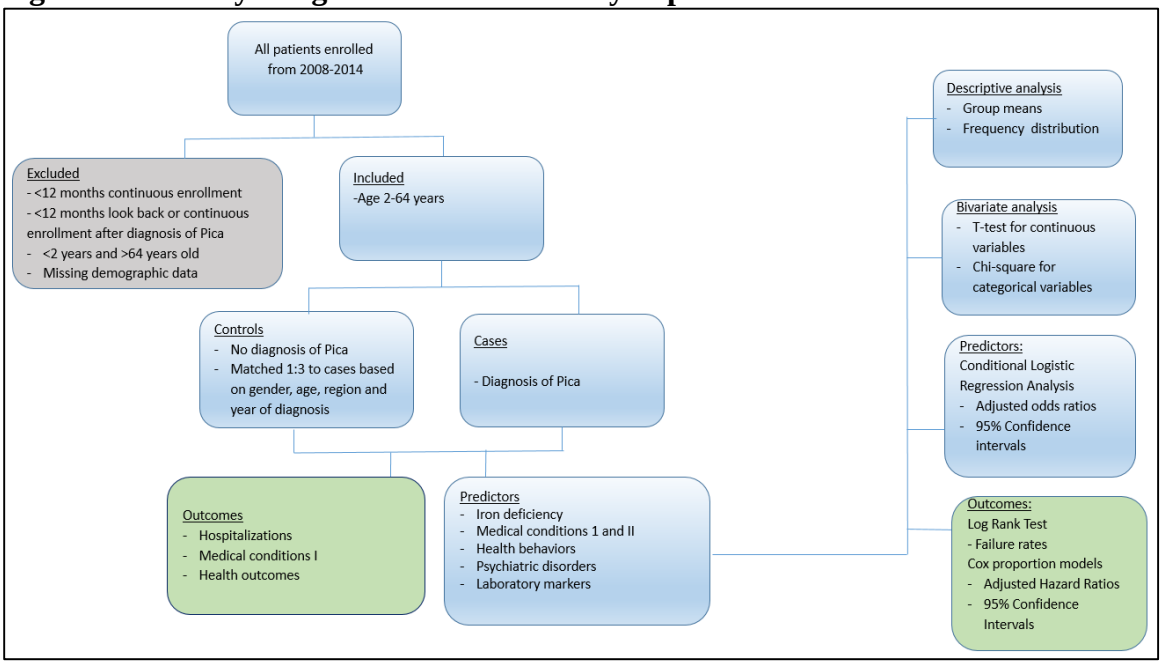
Cases and controls

We conducted a case-control study for aim 1 and the same cases and controls were followed using a cohort study design to assess outcomes for aim 2. This study utilized seven years (2008-2014) of insurance claims data from CDM, as displayed in Figure 2.2. Enrollees from 2 to 64 years of age, both inpatients and outpatients, with any diagnosis of pica were selected as cases. Cases without 12 months of continuous enrollment ove+r the look-back period prior to the first diagnosis of pica (index date) or after diagnosis of pica were excluded from this study. Controls were defined as those who did not have pica diagnoses during the study period (2008-2014). Controls were randomly assigned an index date corresponding to the distribution of diagnosis month and year of pica cases. Those without 12 months of continuous enrollment over the look-back period from or after the index date were excluded from this study. For each case, three controls were randomly selected by matching of age, gender, region, and year and month of diagnosis.

A second case-control cohort was designed to include cases who had at least one laboratory value including serum iron, ferritin, total iron binding capacity (TIBC), percent transferrin saturation (% sat), white blood cell count (WBC), red blood cell count (RBC),

hemoglobin, hematocrit, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count or mean platelet volume (MPV) in the 12 months look-back period or 6 weeks after diagnosis of pica. A second set of controls were also obtained based on presence of one of the above listed lab results in the 12 month look-back period or within 6 weeks after index date. Controls with less than one year continuous enrollment were excluded from the study. Moreover, lab results without a recorded unit of measure outliers that were deemed laboratory reporting error based on clinical determination of plausibility were excluded from this study. Controls were matched 1:3 to cases with at least one lab result based on age, gender, region and month and year of diagnosis.

Figure 2.2: Study design and statistical analysis plan for Aims 1 and 2



Pregnancy

Pregnancy was included as a demographic variable of interest in this study. It was identified in women based on an algorithm designed and modified by Nelway et al.

This algorithm utilizes medical and administrative records to comprehensive pregnancy related diagnostic and procedure codes, including ICD-9 diagnosis codes, procedures, HCPCS codes and DRG codes, to identify pregnancies. This algorithm was used to identify normal pregnancies as well as abnormal pregnancies that may have resulted in early termination. This method was utilized to assign pregnancy start date.[70]

Aim 1: Predictors of pica

Exposure variables for aim 1 included iron deficiency, eating disorders, malnutrition, gastrointestinal (GI) disorders and infections, lead poisoning, parasitic infections, menstrual bleeding disorders (female), restless leg syndrome, GI bleeding disorders, non-GI bleeding disorders, psychiatric disorders (ASD, mood disorders, anxiety disorders, schizophrenia and OCD), and behavior disorders (smoking, alcoholism and obesity) as listed in Table 2.2. These variables were included in the study based on ICD-9-CM codes listed in Appendix A. All exposure variables were extracted from CDM during the12 month look-back period from the diagnosed date for cases or index date for controls using diagnosed codes listed at any positions in both inpatient and outpatient claims. Moreover, laboratory variables including, serum iron, ferritin, TIBC, % sat, WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelet count and MPV results were included in the study based on CPT and LOINC codes, as listed in Appendix A.

Aim 2: Outcomes of pica

The cases and controls utilized in Aim 1 were followed for 12 months to assess incidence of the following outcomes: Medical Conditions I (eating disorders,

malnutrition, GI disorders and infections, lead poisoning and parasitic infections), dental complications, intestinal obstructions, fluid and electrolyte imbalance and cardiac dysrhythmias, as listed in Table 2.2. These variables were included in this study based on ICD-9-CM codes listed in Appendix A. Any cases and controls that had any of the disorders from Medical Conditions I in the 12 month look-back period were removed from aim 2 analysis for only that specific medical condition. All outcome variables were extracted from the CDM database during 12 month follow up from the date of diagnosis of pica for cases and the index date for controls in both inpatient and outpatient claims. Moreover, all cause hospitalizations was an additional outcome variable that was measured. The top 10 primary diagnoses for the hospitalizations between pica cases and controls were compared. Cases and controls that did not have the studied outcomes were censored at 12 month of follow-up.

STATISTICAL ANALYSIS

Descriptive analysis was conducted for demographic variables, predictors of pica (Aim 1) and outcomes of pica (Aim 2) and means, standard deviation, and frequency distributions were reported. The differences between cases and controls were compared by t-test for continuous variables and chi-square test for categorical variables. For Aim 1, multivariable conditional logistic regression analysis was conducted to report adjusted odds ratios (aORs) with 95% confidence intervals (CI) for the association between pica and predictors. Moreover, association of different predictors of pica as mediated by iron deficiency was also evaluated by comparing conditional logistic regression models with and without iron deficiency. A mediator is a variable that transmits some or all of the effect of a predictor or independent variable to a dependent or outcome variable.

Mediation analysis is performed to measure the effect of predictor variable on outcome variable that is due to an intermediate variable called the mediator.[71] In other words, it measures the change in effect of a predictor on an outcome in the presence of the mediator. If iron deficiency was a mediator of a predictor disorder, addition of iron deficiency as a variable resulted in decreasing the odds ratio for the variable. For Aim 2, log rank test was used for comparing the occurrence of each of the outcome variables between patients with and without diagnosis of pica. Failure rate is the rate of occurrence of an outcome estimated by Kaplan Meier method. Failure curves, plotting days since diagnosis of pica or index date (for controls) vs. rate of outcome condition, were constructed for each of the outcome variables. Cox proportional hazard models were used to examine whether risk of outcomes was different between patients with and without a pica diagnosis, adjusted for demographic variables and significant predictors of pica identified in Aim 1 analysis. Proportional hazard assumption was examined using graphical check and simulated cumulative martingale residual curves (available in SAS). Any violation of the assumption was addressed by generating time-dependent Cox models that allow for the effect of the covariate varied by follow-up time. All analysis was conducted using SAS Software (version 9.4; SAS Institute, Cary, NC).

Exploratory analysis

Hospitalization was an outcome that was studied for Aim 2. However, hospitalizations due to disorders other than pica were not accounted for in our analysis. Therefore, we created Cox proportional hazard models to evaluate whether these hospitalizations were due to pica resulting from other disorders such as eating disorders and GI disorders and infections. Pica was added to these models to examine its mediation

effect on hospitalizations. Moreover, we also examined the impact of selection bias for identification of patients diagnosed with pica in our data. Patients with pica may utilize more healthcare services than controls leading to increased diagnosis of outcomes. In order to perform this analysis, Cox proportional hazard models were created for control outcomes, including otitis media and peri-orbital and orbital cellulitis for children, as well as fractures and ischemic heart disease for adults. These are outcomes that are not related to pica. Adjusted hazard ratios with 95% confidence interval were reported for each of the control outcomes.

Power analysis

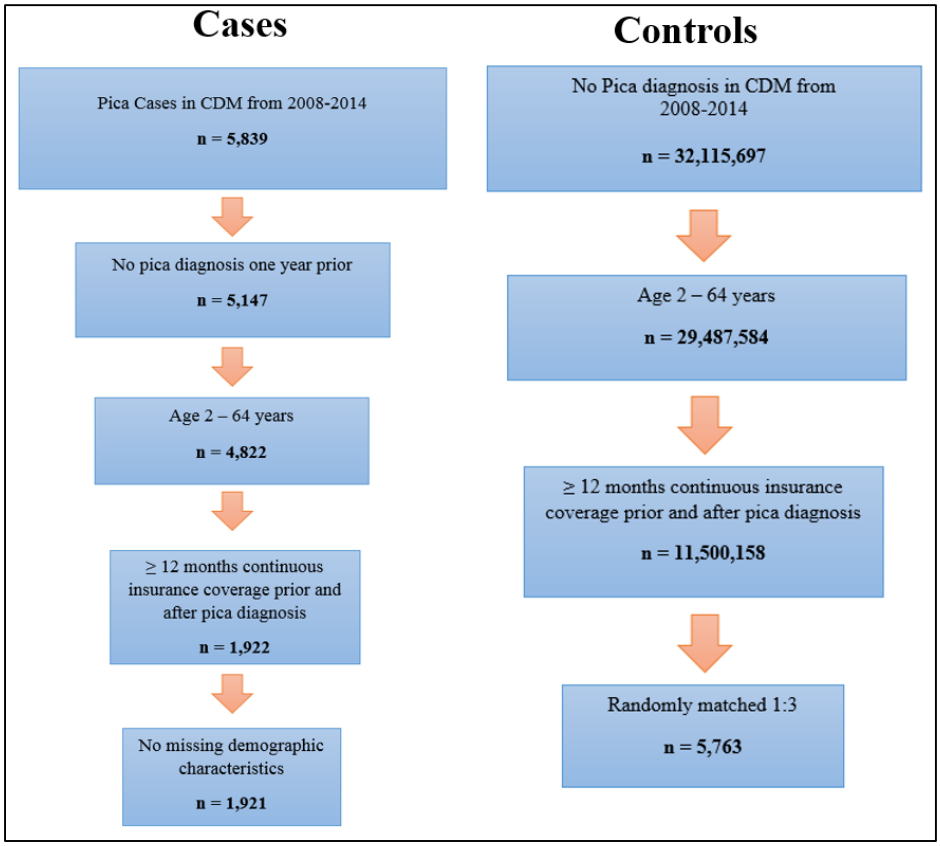
A preliminary query of 2012 Clinformatics data was run with a conservative estimate of 60% patients being continuously enrolled in the 12 month look-back period to study the association between iron deficiency and pica. This resulted in an estimate of 1,058 patients with a primary diagnosis of pica in 4 years. With the 1:3 match, these analyses reached power of 87% to detect the difference of iron deficiency as 4% in the control group and 6.5% in the pica group, based on chi-square test at a 0.05 two sided significant level. We expect only 30% of patients to have lab results available. This sample size reached a power of 85% to detect the odds ratio of 1.55 for each unit lower of ferritin associated with pica, based on a logistic regression model at a 0.05 two sided significant level. For Aim 2, a conservative estimate of 60% patients being continuously enrolled in a 12 month look-back period resulted in 793 patients with a primary diagnosis of pica in 3 years. This sample size reached a power of 93% to detect a hazard ratio of 1.20 for the risk of hospitalization associate with pica, based on a log rank test at a 0.05

two sided significant level and assuming the rate of hospitalization being 5%. Above calculation was made using the power software n-Query 7.0.

Chapter 3: Aim 1 Results

There were about 32 million enrollees in Clinformatics Data Mart from 2008 to 2104. Of these 1,921 were diagnosed with pica and met the inclusion and exclusion criteria of this study (Figure 3.1). Among members without a diagnosis of pica who met the inclusion criteria, 5,763 were selected as controls by matching 1:3 to cases for age, gender, region and month and year of diagnosis.

Figure 3.1: Summary of exclusions in the selection of study cohorts of pica cases and controls



A summary of the case and control cohort demographic variables is listed in Table 3.1. A total of 1,921 cases and 5,673 controls were included in the study for a complete cohort of 7,684. The distribution of age, gender, region and year of diagnosis

was identical in both cases and controls due to matching. The majority of cases were children under the age of 18 years with 33.73% between the age of 2 and 5 years, as displayed in Figure 3.2. 30% of cases and controls were male and 70% were female. As far as regional distribution was concerned, the majority (53.05%) of cases and controls were from the Southern United States followed by the Midwest (27.95%), West (12.34%) and Northeast (6.66%).

The distribution of cases and controls based on pregnancy in females between 13 and 49 years of age are displayed in Table 3.2. The majority of women in our study were not pregnant. Overall, 13.3% of cases and 7.8% of controls were pregnant females between 13 to 49 years of age and the difference in the two groups was significant ($p<0.0001$). Among females aged 18 to 29 years of age, around 17% of cases and 3% of controls were pregnant which was a significant difference ($p<0.0001$). Among females 30 to 39 years of age around 25% of cases and 19% of controls were pregnant which was not significant ($p=0.0824$). In addition, among females 40 to 49 years of age around 2% of cases and 3% of controls were pregnant which was not significant ($p=0.5865$). Overall, the difference in rate of pregnancy was larger in the 18 to 29 year age group.

The majority of pica cases were children under the age of 18 years. As discussed in chapter 1, certain medical conditions often associated with pica, such as eating disorders and lead poisoning, which are more prevalent in children, may also be stronger predictors of pica in children than in adults. Therefore, these conditions were examined separately in children and adults as predictors of pica. Also geophagy was more common in children than pagophagy, which was more common in adults, and these might have somewhat different health consequences.[1,8,9,11,12]

Table 3.1: Demographic characteristics of cases and controls included in the study

Variables	*Total n (%) n= 7,684*	*Matched Controls n (%) n=5,763*	*Cases n (%) n= 1,921*
All	7,684 (100)	5,763 (100)	1,921 (100)
Age, mean	21.96 years (SD=19.77)		
Age group (years) at diagnosis			
<18	4,204 (54.71)	3,153 (54.71)	1,051 (54.71)
2 to 5	2,592 (61.66)	1,944 (33.73)	648 (33.73)
6 to 9	888 (21.12)	666 (11.56)	222 (11.56)
10 to 14	472 (11.23)	354 (6.14)	118 (6.14)
15 to 17	252 (5.99)	189 (3.28)	63 (3.28)
18-29	572 (7.44)	429 (7.44)	143 (7.44)
30-39	824 (10.72)	618 (10.72)	206 (10.72)
40-49	1,208 (15.72)	906 (15.72)	302 (15.72)
50-64	876 (11.40)	657 (11.40)	219 (11.40)
Gender			
Male	2,332 (30.35)	1,749 (30.35)	583 (30.35)
Female	5,352 (69.65)	4,014 (69.65)	1,338(69.65)
Region of U.S.			
Midwest	2148 (27.95)	1611 (27.95)	537 (27.95)
Northeast	512 (6.66)	384 (6.66)	128 (6.66)
South	4,076 (53.05)	3,057 (53.05)	1,019 (53.05)
West	948 (12.34)	711 (12.34)	237 (12.34)
Year of diagnosis			
2009	1,252 (16.29)	939 (16.29)	313 (16.29)
2010	1,488 (19.36)	1,116 (19.36)	372 (19.36)
2011	1,676 (21.81)	1,257 (21.81)	419 (21.81)
2012	1,788 (23.27)	1,341 (23.27)	447 (23.27)
2013	1,480 (19.26)	1,110 (19.26)	370 (19.26)

Figure 3.2: Distribution of pica cases expressed as percent of total cases by age

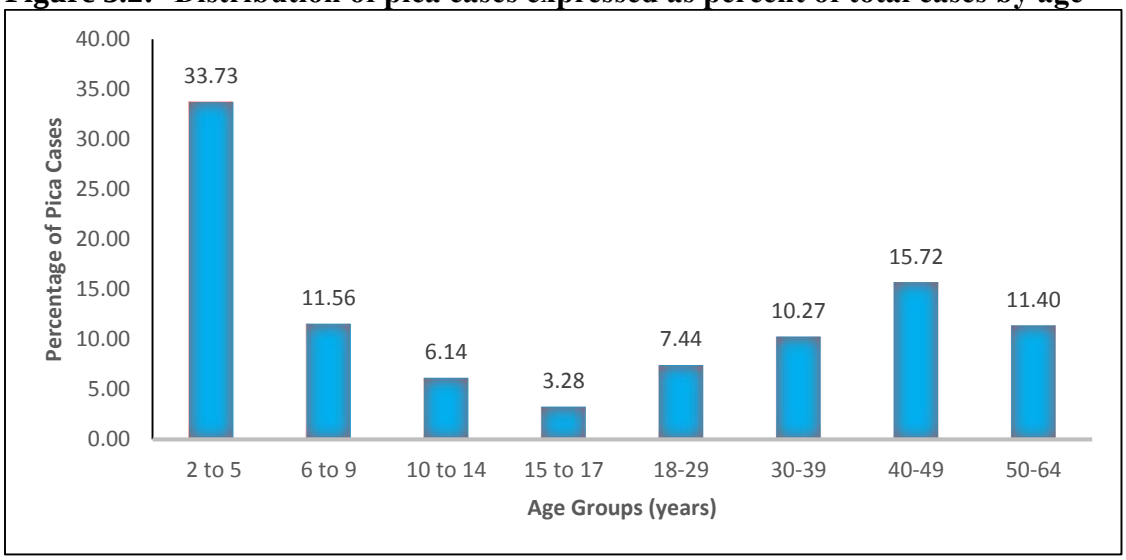


Table 3.2: The number (percentage) of female cases and controls between 13 and 64 years of age that were pregnant

Variables	***Total n (%)***	***Matched Controls n (%)***	***Cases n (%)***	***p-value***
Pregnant (13 -49 yrs. old)	237 (9.17)	151 (7.79)	86 (13.31)	<0.0001
18-29 yrs. old	50 (6.61)	18 (3.17)	32 (16.93)	<0.0001
30-39 yrs. old	133 (20.15)	92 (18.59)	41 (24.85)	0.0824
40 - 49 yrs. old	29 (2.85)	23 (3.02)	6 (2.36)	0.5865

Abbreviations: yrs., years

PREDICTORS OF PICA IN CHILDREN

The study cohort included 4,204 children under the age of 18 years, including 1,051 cases and 3,153 controls. The data was stratified into four age groups and the number and percentage of cases and controls for medical exposures are displayed in Table 3.3. These exposures include iron deficiency, Medical Conditions 1 (eating disorders, malnutrition, GI disorders and infections, lead poisoning, parasitic infections) and medical conditions II (menstrual bleeding - female, restless legs Syndrome (RLS), gastrointestinal bleeding disorders, and non-GI bleeding disorders).

