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Ascertainment of Iron Deficiency and Depletion in Blood Donors through Screening Questions for Pica and Restless Legs Syndrome

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Abstract

Background—Pica and restless legs syndrome (RLS) are associated with iron depletion and deficiency. The presence of pica and RLS was prospectively assessed in blood donors.

Methods—During a 39-month period, 1236 donors deferred for fingerstick hemoglobin <12.5 g/dL and 400 non-deferred "control" donors underwent health screening and laboratory testing (CBC, ferritin, iron, transferrin). Pica and RLS were assessed by direct questioning. Deferred donors and iron-deficient control donors were given ferrous sulfate 325 mg daily for 60 days. Reassessments were performed and additional iron tablets dispensed at subsequent visits.

Results—Pica was reported in 11% of donors with iron depletion/deficiency, compared with 4% of iron-replete donors ($p<0.0001$). Pagophagia (ice pica) was most common and often of extraordinary intensity. Female sex, younger age, and lower MCV and transferrin saturation values were strongly associated with pica. Donors with pica given iron reported a marked reduction in the desire to consume the non-nutritive substance by day 5–8 of therapy, with disappearance of symptoms by day 10–14. RLS was reported in 16% of subjects with iron depletion/deficiency compared with 11% of iron-replete donors ($p=0.012$). Iron replacement generally resulted in improvement of RLS symptoms, however, at least 4–6 weeks of iron therapy was necessary.

Conclusion—The presence of pica is associated with a high probability of iron depletion/deficiency in blood donors; however, RLS lacks a strong correlation in this population. Screening questions for pagophagia may be useful in the ascertainment of iron deficiency in donors and may identify those who would benefit from oral iron.

INTRODUCTION

Pica is the compulsive craving and persistent consumption of non-nutritive substances. The word pica comes from the Latin word for Magpie, a small bird that has a voracious appetite

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and indiscriminating diet. Pica has been recognized for centuries, from Hippocrates' early description of "craving to eat earth" due to "disruption of the blood" to modern day medical practice.[1–3] The etiology of pica is poorly understood; nutritional, cultural, sensory, psychosocial, and religious theories have been proposed to explain the compulsion and behavior. Pica has also been characterized as a mental health disorder in the Diagnostic and Statistical Manual of Mental Disorders (DMS-IV-TR).[4] Individuals are often reluctant to disclose or discuss unusual cravings and ingestion of abnormal substances with their physicians. The ingested materials are quite varied and can include almost any substance. More commonly reported picas involve ingestion of dirt, clay, chalk, laundry starch, ice, and paper. Pagophagia, the pathological consumption of ice, is a specific pica strongly associated with iron deficiency.

Restless legs syndrome (RLS) is a neurological movement disorder characterized by uncomfortable sensations in the lower extremities, with a compelling urge to move the affected extremities to relieve the discomfort. The mild to intolerable sensations are often described as creeping, crawling, burning, itching, searing, pulling, aching, painful, electrical-like, and worms or bugs crawling under the skin. The sensory and motor symptoms occur or intensify mainly at times of rest, resulting in disturbed sleep patterns.[5–8] Primary RLS is a central nervous system disorder; however, secondary RLS may be caused or exacerbated by iron deficiency.[9,10]

The occurrence of iron depletion and deficiency in first-time and repeat blood donors is well-documented in the transfusion medicine literature.[11–13] With each whole blood (WB) donation, male donors lose 242 ± 17 mg and female donors lose 217 ± 11 mg of iron.[11] Given that normal iron stores in men and women are 1000 mg and 350 mg, respectively, maintenance of iron balance is a challenge in the blood donor population.

Both pica and RLS have been reported to occur in blood donors.[14–16] The purpose of the current study was to prospectively assess the prevalence of pica and RLS in blood donors presenting to a hospital-based donor center, to correlate the findings with donor hemoglobin and iron levels, and to study the effects of iron replacement therapy on the resolution of symptoms.

