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Iron and Infection: An Investigation of the Optimal Iron Hypothesis in Lima, Peru

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Abstract

Aim—This paper explores the optimal iron hypothesis through secondary data analysis of the association between hemoglobin levels and morbidity among children living in Canto Grande, a peri-urban community located on the outskirts of Lima, Peru.

Methods—Risk ratios were used to test whether lower iron status, assessed using HemoCue B-Hemoglobin System, was associated with an increased relative risk of having morbidity symptoms compared to iron replete infants, controlling for infant age, sex, weight for height z-score, maternal education, and repeated measures in 515 infants aged 6–12 months.

Results—Infants with low iron deficiency had a lower risk of current respiratory and diarrhea morbidity symptoms compared to participants who were iron-replete ($p < 0.10$). Infants with moderate iron deficiency had a statistically significant ($p < 0.05$) reduction in risk of current respiratory infection symptoms compared to infants who were iron-replete.

Conclusion—In this study, iron deficient status was not predictive of morbidity symptoms over a 6-month interval period but non-replete iron status was shown to be associated with current morbidity symptoms. These results support investigating iron status as an allostatic system that responds to infection adaptively, rather than expecting an optimal-pre-infection value.

Keywords

The Optimal Iron Hypothesis; Iron Deficiency; Child Morbidity; Peru

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Author Contributions

AD analyzed the data and drafted the manuscript. MP, RK, and CD played active and significant roles in the design of the study, and directed implementation and data collection. AT, MP, RK, and CD edited the manuscript for intellectual content and provided critical comments on and suggestions for the manuscript.

Disclosure Statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Introduction

Iron deficiency is the most common and widespread nutritional disorder in the world, affecting 1.62 billion people or 24.8% of the world's population (WHO, 2009). Despite interventions, global and local efforts to improve iron status among women and children have not led to a significant decrease in the burden of iron deficiency (Black et al., 2008). One explanation for this lack of effect comes from the field of evolutionary medicine, which proposes that some manifestations of disease may act as adaptive defenses against other types of infection (Ewald, 1994, Williams and Nesse, 1991). While low levels of iron are associated with negative health outcomes, such as general fatigue, dizziness, and irregular heartbeat, iron withholding is an important component in immune defense against infectious disease (WHO 2009). Building on prior biomedical and archaeological work that showed links between iron and infection (Stuart-Macadam, 1992; Kluger & Bullen, 1987; Kochan, 1973), Wander et al. (2009) propose the Optimal Iron Hypothesis (OIH), which states that an individual's optimal iron status is contingent on local disease ecology. In environments with high levels of endemic infectious diseases, the authors hypothesize that restricted iron intake, utilization, and absorption may protect against infection.

Evidence for the OIH has so far been weak. Wander et al. (2009) found mild to moderate iron deficiency (assessed by transferrin receptor and zinc protoporphyrin) in Kenyan children was associated with lower rates of infection compared to children with standard levels of iron when controlling for age and triceps skinfold thickness. Severe iron deficiency and anemia were not associated with protective effects. These results were not replicated in Tanzanian children, where low iron (assessed by measurements of transferrin receptor and hemoglobin) was not associated with a lower likelihood of elevated C-reactive protein compared to iron-replete children (Hadley and DeCaro, 2015). Hadley and DeCaro (2015) argue that it may be more beneficial to investigate iron regulation as an allostatic system that responds to infections adaptively, rather than to expect an optimal pre-infection value.

Therefore the aim of this study was to investigate whether higher hemoglobin levels were associated with a greater occurrence of morbidity among children living in Canto Grande, a peri-urban community located on the outskirts of Lima, Peru. Peru provides a unique context for this research since the country suffers from persistent severe iron deficiency rates despite programs that distribute oral iron supplements (Ministerio de Salud, 2015). Here, we test the predictions of OIH using hemoglobin measurements and reported morbidity symptoms. If the predictions of the OIH are reflected in the results of this study, we expect to find that infants with low or moderate hemoglobin levels would have a lower likelihood of reported diarrheal disease symptoms and reported respiratory infection symptoms at the time of iron assessment and over an interval of six months.