Cases had a higher percentage of children with all of these disorders with the exception of menstrual bleeding which was only studied in female children between 10 and 17 years of age. The distribution of iron deficiency was 3.14% in cases and 0.54% in controls ($p<0.0001$) among all childhood age groups. Similar distribution was seen for GI disorders and infections with 20.93% in cases and 8.66% in controls ($p<0.0001$). However, prevalence of eating disorders was 5.14% among cases and 0.79% among controls ($p<0.0001$) but the difference was only statistically significant in children 2 to 14 years of age. Moreover, prevalence of malnutrition was 1.24% in cases and 0.35% in controls ($P=0.0009$) but was only statistically significant in children ages 6 to 9 years of age. There were very few cases ($n<10$) of lead poisoning and RLS in children, but for RLS we found a significantly higher prevalence in cases than in controls. Parasitic infections were more prevalent in cases (1.52%) compared to controls (0.54%) and the difference was statistically significant ($p=0.0018$) mostly due to the increased prevalence in those that were 2 to 5 years old ($p=0.0011$). GI bleeding was 1.14% in cases and 0.35% in controls ($p=0.0025$) while non-GI bleeding was 3.52% in cases and 1.59% in

controls (p=0.0001) and both were highly significantly different in 2 to 5 year olds. For menstrual bleeding in female children, the distribution was very similar in cases and controls (p=0.8993).

Table 3.3: Distribution of studied medical conditions in children 2 – 17 years of age, stratified by pica cases and controls

Variables	***Matched Controls n(%) n=3,153***	***Cases n(%) n= 1,051***	***p- value***
Iron Deficiency	17 (0.54)	33 (3.14)	<0.0001
2 to 5 yrs.	15 (0.77)	19 (2.93)	<0.0001
6 to 9 yrs.	0 (0)	4 (1.8)	0.0038*
10 to 14 yrs.	0 (0)	4 (3.39)	0.0038*
15 to 17 yrs.	2 (1.06)	6 (9.52)	0.0033*
Medical Conditions I			
Eating disorders	25 (0.79)	54 (5.14)	<0.0001
2 to 5 yrs.	24 (1.23)	36 (5.56)	<0.0001
6 to 9 yrs.	1 (0.15)	11 (4.95)	<0.0001*
10 to 14 yrs.	0 (0)	5 (4.24)	0.0009*
15 to 17 yrs.	0(0)	2 (3.17)	0.0618*
Malnutrition	11 (0.35)	13 (1.24)	0.0009
2 to 5 yrs.	6 (0.31)	5 (0.77)	0.0801*
6 to 9 yrs.	0 (0)	4 (1.8)	0.0038*
10 to 14 yrs.	5 (1.41)	2 (1.69)	0.3139*
15 to 17 yrs.	0 (0)	2 (3.17)	0.0618*
GI disorders and infections	273 (8.66)	220 (20.93)	<0.0001
2 to 5 yrs.	212 (10.91)	145 (22.38)	<0.0001
6 to 9 yrs.	44 (6.61)	50 (22.52)	<0.0001
10 to 14 yrs.	12 (3.39)	11 (9.32)	0.0095
15 to 17 yrs.	5 (2.65)	14 (22.22)	<0.0001*
Lead Poisoning	2 (0.06)	3 (0.29)	0.1034*
2 to 5 yrs.	2(0.1)	2 (0.31)	0.2110*
6 to 9 yrs.	0 (0)	1 (0.45)	0.250*
10 to 14 yrs.	0 (0)	0 (0)	
15 to 17 yrs.	0 (0)	0 (0)	
Parasitic infections	17 (0.54)	16 (1.52)	0.0018
2 to 5 yrs.	12 (0.62)	11 (1.7)	0.0111
6 to 9 yrs.	2 (0.3)	2 (0.9)	0.2111*
10 to 14 yrs.	3 (0.85)	1 (0.85)	0.4237*
15 to 17 yrs.	0 (0)	2 (3.17)	0.0618*

Medical Conditions II			
Menstrual bleeding (female)	16 (0.96)	5 (0.9)	0.8993
RLS	0 (0)	3 (0.29)	0.0156*
GI bleeding disorders	11 (0.35)	12 (1.14)	0.0025
2 to 5 yrs.	6 (0.31)	8 (1.23)	0.008*
6 to 9 yrs.	2 (0.3)	1 (0.45)	0.4227*
10 to 14 yrs.	0	1 (0.85)	0.250*
15 to 17 yrs.	3 (1.59)	2 (3.17)	0.2658*
Non-GI bleeding dis.	50 (1.59)	37 (3.52)	0.0001
2 to 5 yrs.	26 (1.34)	25 (3.86)	<0.0001
6 to 9 yrs.	14 (2.10)	5 (2.25)	0.2046*
10 to 14 yrs.	6 (1.69)	6 (5.08)	0.0389*
15 to 17 yrs.	4 (2.12)	1 (1.59)	0.3987*

*p-value is based on Fisher's Exact Test instead of Chi-Square.
Abbreviations: GI, gastrointestinal; RLS, Restless Leg Syndrome

The distribution of health behavior variables to include smoking, alcoholism and obesity among cases and controls in children under the age of 18 years, as displayed in Table 3.4, suggest that there were very few cases of smoking and alcoholism among children which made it difficult to analyze these variables. However, cases had a higher percentage (2.09%) of obesity in children than controls (0.82%) which was statistically significant (p=0.0008) only in children ages 10 to 17 years old.

Table 3.4: Distribution of health behaviors in children 2 – 17 years of age, stratified by pica cases and controls

Health Behavior Variables	Matched Controls n(%) n=3,153	Cases n(%) n= 1,051	p- value
Smoking	2 (0.06)	1 (0.1)	0.422*
Alcoholism	1 (0.03)	0 (0)	0.750*
Obesity	26 (0.82)	22 (2.09)	0.0008
Obesity by age			
2 to 5 yrs.	8 (0.41)	3 (0.46)	0.2587*
6 to 9 yrs.	9 (1.35)	7 (3.15)	0.0517*
10 to 14 yrs.	8 (2.26)	8 (6.78)	0.0184*
15 to 17 yrs.	1 (0.53)	4 (6.35)	0.0138*

*p-value is based on Fisher's Exact Test instead of Chi-Square

Interestingly, the distribution of psychiatric disorder variables among cases and controls in children under the age of 18 years, as displayed in Table 3.5, suggest that cases had a significantly higher percentage of all the psychiatric disorders than controls. The distribution of autism spectrum disorders (ASD) was 8.85% in cases and 0.79% in controls (P<0.0001) and was statistically significant in all childhood age groups. There were very few cases of OCD among children, and the, distribution was 1.52% among cases and 0.13% among controls, with a statistical significance observed only for the entire group and for those 6 to 14 years old (p<0.0001). Prevalence of mood disorders was 5.71% in cases and 1.93% in controls. Schizophrenia was more prevalent in cases (1.52%) compared to controls (0.19%) and this difference was statistically significant (P<0.0001). Anxiety disorders were more prevalent in cases (4.47%) than in controls

(1.36%) which was a statistically significant difference (<0.0001) seen especially in 10 to 14 year old children with pica.

Four predictive models were created to test Hypothesis 1 through 3 for prediction of pica. Conditional logistic regression was used to estimate the association of pica in children with several exposure variables, expressed as odds ratios (OR) with 95% confidence intervals (CI) in Table 3.6. Only variables that were clinically indicated in children and/or had a p-value of less than 0.20 in descriptive analysis were included in these models. The first model showed that pica cases were 6 times more likely to be iron deficient (OR: 6.08, 95% CI: 3.34-11.06) than controls, as stated in Hypothesis 1. Model 2 included exposure variables from Medical Conditions I and indicated that pica cases were 6 times more likely to have another eating disorder (OR: 6.40, 95%CI: 3.88-10.52) and were about 3 times more likely to have GI disorders and infections (OR: 2.77, 95% CI: 2.27-3.40) compared to controls, as stated in Hypothesis 2. Model 3 was used to study mediation of exposure variables included in Medical Conditions I by iron deficiency for outcome of pica. The difference in odds ratios of exposure variables between Models 2 and 3, as displayed in Tables 3.6 and 3.7, suggests that there was only slight decrease in odds ratio for malnutrition, GI disorders and infections and parasitic infections due to iron deficiency. Odds ratio for eating disorder and lead poisoning actually increased from Model 2 to 3. Therefore, iron deficiency was not a mediator for eating disorders and lead poisoning for outcome of pica. Model 4 included the exposure variables included in Model 3 as well as GI bleeding and non-GI bleeding that are a part of Medical Conditions II, psychiatric disorders including ASD, mood disorders, schizophrenia, anxiety disorders, OCD, and obesity. Results of multivariate conditional

logistic regression suggest that pica cases were about 5 times more likely to be iron deficient (OR: 4.83, 95% CI: 2.55-9.13) or to have another eating disorder (OR: 4.77, 95% CI: 2.83-8.03) compared to controls which is a decrease from OR of about 6.0 after adjusting for other medical conditions. Of note, pica cases were almost 7 times more likely to be autistic (OR: 6.86, 95% CI: 4.19-11.23) and were twice as likely to have gastrointestinal disorders or infections (OR: 2.46, 95% CI: 1.99-3.05), non-gastrointestinal bleeding (OR: 1.97, 95% CI: 1.24-3.13) and mood disorders (OR: 2.14, 95% CI: 1.34-3.42) than controls. Finally, pica cases were about 3 times more likely to be obese (OR: 2.73, 95% CI: 1.45-5.14) than those without pica.

Table 3.5: Distribution of psychiatric disorders in children 2 – 17 years of age, stratified by pica cases and controls

Psychiatric Disorder Variables	Matched Controls n(%) n=3,153	Cases n(%) n= 1,051	p- value
ASD	25 (0.79)	93 (8.85)	<0.0001
2 to 5 yrs.	15 (0.77)	25 (3.86)	<0.0001
6 to 9 yrs.	7 (1.05)	41 (18.47)	<0.0001
10 to 14 yrs.	3 (0.85)	20 (16.95)	<0.0001
15 to 17 yrs.	0 (0)	7 (11.11)	<0.0001*
OCD	4 (0.13)	16 (1.52)	<0.0001
2 to 5 yrs.	0 (0)	0 (0)	
6 to 9 yrs.	2 (0.3)	10 (4.5)	<0.0001*
10 to 14 yrs.	1 (0.28)	4 (3.39)	0.0142*
15 to 17 yrs.	1 (0.53)	2(3.17)	0.1401*
Mood Disorders	61 (1.93)	60 (5.71)	<0.0001
2 to 5 yrs.	4 (0.21)	14 (2.16)	<0.0001*
6 to 9 yrs.	23 (3.45)	15 (6.76)	0.0352
10 to 14 yrs.	15 (4.24)	19 (16.1)	<0.0001
15 to 17 yrs.	19 (10.05)	12 (19.05)	0.0598

Schizophrenia	6 (0.19)	16 (1.52)	<0.0001
2 to 5 yrs.	2 (0.1)	3 (0.46)	0.0878*
6 to 9 yrs.	2 (0.3)	7 (3.15)	0.0012*
10 to 14 yrs.	1 (0.28)	4 (3.39)	0.0142*
15 to 17 yrs.	1 (0.53)	2 (3.17)	0.1401*
Anxiety	43 (1.36)	47 (4.47)	<0.0001
2 to 5 yrs.	5 (0.26)	3 (0.46)	0.2079*
6 to 9 yrs.	18 (2.7)	17 (7.66)	0.001
10 to 14 yrs.	11 (3.11)	19 (16.1)	<0.0001
15 to 17 yrs.	9 (4.76)	8 (12.7)	0.0296

*p-value is based on Fisher's Exact Test instead of Chi-Square.
Abbreviations: ASD, autism spectrum disorder; OCD, obsessive compulsive disorder

Table 3.6: Odds ratios for predictors of pica estimated by Conditional Logistic Regression Models in children 2 to 17 years of age

Variables	Multivariate OR (95% CI)			
	Model 1	**Model 2**	**Model 3**	**Model 4**
Iron deficiency	6.08 (3.34,11.06)*		4.93 (2.64,9.19)*	4.829 (2.55,9.13)*
Eating disorder		6.40 (3.88,10.52)*	6.51 (3.95,10.72)*	4.77 (2.83,8.03)*
Malnutrition		2.107 (0.89,5.02)	1.98 (0.83,4.72)	0.86 (0.30,2.47)
GI disorders/infections		2.77 (2.27,3.40)*	2.67 (2.17,3.27)*	2.46 (1.99,3.04)*
Lead poisoning		5.29 (0.87-32.40)	6.26 (1.01,38.85)*	4.64 (0.68,31.77)
Parasitic infection		2.15 (1.05-4.41)	1.99 (0.96,4.10)	1.80 (0.83,3.86)
GI bleeding				1.93 (0.76,4.88)
Non-GI bleeding				1.97 (1.24,3.13)*
ASD				6.86 (4.19,11.23)*
Mood disorder				2.14 (1.34,3.42)*
Schizophrenia				2.30 (0.77,6.91)
Anxiety disorder				1.12 (0.64,1.96)
OCD				3.10 (0.88,10.89)
Obesity				2.73 (1.45,5.14)*

*Results are statistically significant
Abbreviations: ASD = autism spectrum disorders, OCD = obsessive compulsive Disorder, GI = gastrointestinal

Table 3.7: Difference in the odds ratios between Conditional Logistic Regression Models 2 (excluding iron deficiency) and 3 (including iron deficiency) in children 2 to 17 years of age

Variables	*Change in OR due to iron deficiency*
Eating disorder	0.11
Malnutrition	-0.132
GI disorder	-0.104
Lead poisoning	0.966
Parasitic infection	-0.166

Abbreviation: GI, gastrointestinal

The results of this multivariate regression analysis indicates that ASD followed by iron deficiency and other eating disorders are the strongest predictors of pica in children under the age of 18 years. Other significant predictors include GI disorders and infection, non-GI bleeding, mood disorders and obesity. All other disorders including malnutrition, lead poisoning, parasitic infections, GI bleeding, schizophrenia, anxiety disorder and OCD were not significant predictors of pica in children.

PREDICTORS OF PICA IN ADULTS

The study cohort of adults, ages 18 to 64 years old, comprised 3,480 participants, including 870 cases and 2,610 controls. The number and percentage of cases and controls with exposures including iron deficiency, Medical Conditions I, Medical Conditions II, psychiatric disorders and behavior disorders, are displayed in Table 3.8. Data for eating disorders, malnutrition and GI disorders and infections were also reported by age group to observe differences between younger vs. older adults, because we expected these disorders to be more prevalent in younger than older adults.

Cases had a significantly higher percentage of adults with iron deficiency, eating disorders, GI disorders and infections, GI bleeding disorders, non-GI bleeding disorders,

ASD, mood disorders, anxiety disorders, smoking and obesity than controls. Prevalence of iron deficiency among cases was 23.56% versus 2.49% in controls, which was a statistically significant difference ($p<0.0001$). Among Medical Conditions I, prevalence of eating disorders was 3.56% among cases and 0.46% among controls ($p<0.0001$), prevalence of malnutrition was 11.49% in cases and 5.82% in controls ($p<0.0001$), and prevalence of GI disorders and infections was 18.05% in cases compared to 10.19% in controls ($p<0.0001$), and as indicated by the P values, the differences were statistically significant. The distribution of adults with lead poisoning and parasitic infections did not differ significantly between cases and controls. Among Medical Conditions I, eating disorders were most significantly prevalent in adult cases under the age of 40 years ($p<0.0001$) while malnutrition was significantly prevalent in cases under the age of 30 years ($p<0.0001$ for all age groups under 30 years of age) compared to controls. Moreover, malnutrition was also more prevalent in adults cases between 50 to 64 years of age compared to controls ($p=0.0012$). GI disorders and infections were more significantly prevalent in adult cases over 50 years of age compared to controls ($p<0.0001$) but were also significant in adults ages 18-29 years ($p=0.0001$). Among Medical Conditions II, females with pica had a significantly higher prevalence of menstrual bleeding and RLS than controls. Among females, prevalence of menstrual bleeding disorders was 21.91% in cases and 8.45% in controls ($p<0.0001$). Moreover, prevalence of RLS was 1.27% in female cases and 0.47% in female controls ($p=0.0066$). GI bleeding was reported in 5.06% cases and 2.15% controls which was also a statistically significant difference ($p<0.0001$). Also significant was non-GI bleeding with a prevalence of 9.66% in cases and 5.98% in controls ($p=0.0002$).

Among psychiatric disorders, 19.08% of adult pica cases and 11.03% of controls had mood disorders (P<0.0001). Moreover, 13.45% of cases and 7.51% of controls reported anxiety disorders (p<0.0001). There were very few adult study subjects with ASD and schizophrenia but the difference in cases and controls was significant based on Fisher's exact test. Finally, as reported in Table 3.8, the distribution of OCD among cases and controls was not significant.

Among health behavior disorders, prevalence of smoking was 7.01% in cases and 3.07% in controls (p<0.0001). Moreover, 15.4% of cases and 5.63% of controls were obese which was a statistically significant difference (p<0.0001). However, the distribution of alcoholism among cases and controls did not show a significance.

Seven predictive models were created to test Hypothesis 1 through 3 for prediction of pica. Conditional logistic regression was used to estimate the association of pica in adults between 18 and 64 years of age with several exposure variables, expressed as odds ratios (OR) with 95% confidence intervals (CI), as shown in Table 3.9. Only variables that might be clinically related in adults and had a p-value of less than 0.20 in descriptive analysis were included in these models.