MATERIALS AND METHODS

Donor Selection and Evaluation

The study was conducted at a single hospital-based donor center as part of an Institutional Review Board-approved protocol to investigate the incidence and operational impact of iron depletion/deficiency in blood donors and to evaluate the safety and efficacy of iron replacement therapy in donors 18 years of age and older.[12] Approximately 4500 blood donors make 12,000 visits per year at this facility, donating 7000 whole blood units, 3500 plateletpheresis and 1500 leukapheresis concentrates.

Prospective blood donors deferred for fingerstick hemoglobin of <12.5 g/dL, but otherwise meeting AABB, FDA, and local blood donor center criteria for donation, were consecutively approached to participate in the study. This group of donors constituted the "low hemoglobin group." A concurrent group of "control donors" who were not deferred for a low fingerstick hemoglobin value were approached in order of presentation to the donor center during the first 12 months of the study, such that they comprised a 1:3 ratio with the low hemoglobin donors. Control donors were not matched for age, race, or gender. Exclusion criteria in both groups included age less than 18 years or a prior diagnosis of hemochromatosis. In addition, control donors were excluded if they were taking oral iron supplements.

All participants underwent an additional health history screening and record review to determine blood donation frequency, history of low fingerstick hemoglobin values, current or past iron therapy, history of gastrointestinal or genitourinary blood loss, obstetric and gynecologic history, medications, diet, and personal or family history of anemia, clotting or bleeding disorders, hemochromatosis, hemoglobinopathy, or cancer. Participants were directly questioned for symptoms of pica (craving and eating unusual or non-nutritive substances) and RLS. Donors answering affirmatively to the pica questions were further prompted to elaborate on type of substance craved, frequency of symptoms, and quantity of substance consumed.

Laboratory Testing

Capillary fingerstick hemoglobin values were obtained using a portable hemoglobin screening device (HemoCue Hb 201+, HemoCue, Cypress, CA). Samples for complete blood counts (CBC) were collected by venipuncture and analyzed with use of an automated hematology instrument (Cell-Dyn 4000, Abbott Laboratories, Abbott Park, IL). Serum iron determinations were performed with use of an automated chemistry analyzer (LX20, Beckman-Coulter, Inc., Brea, CA) as were ferritin and transferrin levels (Immulite 2500, Diagnostics Product Corporation, Los Angeles, CA). Transferrin saturation (%) was calculated as [Iron/Transferrin] x 71.2.

Oral Iron Replacement Therapy

Donors in the low hemoglobin group were given 60 tablets of ferrous sulfate 325 mg (65 mg of elemental iron) at the time of their deferral. Tablets were dispensed in child-resistant blister packs. Donors were instructed to take one tablet by mouth daily, 30 minutes before bedtime, with a half glass of water. Donors with a history of sensitivity to ferrous sulfate, or who developed intolerance to the tablets during the study, were given ferrous gluconate 325 mg tablets (38 mg of elemental iron) to take once daily. Subjects were instructed to notify a study physician promptly if adverse effects occurred.

Within 10 days of the initial visit, a study physician informed donors of their laboratory results by telephone and inquired about compliance with and tolerance to iron therapy. Control donors found to have iron deficiency (ferritin values below the reference range) were offered iron replacement tablets at the time they were notified of their laboratory results. Donors whose responses to health history screening questions and/or laboratory test results indicated a potentially serious health concern were referred to their primary care physician for follow-up.

Subsequent Donations by Study Donors

“Low hemoglobin” donors were deferred from subsequent WB donation for at least 60 days and apheresis donations for 30 days, following which they could be contacted by telerecruitment staff whenever their names came up on routine recruitment lists. Subsequent donations were encouraged but not required. Interim medical history, assessment of oral iron compliance and tolerance, and laboratory evaluation were performed on all subsequent visits. Pica and RLS symptoms were reassessed, and the time to improvement and/or cessation of symptoms was documented. Another 60-pack of iron tablets was dispensed at the time of each subsequent WB donation in order to offset the iron lost through donation. Since donation-related red cell losses were more modest in apheresis donors, iron replacement therapy was stopped when iron stores were replete, as reflected in a ferritin level exceeding 50 mcg/L in females and 100 mcg/L in males on two consecutive apheresis donation visits. Control donors were not given iron tablets at subsequent visits unless they had been found to be iron deficient on a previous visit.