Methods

Sample

Data come from a randomized supplementation infant cereal trial conducted by the Institute of Nutritional Research in 1999–2000 (Duggan et al., 2003). This study provided fortified cereals to infants in Canto Grande and was designed to evaluate the effects of dietary

supplementation of prebiotics both with and without zinc on the prevalence of diarrhea in Canto Grande, a community with a high burden of gastrointestinal and other infections. Researchers performed two consecutive randomized, blinded, and controlled clinical trials. The first trial compared an infant cereal supplemented with prebiotics to non-supplemented cereal. During the second trial, zinc was added to both supplemented and control cereals.

Enrollment for the first trial lasted began in July 1999 and enrollment for the second trial began in January 2000. Both trials lasted six months. Researchers enrolled a combined total of 515 infants aged 6–12 months. This study excluded children that had chronic illnesses or congenital anomalies, had severe acute malnutrition (weight-for-height z-score < -2), those that were exclusively breastfed, or those who were receiving chronic corticosteroids or antibiotics (as defined by >6 consecutive weeks of therapy before enrollment).

Identical protocols were followed for the two trials. Fieldworkers recruited eligible subjects from the community and referred them to the central study site. Eligibility was then confirmed with a screening history, physical examination, and anthropometric measurements. Enrolled infants returned to the study clinic at four and six months after enrollment for repeat anthropometric measurements and assessment of iron status. Fieldworkers visited the family five times per week during the first two months of the study and two times per week during months three through six. Each infant's caretaker was asked about the presence of symptoms and signs of illness at each visit, including the presence of difficulty breathing, cough, and diarrheal symptoms.

Iron Level

Hemoglobin was measured using HemoCue B-Hemoglobin System (Hemocue, Mission Viejo CA) at the beginning of the study and at months 4 and 6. For this analysis, hemoglobin was used as a proxy for iron status. Due to the distribution of the sample, the four anemia categories employed by Hadley and DeCaro (2015) were not used. Iron status was categorized into three groups: iron-replete (≥ 11.0 g/L), mild iron deficiency (9.4–10.9 g/L), and moderate iron deficiency (7.0–9.3 g/L) (WHO, 2011). No iron levels below 7.0 were included in the sample.

Morbidity

Morbidity was defined using 24-hour recalls of illness symptoms 2–5 times/week. Two variables were created: current morbidity and interval morbidity. Current morbidity is a dichotomous variable measuring whether children had symptoms at the time of iron assessment. Interval morbidity is a dichotomous variable measuring whether children had symptoms in the time between iron assessments (4 months and 2 months). Because the number of days sick was non-normally distributed, interval morbidity was dichotomized into having or never having experienced respiratory or diarrheal disease symptoms between visits. Respiratory infection symptoms included caregiver reports of difficulty breathing or rapid breathing. Diarrheal disease symptoms were defined as passing liquid stools.

Statistical analysis

All statistical analyses were performed using STATA 13. Risk ratio (RR) was used to test the probability of current and interval morbidity in children with low or moderate iron deficient to the probability of current and interval morbidity in iron-replete children. Risk ratio (RR) allows for the comparison of the risk or morbidity between iron deficiency (low or moderate) and iron-replete, putting the risk or morbidity in context. Models on diarrheal disease and respiratory infection symptoms were run separately for both current and interval morbidity. All models controlled for infant age, sex, weight for height z-score, maternal education, and repeated measures.

Results

In this sample, the average child age at enrollment was 8.7 months (SD=1.89) and half the sample (50.7%) was female. The mean weight for height z-score was 0.54 (SD=0.89). Mothers were an average of 25.51 years of age (SD=7.58). 43.8% of mothers had completed high school and about 40% of homes had earth floors.