Table 3.8: The distribution of medical conditions, psychiatric disorders and health behaviors in adults 18 to 64 years of age, stratified by pica cases and controls

Variables	*Total n = 3,480*	*Matched Controls n=2,610 n (%)*	*Cases n=870 n (%)*	*P-value*
Iron Deficiency	270	65 (2.49)	205 (23.56)	<0.0001
Medical Conditions 1				
Eating disorders	43	12 (0.46)	31 (3.56)	<0.0001
18-29	11	0 (0)	11 (7.69)	<0.0001
30-39	19	5 (0.81)	14 (6.8)	<0.0001
40-49	10	5 (0.5)	5 (1.66)	0.0668
50-64	3	2 (0.3)	1 (0.46)	0.7385
Malnutrition	252	152 (5.82)	100 (11.49)	<0.0001
18-29	18	6 (1.4)	12 (8.39)	<0.0001
30-39	49	31 (5.02)	18 (8.74)	0.0505
40-49	89	56 (6.18)	33 (10.93)	0.0063
50-64	96	59 (8.98)	37 (16.89)	0.0012
GI disorders and infections	423	266 (10.19)	157 (18.05)	<0.0001
18-29	42	21 (4.9)	21 (14.69)	0.0001
30-39	75	49 (7.93)	26 (12.62)	0.0426
40-49	139	97 (10.71)	42 (13.91)	0.1311
50-64	167	99 (15.07)	68 (31.05)	<0.0001
Lead Poisoning	1	0 (0)	1 (0.11)	0.25
Parasitic infections	21	13 (0.5)	8 (0.92)	0.1645
Medical Conditions 2				
Menstrual bleeding (female)	371	199 (8.45)	172 (21.91)	<0.001
RLS (female)	21	11 (0.47)	10 (1.27)	0.0066
GI bleeding disorders	100	56 (2.15)	44 (5.06)	<0.0001
Non-GI bleeding dis.	240	156 (5.98)	84 (9.66)	0.0002
Psychiatric Disorders				
Autism Spectrum Dis. (ASD)	7	0 (0)	7 (0.8)	<0.0001*
OCD	16	10 (0.38)	6 (0.69)	0.1101
Mood disorders	454	288 (11.03)	166 (19.08)	<0.0001
Schizophrenia	3	1 (0.04)	2 (0.23)	0.1406*
Anxiety	313	196 (7.51)	117 (13.45)	<0.0001
Health Behaviors				
Smoking	141	80 (3.07)	61 (7.01)	<0.0001
Alcohol	21	12 (0.46)	9 (1.03)	0.058

Obesity	281	147 (5.63)	134 (15.4)	<0.0001

*p-value is based on Fisher's Exact Test instead of Chi-Square
Abbreviations: ASD, autism spectrum disorders; OCD, obsessive compulsive disorder; GI, gastrointestinal; RLS, restless leg syndrome

The first model was created to test Hypothesis 1 and the results suggest that pica cases were 13 times more likely to be iron deficient (OR: 13.05, 95% CI: 9.00, 18.15) than controls. Model 2 includes exposure variables included in Medical Conditions 1 and indicates that pica cases were 8 times more likely than controls to occur with another eating disorder (OR: 8.15, 95%CI: 3.94-16.83) and about twice as likely to be associated with malnutrition (OR: 2.02, 95%CI: 1.52-2.67) and with GI disorders and infections (OR: 1.88, 95%CI: 1.50-2.37). Model 3 was used to study mediation by iron deficiency of exposure variables included in Medical Conditions I for the outcome of pica. The difference in odds ratios of these exposure variables between Models 2 and 3, as displayed in Table 3.8 and 3.9, were negligible, and therefore resulted in no change between the two models. Therefore, iron deficiency was not a mediator for other eating disorders, malnutrition, GI disorders and infections, lead poisoning and parasitic infections for the outcome pica. Model 4 only contained predictor variables relevant to adult females, including menstrual bleeding disorders and RLS. Cases with pica were about 3 times more likely to have menstrual bleeding disorders (OR: 3.17, 95%CI: 2.51-4.01) and RLS (OR: 2.62, 95%CI: 1.10-6.28) than controls. This model was also tested for mediation by iron deficiency in Model 5, as indicated in Hypothesis 5, by comparing odds ratios of the predictor variables with and without adjustment for iron deficiency. This model indicated slight mediation due to iron deficiency resulting in a decrease in the odds ratio for menstrual bleeding disorders, as displayed in Table 3.10, from 3.18 to 2.17

for menstrual bleeding disorders (Hypothesis 3). Moreover, inclusion of iron deficiency in this model suggested that RLS was no longer a statistically significant predictor for pica. Model 6 included the exposure variables included in Models 1 through 5 as well as GI bleeding and non-GI bleeding that are a part of Medical Conditions II, psychiatric disorders to include mood disorders, schizophrenia, anxiety disorders and OCD, and behavior related disorders including smoking, alcoholism and obesity. Results of multivariate conditional logistic regression suggested that pica cases were close to 12 times more likely to be iron deficient (OR: 12.01, 95% CI: 8.53-16.90) and about 5 times more likely to have another eating disorder (OR: 5.33, 95% CI: 2.41-11.78) compared to controls. Of note, pica cases were about 1.8 times more likely to be smokers (OR: 1.78, 95% CI: 1.19-2.67) and 2.5 times more likely to be obese (OR: 2.45, 95% CI: 1.81-3.30) than controls. Finally, pica cases were about 1.5 times more likely to have GI disorders and infection, and mood or anxiety disorders compared to controls. Model 7 included female participants only, in order to explore predictors in females vs. the entire cohort (model 6). The predictors that were significant in model 6 were also significant in model 7 indicating that these is no strong modification effect by gender.

Table 3.9: Odds ratios of predictors of pica estimated by Conditional Logistic Regression Models in adults 18 to 64 years of age

	Multivariate OR (95% CI)						
Variables	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**
Iron deficiency	13.09 (9.44, 18.15)*		12.15 (8.72, 16.93)*		10.85 (7.75,15.20)*	12.01 (8.53, 16.90)*	10.15 (7.15, 14.3)*
Eating disorder		8.15 (3.94, 16.83)*	8.21 (33.82, 17.61)*			5.33 (2.41, 11.78)*	5.33 (2.36, 12.05)*
Malnutrition		2.02 (1.52, 2.67)*	1.70 (1.24, 2.34)*			1.51 (1.09, 2.10)*	1.39 (0.98, 1.97)
GI disorders/infections		1.88 (1.50, 2.37)*	1.64 (1.27, 2.11)*			1.47 (1.11, 1.94)*	1.34 (0.99, 1.82)
Parasitic infections		1.38 (0.55, 3.46)	1.12 (0.41, 3.11)			0.95 (0.33, 2.75)	0.80 (0.25, 2.46)
Menstrual bleeding (female)				3.17 (2.51, 4.01)*	2.18 (1.67, 2.84)*		2.34 (1.73, 3.14)*
RLS (female)				2.62 (1.10, 6.28)*	2.47 (0.92, 6.61)		1.83 (0.63, 5.28)
GI bleeding						0.99 (0.59, 1.64)	1.09 (063, 1.91)
Non-GI bleeding						1.28 (0.92, 1.80)	0.77 (0.52, 1.13)
Mood disorder						1.51 (1.17, 1.95)*	1.52 (1.17, 1.99)*
Schizophrenia						0.44 (0.03, 5.96)	0.25 (0.01, 4.96)
Anxiety disorder						1.55 (1.14-2.10)*	1.51 (1.09, 2.07)*
OCD						0.74 (0.21, 2.56)	0.83 (0.25, 2.79)
Smoking						1.78 (1.19, 2.67)*	1.68 (1.09, 2.60)*
Alcoholism						1.11 (0.38, 3.28)	1.03 (0.32, 3.37)
Obesity						2.45 (1.81, 3.30)*	2.29 (1.67, 3.14)*

*Results are statistically significant

ASD, Autism Spectrum Disorders; OCD, Obsessive Compulsive Disorder; GI, Gastrointestinal

Models 4, 5 and 7 are based on adult females

Table 3.10: Difference in the odds ratios between Conditional Logistic Regression Models 2 (excluding iron deficiency) and 3 (including iron deficiency), and Models 4 (excluding iron deficiency) and 5 (including iron deficiency) in adults

Variables	***Change in OR due to iron deficiency***
Eating disorders	0.061
Malnutrition	-0.317
GI disorders	-0.244
Parasitic infections	-0.255
Menstrual bleeding (female)	0.995
RLS (female)	0.157

Abbreviations: GI, gastrointestinal; RLS, Restless Leg Syndrome

The results of this multivariate regression analysis indicates that iron deficiency followed by other eating disorders were the strongest predictors of pica in adults between the age of 18 and 64 years. Other significant predictors include GI disorders and infections, mood disorders, anxiety disorders, smoking and obesity. All other disorders including malnutrition, parasitic infections, GI and non-GI bleeding, schizophrenia, ASD, OCD and alcoholism were not significant predictors of pica in adults.

LABORATORY PREDICTORS OF PICA

Of the original study population only 544 cases and 800 controls had lab results available. Majority of cases (n=1,377) did not have lab results available in the Clinformatics Data Mart. The cases in this cohort that contained lab results and those that had no available lab data were similar with respect to selected medical conditions, as shown in Table 3.11 but were different for demographic variables such as age, gender and region. Mean age of study cases with labs was 27.67 years and was 19.7 years of the cases without labs. Cases with lab data were more likely to be female (77.57%) compare to those without lab data (66.52%). 70% of cases with lab data came from the Southern U.S compared to those without lab results (46%) without lab results, which was significant. Cases with lab data were significantly more likely to be pregnant, and to have iron deficiency, malnutrition, menstrual bleeding, GI and non-GI bleeding disorders, anxiety disorders and obesity. Therefore, these individuals had a greater likelihood of being included in the case group for this study of lab results.

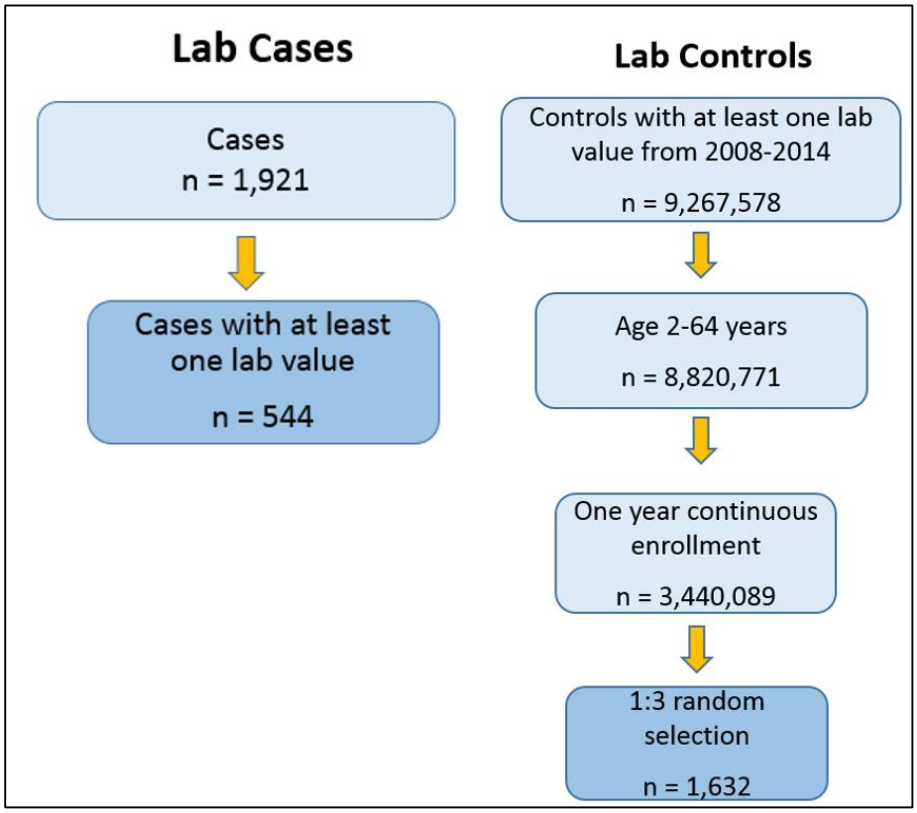
Table 3.11: Distribution of demographics, medical conditions, psychiatric disorders and health behaviors, stratified by pica cases with or without available lab results

Variables	***Cases with labs n(%) n=544***	***Cases without labs n(%) n=1,377***	***p-value***
Mean Age (yrs.)	27.67	19.7	<0.0001
Gender			
Female	422 (77.57)	916 (66.52)	<0.0001
Male	122 (22.43)	461 (33.48)	
Region			
Midwest	50 (9.19)	487 (33.57)	<0.0001
Northeast	39 (7.17)	89 (6.46)	
South	381 (70.04)	638 (46.33)	
West	74 (13.6)	163 (11.84)	
Pregnant	48 (8.82)	39 (2.83)	<0.0001
Year of diagnosis			0.0195
2009	77 (14.15)	236 (17.14)	
2010	104 (19.12)	268 (19.46)	
2011	120 (22.06)	299 (21.71)	
2012	114 (20.96)	333 (24.18)	
2013	129 (23.71)	241 (17.50)	
Iron Deficiency	111 (20.40)	127 (9.22)	<0.0001
Eating disorders	22 (4.04)	63 (4.58)	0.6101
Malnutrition	53 (9.74)	60 (4.36)	<0.0001
GI disorders and infections	112 (20.59)	265 (19.24)	0.5041
Lead Poisoning	2 (0.37)	2 (0.15)	0.3353
Parasitic infections	6 (1.1)	18 (1.31)	0.7165
Menstrual bleeding (female)	81 (19.19)	96 (10.48)	<0.0001
RLS	5 (0.92)	9 (0.65)	0.53376
GI bleeding disorders	26 (4.78)	30 (2.18)	0.0023
Non-GI bleeding dis.	52 (9.56)	69 (5.01)	0.0002
Autism Spectrum Dis. (ASD)	25 (4.60)	75 (5.45)	0.44933
OCD	4 (0.74)	18.(1.31)	0.2885
Mood disorders	67 (12.32)	159 (11.55)	0.6373
Schizophrenia	5 (0.92)	13 (0.94)	0.9592
Anxiety disorders	61 (11.21)	103 (7.48)	0.0083
Smoking	21 (3.86)	41 (2.98)	0.3239
Alcohol	3 (0.55)	6 (0.44)	0.7379
Obesity	56 (10.29)	100 (7.26)	0.0284

Abbreviations: ASD = Autism Spectrum Disorders, OCD = Obsessive Compulsive Disorder, GI = gastrointestinal

This case control cohort with lab results was created to include cases and controls for whom at least one of the studied laboratory test result was available. All were enrolled between 2008 and 2014. The cohort comprised 2,176 participants, including 544 cases and 1,632 matched controls, as shown in Figure 3.3. The controls were matched 1:3 to cases for age, gender, region and year and month of diagnosis.

Figure 3.3: Summary of selection of study cohorts for pica cases and controls for those with lab results



The mean of red blood cell measurements including RBC count, hemoglobin, hematocrit, MCV, MCH and MCHC were significantly lower, whereas RDW was higher in cases compared to controls ($p<0.0001$), as shown in Table 3.12. Mean platelet counts

and mean blood lead levels were significantly higher in cases than in controls. Means of serum iron, transferrin saturation and ferritin were significantly lower while mean TIBC was significantly higher in cases than in controls.

Table 3.12: Distribution of laboratory results, stratified by pica cases and controls

Variables	*Number of Controls*	*Controls Mean (SD)*	*Number of Cases*	*Cases Mean (SD)*	*p value*
WBC (x 10^3/uL)	1,487	7.15 (2.34)	465	7.20 (2.50)	0.6978
RBC ((x 10^6/uL)	1,480	4.51 (0.40)	459	4.40 (0.49)	<0.0001
Hemoglobin (g/dL)	1,526	13.02 (1.30)	471	11.19 (2.22)	<0.0001
Hematocrit (%)	1,516	38.98 (3.57)	472	34.68 (5.26)	<0.0001
MCV (fL)	1,469	86.75 (6.79)	455	79.05 (9.45)	<0.0001
MCH (pg)	1,460	28.98 (2.58)	439	25.48 (4.36)	<0.0001
MCHC (g/dL)	1,471	33.36 (1.56)	458	31.87 (2.57)	<0.0001
RDW (%)	1,433	13.89 (1.26)	448	16.02 (3.24)	<0.0001
Platelets (x 10^3/uL)	1,448	281.03 (71.91)	446	313.26 (84.77)	<0.0001
MPV (fL)	55	10.00 (1.17)	22	10.17 (1.09)	0.5625
Iron, Serum (ug/dL)	146	81.86 (43.23)	223	48.14 (48.84)	<0.0001
Ferritin, Serum (ng/mL)	136	51.83 (63.30)	206	22.53 (37.86)	<0.0001
Transferrin Saturation (%)	101	26.02 (14.00)	167	12.57 (13.05)	<0.0001
TIBC (ug/dL)	107	338.83 (61.72)	180	390.49 (80.69)	<0.0001
Blood Lead (ug/dL)	203	0.98 (1.26)	117	2.00 (5.23)	0.0084

SD = standard deviation, WBC = white blood cell count, RBC = red blood cell count, MCV = mean cell volume, MCH = mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW = red cell distribution width, MPV = Mean platelet volume, TIBC = Total iron binding capacity

Conditional logistic regression was conducted to evaluate the predictability of each of the laboratory variables listed in Table 3.12 for the outcome pica. Unadjusted odds ratios with 95% confidence intervals for each of the variables are recorded in Table 3.13. The number cases and controls that were tested for CBC parameters were much higher than those that were tested for iron panel parameters, MPV or blood lead (Table 3.12). Therefore, the conditional logistic regression model created for prediction of laboratory results for the outcome of pica did not include iron panel parameters or blood lead. Moreover, a correlation coefficient (r) was calculated for each the variables, indicating that the following variables were highly correlated: hemoglobin and hematocrit ($r = 0.958$), MCV and MCH ($r = 0.948$), and serum iron and transferrin saturation ($r = 0.958$). Therefore, of these correlated variables, only hemoglobin and MCV were included in the conditional logistic regression model. Furthermore, RBC was not included in the model since it is clinically correlated to hemoglobin.

Adjusted odds ratios with 95% confidence intervals are displayed in Table 3.12. These results indicate that pica cases were 64% more likely to have a one unit (1g/dL) decrease in hemoglobin of at least 1g/dL and 24% more likely to have a one unit increase (1%) in RDW of at least 1% and these results were statistically significant.

Table 3.13: Odds ratios of laboratory predictors of pica estimated by Conditional Logistic Regression

Lab Variables	*Unadjusted OR*	*95% CI*	*Adjusted OR*	*95% CI*
WBC (x 10^3/uL)	0.99	0.947-1.043		
RBC ((x 10^6/uL)	0.47	0.359-0.622		
Hemoglobin (g/dL)	0.48	0.439-0.533	0.64	0.552-0.739*
Hematocrit (%)	0.76	0.731-0.788		
MCV (fL)	0.89	0.871-0.902	0.98	0.953-1.005
MCH (pg)	0.75	0.715- 0.779		
MCHC (g/dL)	0.58	0.529-0.628	0.98	0.838-1.134
RDW (%)	1.75	1.610-1.908	1.24	1.105-1.382*
Platelets (x10^3/uL)	1.01	1.00-1.007	1.00	0.999-1.003
MPV (fL)	0.73	0.304-1.764		
Iron, Serum (ug/dL)	0.98	0.968-0.992		
Ferritin, Serum (ng/mL)	0.99	0.976-0.997		
TIBC (ug/dL)	1.06	1.009-1.108		
Transferrin Saturation (%)	0.93	0.884- 0.980		
Blood Lead (ug/dL)	1.10	0.928- 1.314		

*Results are statistically significant
WBC = white blood cell count, RBC = red blood cell count, MCV = mean cell volume, MCH = mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW = red cell distribution width, MPV = mean platelet volume, TIBC = Total iron binding capacity

COMBINED MODEL FOR PREDICTION OF PICA

A combined logistic regression model was created to include medical conditions and one laboratory variable that were significant predictors of pica in both children and adults. Multivariate odds ratios with 95% confidence intervals are shown in Appendix B.

The results of this combined model were very different from the original model perhaps due to the fact that only a fraction of the study group had lab results. This is evident from the odds ratio for obesity which was about 2.5 in the children and adult models as shown in Tables 3.5 and 3.8 and was about 12.0 in the combined model. Therefore, the results of combined model should be interpreted with caution and cannot be generalized to the whole study population.

Overall, we found in this study that iron deficiency, eating disorders, GI disorders and infections, mood disorders and obesity are strong predictors of pica in both adults and children. In addition, ASD and non-GI bleeding in children and anxiety disorders and smoking were significant predictors of pica in adults18 to 64 years of age. Moreover, decreased hemoglobin levels and increased RDW were significant laboratory predictors of pica.

Chapter 4: Aim 2 Results

OUTCOMES OF PICA

Cases from the original case control cohort with a pica diagnosis dated between 2009 and 2013 and their matched controls were followed for a period of 12 months (cases: n = 1,921, controls: n = 5,763) to assess potential clinical outcomes of pica. Outcome variables that were studied include hospitalizations, Medical Conditions I (eating disorders, malnutrition, GI disorders and infections, lead poisoning and parasitic infections), dental complications, intestinal obstruction, fluid and electrolyte imbalances and cardiac dysrhythmias. Cases with any of the conditions included in the category of Medical Conditions 1 in the 12 month look-back period were excluded from the outcomes analysis only for that specific pre-existing condition. As discussed in chapter 3, the majority of pica cases were children under the age of 18 years. Therefore, it was of interest to analyze data from children and adults separately and compare the pica outcome rates among these two groups.