Outcome Objectives

The primary outcome of this study was to determine the prevalence of pica and RLS as indicators of symptomatic iron depletion/deficiency and to characterize the clinical response, pace, and extent of symptom resolution with oral iron therapy.

Statistical Analyses and Definitions

Iron deficiency was defined as a ferritin level below the institutional reference range of 9 mcg/L in females and 18 mcg/L in males. Iron depletion was defined as a ferritin of 9 – 19 mcg/L in females and 18 – 29 mcg/L in males. We used two categories to describe low iron levels, in accord with prior studies of iron deficiency in donors. Levels below the reference range would be expected to cause iron-deficient erythropoiesis and symptomatic iron-deficiency anemia; this level was referred to as “iron-deficient.” Less extreme depletion of iron stores might be expected to cause milder symptoms and have lesser effect on erythropoiesis; this level was referred to as “iron-depleted.”

Analyses were stratified by gender and iron status among the low hemoglobin and control groups. Group outcomes were compared using Student’s t-test and proportions among groups compared using a Chi-square analysis for two by two contingency tables. When appropriate, paired t-tests were used, with statistical significance defined as $p<0.05$. Multivariate analyses were performed using step-wise forward logistic regression, based on parameters having significance in univariate analysis, using a commercial statistics program (JMP software, SAS Institute, Cary, NC).

RESULTS

Donor Accrual, Donor Demographics, and Incidence of Iron Depletion and Deficiency

During a 39-month period between 02/18/06 and 05/26/09, there were 40,422 visits to the blood center made by 7121 donors: 5651 WB and 1470 apheresis donors. Of these donors, 1236 deferred for low fingerstick hemoglobin values (1031 WB, 205 apheresis) and 400 control donors (366 WB, 34 apheresis) were enrolled. Enrolled donors represented greater than 90% of all donors deferred for low screening hemoglobin during the study period.

In the low fingerstick hemoglobin group, 30% and 8% of the women and men, respectively, were iron depleted, and 23% and 53% of the women and men, respectively, were iron deficient. In the control group, 29% and 18% of the females and males, respectively, were iron depleted and 10% and 21% of the women and men, respectively, were iron deficient. Overall, 54% of donors in the low hemoglobin group and 39% in the control group were iron depleted or deficient. The demographics and incidence of iron depletion and deficiency in the 1636 study participants are shown in Table 1.

Prevalence of Pica and RLS on Study Enrollment

Responses to questions concerning pica and RLS were obtained in 1618 (1199 female, 419 male) donors. In 18 of the 1636 study participants, responses to questions about pica and RLS were not recorded at the time the initial protocol medical history was obtained (protocol entry point), therefore these 18 subjects (15 low hemoglobin females, 2 control females, 1 control male) were excluded from further analysis.

The most common type of pica was pagophagia (94%), followed by geophagia (dirt, chalk, and clay), amylophagia (laundry starch) and cravings for raw pasta and coal. Pagophagia was often of extraordinary intensity with donors reporting consumption of as much as 200 ounces of crushed ice per day (32 ounces six times per day; upon waking, arriving at work, after lunch, driving home, after dinner, and during the night). Many individuals with pica

were hesitant to admit to this behavior, and answered negatively if asked whether they craved ice. However, if asked more directly, "How much crushed ice do you eat every day," donors were more likely to answer openly and without censoring their responses. Donors with pagophagia could describe the location of the "best ice in the building" and had devised methods of concealing their "ice habit" from family, friends, and coworkers (eating ice in closets and bathrooms, hiding ice in desk drawers and file cabinets, etc.). They described their craving for ice as compulsive and non-relenting.