Iron deficiency was common in the sample over all three clinic visits (Table 1). At enrollment, 138 infants had moderate iron deficiency, 294 infants had low iron deficiency, and 118 infants were iron-replete. At the second clinic visit, 99 infants were moderately iron deficient, 326 had low iron deficiency, and 124 were iron-replete. At the conclusion of the study, 83 infants were moderately iron deficient, 320 had low iron deficiency, and 144 were iron-replete. Reported respiratory infection symptoms were less common than reported diarrheal disease symptoms at all three-clinic visits (Table 1). At recruitment 79 (12.52%) infants experienced diarrheal disease symptoms while only 57 (9.03%) had respiratory infection symptoms. These numbers fluctuated across the course of the study, with 44 (7.6%) infants experiencing diarrheal disease symptoms and 17 (2.93%) experiencing respiratory infection symptoms at second clinic visit and 91 (14.42%) infants experiencing diarrheal disease symptoms and 27 (4.28%) experiencing respiratory infection symptoms at the third clinic visit.

Iron levels and current morbidity showed some association (Table 2). Infants having current diarrheal disease or respiratory infection symptoms did not have a statistically significant reduced risk of low iron deficiency compared to being iron-replete in adjusted models, 0.73 (0.51–1.04) and 0.61 (0.37–1.01), respectively. Infants categorized with current diarrheal disease symptoms did not have a statistically significant reduced risk of having moderate iron deficiency compared to being iron-replete in adjusted models, 0.74 (0.46–1.20). Given the presence of current respiratory infection symptoms the relative risk of being in the moderate iron deficiency group would be 0.44 (CI: 0.21–0.92) times more likely than when the other variables in the model are held constant ($p<0.05$). More generally, infants with moderate iron deficiency had a reduced risk of respiratory infection in adjusted models.

From recruitment to the second clinic visit, 475 (75.28%) infants experienced diarrheal disease symptoms and 494 (78.29%) had respiratory infection symptoms (Table 1). There was a decrease in the number of infants experiencing morbidity symptoms from the second clinic visit to the final clinic visit. During this interval, 384 (66.21%) infants experienced

diarrheal disease symptoms and 203 (32.17%) infants experienced respiratory infection infections (Table 1). Fluctuations in disease symptoms over the course of this study may be due to seasonal patterns of infectious disease occurrence.

There were no significant associations between interval morbidity measures and iron status (Table 2). Infants having interval diarrheal disease or respiratory infection symptoms did not have a statistically significant reduced risk of having low iron deficiency compared to being iron-replete in adjusted models, 0.93 (0.66–1.31) and 0.81 (0.60–1.09), respectfully, or moderate iron deficiency compared to being iron-replete in adjusted models 0.86 (0.57–1.31) and 0.76 (0.53–1.08), respectfully.

For all current and interval models, infants with educated mothers had a statistically significant reduced risk of being moderately iron deficient compared to infants with led educated mothers in adjusted models (Table 2). Girls also showed a reduced risk of being moderately iron deficient compared to boys in all current and interval adjusted models (Table 2).

Discussion and Conclusion

The results of this study are inconsistent with the OIH proposed by Wander et al. (2009). We found no evidence that infants with low or moderate hemoglobin levels had a lower likelihood of reported respiratory infection or diarrheal disease symptoms over an interval of six months. The lack of evidence for the relationship between hemoglobin level and interval infection symptoms suggest that a mild to moderate hemoglobin level does not protect against future acute infections.

While we do not find evidence that infants with low or moderate hemoglobin levels had a lower likelihood of reported diarrheal disease symptoms at the time of iron assessment, we do find evidence that infants with moderate hemoglobin have a reduction in risk of current respiratory infection symptoms compared to infants who were iron-replete. These results show mixed support for Hadley and DeCaro's (2015) proposal to investigate iron status as an allostatic system that responds to infection adaptively. Wander et al. (2016) also found a lower incidence of respiratory infections among iron deficient children. Research on the relationship between iron and infectious disease is highly variable; more research is needed to understand why there was a statistically significant reduction in risk of current respiratory infection symptoms and not diarrheal disease symptoms.