OUTCOMES OF PICA IN CHILDREN

The rate of clinical outcomes of pica in children under the age of 18 years (cases: n=1,051, controls: n=3,153) including hospitalizations, Medical Conditions I (eating disorders, malnutrition, GI disorders and infections, lead poisoning and parasitic infections), dental complications, intestinal obstructions, fluid and electrolyte imbalance and cardiac dysrhythmias were computed using log rank tests, and the results are shown in Table 4.1. Children with pica had significantly higher rates of all of these outcomes

compared to controls with the exception of dental complications and cardiac dysrhythmias.

There were very few patients ($n < 10$) that developed intestinal obstruction in our study population, so this outcome could not be further analyzed. Among pica cases, 13% developed GI disorders or infections compared to 7% controls ($p<0.0001$), 4% were hospitalized compared to 1% controls ($p<0.0001$), 3% developed eating disorders compared to 0.4% controls ($p<0.0001$), 2% developed fluid/electrolyte imbalance compared to 1% controls ($p=0.0022$), 1% developed parasitic infections ($p=0.0077$) and malnutrition ($p=0.0034$) compared to less than 0.5% controls. About 0.5% developed lead poisoning compared to 0.06% controls ($p=0.0011$). The corresponding Kaplan Meier failure curves are shown in Figures 4.1a and 4.1b, including those for intestinal obstructions and dental complications, which are questionable because very few ($n<10$) children experienced these outcomes. The failure curves for all outcomes except dental complications indicate that their rates were higher in cases than controls during the entire follow-up period. The GI disorder curve indicates an equivalent increase in both cases and controls for the first 3 months followed by an increase in the rate for cases, which was almost double that of controls. There was a steady increase in hospitalizations for controls but cases increased at a much higher rate. After a sharp increase in rate of hospitalizations in cases for the first 75 days, the increase was slower for the rest of the study period. After a steady increase in the rate of eating disorders during the first 6 months in cases, there was a slower rate of increase for rest of the study period but an increased rate for controls (Figure 4.1a). The curve for malnutrition for cases also shows a higher rate of increase for the first 6 months followed by a slower increase when

compared to controls. The failure curve for parasitic infection in pica cases shows an early rise in rate for the first 30 days after diagnosis followed by a slower rate of increase, while the rate for controls increased steadily, but at a lower rate than for cases. Rate of cardiac dysrhythmias increased throughout the 12 month follow up period, but the rate was only slightly higher than that for controls, and the difference was not statistically significant. The rate for fluid and electrolyte imbalances also increased steadily in both cases and controls, and was significantly higher in the pica cases. Finally, there were very few children with lead poisoning; but the failure curve shows that the rate was about 10 times greater in pica cases than in controls, with the increase occurring in lead poisoning in pica cases occurring during the first 90 days of follow up.

Table 4.1: Failure rates for outcomes under the age of 18 years estimated by Kaplan Meier method, stratified by pica cases and controls

	Controls			*Cases*			
Outcomes	*Total*	*Failed n(%)*	*Censored n(%)*	*Total*	*Failed n(%)*	*Censored n(%)*	*p-value*
Eating disorders	3,128	12 (0.38)	3,116 (99.62)	997	30 (3.01)	967 (96.99)	<0.0001
Malnutrition	3,142	10 (0.32)	3,132 (99.68)	1,038	11 (1.06)	1,027 (98.94)	0.0034
GI disorders/infections	2,880	188 (6.53)	2692 (93.47)	831	105 (12.64)	726 (87.36)	<0.0001
Lead Poisoning	3,151	2 (0.06)	3,149 (99.94)	1,048	6 (0.57)	1,042 (99.43)	0.0011
Parasitic infections	3,136	15 (0.48)	3,121 (99.52)	1,035	13 (1.26)	1,022 (98.74)	0.0077
Dental complications	3,149	2 (0.06)	3,147 (99.94)	1,048	1 (0.10)	1047 (99.90)	0.7388
Intestinal Obstruction	3,151	0 (0)	3,151 (100)	1,045	4 (0.38)	1041 (99.62)	*
Fluid/Electrolyte imbalance	3,116	29 (0.93)	3,087 (99.07)	1,027	25 (2.43)	1,002 (97.57)	0.0002
Cardiac Dysrhythmias	3,058	67 (2.19)	2,991 (97.81)	992	23 (2.32)	969 (97.68)	0.8046
Hospitalization	3,153	32 (1.01)	3,121 (98.99)	1,051	39 (3.71)	1,012 (96.29)	<0.0001

*p-value could not be calculated
GI = gastrointestinal

Figure 4.1a: Percent of patients under the age of 18 years that developed study outcomes in the 12 month follow-up period estimated by Kaplan Meier failure curves, stratified by pica cases and controls

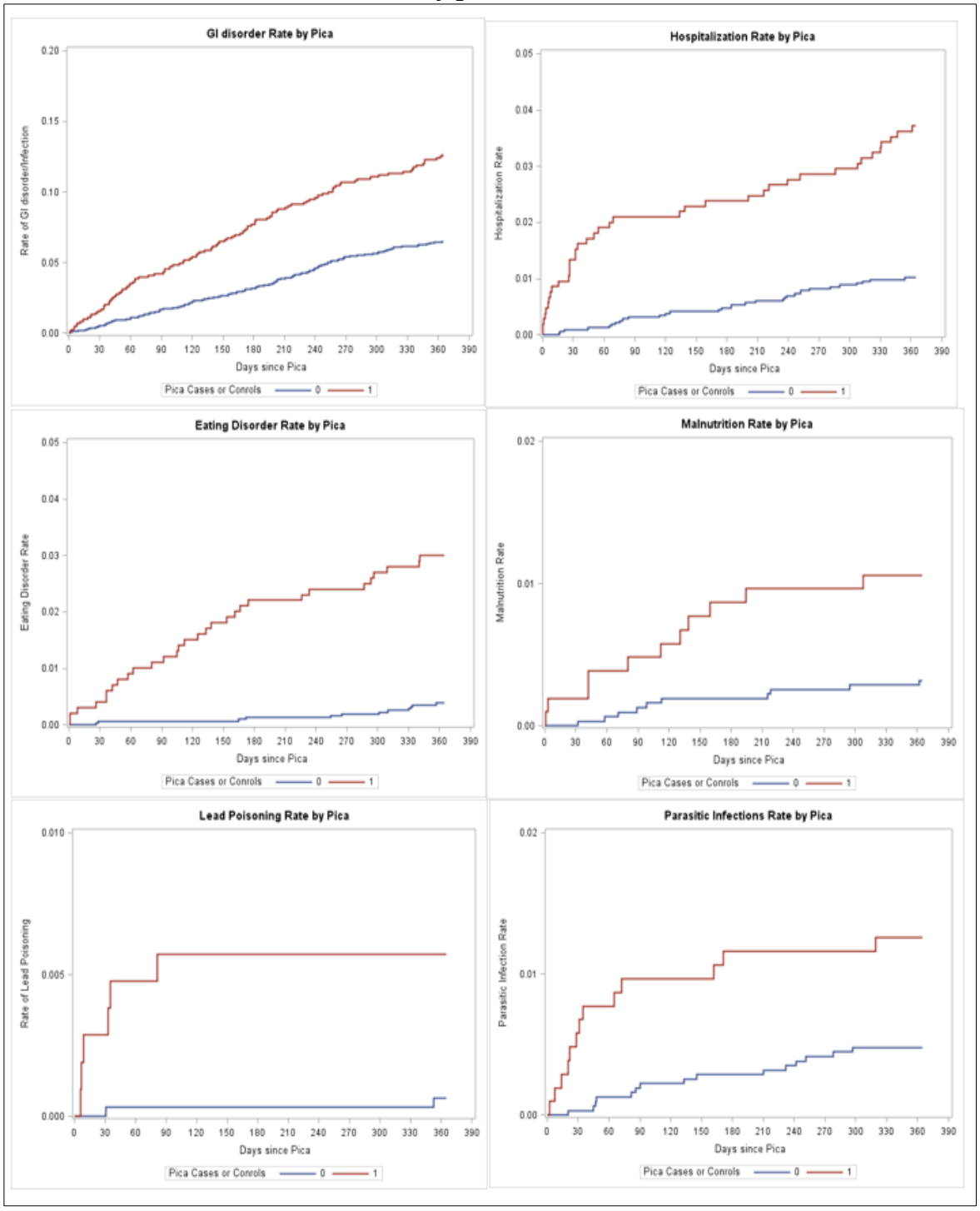
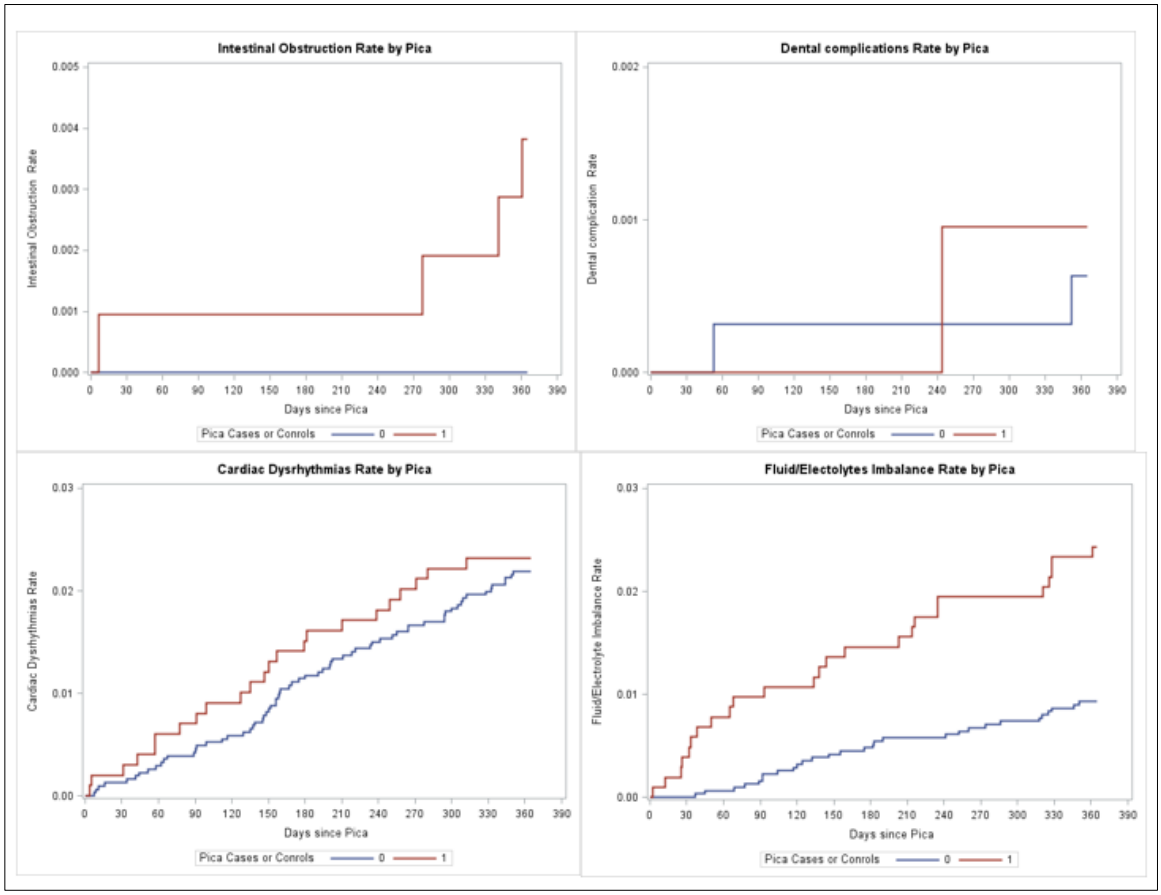


Figure 4.1b: Percent of patients under the age of 18 years that developed study outcomes in the 12 month follow-up period estimated by Kaplan Meier failure curves, stratified by pica cases and controls



Cox proportional hazards regression models were constructed to estimate hazard ratios (HRs) and 95% confidence intervals for the risk of health outcomes associated with pica. Multivariate adjustment was performed for demographic variables (gender, age, year of diagnosis and region) followed by addition of iron deficiency, which is a key predictor of pica, to the models. Finally, the models were adjusted for significant predictors of pica (as discussed in chapter 3) for children to include non-GI bleeding, ASD, mood disorder and obesity. Unadjusted and multivariate hazard rates yielded by a Cox proportional hazards model for all of the outcomes of pica for children under the age

of 18 years are shown in Table 4.2. The data suggest that children with pica were more likely than controls to develop lead poisoning in both unadjusted and adjusted models. After controlling for demographic variables, iron deficiency and significant predictors including non-GI bleeding, mood disorder, ASD and obesity, children with pica were about 11 times more likely to have lead poisoning (HR: 10.74, 95%CI: 2.16, 53.50), 7 times more likely to have other eating disorders (HR: 6.83, 95%CI: 3.42, 13.63), about 3 times more likely to have parasitic infections (HR: 2.79, 95%CI: 1.32, 5.92) and fluid or electrolyte imbalances (HR: 2.80, 95%CI: 1.62, 4.81), and twice as likely to have GI disorders or infection (HR: 1.87, 95%CI: 1.46, 2.40) compared to controls without pica. Hazard ratios for lead poisoning and parasitic infections actually increased after adjustment for demographic variables, iron deficiency, non-GI bleeding, mood disorder and obesity demonstrating that these outcomes were confounded by adjusted variables. These models were evaluated for proportional hazard violations and were found to have no violations. However, a violation of proportional hazard was found for hospitalizations. Therefore, time dependent hazard models were created to examine this outcome variable. The cutoff of 75 days was determined by examining the hospitalization failure curve, as displayed in Figure 4.1a. Children with pica were 7 times more likely to be hospitalized compared to controls, as stated in Hypothesis 4, in the first 75 days (HR: 7.06, 95%CI: 3.09, 16.10) after pica diagnosis which was statistically significant. However, the likelihood of hospitalization after the first 75 days was not significantly different from controls (OR: 1.88, 95%CI: 0.99, 3.57). The results of this analysis are shown in Table 4.3. We were not able to test Hypothesis 5 for children due to very few number of cases and no controls with gastrointestinal obstruction in our study

population. Moreover, malnutrition, dental complications and cardiac dysrhythmias were not significant outcomes of pica in children in our study.

Table 4.2: Hazard ratios for outcomes of pica in children under the age of 18 years estimated by Cox Proportional Hazards Regression Models

Models	*Outcomes*	*Unadjusted HR (95% CI)*	*Multivariate HR* (95% CI)*	*Multivariate HR^ (95% CI)*	*Multivariate HR# (95% CI)*
1	Eating disorders	7.97 (4.08, 15.56)	8.00 (5.00, 15.63)	8.02 (4.10, 15.69)	6.83 (3.42, 13.63)
2	Malnutrition	3.34 (1.42, 7.87)	3.41 (1.45. 8.03)	3.01 (1.24, 7.31)	2.50 (0.97, 6.42)
3	GI disorders/infections	2.02 (1.59, 2.56)	2.02 (1.59,2.57)	2.03 (1.59, 2.57)	1.87 (1.46, 2.40)
4	Lead poisoning	9.05 (1.83, 44.81)	9.04 (1.83, 44.79)	9.21 (1.86, 45.61)	10.74 (2.16, 53.50)
5	Parasitic infections	2.64 (1.26, 5.55)	2.67 (1.27, 5.61)	2.59 (1.22, 5.49)	2.79 (1.32, 5.92)
6	Fluid/Electrolyte Imbalance	2.94 (1.80, 4.82)	2.64 (1.55, 4.50)	2.71 (1.59, 4.62)	2.80 (1.62, 4.81)
7	Cardiac Dysrhythmias	1.06 (0.66, 1.71)	1.06 (0.66, 1.70)	1.03 (0.64, 1.67)	1.05 (0.64, 1.72)

*Adjusted for demographic variables (age, gender, region and year of diagnosis)
^Adjusted for demographics and Iron deficiency
#Adjusted for demographics, Iron deficiency, Non-GI bleeding, ASD, Mood disorders and Obesity
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; GI, gastrointestinal

Table 4.3: Hazard ratios of hospitalizations associated with pica in children under the age of 18 years estimated by time dependent Cox Proportional Hazards Regression Models

Outcomes	*Time dependent HR#*	*95% CI*
Hospitalization		
<75 days after pica diagnosis	7.06	3.09-16.10
75 - 365 days after diagnosis	1.88	0.99-3.57

#Adjusted for demographics, Iron deficiency, Non-GI bleeding, ASD, Mood disorders and Obesity
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval

Mediation for hospitalization:

As discussed above, children with pica are 7 times more likely to be hospitalized in the first 75 days after diagnosis, 7 times more likely to be found to have an eating disorder and twice as likely to have a GI disorder or infection as the controls without pica. Eating disorders and GI disorders and infections may be independent outcomes of hospitalization in our study population with or without pica. In order to test this Hypothesis, failure rates were computed for these disorders and Cox proportional hazard regression models were created to test the direct relationship of eating disorders and GI disorders and infections in the look-back period with hospitalization in the follow-up period. Moreover, pica was added to the models to evaluate the effect of mediation due to pica in this relationship. The results of this analysis, as shown in Table 4.4 indicate that patients with eating disorders and GI disorders had significantly higher rates of hospitalization compared to controls. Cox proportional hazard models, as shown in Table 4.4, indicate that hospitalization was not a significant outcome of eating disorders in the children in our study population after adjusting for demographic variables (age, gender, region and year of diagnosis), but was a significant predictor of pica in children, as discussed in chapter 3. However, children with GI disorders and infections were almost twice as likely to be hospitalized (HR: 2.50, 95%CI: 1.44, 4.34) than those without these disorders and this relationship was also slightly mediated by pica (HR: 1.99, 95%CI: 1.14, 3.48).

Table 4.4: Failure rates for hospitalizations estimated by Kaplan Meier method and hazard ratios estimated by Cox Proportional Hazards Regression Models in cases and controls under the age of 18 years with and without eating disorders and GI disorders and infections in the look-back period

	Without disorders			*With disorders*					
Variables	*Total*	*Failed n (%)*	*Censored n (%)*	*Total*	*Failed n (%)*	*Censored n (%)*	*p-value*	*HR* (95%CI)*	*aHr (95%CI)*
Eating disorder	4,125	67 (1.62)	4,058 (98.38)	79	4 (5.06)	75 (94.94)	0.0147	1.62 (0.54, 4.92)	1.12 (0.38, 3.33)
GI disorders/infection	3,711	53 (1.43)	3,658 (98.57)	493	18 (3.65)	475 (96.35)	0.0003	2.50 (1.44, 4.34)	1.99 (1.14, 3.48)

HR* = Hazard Ratio adjusted for demographic and significant predictor variables, Abbreviations: aHR, Hazard Ratio adjusted for pica; CI, Confidence Interval

OUTCOMES OF PICA IN ADULTS

Rate of clinical outcomes of pica in adults between 18 and 64 years of age (cases: n = 2,610, Controls: n= 870) including hospitalizations, Medical Conditions I (eating disorders, malnutrition, GI disorders and infections, and parasitic infections), intestinal obstructions, fluid and electrolyte imbalance and cardiac dysrhythmias are shown in Table 4.5. Lead poisoning and dental complications were not included because there were no cases for these disorders in this age group. Adults with pica had a significantly higher rate of all other outcomes that were studied compared to controls with the exception of cardiac dysrhythmias. Among cases, 17% developed GI disorders or infections compared to 9% of controls ($p<0.0001$) and approximately 17% were hospitalized compared to 5% of controls ($p<0.0001$), 11% developed malnutrition compared to around 5% controls ($p<0.0001$), 5% developed fluid or electrolyte imbalance compared to 2% controls ($p<0.0001$), approximately 2% developed eating disorders compared to 0.3% controls ($p<0.0001$), 2% developed intestinal obstructions compared to 0.5% controls ($p=0.0029$), and approximately 1% developed parasitic

infections compared to 0.4% controls (p=0.0035). The corresponding failure curves are shown in Figures 4.2a and 4.2b.