Pica was reported in 11% (91/809) of donors with iron depletion or deficiency, compared to 4% (34/809) of donors who were not iron depleted or deficient ($p<0.0001$). In univariate regression analysis of the entire study population (n=1618), the single factor most strongly associated with the presence of pica was a low MCV. Lower venous hemoglobin, lower transferrin saturation, lower ferritin, female sex, younger age, and a lesser number of total prior blood donations (but not donations in the prior 12 months), were also associated with pica in univariate analysis (Table 2). There was no association of donor race with pica. In a stepwise multivariate model, once MCV was in the model, only lower transferrin saturation, female sex, and younger age remained independently associated with pica. Venous hemoglobin and ferritin levels were so closely associated with MCV and transferrin saturation values that they no longer showed independent associations with pica once the contributions of the MCV and transferrin saturation were in the model. Donors with pica had a higher rate of prior deferral for low screening hemoglobin than donors without pica.

Focusing only on the 608 female iron depleted/deficient donors, those with pica were younger (mean age 34.6 vs. 38.7 years, $p=0.003$) and had a lower mean MCV (83.6 vs. 86.3 fL, $p<0.001$), ferritin (7.9 vs. 10.6 mcg/L, $p <0.0001$), transferrin saturation (12.0 vs. 16.1%, $p<0.001$), and venous hemoglobin (11.9 vs. 12.2 g/dL, $p=0.014$), than those without pica. There was no difference in race or in number of prior donations among female iron depleted/ deficient donors with and without pica.

The association of pica with fingerstick hemoglobin levels was significant in females with hemoglobin levels of less than 11.5 g/dL and in males with hemoglobin levels less than 12.5 g/dL (Tables 3 and 4). Among women in the low hemoglobin group, 8% (26/310) with iron depletion and 21% (50/242) with iron deficiency reported pica compared to 5% (25/506) of those who were iron replete ($p<0.05$ for both comparisons, Table 5). Similar findings were seen in the control group, where 21% (3/14) of iron deficient versus 4% (3/85) of iron replete women reported pica ($p=0.009$, Table 6). In contrast, there was no significant association of pica with iron status in male donors in either the low hemoglobin or the control group (Tables 7 and 8). Although the sensitivity of pica in identifying donors with iron depletion or deficiency was low (14% in female and 8% in male donors), the specificity of pica in females was high (95%), indicating that the presence of pica was associated with a high probability that a female donor was iron depleted or deficient (Table 5).

RLS was reported in 16% (127/809) of donors with iron depletion or deficiency, compared to 11% (92/809) of donors who were not iron depleted or deficient ($p=0.012$). The association of RLS with fingerstick hemoglobin levels was significant only in males with hemoglobin levels of less than 12.0 g/dL (Tables 3 and 4). In the low hemoglobin group, there was no significant association of RLS with iron status in women (Table 5); however, 21% (18/87) of iron deficient versus 6% (4/63) of iron replete men in this group ($p= 0.014$) had RLS (Table 7). In contrast, in the control group, RLS was significantly associated with iron deficiency in female but not in male donors (Tables 6 and 8).

The positive predictive value of pica and RLS in iron deficient and depleted blood donors was 73% and 58%, respectively.

Response to Iron Replacement Therapy

Seventy-two percent of donors deferred for low fingerstick hemoglobin levels and given oral iron replacement therapy returned for at least one subsequent visit. Compliance with oral iron replacement therapy, defined as the percentage of the 60 tablets of iron taken before the next donation visit or the percentage of daily iron tablet ingestion for apheresis donation intervals less than 60 days, was 68% (range 0–100%). Donors taking iron supplements showed steady and consistent improvement and normalization of iron-related laboratory parameters on subsequent donations, even as they continued to donate whole blood and apheresis components. Fingerstick hemoglobin, venous hemoglobin, mean corpuscular volume (MCV), red cell distribution width (RDW), serum ferritin, and transferrin saturation all normalized in this cohort.[12] Donors in the control group who were given oral iron replacement for documented iron deficiency had a similar response.