A key limitation to this study is the use of hemoglobin as a measure for iron level. Measuring iron level requires the use of multiple sensitive biomarkers that can identify iron level across the range of mild to severe deficiency and to measure iron status that is not confounded with concurrent infection (Shell-Duncan and McDade 2004). Other limitations include the reliance on caretaker reports of morbidity. While self- and caretaker reports of infection symptoms are an appropriate standard to evaluate disease occurrence, they do not capture chronic low-grade inflammation. Excluding EBF children may have impacted the study as breastfeeding has been shown to protect infants from diarrheal disease and acute respiratory infections (Raheem et al. 2017). Excluding sick children may have impacted the

study, as this did not allow for an examination of hemoglobin level relative to more advanced forms of illness.

Nonetheless, the association between moderate hemoglobin and a reduction in risk of current respiratory infection symptoms illustrate the complexity of the relationship between iron status and infection, demonstrating the need for further research with finer measures.

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Table 1:

Descriptive Statistics for Iron Level and Morbidity

Sample Characteristic	Clinic Visit 1 <i>Frequency (%)</i>	Clinic Visit 2 <i>Frequency (%)</i>	Clinic Visit 3 <i>Frequency (%)</i>
<i>Iron</i>			
Iron-Replete^a	118 (21.45)	124 (22.59)	144 (26.33)
Low Iron Deficiency^b	294 (53.45)	326 (59.38)	320 (58.50)
Moderate Iron Deficiency^c	138 (25.09)	99 (18.03)	83 (15.17)
<i>Morbidity Symptoms Present</i>			
<i>Current</i>			
Diarrhea	79 (12.52)	44 (7.60)	91 (14.42)
Respiratory	57 (9.03)	17 (2.93)	27 (4.28)
<i>Interval</i>			
Diarrhea	475 (75.28)		384 (66.21)
Respiratory	494 (78.29)		203 (32.17)

^aIron-Replete: 11.0 g/L^bLow Iron Deficiency: 9.4–10.9 g/L^cModerate Iron Deficiency: 9.3 g/l

Table 2:

Risk Ratios for Low and Moderate Iron Deficiency in Comparison to Normal Iron

Morbidity Symptom	Low Iron Deficiency ^a RR ^c , (95% CI)	Moderate Iron Deficiency ^b RR ^c , (95% CI)
<i>Current Diarrhea Model</i>		
Diarrhea	0.73 (0.51–1.04) *	0.74 (0.46–1.20)
Child Sex	0.84 (0.61–1.15)	0.59 (0.38–0.92) **
Maternal Education	0.86 (0.74–1.00) *	0.77 (0.64–0.94) **
<i>Current Respiratory Model</i>		
Respiratory	0.61 (0.37–1.01) *	0.44 (0.21–0.92) **
Child Sex	0.85 (0.62–1.17)	0.60 (0.39–0.93) **
Maternal Education	0.75 (0.55–1.03) *	0.60 (0.38–0.92) **
<i>Interval Diarrhea Model</i>		
Diarrhea	0.93 (0.66–1.31)	0.86 (0.57–1.31)
Child Sex	0.81 (0.57–1.15)	0.60 (0.38–0.94) **
Maternal Education	0.87 (0.74–1.02) *	0.78 (0.64–0.95) **
<i>Interval Respiratory Model</i>		
Respiratory	0.81 (0.60–1.09)	0.76 (0.53–1.08)
Child Sex	0.81 (0.57–1.15)	0.60 (0.38–0.93) **
Maternal Education	0.75 (0.53–1.06)	0.59 (0.38–0.94) **

^aLow Iron Deficiency: 9.4–10.9 g/L^bModerate Iron Deficiency: 9.3 g/l^cRR for outcome compared to infants with iron-replete status controlling for infant age, sex, weight for height z-score, maternal education, and repeated measures.*
p<0.10**
Significant at p<0.05