The failure curves for all studied outcomes indicated that their rates were higher in cases compared to controls throughout the follow-up period. The rate of malnutrition in cases was about double the rate of controls. The increasing trend was proportional cases and controls throughout the study period. The fluid and electrolyte imbalance curve shows a sharp increase in cases for the first thirty days followed by a steady increase for the rest of the study period, whereas the curve for controls showed a steady increase beginning after about thirty days. The rates for eating disorders increased more rapidly in cases than in the controls, for whom the rate remained consistently low. Rate of parasitic infections increased among cases for the first 90 days followed by a slower rate of increase for the rest of the study period, whereas the increase was lower in controls and occurred mainly from 2 to 4 months and again from 6 to 9 months. The intestinal obstruction curves show steady increases in both cases and controls for the first 9 months followed by a plateau effect, with a higher rate in cases than controls. Cardiac dysrhythmias increased proportionally for both cases and controls with very little difference in rates between the two groups. There was a steady increase in both hospitalizations and GI disorders for controls but cases increased at a much higher rate than controls. There was a sharp increase in rates for these variables in cases for the first 75 days followed by a slower rate of increase for the rest of the study period.

Table 4.5: Failure rates for outcomes for adults' ages 18 to 64 years estimated by Kaplan Meier method, stratified by pica cases and controls

Outcomes	Controls			Cases			p-value
	Total	Failed n(%)	Censored n(%)	Total	Failed n(%)	Censored n(%)	
Eating disorders	2,598	8 (0.31)	2,590 (99.69)	839	13 (1.55)	826 (98.45)	<0.0001
Malnutrition	2,458	135 (5.49)	2323 (94.51)	770	83 (10.78)	687 (89.22)	<0.0001
GI disorders/infections	2,344	219 (9.44)	2,125 (90.66)	713	119 (16.69)	594 (83.31)	<0.0001
Parasitic infections	2,597	10 (0.39)	2,587 (99.61)	862	11 (1.28)	851 (98.72)	0.0035
Intestinal Obstruction	2,601	13 (0.5)	2,588 (99.50)	861	13 (1.51)	848 (98.49)	0.0029
Fluid/Electrolyte imbalance	2,553	54 (2.12)	2,499 (97.88)	823	40 (4.86)	783 (95.14)	<0.0001
Cardiac Dysrhythmias	2,476	99 (4.0)	2,377 (96.0)	874	41 (5.1)	763 (94.9)	0.1797
Hospitalization	2,610	142 (5.44)	2,468 (94.56)	870	150 (17.24)	720 (82.76))	<0.0001

Abbreviation: GI, gastrointestinal

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Cox proportional hazard regression models were constructed to estimate hazard ratios (HRs) and 95% confidence intervals for the risk of health outcomes associated with pica. Multivariate adjustment was performed for demographic variables: gender, age, year of diagnosis and region followed by addition of iron deficiency, which is a key predictor of pica, to the models.

Finally, the models were adjusted for significant predictors of pica (as discussed in chapter 3) for adults to include mood disorders, anxiety disorder, smoking and obesity. Unadjusted and multivariate hazard rates yielded by Cox proportional hazards model for all of the outcomes of pica for adults' ages 18 to 64 years are reported in Table 4.6. The data suggest that pica cases were more likely to have other eating disorders than were controls in both unadjusted and adjusted models.

Figure 4.2a: Percent of patients ages 18 to 64 years that developed study outcomes in the 12 month follow-up period estimated by Kaplan Meier failure curves, stratified by pica cases and controls

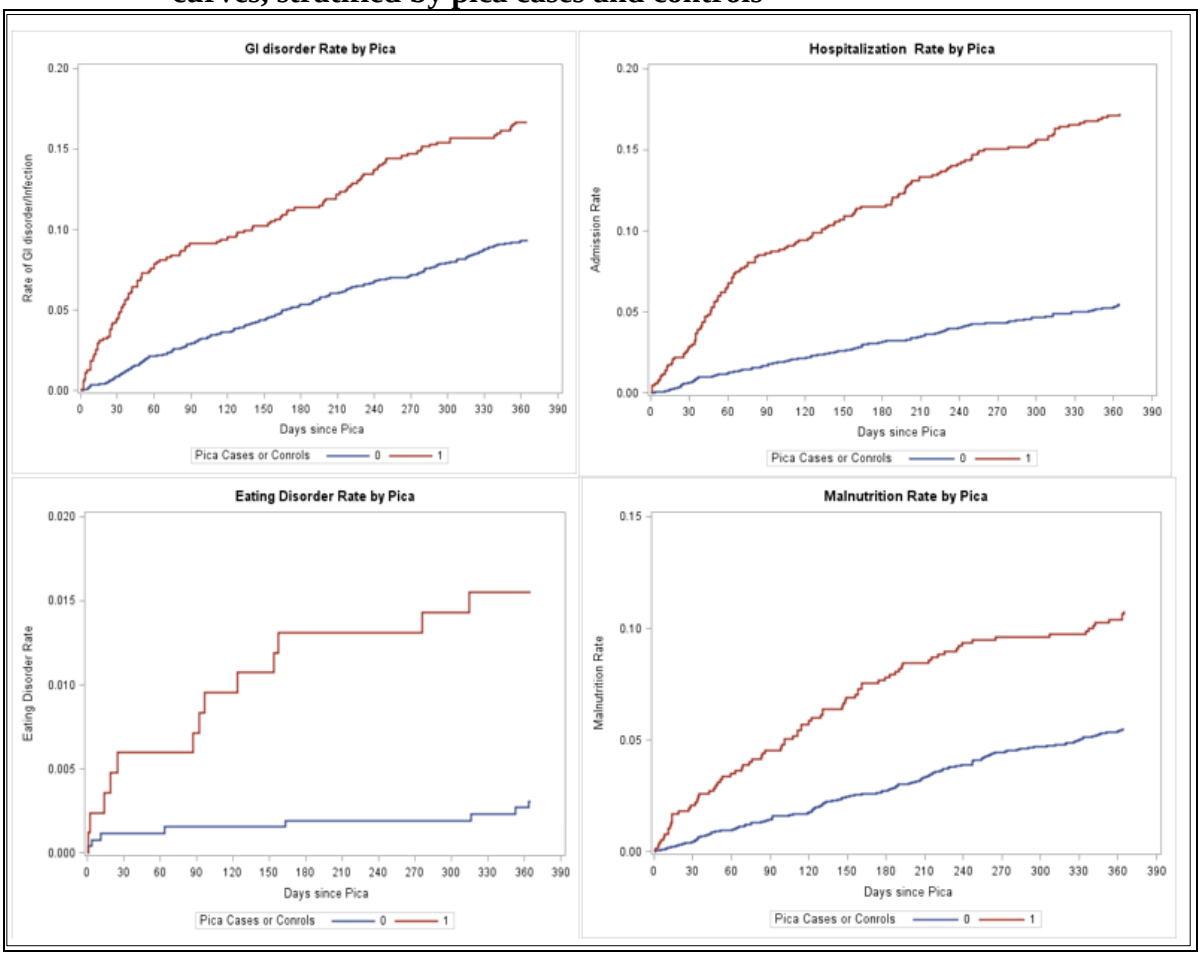
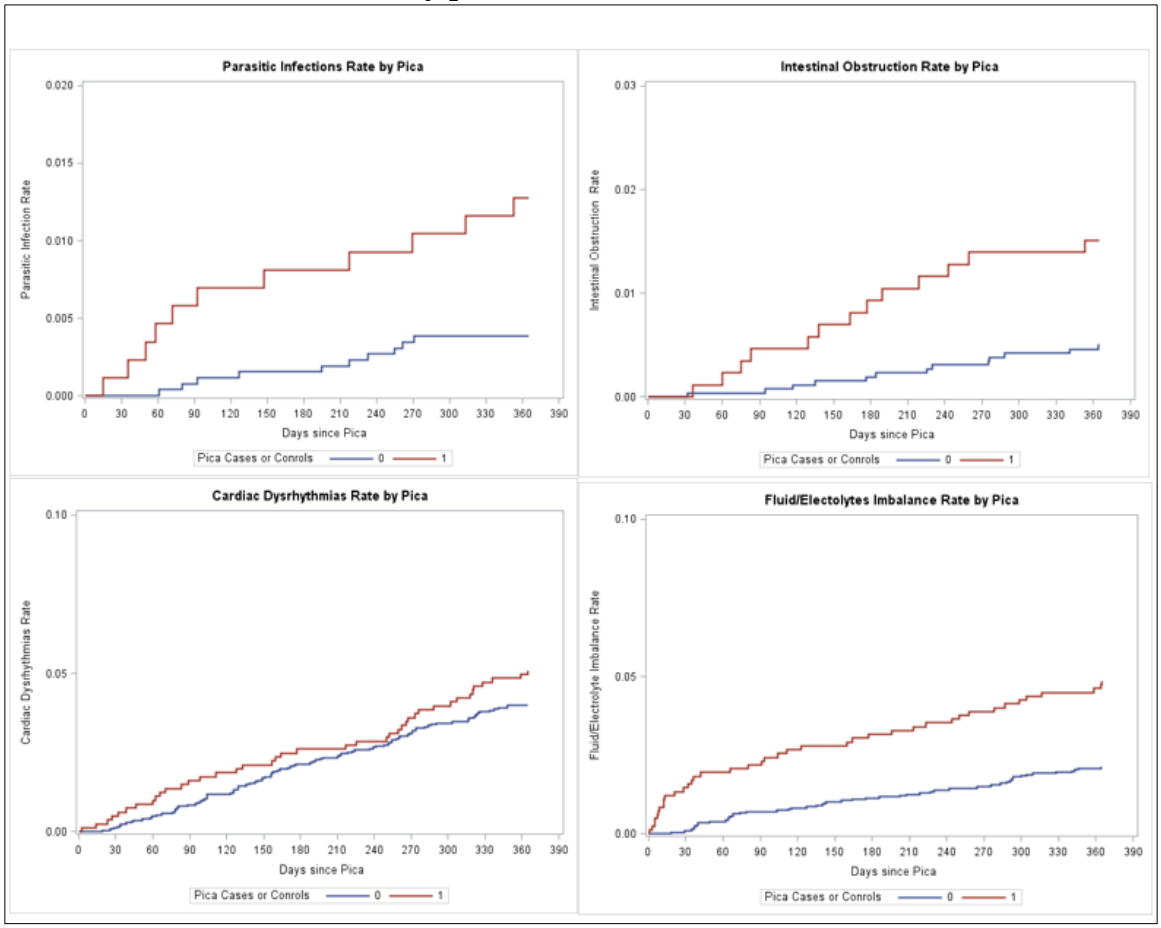


Figure 4.2b: Percent of patients ages 18 to 64 years that developed study outcomes in the 12 month follow-up period estimated by Kaplan Meier failure curves, stratified by pica cases and controls



After controlling for demographic variables, iron deficiency and significant predictors including mood disorder, anxiety disorder, smoking and obesity, adults with pica were about 6 times more likely to have eating disorders (HR: 5.57, 95% CI: 2.22, 13.95), about 3 times more likely to have parasitic infections (HR: 3.12, 95%CI: 1.24, 7.85) and twice as likely to have fluid or electrolyte imbalance (HR: 2.20, 95%CI: 1.41, 3.45), and malnutrition (HR: 2.01, 95% CI: 1.50, 2.70) compared to those without pica. Eating disorders actually exhibited an increase in hazard ratio after adjustment for demographic variables, iron deficiency, mood disorder, anxiety disorder, smoking and

obesity demonstrating that this outcome was confounded by these adjusted variables. These models were evaluated for proportional hazard violations, as discussed in chapter 2, and were found to have no violations. However, there was a violation of proportional hazard for hospitalizations and GI disorders and infections. Therefore, time dependent hazard models were created to examine these outcome variables. We found that adults with pica were about 6 times more likely to be hospitalized in the first 75 days (HR: 5.56, 95%CI: 3.71, 8.34) after pica diagnosis, as displayed in Table 4.7, and about three times as likely to be hospitalized after the first 75 days (HR: 2.50, 95% CI: 1.84, 3.39) compared to controls, as suggested by Hypothesis 4. Moreover, adults with pica were three time more likely to have GI disorders and infections in the first 75 days (HR: 2.78, 95% CI: 2.05, 3.76), which was significant, compared to controls but this association was not significant after the first 75 days. The results of this analysis are displayed in Table 4.6. Moreover, intestinal obstructions (Hypothesis 5) and cardiac dysrhythmias were not significant outcomes of pica in adults.

Table 4.6: Hazard ratios for outcomes of pica in adults 18 to 64 years of age estimated by Cox Proportional Hazards Regression Models

Models	*Outcomes*	*Unadjusted HR (95% CI)*	*Multivariate HR* (95% CI)*	*Multivariate HR^ (95% CI)*	*Multivariate HR# (95% CI)*
1	Eating disorders	5.06 (2.10, 12.22)	5.24 (2.17, 12.64)	5.80 (2.35, 14.32)	5.57 (2.22, 13.95)
2	Malnutrition	2.04 (1.55 2.68)	2.03 (1.55, 2.67)	2.14 (1.60, 2.85)	2.01 (1.50, 2.70)
3	Parasitic infections	3.33 (1.42, 7.84)	3.34 (1.42, 7.87)	3.31 (1.35, 8.16)	3.12 (1.24, 7.85)
4	Intestinal Obstruction	3.04 (1.41, 6.56)	3.05 (1.42, 6.59)	2.47 (1.06, 5.74)	2.19 (0.92, 5.21)
5	Fluid/Electrolyte Imbalance	2.34 (1.56, 3.52)	2.64 (1.55, 4.51)	2.27 (1.47, 3.50)	2.20 (1.41, 3.45)
6	Cardiac Dysrhythmias	1.28 (0.89, 1.85)	1.29 (0.90, 1.86)	1.17 (0.79, 1.74)	1.14 (0.77, 1.71)

*Adjusted for demographic variables (age, gender and region),

^Adjusted for demographics and iron deficiency

#Adjusted for demographics, iron deficiency, mood disorders, anxiety disorders, smoking and obesity; Abbreviations: HR, Hazard Ratio; CI, Confidence Interval

Table 4.7: Hazard ratios of hospitalizations associated with pica in adults 18 to 64 years of age estimated by time dependent Cox Proportional Hazards Regression Models

Outcomes	*Time dependent HR[#]*	*95% CI*
Hospitalization		
<75 days after pica diagnosis	5.56	3.71-8.34
75 - 365 days after diagnosis	2.50	1.84-3.39
GI disorders and Infection		
<75 days after pica diagnosis	2.78	2.05-3.76
75 - 365 days after diagnosis	0.99	0.76-1.29

[#]Adjusted for demographics, iron deficiency, mood disorders, anxiety disorders, smoking and obesity
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval

Mediation for hospitalization

As discussed above, this study indicates that adults with a diagnosis of pica, when compared to matched controls without this diagnosis, were about 6 times more likely to be hospitalized in the first 75 days after diagnosis and about three times more likely thereafter, 6 times more likely to have an eating disorder (other than pica) and about three times more likely to have a GI disorder or infection within 75 days after a diagnosis of pica. Cox proportional hazard regression models were created to test the direct relationship of eating disorders and GI disorders or infections with hospitalization. Pica was added to the models to evaluate the effect of mediation due to pica in these relationships. The unadjusted rates and adjusted results from Cox proportional hazard models, shown in Table 4.8 indicate that patients with eating disorders and GI disorders or infections did not have a higher rate of hospitalizations compared to controls. Therefore, we conclude that hospitalization is an independent outcome of pica in adults

and pica is not a mediator of hospitalizations due to other disorders such as eating disorders and GI disorders or infections.

Table 4.8: Failure rates for hospitalizations estimated by Kaplan Meier method and hazard ratios estimated by Cox Proportional Hazards Regression Models in cases and controls ages 18 to 64 years with and without eating disorders and GI disorders and infections in the look-back period

	Without disorders			*With disorders*					
Variables	*Total*	*Failed n (%)*	*Censored n (%)*	*Total*	*Failed n (%)*	*Censored n (%)*	*p-value*	*HR* (95%CI)*	*aHr (95%CI)*
Eating disorder	3,437	287 (8.35)	3,150 (91.65)	43	5 (11.63)	38 (88.37)	0.3618	0.99 (0.41, 2.45)	0.66 (0.27, 1.63)
GI disorders/infection	3,057	249 (8.15)	2,808 (91.85)	423	43 (10.17)	380 (89.83)	0.1523	1.17 (0.84-1.63)	1.07 (0.77,1.50)

HR* = Hazard Ratio adjusted for demographic and significant predictor variables, Abbreviations: aHR, Hazard Ratio adjusted for pica; CI, Confidence Interval

STRATIFICATION

Stratified Cox proportional hazards models were created for each study outcome for both children and adults in this is matched case control study. The results of this analysis were similar to the results from the un-stratified models for all variables, with the exception of malnutrition for children, suggesting robustness for our main analyses. We believe that the differing results for malnutrition were due to the small sample sizes. All stratified models for children and adults with adjusted hazard ratios and 95% confidence intervals are described in Appendix C.

EXPLORATORY ANALYSIS

Outcome analysis of data from children and adult suggests that hospitalization was a significant outcome of pica. However, it is not known from this analysis whether these hospitalizations were primarily due to pica or due to other risk factors not accounted for in this analysis that differed in frequency between patients with and without pica. The primary causes of hospitalization for patients in both groups are listed

in Table 4.9. Children with pica were hospitalized mostly for mood disorders and controls mostly for respiratory disorders. We explored the types of mood disorders that were predominant causes of hospitalizations in children with pica and found that manic episodes of bipolar disorders constituted about half of these hospitalizations. It is important to note that mood disorders in children are predictors of future diagnosis of pica, as discussed in chapter 3.

On the other hand, adults with and without pica were mostly hospitalized for pregnancy complications due to abnormalities of uterus, diabetes or trauma to the perineum and vulva due to delivery. As discussed in chapter 3, a higher proportion of women with pica were pregnant compared to those without pica. However, in our study, pica cases were no more likely than controls to be hospitalized due to pregnancy complications, suggesting that pica may or may not be a contributor to these hospitalizations. Therefore, the association of hospitalizations with pica, at least in adults, needs to be further examined.

This study has revealed several significant outcomes of pica which could be accounted for by over-utilization of healthcare services leading to more frequent diagnosis of these outcomes in patients with pica. We explored the possibility of over-diagnosis in patients with pica by comparing acute outcomes that were unrelated to pica between cases and controls. These control outcomes, including otitis media and periorbital and orbital cellulitis for children and ischemic heart disease and fractures for adults, were analyzed by Cox proportional hazard models. Patients with these conditions in the 12 month look back period were excluded from this analysis. The results, as shown in Tables 4.10 and 4.11, suggest that children and adults in this study were at a higher

risk of experiencing some of these control outcomes. This analysis leads us to conclude that our results may be impacted slightly by selection bias for cases who have higher utilization of healthcare service, especially in adults.