Donors with pagophagia who were given oral iron supplements reported a marked reduction in the desire to eat ice by day 5–8 of therapy, with complete disappearance of craving symptoms by day 10–14. The clinical response to iron supplements was not dependent on laboratory evidence of iron deficiency or depletion. Resolution of pagophagia was prompt and complete in all donors receiving iron replacement therapy, including 30 donors whose initial ferritin level was in the normal range for gender (mean ferritin 39, range 22 – 100 mcg/L). Donors exhibiting the other types of picas also reported complete resolution of cravings and consumption by day 14. Iron replacement generally resulted in improvement in RLS symptoms, and in some cases complete resolution, but at least 4–6 weeks of iron therapy was necessary before the full effect was seen.

DISCUSSION

The association of pica and disorders of the blood has been known since antiquity.[1,2] Case reports and studies in the literature have chronicled the resolution of pica after the treatment of iron deficiency.[17–22] However, this is the first study to investigate the role of health history questions related to pica in detecting iron deficiency or depletion in blood donors and to report the prevalence of pica in donors before and after oral iron replacement therapy.

RLS was first described more than 350 years ago, but it was not until 1953 that an association of RLS with iron deficiency was reported.[23,24] Serum ferritin levels below 45–50 mcg/L have been found to exacerbate RLS.[25,26] Blood donation and the onset or exacerbation of RLS have been demonstrated in previous studies.[14,15] Our study is the first to examine the role of iron replacement therapy in the improvement of RLS symptoms in blood donors.

The etiologies of both pica and RLS in the setting of iron deficiency are poorly understood. In pica, the substance craved and consumed is relatively devoid of iron, and thus does not provide any nutritive or restorative properties. The addictive nature of the cravings in pica suggests that addiction centers in the brain may be selectively affected by cerebral iron deficiency, but experimental evidence for this hypothesis is lacking. Iron deficiency and secondary RLS is equally puzzling. Studies have shown that cerebral spinal fluid ferritin levels were decreased by 65% and transferrin levels were increased 3 fold in individuals with RLS compared with control subjects.[27] Magnetic resonance imaging (MRI) of the brain in RLS patients demonstrated decreased iron stores, especially in the substantia nigra (SN).[28] Post-mortem analysis of brain tissue from patients with RLS indicates that transferrin receptor expression in the SN was decreased despite cellular evidence of iron deficiency.[29] RLS may be caused or exacerbated by a combination of brain iron management dysfunction in the setting of peripheral iron deficiency.

Iron depletion and deficiency are well-documented consequences of blood donation and were seen in 54% of donors with a low fingerstick hemoglobin level and 39% of donors in the control group in our study.[12] Hemoglobin concentration alone is a poor indicator of iron stores. Eleven percent and 16% of donors with iron depletion or deficiency reported clinical manifestations of pica and RLS, respectively, compared with 4% and 11% of donors with normal iron stores. Furthermore, 73% of all donors giving a history of pica on health history screening had iron deficiency or depletion. Female donors were largely responsible for this association; 75% of all female but only 57% of male donors giving a history of pica were found to be iron depleted or deficient. We also found a significant association of pica with fingerstick hemoglobins of less 11.5 g/dL in female and less than 12.5 g/dL in male donors.

Other than female sex, younger age was the only demographic factor significantly associated with pica, confirming that young female donors are the population most at risk of this unusual symptom. The finding that donors with pica had a lesser rather than greater number of prior successful blood donations was, on further analysis, found to be due to a higher rate of prior deferrals for low screening hemoglobin in this cohort. The laboratory values most strongly associated with pica were found to be the MCV and the transferrin saturation, with venous hemoglobin and ferritin migrating closely with MCV and saturation. These four lab values are so highly interrelated that the assignment of primacy to any one of them is arbitrary.