Table 4.9: The 5 most frequent causes of hospitalization in children and adults, stratified by patients with and without pica

	Children		Adults	
Reason for Hospitalization	***Cases (n= 39) Rank (%)***	***Controls (n= 32) Rank (%)***	***Cases (n= 150) Rank (%)***	***Controls (n= 142) Rank (%)***
Mental Disorder	1 (39)		5 (7)	4 (6)
Respiratory disease	2 (15)	1 (25)		
Injury Poisoning	4 (5)	2 (16)		4 (6)
Skin Disease		3 (13)		
Genitourinary disease		4 (9)	4 (15)	3 (10)
Digestive disease	3 (5)	4 (9)	3 (12)	3 (10)
Pregnancy Complications			1 (30)	1 (31)
Ill Defined Conditions	4 (5)			
Infectious and parasitic disease	4 (5)			
Nervous ystem disorders	4 (5)			
Neoplasm			2 (18)	2 (11)
Circulatory disease				
Blood Disease	4 (5)			

Table 4.10: Distribution and hazard ratios for Otitis Media and Periorbital and Orbital Cellulitis associated with pica estimated by Cox Proportional Hazards Regression Models in children ages 2 to 17 years

Children's Outcomes	Controls			Cases			p-value	HR	95% CI
	Total	Failed n(%)	Censored n(%)	Total	Failed n(%)	Censored n(%)			
Otitis Media	2,172	362 (16.67)	1,810 (83.33)	639	125 (19.56)	514 (80.44)	0.0994	1.251	1.10-1.42
Periorbital and orbital Cellulitis	3,148	4 (0.13)	3,144 (99.87)	1,048	3 (0.29)	1,045 (99.71)	0.2738	2.25	0.50-10.06

*Adjusted for demographic and significant predictor variables
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval

Table 4.11: Distribution and hazard ratios for ischemic heart disease and fracture associated with pica estimated by Cox Proportional Hazards Regression Models in adults ages 18 to 64 years

Adults Outcomes	Controls			Cases			p-value	HR	95% CI
	Total	Failed n(%)	Censored n(%)	Total	Failed n(%)	Censored n(%)			
Ischemic heart disease	2,553	29 (0.14)	2,524 (98.86)	838	21 (2.51)	817 (97.49)	0.0042	2.27	1.53-3.34
Fracture	2,325	233 (10.02)	2,092 (89.98)	775	90 (11.61)	685 (88.39)	0.1962	1.16	0.94-1.42

*Adjusted for demographic and significant predictor variables
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval

Finally, evaluation of the clinical outcomes of pica that we examined suggest that children and adults with pica are more likely to be hospitalized (Hypothesis 4) in the first 75 days after diagnosis of pica. The likelihood of hospitalization continued to be significantly increased for the rest of the 12 months period in adults but the increase was not significant in children. Intestinal obstruction could not be evaluated in children, but was not a significant outcome of pica in adults (Hypothesis 5). Moreover, eating disorders (other than pica), GI disorders or infections, parasitic infections and fluid or electrolyte imbalances are also significant outcomes of pica. In addition to these outcomes, lead poisoning in children and malnutrition in adults are significant outcomes of pica in adults.

Chapter 5: Discussion

Pica is an eating disorder that has been recognized as abnormal eating behavior for centuries[6] but was included in the DSM criteria as an eating disorder about two decades ago. Pica was associated with iron and other nutritional deficiencies in a number of studies.[1,8,9,18,20] AHRQ studies have suggested associations of eating disorders with a number of medical conditions,[30] but none of these associations have been proven. Our study is the first population based study that included medical conditions, psychiatric disorders, behavior disorders such as smoking and alcoholism, and laboratory biomarkers as possible predictors of pica, which were examined in both in-patient and out-patient settings. Moreover, this study examined the role of iron deficiency as a mediator of pica. Finally, ours is the first population based study to explore subsequent outcomes of pica.

DEMOGRAPHIC VARIABLES AND PICA

Eating disorders, including pica, are more prevalent in females, adolescents and young adults.[1,10,11,30] Our findings are in in agreement with previously published studies[30] in finding a greater frequency of pica cases being women than men. The majority of the pica cases were relatively young rather than older individuals. Most (33%) of the pica cases were children between 2 to 5 years of age rather than adolescents or young adults. We believe it is not plausible that 2 to 5 year age group was consuming large amounts of ice or had pagophagia, the most common form of pica.[1,8-10] It is more likely that these children consumed dirt (geophagia) or other substances that may be accessible to them, rather than ice (pagophagia). This finding was also supported by other studies involving children[11-13,72] including a Jamaican study where the majority (85%) of the children with pica were under 5 years of age and they obsessively consumed dirt by

the handful.[11] In comparison, studies involving adults reported pagophagia as the predominant type of pica.[1,8-10] An exception is in pregnancy where geophagia is reportedly as a common type of pica.[73] Due to the nature of the data examined in this study, the information regarding type of pica was not accessible, but we believe that children with pica, due to their younger age, were more likely to consume dirt and other similar substances, as previously reported, while most adults had pagophagia. Most adults with pica in our study were 40 to 49 years of age, a range that included the mean age of adults with pagophagia reported by Barton and colleagues.[8] In our study, 16% of study participants, as shown in Figure 3.2, were in this age group and most of these adults were females of reproductive age, and therefore prone to developing iron deficiency, which is associated with pica.[47] However, in our study, the association of pica with age could not be measured because age was one of the demographic factors used for matching cases and controls. Nonetheless, the higher representation of pica in certain age groups was very informative in identifying high risk groups.

The regional prevalence of pica in the United States is of interest. The AHRQ report suggested that hospitalizations due to eating disorders were more common in the South than other regions.[14] We found pica to be more prevalent in the southern United States, followed by the Midwest, West and Northeast. Eating of dirt has been described as popular in the South, and has been attributed to nutrient deficiencies, pregnancy and childhood behavior.[5,74] White dirt, known as kaolin, is found on the Georgia coastline and other parts of the world.[74] Therefore, custom of eating dirt may explain the higher prevalence of geophagia in the South. But explanations for other types of pica are lacking. The regional differences we observed cannot be attributed to the study

population in CDM. Comparing to U.S. private insurance population, CDM market penetration was higher in Midwest and Northeast compared to other regions[67] Therefore, our finding of higher rates of pica in Southern United States compared to other regions is very interesting and informative for identifying high risk groups.

Pica in pregnancy

Pregnancy has been associated with pica in several studies.[9,73] This was confirmed in the current study even though pregnancy was not a primary focus. The majority of our study population of individuals with pica were women (69.65%), as shown in Table 3.1, and most were of potential childbearing age. Moreover, a significantly higher percentage of adult women with pica were pregnant compared to women that did not have pica ($p<0.0001$), as shown in Table 3.2. This was particularly true for all women between the ages of 18 and 29 years, of whom 17% of women with pica and 3% without pica were pregnant ($p<0.0001$). A study that is matched based on pregnancy might further elucidate the possible association of pica and pregnancy in these age groups. Cravings for certain foods are common during pregnancy, and include cravings for nutritional substances as well as non-nutritional items such as ice, dirt, corn starch etc. Olfactory cravings for some of these substances are also described.[75] Some of this behavior has been attributed to the nausea and morning sickness that is experienced during pregnancy but there are no physiologic associations that have been suggested.[5] Pregnancy cravings and associations with pica should be explored further by another study design, since specific cravings are not likely to be described in insurance claims databases.

MEDICAL CONDITIONS AND PICA

Iron deficiency and pica

The association of pica with iron deficiency is well established[1,3,8,9,18,72,76] and is confirmed in our study. We observed that, approximately 3% of children with pica and less than 1% of controls ($p<0.0001$), and 24% of adults and approximately 2.5% of those without pica ($p<0.0001$) were iron deficient. A higher prevalence of iron deficiency was found in children of all ages when compared to controls. It is difficult to compare the prevalence of iron deficiency in pica with other studies due to the wide range of reported prevalence in published literature from 44 to 94%, as discussed in chapter 1.[1,8,9,18] We also found that children with pica were 5 times and adults were 12 times more likely to be iron deficient than those without pica, after adjusting for demographic and related medical conditions. These findings were in agreement with the systematic review conducted by Miao at el. who reported similar estimates for pica in children (OR = 4.23, 95% CI 1.52-11.78).[18] To our knowledge, population based studies of the combined prevalence of iron deficiency in both genders and in non-pregnant females have not been reported previously. We found that 25% of women with pica and about 3% of women without pica were iron deficient. These proportions were lower than previously reported prevalence of pica, 13% in iron deficient female blood donors compared to 2% in controls, by Spencer and colleagues.[3] However, blood donors are screened and deferred from donations if they are anemic, which removes the most severe cases of iron deficiency and leads to an underestimation of iron deficiency and pica in the population. Overall, our findings indicate that iron deficient children and adults are high risk groups for pica.

Due to the strong association of pica with iron deficiency and increased demands for iron in females during pregnancy, we wanted to explore the pregnancy status of iron deficient female cases and controls in this study. Among the females in our study that were pregnant, 10% with pica and 10% without pica were iron deficient (p=0.8658). This finding was in agreement with a study conducted by Smulian and colleagues, who found no difference in prevalence of iron deficiency or anemia in pregnant women regardless of their pica status (OR=0.92, p>0.05).[9] Only 237 women between 13 and 49 years of age in our study were pregnant, and cases and controls were not matched based on pregnancy. Therefore, we cannot determine whether or not pica and iron deficiency are related during pregnancy. Further studies are needed to examine the association between pregnancy and pica.

Our study evaluated for the first time, to our knowledge, the mediation effect of iron deficiency on pica. We found that iron deficiency was not a mediator for medical conditions I, including eating disorders, malnutrition, GI disorders and infections, lead poisoning and parasitic infections, in both children and adults. However, it was a mediator for menstrual bleeding disorders in adult women, which will be discussed later in this chapter.

Iron deficiency is a major public health concern and one of the most significant independent predictors of pica in both children and adults, as found in this and previous studies.[77] An association between iron deficiency and diminished cognitive function, which is correcTable by iron repletion, is also well established.[78] In young children, iron deficiency has shown to be associated with poor psychomotor performance and short term memory, changes in behavior, increased irritability, and reduced responsiveness to

stimuli.[79] Iron deficiency anemia is also responsible for poor pregnancy and perinatal outcomes in women.[77] This debilitating nutritional deficiency can be exacerbated by pica. Patients with iron deficiency should be questioned regarding pica and treatment should be provided.

Eating disorders and pica

Eating disorders other than pica include bulimia nervosa, anorexia nervosa, rumination disorder, psychogenic vomiting and other less-specified disorders. These can co-exist with pica, mostly in adolescent females who try to control their weight or suppress their hunger by eating substances that do not contribute calories.[7,33] However, this type of behavior is not likely to occur in children 2 to 9 years old, who comprised 45% of our study population. The prevalence of other eating disorders in our study was approximately 6% in 2 to 5 year old children compared to 1% in control children ($p<0.0001$) and 5% in 6 to 9 year old children compared to 0.2% in controls ($p<0.0001$). In examining the diagnosis codes of eating disorders, we found that 61.1% of 2 to 5 year old and 45.5% of 6 to 9 year old children in our study, with or without pica, were diagnosed with feeding problems. We elected in our study to classify feeding problems in infancy and childhood, including polyphagia (increased appetite), as eating disorders, since they have been found to be predictive of eating disorders. The current consensus in the literature is that feeding and eating disorders should be merged into one category.[13] In particular, picky eating has been shown to be predictive of anorexia and pica has been associated with bulimia in early adolescence.[36] In this manner, we found that children and adults with pica were 5 times more likely to have another eating disorder, after

adjusting for all other variables included in the study. In some cases we found that pica co-existed with multiple eating disorders.

Eating disorders were also evaluated as an outcome of pica in this study. We found that in the 12 month follow-up period 3% of children and 2% of adults with pica, who did not have pre-existing eating disorders, received a diagnosis of an eating disorder after they were diagnosed with pica, compared to <0.5% of controls ($p<0.0001$ for both). We estimated that children with pica were 7 times more likely and adults 6 times more likely than controls to develop another eating disorder, which was also a statistically significant difference.

Eating disorders are both strong predictors and outcomes of pica in our study. This is in agreement with the AHRQ report suggesting that more than one eating disorder can be present at the same time.[30] A diagnosis of an eating disorder is made clinically based on information provided by patients, and symptoms may be present for some time before diagnosis. Our data, which is based on insurance claims that result from physician or other healthcare visits, suggest that pica and other eating disorders often coexist. Therefore, both children and adults with any feeding problems and eating disorders should be monitored and questioned about pica.

Malnutrition and pica

Malnutrition has been associated with eating disorders, including pica, in a number of studies.[11,13,18] In our study, we found no difference in prevalence of malnutrition in cases and controls except in adults 30 to 39 years of age, and children aged 6 to 9 years. Adults with pica were 1.5 times more likely to be malnourished. Therefore, malnutrition was a significant predictor of pica in adults but not in children.

We examined the association of malnutrition with pica in females and found that this association was not statistically significant, after adjustment for menstrual bleeding disorders and all other studied variables (Table 3.9). We also found that the association between malnutrition and pica was not mediated by iron deficiency. This is in agreement with the study by Bay and colleagues, who found that the association of iron deficiency anemia with zinc ($p = 0.97$) and selenium ($p = 0.33$) was not significant. Therefore, based on the above discussed findings, we believe that malnutrition was not a strong predictor of pica.

The AHRQ study previously suggested that malnutrition is often secondary to eating disorders.[30] We found this to be true in adults with pica who were twice as likely to be malnourished than controls as a consequence of pica (HR: 2.01, 95% CI: 1.50, 2.70). Children with pica were about 3 times as likely to have malnutrition (HR: 3.00, 95%CI: 1.24, 7.27) as a consequence of pica, after adjusting for demographic variables and iron deficiency, but the association was not significant after adjusting for significant predictors such as non-GI bleeding, ASD, mood disorders and obesity (HR: 2.46, 95%CI: 0.96, 6.35).

With geophagy, soil consumption can result in decreased absorption of nutrients,[23,25] as discussed earlier, which may result in malnutrition. Moreover, consumption of non-nutritional substances in pica probably prevents consumption of food in appropriate quantities. Therefore, it is not surprising that malnutrition is a significant outcome of pica. However, we do not know if deficiencies in nutrients other than iron occur with pica, and this should be explored in a future studies.

In our study malnutrition was found to be a significant outcome of pica, at least in adults. Therefore, it would be clinically important to recognize and treat both pica and any associated nutritional deficiencies.

Gastrointestinal disorders and infections and parasitic infections in pica

Gastrointestinal disorders including enteric infections have been associated with pica in previous studies.[11,13] More specifically, parasitic infections such as *Giardia*, *Entamoeba* and helminthes, including *Ascaris* and *Trichuris* species, have been associated with geophagia.[11,72] These infections and GI disorders may themselves lead to deficiencies of micronutrients such as iron, and are associated with pica.[11] We studied GI disorders and infections, including enteric non-parasitic infections and GI diseases as discussed in chapter 2, separately from parasitic infections. We found that children with pica were about three times as likely and adults were twice as likely to have GI disorders and infections as were controls without pica. Parasitic infections, on the other hand, were not predictive of pica in either children or adults. Furthermore, the association of these GI disorders and parasitic infections with pica was not mediated by iron deficiency, in contrast to suggestions in other studies.[39,40] Therefore, we conclude that GI disorders and infections are predictors of pica in children and adults, and are independent of iron deficiency.

Disorders of GI tract, whether they are due to bacterial infections, parasitic infections or other reasons, usually cause similar symptoms such as diarrhea, nausea and vomiting. The relationship between parasitic infections and pica may be different from that of other GI disorders. On the other hand, dirt has been known to be used in anti-diarrheal preparations[80] and has been used by pregnant women to relieve their symptoms

of morning sickness.[22] It is also possible that the protective effect of microbes and toxins entering the gut, discussed in chapter 1, with dirt works better for parasites than other types of organisms. These relationships need to be explored further with different types of pica and enteric parasites, in a future study.

On the other hand, GI disorders and infections and parasitic infections can be a consequence of pica due to consumption of bacteria, parasites and toxins contaminating dirt or soil.[11-13,38] We found that children with pica were twice as likely to develop GI disorders and infections. Moreover, adults with pica were 4 times likely to get GI disorders within the first 75 days of a pica diagnosis, compared to controls, which was a statistically significant difference. However, development of GI disorders and infections in adults after the first 75 days was not significantly different in pica cases and controls, leading us to believe that GI disorders and infections are acute outcomes of pica and mostly occur soon after a diagnosis of pica. Moreover, children and adults with pica were three times as likely to acquire parasitic infections as those without pica. These findings are not surprising and are in agreement with the AHRQ data suggesting that GI disorders and infections are often secondary to eating disorders.[30] However, it is difficult to draw conclusions regarding pagophagia, because we did not have information on the types of pica in our study.

Our data suggest that GI disorders are an acute outcome of pica in children and adults, and also a predictor of pica in children. However, parasitic infections were an outcome of pica. Our study is based on claims data, so we only captured pica diagnoses resulting from patient visit to practitioners. However, pica may not be reported until after the diagnosis of a GI disorder or infection, which may lead us to believe that they are

predictors of pica. Based on our analysis, we can report that GI disorders and infections and parasitic infections are significant outcomes of pica. This is biologically plausible since dirt contains bacteria and parasites that can cause infections. Longitudinal studies are suggested to clarify temporal sequences of pica and GI disorders and infections.

Lead Poisoning and pica

Lead poisoning can lead to iron deficiency anemia which is a predictor of pica. We had very few (n<10) children and only one adult with lead poisoning in our predictor study. We found that lead poisoning was not a predictor of pica in children. We could not study the association of pica with lead poisoning in adults due to the small sample size.

Lead poisoning can be an outcome of pica particularly with consumption of dirt contaminated with lead or old lead paint in children. We found that a significantly higher number of children with pica were later diagnosed with lead poisoning compared to controls. There were no adults that were diagnosed for lead poisoning as a consequence of pica in our study. Children with pica were 11 times more likely to be diagnosed with lead poisoning compared to controls, after adjustment for iron deficiency and other predictor variables. This is in agreement with the AHRQ data suggesting that lead poisoning is often secondary to eating disorders.[30] Therefore, we believe that lead poisoning is a significant outcome of pica in children. Lead is associated with anemia, GI disturbances and cognitive impairment in children.[43] Iron deficient children that are exposed to lead can have higher blood lead levels than those that were not iron deficient.[81] Therefore, all children who consume dirt or other non-nutritional substances should be screened for lead toxicity.

GI and Non-GI Bleeding in pica

We explored the predictability of GI and non-GI bleeding for pica. GI and non-GI bleeding were found to be more prevalent in children and adults with pica compared to controls ($p<0.0001$ for both children and adults). Among children, the increased prevalence of these pica-associated disorders was seen in those that were 2 to 5 years old. Moreover, children with pica were twice as likely to have non-GI bleeding which was also statistically significant. However, the association of GI bleeding with pica in children did not show statistical significance, after adjusting for other predictor variables. In adults, the association of GI and non-GI bleeding with pica was not statistically significant. The relative weak association of non-GI bleeding with pica in children alone was puzzling. We examined the diagnosis codes that were most prevalent for non-GI bleeding and found that hematuria (blood in urine) and epistaxis (nose bleed) were included. To our knowledge, these conditions are not directly related to pica in published studies. In fact, we found no studies of a possible association between pica and GI and non-GI bleeding. Any future studies of pica should distinguish various types of non-GI bleeding disorders, particularly in children.