The symptoms of pica described by iron-deficient donors were intense, pervasive and disruptive, taking the form of addictive-like cravings that significantly affected quality of life. Donors in our study were embarrassed and ashamed of these cravings, rarely if ever discussed them with friends, family, or healthcare providers, and thus did not seek help or recognize their symptoms as those of a disorder amenable to medical therapy. This study not only demonstrates a clear association of pica with iron deficiency in female blood donors, but emphasizes that the recognition of iron deficiency should be an imperative in this at-risk population, as diagnosis is likely to lead to prompt, accessible, and effective treatment. An increased appreciation of the frequency and intensity of symptoms of iron deficiency in donor populations is likely to accelerate efforts to mitigate this undesirable donor outcome, either through adjustments in maximum allowable frequency of donation, modification of hemoglobin eligibility criteria, or routine distribution of a short course of iron replacement supplements after donation.[30]

Thirty-four donors reporting pica were considered iron replete by initial ferritin testing. Oral iron supplements were given to 30 of these donors since they had fingerstick hemoglobin values of < 12.5 g/dL. All 30 of these donors experienced complete resolution of pica symptoms. This observation, together with our prior findings that iron replete donors taking iron had significant increases in both hemoglobin and MCV, demonstrates that neither hemoglobin nor ferritin alone are robust indicators of iron stores, and that even seemingly iron “replete” donors may benefit from iron replacement therapy.[12]

Although the presence of pica was associated with a high probability of iron depletion and deficiency in blood donors, particularly in female donors, we found that symptoms of RLS were not strongly or consistently correlated with iron deficiency in this population. Pica symptoms abated rapidly and resolved completely with oral iron supplements, whereas RLS symptoms improved more slowly and less completely with oral iron. As iron deficiency is not the only cause or contributor to the development of RLS, and our study showed no difference in self-reporting of RLS symptoms among iron deficient versus iron replete donors, we do not recommend the use of a screening question for RLS to ascertain iron status in volunteer blood donors. In contrast, screening questions for pica, in particular pagophagia, may be useful in the ascertainment of iron depletion and deficiency in blood

donors and help to identify at least some of those who would benefit from oral iron therapy. We recognize that most donor centers are unlikely to include pica in their screening questions, but we recommend that centers inform donors who fail the screening hemoglobin test that symptoms of iron deficiency include pica, in particular, pagophagia.

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Table 1

Donor Demographics and Incidence of Iron Depletion and Deficiency at Study Enrollment

		Low Hemoglobin Group* (n= 1236)	Control Group (n =400)	p value
Females	Number of donors	1073 (89%)	143 (37%)	<0.0001
	Age (range)	39 (17–82)	46 (23–69)	<0.0001
Males	Number of donors	163 (11%)	257 (63%)	<0.0001
	Age (range)	53 (22–85)	49 (18–80)	0.0005
Race	Caucasian	832 (65%)	331 (80%)	<0.0001
	African American	215 (19%)	21 (6%)	<0.0001
	Asian	76 (7%)	31 (9%)	0.14
	Hispanic	51 (4%)	7 (2%)	0.04
	Other	62 (5%)	10 (3%)	0.03
Iron Depletion	Females	318 (30%)	42 (29%)	0.25
	Males	13 (8%)	47 (18%)	<0.0001
Iron Deficiency	Females	244 (23%)	14 (10%)	<0.0001
	Males	87 (53%)	54 (21%)	<0.0001

* Fingerstick hemoglobin < 12.5 g/dL.