Menstrual bleeding disorders and pica

Menstrual bleeding disorders were studied in female children from 13 to 19 years old but very few ($n<10$) were given this diagnosis. Therefore, the predictability of this disorder for pica in children could not be further evaluated.

Among adult females, the prevalence of menstrual bleeding disorders was 22% in those with pica compared to around 9% in controls which was statistically significant ($p<0.0001$). However, this relationship is partially mediated by iron deficiency as

demonstrated by the decrease in odds ratio when iron deficiency was added to the model in females. But after adjustment for all predictor variables, as shown in Table 3.9, women with pica were still twice as likely to have a menstrual bleeding disorder compared to controls which was a statistically significant difference. Comparable data was not available, because to our knowledge, no previous studies have looked at the relationship of menstrual bleeding disorders with pica.

A European study that explored the association of iron deficiency with menstrual bleeding disorders suggested that the prevalence of heavy menstrual bleeding was 27% in women 18 to 57 years of age and 63% of these women were iron deficient.[47] This prevalence of iron deficiency was probably an underestimate because all women with menstrual bleeding disorders do not seek treatment for iron deficiency.[47,48] If that were true in our study, it would result in decreased number of claims filed in the Clinformatics Data Mart. Whether this possible underestimation of iron deficiency will impact the association of menstrual bleeding disorders with pica is unknown. Moreover, the mediationed of this association by iron deficiency should be explored in future studies. But we conclude from this study that menstrual bleeding disorders are strong predictors of pica.

RLS and pica

RLS and pica are both associated with iron deficiency and can coexist, particularly in women.[1,3] We had very few children ($n<10$) with RLS in our study. Therefore, its predictability for pica could not be explored in children. However, in adult women the proportion of pica was significantly higher compared to controls ($p<0.0066$).

Adult females with pica were about 3 times more likely to have RLS compared to those without pica (OR: 2.62, 95%CI: 1.10-6.61) but this association was much weaker and not significant after adjustment for other predictor variables. We also found that the relationship of pica and RLS was not mediated by iron deficiency in adult women. This is contrary to the study of Allen and Early in which RLS was highly associated with iron deficiency, particularly cerebral iron deficiency (decreased iron in cerebrospinal fluid), and is relieved with iron repletion.[50] Our results are in agreement with those of the Bryant and colleagues, who did not find a strong correlation of RLS with iron deficiency.[1] Therefore, we conclude that RLS is not a predictor of pica.

Intestinal obstruction and pica

Intestinal obstruction have been reported as a complication of pica.[38,51,52] Because we had very few children (n<10) with intestinal obstruction in our study, we could not study the association of intestinal obstructions with pica in children. We found a significantly higher prevalence of intestinal obstruction in adults with pica than in controls ($p = 0.0029$). However, intestinal obstruction was not a significant outcome of pica in adults after adjustment for demographic and significant predictor variables. Cases of intestinal obstruction that were previously reported as a consequence of pica were mostly in individuals with mental retardation[51] but also in other groups.[52]

Intestinal obstruction in patients with pica can be attributed to consumption of clothing, dirt and other substances. We did not ascertain such cause and effect relationships in our study, and, to our knowledge, there are no studies exploring intestinal obstructions as an outcome of pica. Therefore, at present we conclude that intestinal obstructions are not a common or significant outcome of pica.

Dental complications and pica

In children we found no difference in cases and controls with respect to dental complications, and dental complications were not a significant outcome of pica. In adults, there were no cases or controls with dental complications in our study, perhaps because patients customarily see their dentists for such complications, and these visits are covered by dental rather than medical health insurance. Clinformatics databases only include claims for medical insurance. Also, we may have fewer study participants with pagophagia than other types of pica, and pagophagia is the only type of pica reported to cause dental complications.[53,54] Therefore, we were unable to draw any conclusions about the association of dental conditions with pica.

Fluid and electrolyte imbalances and pica

Fluid and electrolyte imbalances are well-recognized complications of eating disorders[30,56,57] but have not been associated with pica to our knowledge. In this study, we found that children and adults with pica had more episodes of fluid and electrolyte imbalance than did controls. Moreover, children with pica were about 3 times and adults with pica were about twice as likely to develop fluid and electrolyte imbalances compared to controls. Fluid and electrolyte imbalances such as hypokalemia, hypoglycemia, and acid base imbalances can be mild or severe and life-threatening.[57] Based on our findings, it is important to monitor patients with eating disorders, including pica, for these outcomes. Future studies should explore specific fluid and electrolyte abnormalities as outcomes of pica. We conclude that fluid and electrolyte imbalances are a significant outcome of pica in both adults and children.

Cardiac dysrhythmias and pica

The AHRQ report suggested that cardiac dysrhythmias occur in patients with eating disorders, but this, and to our knowledge other studies, did not examine dysrhythmias as outcomes of pica.[30] Their findings were based only on hospitalized patients and included those with any eating disorders and not specifically pica. We found that children and adults with pica did not have a higher frequency of cardiac dysrhythmias compared to controls, and therefore dysrhythmias were not a significant outcome of pica. Therefore, at present there is no evidence of an association between pica and cardiac dysrhythmias.

PSYCHOLOGICAL CONDITIONS AND PICA

The AHRQ data suggested that 31% of hospitalized children with pica had autism spectrum disorders (ASD), and that other psychological disorders may also coexist with pica.[30] We found that 9% of children with pica compared to less than 1% of controls had ASD, 6% of cases compared to 2% of controls had mood disorders, 5% of pica cases compared to less than 2% of controls had anxiety disorders, and 1.5% of cases compared to less than 0.2% of controls had OCD and schizophrenia ($p<0.0001$ for all comparisons). Among adults mood and anxiety disorders were most prevalent psychological disorders, 19.08% cases compared to 11.03% controls had mood disorders and 13.45% cases and 7.51% controls had anxiety disorders($p<0.0001$).

We also found that children with pica were 7 times more likely to be autistic compared to controls, after adjustment for demographic and other predictor variables, and this difference was statistically significant. Reasons for an association between ASD and pica are not clear. But autistic children often struggle with feeding problems[82] which is a

risk factor for pica. However, we found ASD to be a highly significant predictor of pica in children even after adjusting the final model for eating disorders. A future study should explore the mechanisms of the relationship of ASD and pica.

We found adults and children with pica to be about twice as likely to have mood disorders compared to controls. Also, adults with pica were about twice as likely to have anxiety disorders compared to controls. A future study to focus on pica as related to specific mood disorders that are more common in adults versus children would be of interest. But, in this study and in contrast to what was suggested in some studies,[61] OCD was not a predictor of pica in children or adults.

Associations of pica with psychological disorders suggest a need to study the neural pathways that are common to these disorders. Treatment with SSRIs for depression and other disorders can also relieve pica, which further supports common neural relationships.[61,62] Our study was the first to our knowledge to measure the association of psychological disorders with pica. However, longitudinal studies of individuals with these disorders will be necessary to define these relationships. Overall, based on our findings, ASD and mood disorders are strong predictors of pica in both adults and children, and anxiety disorders are strong predictor of pica in adults.

BEHAVIOR DISORDERS AND PICA

Smoking and alcohol are addictive behaviors with features similar to pica. We explored the association of these behaviors with pica. Very few ($n<10$) of the children included in our study were smokers or consumed alcohol. A higher proportion of adults with pica were smokers ($p<0.0001$) and alcoholics ($p=0.058$) compared to controls. Moreover, even after adjustment for demographic and other predictor variables, adults

with pica were twice as likely to smoke compared to those without pica. However, alcoholism was not significantly associated with pica in multivariate analyses. Smokers are accustomed to putting things in their mouths, which may encourage pica behavior. Alcohol and smoking may satisfy the same or different addiction centers in the brain. We found no prior studies examining the relationship of smoking and alcohol with pica. Based on our findings, we conclude that smoking is a predictor of pica in adults.

We also found that a higher proportion of children ($p=0.0008$) and adults ($p<0.0001$) with pica were obese compared to controls. The prevalence of obesity was significantly higher in older children with pica, especially 6 to 17 years of age comparing to their controls. Moreover, children with pica were 3 times more likely and adults with pica twice as likely to be obese compared to controls. The possibility that older children and adults are using pica as a weight control method could not be ascertained in this study, but has been described in previous studies.[31,35] A longitudinal study that follows children and adults with addictive behaviors up to diagnosis of an eating disorder such as pica would be better inform these associations. For the present we conclude that obesity is a significant predictor of pica in children and adults.

HOSPITALIZATIONS AND PICA

The AHRQ report suggests that pica is the only eating disorder with a trend for increasing hospitalizations. We found that a higher proportion of children and adults with pica were hospitalized compared to controls. Moreover, the rate of all cause hospitalizations in both children and adults with pica was higher in the first 75 days compared to the rest of the follow up year, which indicates that hospitalization is a short term outcome of pica. For example, time dependent hazard models for hospitalization

suggest that children with pica were 7 times more likely to be hospitalized compared to controls in the first 75 days, which was statistically significant, and only twice as likely as controls in the remaining part of the year, which was not significant, after adjustment for demographic and significant predictor variables. Moreover, adults with pica were 6 times more likely to be hospitalized compared to controls in the first 75 days and about 3 times more likely than controls thereafter, after adjustment for demographic and significant predictor variables. Further examination of reasons for these hospitalizations suggest that most children with pica were often hospitalized for mood disorders such as manic episodes of bipolar disorders. Adults with and without pica were mostly hospitalized for complications of pregnancy. It is not known whether the complications of pregnancy in cases and controls were different, but this could be examined in future studies.

Because we were initially skeptical that hospitalizations in pica cases might be more related to other disorders, such as another eating disorder, GI disorders or infections that may coexist with pica, we analyzed the cases and controls in our study for hospitalizations as an outcome of eating disorders and GI disorders and infections. The results indicate that eating disorders were not associated with increased likelihood of hospitalizations. Moreover, adult cases with GI disorders were not more likely to be hospitalized compared to adult cases without GI disorders. However, pica cases aged 2 to 17 years with GI disorders were twice as likely to be hospitalized compared to those without GI disordrs and this relationship was only slightly mediated by pica.

The above findings lead us to conclude that hospitalization is a significant outcome of pica in children and adults. However, rates of hospitalization in pica may be

overestimated as a result of other coexisting acute disorders in our case control cohort. Hospitalizations suggest that pica is not just a disorder of consuming inappropriate substances, but can also lead to complications that may require hospitalization. These hospitalizations are of public health concern and a burden for patients and our healthcare system.

LABORATORY PREDICTORS OF PICA

As discussed earlier, iron deficiency, with or without anemia, is a significant predictor of pica. However, only 28.3% of cases in our cohort had results for biomarkers such as hemoglobin and ferritin which are common and useful indicators of iron deficiency and anemia. This may be due in part to inclusion in the database only of those tests conducted in the labs contracted with Clinformatics. It is important to note that patients with lab results in our study were older, predominantly female and mostly from the southern United States. Also, cases that were pregnant, iron deficient or malnourished, had GI bleeding, non-GI bleeding, menstrual bleeding, and anxiety disorders, or were obese were more likely to have lab results.

Overall, we observed that patients with pica had significantly lower mean RBC count, hemoglobin, hematocrit, MCV, MCH, MCHC, total iron, transferrin % saturation and ferritin compared to controls. The mean hemoglobin level for cases was only 11.19 g/dL (SD: 2.22) compared to 13.02 g/dL (SD: 1.30) for controls. The reference range for hemoglobin is 12.0 to 13.5 g/dL for women and 13.5 to 17.5 g/dL for men.[78] Considering that women were the majority in the case control cohort, mean hemoglobin levels of 11.19 g/dL (SD: 2.22) for cases indicates that some of these individuals had

normal hemoglobin levels but were probably iron deficient without anemia. This is also evident from the mean MCV levels that do not clearly indicate microcytic anemia. However, the mean hemoglobin is not as low as 6 g/dL, as reported in other pica studies,[20,65] which indicates severe anemia. Therefore, based also on the significantly lower levels of ferritin and percent transferrin saturation in cases compared to controls, it is likely that iron deficiency, even without anemia, was a significant predictor of pica in our study, as discussed in Chapter 3. Moreover, cases had significantly higher RDW indicating increased variation in their red blood cell sizes, which is an early, although nonspecific, indicator of iron deficiency. We found that pica cases were 64% more likely to have a one unit (1g/dL) decrease in hemoglobin and 24% more likely to have one unit increase (1%) in RDW compared to controls without pica. Therefore, decreased hemoglobin and increased RDW are significant predictors of pica. These results are in agreement with other studies of iron deficiency in pica.[8]

We did not find serum ferritin to be a significant predictor of pica. This may be due to the fact that less than half of the cases and less than 10% of controls that were tested for hemoglobin also had a ferritin test. The majority of patients with decreased hemoglobin due to iron deficiency would also have decreased ferritin levels. If more patients had ferritin results available in our study, we believe this would have been found to be a significant biomarker, along with hemoglobin and RDW, and therefore useful for screening high risk patients for pica. Serum ferritin needs to be explored further in a future study in patients with pica.

The analysis of laboratory markers in patients with pica has indicated that iron deficiency manifests at some point during one of the long recognized three stages of iron

deficiency and anemia.[78,83] Stage one involves decreased iron stores, which is clinically diagnosed by decrease in serum ferritin. There is no significant decrease in hemoglobin level at this stage. Stage two of iron deficiency is characterized by iron deficient erythropoiesis. Although there is no anemia at this stage, ferritin is decreased, as in stage 1, transferrin saturation is decreased, and there is evidence of decreased hemoglobin within the erythrocytes, as manifested by decreases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). Stage three is characterized not only by decreased iron stores but by the development of iron deficiency anemia.[78]

Our results indicate that, as might be expected in a population prone to develop iron deficiency, that we have a mix of subjects at any of these three stages of iron deficiency. Our study was not designed to examine the association of pica with each stage of iron deficiency. But it would be informative to conduct a future study that correlates the various indicators of iron deficiency so that these stages could be recognized in the individual subjects. A prospective study might also define the stages of iron deficiency where pica manifests itself. In addition to the biomarkers discussed above other biomarkers that are generally not measured for clinical diagnosis such as red cell protoporphyrin and transferrin receptor may also be included to study their relationship with pica. Moreover, other nutritional biomarkers should also be studied in relation to pica, including other essential metals such as zinc. This would provide a more complete understanding of the nutritional manifestations of this eating disorder.

SELECTION BIAS

We were concerned that our results might be biased, with the proportion of outcomes in cases being higher in cases with pica than in controls due to overutilization

of healthcare services by subjects with pica. Therefore, we defined other acute outcomes as controls that are unrelated to pica, such as otitis media, periorbital and orbital cellulitis, ischemic heart disease and fractures, and analyzed these as outcomes of pica. We found two out of four control outcomes to be weakly significant outcomes of pica, which suggests that overutilization of healthcare resources may have introduced some selection bias in our study. Future studies can include additional sensitivity analyses, such as adjusting for number of visits, number of hospitalizations, and whether patients had any mental health provider visits in the 12 months before diagnosis date or index date in the multivariable analyses to address this issue. Furthermore, matching based on number of visits in the 12 month before diagnosis date and index date between cases and controls can also be included in future studies.

CLOSING REMARKS

Our study is the first comprehensive population based study that evaluated the predictors and outcomes of pica in both children (age 2 to 17 years) and adults (age 18 to 64 years), and with findings are potentially generalizable, having been drawn from a large national health claims database. We found iron deficiency, mood disorders and obesity to be predictors of pica in both children and adults. Moreover, ASD was an additional significant predictor of pica in children. In adults, additional significant predictors of pica were anxiety disorders, female menstrual bleeding disorders and smoking. We also observed that iron deficiency mediated the association of pica with menstrual bleeding disorders, which to our knowledge was not previously studied. However, iron deficiency did not mediate the association of pica with eating disorders, GI disorders and infections, malnutrition, lead poisoning and parasitic infections.

The outcomes of pica over time have not been previously studied, to our knowledge. We were able to identify important outcomes of pica, over a 12 month study with retrospective follow-up of cases and controls in a cohort study design, such as acute hospitalizations, GI disorders and infections, and fluid and electrolyte imbalances, and these were observed in both adults and children. Moreover, lead poisoning was noted to be a highly significant outcome of pica in children. These outcomes suggest that pica is a condition that requires ongoing attention by the medical community, with early interventions to prevent adverse outcomes. Finally, we found that eating disorders were both predictors and outcomes of pica, and are likely to co-exist at all stages of pica.

This study also identified a number of important predictors of pica that were not previously reported, to our knowledge, such as psychiatric disorders, eating disorders, obesity and smoking. However, we were not able to explore associations based on the different types of pica such as pagophagia and geophagia. A future study to explore predictors and outcomes of different types of pica would be of interest.

Overall, this study was successful in accomplishing its aims, which were to study predictors and outcomes of pica in the general population. Additionally, we were able to study predictors and outcomes specific to children and adults and to identify laboratory markers that can be utilized for screening for pica. These predictors and outcomes contribute to an enhanced understanding of this disorder.

Chapter 6: Conclusion

Pica still remains an incompletely understood and heterogeneous condition. We examined 5 hypotheses in this study and reached some important conclusions that allow us to bridge gaps in our understanding of pica. Firstly, patients with pica were significantly more likely to be iron deficient than those without pica. Secondly, the association between menstrual bleeding disorders in adult females and pica was mediated by iron deficiency, which strengthens the evidence that iron deficiency at any one of its three stages, is a strong predictor of pica. Thirdly, children (ages of 2 and 18 years) with pica were more likely to have gastrointestinal disorders or infections than those without pica. Moreover, GI disorders and infections were also significant outcomes of pica in both adults and children. Patients with pica were more likely to be hospitalized than those without pica and hospitalization over a 12 month study period, and was most likely to occur in the first 75 days after a pica diagnosis suggesting that complications of pica or associated conditions are likely in the short term. Finally, patients with pica were no more likely to have intestinal obstruction than those without pica.

While testing predefined hypotheses, we also found that pica was associated with a high probability of mood disorders and obesity in both children between 2 to 18 years of age and adults younger than 65 years of age. Also, ASD was an additional predictor of pica in children that was highly significant. Anxiety disorders, female menstrual bleeding disorders and smoking were additional predictors in adults. Finally, associations of medical conditions such as eating disorders, malnutrition, GI disorders and infections, lead poisoning and parasitic infections with pica were not mediated by iron deficiency. Our major findings are summarized in Table 6.1.

Table 6.1: Summary of predictors and outcomes of pica in children ages 2 to 17 years and adults ages 18 to 64 years.

Variables	Children		Adults	
	Predictors	Outcomes	Predictors	Outcomes
Iron deficiency	X		X	
Eating disorder	X	X	X	X
Malnutrition				X
GI disorder/infection		X		X
Lead Poisoning		X		
Parasitic infection		X		X
Menstrual bleeding (female)			X	
Non GI bleeding	X			
ASD	X			
Mood disorder	X		X	
Schizophrenia				
Anxiety disorder			X	
Smoking			X	
Obesity	X		X	
Fluid and electrolyte imbalance		X		X
Hospitalization		X		X

X = Significant predictor or outcome

Laboratory indicators of iron deficiency such as complete blood counts, red blood cell indices, iron studies and serum ferritin were studied as predictors of pica. We concluded that decreased hemoglobin (i.e. anemia) and increased RDW were significant predictors of pica. These parameters can be used to screen for pica associated with iron deficiency, particularly in high-risk groups such as patients with mental disorders and abnormal eating behaviors. Moreover, ferritin is an earlier marker of iron deficiency and finding a low serum ferritin level may allow for earlier diagnosis of both iron deficiency and pica. Less than half of the patients with hemoglobin results had a ferritin test, which

suggests that this biomarker is underused for establishing iron deficiency as the cause for anemia.

Hospitalization, GI disorders and infections, parasitic infections and fluid and electrolyte imbalances were also outcomes of pica in children ages 2 to 18 and adults under 65 years of age. Moreover, lead poisoning was a significant outcome of pica in children, and malnutrition was a significant outcome in adults. It is unclear from our results whether eating disorders, which are clearly associated with pica, are predictors or outcomes of pica.

Overall, our study findings with respect to predictors and outcomes of pica are solider for children than adults, at least in part because there were more children than adults in our case control cohort. Moreover, bias may be somewhat less because geophagia is more common in children than adults, and may be more likely to require a physician visit than pagophagia, which is more common in adults. However, these have not been studied as potential sources of bias.

Clinical Implications

Previous studies have reported on a number of disorders that co-exist with pica. This population based study is the first of its kind to focus on pica, and has enhanced our understanding of clinical predictors and consequences of pica. Our results indicate that the substances consumed in pica, such as dirt, may be sources of contamination with infections, parasites and toxins. These associations have important clinical and public health implications. Psychiatric conditions such as mood disorders which were leading reasons for hospitalizations in children in our study were also concerning. Therefore, it may be medically important to screen patients with psychiatric disorders for pica.

Patients with other eating disorders are also at risk for pica and should be screened using patient history and other appropriate diagnostic tools. Moreover, iron deficiency should be identified and treated as early as possible in individuals with pica to prevent future complications. After a diagnosis of pica, it is important to assess for iron deficiency and if found treat with iron replacement.

Policy Implications

Pica is diagnosed based on DSM-V criteria, as discussed in chapter 1. However, it requires an astute health care professional to ask questions that can lead to a diagnosis or exclusion of pica. Other psychological and eating disorders are diagnosed based on clinical instruments that can provide more comprehensive information for diagnosis of pica. Such an instrument can be used for screening high risk for pica among groups such as those with iron deficiency, eating disorders or ASD. Inclusion of such an instrument as a DSM-V criterion for diagnosis of pica will not only provide a tool for diagnosis but will also standardize the diagnostic process in many clinical settings.

Limitations

The diagnosis of pica in this study was based on ICD-9-CM codes. It is generally understood that diagnosis codes may be underutilized in clinical practice and not include all patients with a condition, or used inconsistently or incorrectly when doctors' notes are translated for billing purposes.[84] Moreover, the codes may or may not consistently reflect the DSM-V definition of pica. Also, different types of pica are not included within the pica diagnosis, which limits our understanding of type-specific predictors and outcomes. This issue stays the same with ICD-10-CM diagnosis codes for pica comparing to ICD-9-

CM. Less than 30% of the cases in our study had lab results, which limits the reliability of laboratory predictors. The different stages of iron deficiency as associated with pica could also not be studied in our study. Most importantly, this was a case control study which, by nature, has inherent selection biases, which may or may not be recognized. Despite these limitations, this study has a number of strengths including a large population-based sample size, matching cases with controls based on gender, age, region and year of diagnosis, and adjustments for confounding medical conditions. This is the only population-based study that measured predictability of multiple exposures for pica and also looked at outcomes of this eating disorder over a 12-month period.

Future Directions

Past research on pica was limited and mainly focused on the association with iron deficiency. We have expanded the scope of research on pica and reported additional predictors and outcomes of pica. More detailed studies of this kind, for example, to better define the various stages of iron deficiency in pica patients, would be of interest. Also, prospective cohort studies of children and adults with specific types of pica would be informative regarding the specific predictors and outcomes of pica, particularly of pagophagia and geophagia, and would better define effective treatment and follow up.

Appendix A

ICD-9 and CPT-4 codes for studied variables:

Variables	ICD-9-CM or CPT codes/LOINC
Pica	307.52[30,85,86]
Iron deficiency	280.x,[86-89] 648.2
Eating disorders	783.0,[86] 783.00, 783.3, 783.6, 307.1,[30,86] 307.10, 307.50,[30,86] 307.51,[30,86] 307.53,[30,86] 307.54,[30,86] 307.59[30,86]
Menstrual bleeding disorders	626.2,[86,90] 626.20, 626.3, 626.5, 626.6,[86] 626.60, 626.8,[86] 626.80, 626.9,[86] 626.90, 627,[86,90] 627.0, 627.00, 627.1
Restless legs syndrome	333.94[86]
GI bleeding	456.0, 531.0, 531.1, 531.4, 531.6,532.0, 532.4, 532.6, 533.0, 534.4, 535.41, 535.51, 535.61, 537.83, 569.3, 578.0, 578.00, 578.1, 578.10, 578.9,[86,89,91] 578.90
Non-GI bleeding	360.43, 363.61, 364.41, 372.72, 379.32, 459.0, 568.81, 596.7, 599.7, 626.5, 626.6, 626.9, 627.0, 627.1, 719.10, 719.11, 719.12, 719.15, 719.16, 782.7, 784.7, 786.3, 998.1
Malnutrition	260-269[86], 760.4[86]
GI disorders and infections	455[88], 555-558,[88] 560-569,[86,88] 001-005, 006.0-006.2, 007-009,[86] 022.2, 039.2, 047, 048, 112.85
Lead poisoning	984, 984.0, 948.1, 984.8, 984.9[86]
Parasitic infections	120-129, 130-139,[86] 647.8[86]
Smoking	Elixhauser comorbidity method[92]
Alcoholism	Elixhauser comorbidity method[92]
Obesity	Elixhauser comorbidity method[92]
Pregnancy	Pregnancy algorithm[70]
Autism spectrum disorder	299.0, 299.00, 299.8, 299.80, 299.81, 299.9[30,86]
Obsessive Compulsive disorder	300.3, 300.30, 301.4, 303.0[86]
Mood disorder	290.43, 292.84, 293.83, 296.0[86,88], 309[86,88] 311
Schizophrenia	295.xx,[93] 299.9, 299.90
Anxiety disorder	293.84, 300.0, 300.00, 300.01, 300.02, 300.09, 309.24, 313.0[94]
Dental complications	873.63, 873.73, 521.81
Intestinal Obstruction	552.x, 560.x[88]
Fluid and electrolyte imbalance	276.x[92]
Cardiac dysrhythmias	426, 427, 37.7-37.9x[95]
Complete blood count and platelets	CPT: (85025, 85027, 85032,85041, 85048, 85049, 85004, 85007, 85008, 85014, 85018)[96]

	LOINC: (584102,554295, 570226,577825, 570218,697425, 45443, 7187, 7898, 66902, 7773, 7864, 7872, 7880, 7856)[97]
Iron and Iron binding capacity panel	CPT: (83540, 83550, 82728, 84466)[96] LOINC: (24984-iron, 25007-TIBC, 25023-% Sat, 25015-UIBC, 2276-4-Ferritin))[97]
Ferritin (serum/plasma)	CPT: 82728,[96] 83540 LOINC: (2276-4, 20567-4)[97]
Transferrin	CPT: 84466 LOINC: 22674-6, 75689-0, 3034-6[97]
Otitis Media	381-382
Peri-orbital and Orbital Cellulitis	373.13, 376.01
Heart disease	410-413
Fractures	800-869

Appendix B

Combined Conditional Logistic Regression Model predicting Pica

Variables	***Multivariate OR***	***95% CI***
Iron deficiency	2.72	1.010-7.315*
Eating disorder	0.97	0.109-8.514
GI disorder	0.83	0.405-1.702
Mood disorder	1.28	0.582-2.820
Obesity	12.03	2.396-60.419*
Hemoglobin	0.43	0.338-0.545*

*Results were statistically significant

Combined: Significant medical, psychiatric, behavioral and laboratory predictors of pica

Appendix C

Stratified Cox Proportional Hazards Regression Models for Outcomes of Pica in children under the age of 18 years

Models	*Outcomes*	*Multivariate HR (95% CI)*
1	Hospitalization	3.09 (1.80, 5.31)*
2	Eating disorders	7.06 (3.24, 15.38)*
3	Malnutrition	3.10 (1.13, 8.53)*
4	GI disorders and infections	2.30 (1.77, 2.99)*
5	Lead poisoning	9.0 (1.82, 44.59)
6	Parasitic infections	2.79 (1.32, 5.92)*
7	Fluid and electrolyte Imbalance	2.91 (1.65, 5.15)*
8	Cardiac Dysrhythmias	1.03 (0.61, 1.71)*

* Adjusted for demographics, Iron deficiency, Non-GI bleeding, ASD, Mood disorders and Obesity

Stratified Cox Proportional Hazards Regression Models for Outcomes of Pica in adults over the age of 18 years

Models	*Outcomes*	*Multivariate HR (95% CI)*
1	Hospitalization	3.31 (2.61, 4.18)
2	Eating disorders	5.47 (2.18, 13.71)
3	Malnutrition	2.08 (1.56, 2.77)
4	GI disorders and infections	1.95 (1.53, 2.48)
5	Parasitic infections	4.13 (1.66, 10.26)
6	Intestinal Obstruction	3.00 (1.39, 6.47)
7	Fluid and electrolyte Imbalance	2.31 (1.53, 3.50)
8	Cardiac Dysrhythmias	1.33 (0.92, 1.93)

* Adjusted for demographics, Iron deficiency, Mood disorder, Anxiety disorder, smoking and Obesity

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76. Kettaneh A, Eclache V, Fain O, et al. Pica and food craving in patients with iron-deficiency anemia: a case-control study in France. *Am J Med.* 2005;118(2):185-188.
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92. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130-1139.
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94. Eisenberg ML, Li S, Cullen MR, Baker LC. Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. *Fertil Steril.* 2015.
95. Patt DA, Goodwin JS, Kuo YF, et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol.* 2005;23(30):7475-7482.
96. Tsai AG, Hosokawa P, Schoen J, Prochazka AV. Frequency of laboratory testing among gastric bypass patients. *Surg Obes Relat Dis.* 2014;10(2):340-345.
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EDUCATION:

2017 (Expected)	PhD, Clinical Science University of Texas Medical Branch, Galveston, TX
2016	MPH, Public Health University of Texas Medical Branch, Galveston, TX
2001	M.S., Healthcare Administration Texas Women's University, Houston, TX
1996	B.S., Biology--Medical Technology Minor: Chemistry University of Houston, Houston, TX
1996	Certificate – Medical Technology Methodist Hospital, Houston, TX

BOARD CERTIFICATION:

1996	MT(ASCP) #201624

PROFESSIONAL AND TEACHING EXPERIENCE:

2009 – present	Assistant Professor Department of Clinical Laboratory Sciences School of Health Professions Univ. of Texas Medical Branch Galveston, Texas

2004 – 2008	Assistant Professor Department of Medical Laboratory Sciences School of Health Professions Univ. of Texas Southwestern Medical Center Dallas, Texas
2002 – 2004	Chief Medical Technologist Department of Pathology Aston pathology Laboratory Univ. of Texas Southwestern Medical Center Dallas, Texas
2003 – 2004	Medical Technologist-PRN Department of Pathology Charlton Methodist Hospital Dallas, Texas
2001 – 2002	Senior Medical Technologist Department of Pathology Aston pathology Laboratory Univ. of Texas Southwestern Medical Center Dallas, Texas
2000 – 2001	Laboratory Manager Cancer Center Associates Dallas, Texas
1996 – 2000	Medical Technologist III Department of Pathology Ben Taub General Hospital Harris County Hospital District Houston, Texas

SCHOLARLY/RESEARCH ACTIVITIES

AREAS OF RESEARCH	Pica Eating disorders Iron deficiency Clinical Laboratory Science education Audience response systems Interactive teaching/learning tools

GRANTS:

H-1B Technical Skills Training Grant, Clinical Laboratory Initiative to Mentor Baccalaureate Students (CLIMBS), Department of Labor, Primary Investigator: Dr. V. Freeman, $4,947,159, 2013-2016, 10% effort/year.

TEACHING RESPONSIBILITIES

TEACHING RESPONSIBILITIES AT UTMB -- CURRENT:

Primary Instructor

2009 –	CLLS 3514	Clinical Chemistry I 5 credit hours
2009 --	CLLS 3320	Intermediate Case Studies (on campus and web course) 3 credit hours
2009 --	CLLS 4310	Clinical Chemistry II (on campus and web course) 3 credit hours
2009 --	CLLS 3414	Biochemistry (on campus and web course) 4 credit hours
2011--	CLLS 5414	Biochemistry 4 credit hours
2012--	CLLS 5506	Clinical Chemistry I 5 credit hours
2012-	CLLS 6310	Clinical Chemistry II 3 credit hours
2013	CLLS 5093	Independent Investigative Studies 1-3 credit hours

Secondary Instructor

2014-	CLLS 5329	CLS Research
2015-	CLLS 5311	Clinical Correlations

Guest Lectures

2009 --	CLLS 3100	Basic Methods and Intro. to Lab Operations 6 hours
2009 --	CLLS 4107	Seminar 6 hours
2012-	CLLS 4311	Case Studies in Clinical Laboratory Science 1 hour
2013-	CLLS 4327	Method Development and Assessment I 4 hours
2013-	CLLS 4328	Method Development and Assessment II

4 hours

SMALL GROUP TEACHING:

2015--	Inter-professional Education (IPE) Facilitator

TEACHING RESPONSIBILITIES AT UTMB -- PREVIOUS

Primary Instructor

2009 – 2011	CLLS 5406	Clinical Chemistry I for Physician Assistant 4 credit hours

Guest Lectures

2009 -- 2014	SBB	Laboratory Mathematics 2 hours

STUDENT MENTORING/ADVISING:

2009- 2013	CLLS 4326	Advisor and mentor for undergraduate student research
2009-		Academic advisor of CLS students
2012 -		Thesis Chair and advisor for graduate students

TEACHING RESPONSIBILITIES AT OTHER UNIVERSITIES

Primary Instructor –*University of TX Southwestern Medical Center*

2006 – 2008	MT 4101	Introduction to MLS 1 credit hour
2004 – 2008	MT 3302	Clinical Chemistry I 3 credit hours
2004 – 2008	MT 4202	Clinical Chemistry II 3 credit hours
2004 – 2008	MT 4411	Clinical Chemistry Practicum 4 credit hours
2008	MT 4210	Professional Issues 2 credit hours
2005 -- 2007	MT 3310	Biochemistry of Human Metabolism 3 credit hours
2004	MT 4118	Urinalysis Practicum

1 credit hour

Guest Instructor-- *University of TX Southwestern Medical Center*

2008		Laboratory session for high school camp UTSW Graduate School "Sickle Cell Anemia- a mutation story" 3 hours
2008		Physical Therapy seminar course "Clinical Laboratory Values and Implications for PT" 2 hours
2005	HCS 3324	Introduction to Management 3 hours

COMMITTEE RESPONSIBILITIES:
University of Texas Medical Branch

University
University Student Conduct and Discipline Panel, 2016-present

School of Health Professions
Member, Grievance and Appeals Committee, 2016-present
Secretary, Faculty Assembly, 2009-2010

Department of Clinical Laboratory Science
Chair, Grading and Promotions, 2013—present
Member, Master's Thesis, 2012--present
Member, Curriculum, 2009 – present
Member, Admissions, 2010 – present
Chair, faculty search committee, 6/2014
Member, Grading and Promotions, 2009 - 2013
Co-Coordinator, Preceptorship, 2009 – 2012

University of Texas Southwestern Medical Center

University
Member, Faculty Senate, 2008
Member, campus relations and security, 2006-2008

School of Health Professions
President, Faculty Assembly Executive Council, 2008
President Elect, Faculty Assembly Executive Council, 2007-08
Member, Faculty Assembly Executive Council, 2005-07
Member, Faculty Council, 2008
Member, Academic affairs, 2008
Member, Admissions, 2007-2008

Department of Medical Laboratory Sciences
Chair, Admissions and recruiting, 2007 -- 2008

MEMBERSHIP IN SCIENTIFIC SOCIETIES/PROFESSIONAL ORGANIZATIONS:
Member, American Society of Clinical Pathologist (ASCP), 1996 - present
Member, American Society of Clinical Chemistry (AACC), 2003 - present
Member, American Society of Clinical Lab Science (ASCLS), 2004 - present
Member, Texas association of Clinical Laboratory Science (TACLS), 2004 – present
Member, American college of Healthcare Executives (ACHE), 1999-2001

HONORS AND AWARDS:
Dean's faculty travel grant, UTMB School of Health Professions (2013, 2014, 2015, 2016)
Alpha Eta Honor Society. Inducted in 2015
Herzog Educational Enrichment Award (2012-13, 2013-2014, 2014-15, 2015-16)

PUBLICATIONS:

ARTICLES IN PEER –REVIEWED JOURNALS:
Esani M. The Physiological Sources of, Clinical Significance of, and Laboratory-Testing Methods for Determining Enzyme Levels. Lab Medicine. 45(1): 16-18:2014.

Esani M. Educational Technology: Moving from Face-to-Face to Online Teaching. *Clinical Laboratory Science*. 23 (3): 187-190: 2010.

OTHER:

POSTER PRESENTATIONS:
Iron Status of Blood Donors in the United States. Public Health Symposium, Preventive Medicine and Community Health (PMCH), University of TX Medical Branch, Galveston, TX, April 7, 2016.

Masters in Clinical Laboratory Science at University of Texas Medical Branch, a Success Story. Clinical Laboratory Educators Conference, Minneapolis, MN. February 26, 2016

Formula for success in a Clinical Laboratory Science Program. Clinical Laboratory Educators Conference, San Jose, CA. February 31, 2014

Impact of clickers or student response systems on student learning, UTMB Academy of Master Teachers symposium, Galveston, TX. May 20, 2011.

DEMONSTRATIONS:
Learning Objects, AMT Spring Education Symposium, Galveston, TX. May 18, 2012.

BOOK REVIEWS:
Reviewer, Clinical Chemistry – A Laboratory Perspective, F. A, Davis, PA. 2007

VARIA:
Learning objects – Lab Math, Competitive Immunoassay, Acid base disorders, Membranes and Transport. & Calcium Homeostasis. UTMB webcls learning objects repository. 2011

ABSTRACTS:
Iron Status of Blood Donors in the United States. Public Health Symposium, Preventive Medicine and Community Health (PMCH), University of TX Medical Branch, Galveston, TX, April 7, 2016.

Masters in Clinical Laboratory Science at University of Texas Medical Branch, a Success Story. Clinical Laboratory Educators Conference, Minneapolis, MN. February 26, 2016

Freeman VS, Esani M. Predictors of Success for MLS Students. Regional European Biomedical Laboratory Science Congress and the 4th Medical Laboratory Technologists Conference, Athens, Greece. Dec 5, 2013.

PAPERS AND CONTINUING EDUCATION PROGRAMS PRESENTED/ INVITED LECTURES AT SYMPOSIA AND CONFERENCES:

Pica, Student Organization for Clinical Laboratory Sciences (SOCLS), School of Health Professions, University of Texas Medical Branch, Galveston, TX, July 9, 2015.

Pica, Texas Association of Clinical Laboratory Science Conference, Houston, TX. April 10, 2015

Diagnosis of Diabetes using Hemoglobin A1c, Texas Association of Clinical Laboratory Science Conference, Austin, TX. Apr 8, 2011.

Future Fields of Studies, Aga Khan Education Board. Jan 7, 2011 (Sugarland, TX) & August 26, 2011 (San Antonio, TX).

Challenges in Clinical Chemistry Practica, Clinical Laboratory Educators Conference. Feb. 23, 2007.

Laboratory analysis in diagnosis and management of Diabetes Mellitus, UT Southwestern Allied Health Sciences School Research Symposium. April 17, 2006.

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