Table 2

Analysis of Factors Associated with Pica in 1618 Blood Donors

Parameter	Univariate Regression Analysis		Comparison Among Donors (T-test)		
	Chi-square*	p*	Donors with Pica Mean (SD)	Donors without Pica Mean (SD)	p**
MCV (fL)	47.8	<0.00001	84.5 (7.4)	88.4 (5.7)	<0.001
Venous hemoglobin (g/dL)	31.0	<0.00001	12.2 (1.1)	12.8 (1.1)	<0.001
Transferrin saturation (%)	25.9	<0.00001	15.1 (9.5)	20.2 (10.9)	<0.001
Age (years)	16.8	<0.0001	37.8 (14.0)	43.4 (14.7)	<0.001
Sex (female vs. male)	15.2	<0.0001	89% female	73% female	<0.001
Ferritin (mcg/L)	11.5	0.0007	21.6 (35.9)	34.8 (42.1)	<0.001
Number of prior blood donations	4.5	0.034	6.7 (14.8)	10.9 (21.4)	0.002
Number donations in past 12 months	2.8	0.094	1.5 (1.6)	1.8 (1.9)	0.03
Race (Caucasian vs. non-Caucasian)	3.3	0.070	36% non-Caucasian	28% non-Caucasian	0.08

*Strength and significance of the association of each parameter with pica. In stepwise multivariate analysis, once MCV was in the model, only transferrin saturation, sex, and age remained independently associated with pica.

**Significance of differences among donors with and without pica.

Table 3

Association of Fingerstick Hemoglobin Levels with Pica and RLS in Women

	Fingerstick Hemoglobin Levels (g/dL)				
	< 11.5 (n=253)	**11.5 – 11.9 (n=299)**	**12.0 – 12.4 (n=506)**	**< 12.5 (n=1058)**	**≥ 12.5 (n=141)**
Pica present	15%* (38)	9% (26)	7% (37)	10% (101)	7% (10)
p vs. Hb ≥ 12.5	0.021	0.568	0.929	0.345	
RLS present	15% (37)	16% (48)	14% (69)	15% (154)	13% (19)
p vs. Hb ≥ 12.5	0.743	0.475	0.948	0.719	

RLS=Restless Legs Syndrome, Hb=hemoglobin

*Data shown as percent (number) of donors in each fingerstick hemoglobin column who reported pica or RLS.

Table 4

Association of Fingerstick Hemoglobin Levels with Pica and RLS in Men

	Fingerstick Hemoglobin Levels (g/dL)					
	< 12.0 (n=74)	**12.0–12.4 (n=89)**	**12.5–13.4 (n=28)**	**≥ 13.5 (n=228)**	**< 12.5 (n=163)**	**≥ 12.5 (n=256)**
Pica present	11%* (8)	5% (4)	0% (0)	0.9% (2)	7% (12)	0.8% (2)
p vs. Hb ≥ 12.5	<0.001	0.021			<0.001	
RLS present	19% (14)	9% (8)	0% (0)	11% (24)	14% (22)	9% (24)
p vs. Hb ≥ 12.5	0.023	0.914			0.189	

RLS=Restless Legs Syndrome, Hb=hemoglobin

*Data shown as percent (number) of donors in each fingerstick hemoglobin column who reported pica or RLS.

Table 5

Association of Iron Status with Pica and RLS in Women in the Low Hemoglobin Group

	Iron Status		
	Iron Deficient (Ferritin <9 mcg/L) (n=242)	**Iron Depleted (Ferritin 9–19 mcg/L) (n=310)**	**Iron Replete (Ferritin > 19 mcg/L) (n=506)**
Pica present	21%* (50)	8% (26)	5% (25)
p vs. Iron Replete	<0.001	0.048	
RLS present	17% (41)	16% (50)	12% (63)
p vs. Iron Replete	0.099	0.149	

RLS=Restless Legs Syndrome

* Data shown as percent (number) of donors in each iron status column who reported pica or RLS.

Table 6

Association of Iron Status with Pica and RLS in Women in the Control Group

	Iron Status		
	Fe Deficient (Ferritin <9 mcg/L) (n=14)	**Fe Depleted (Ferritin 9–19 mcg/L) (n=42)**	**Fe Replete (Ferritin > 19 mcg/L) (n=85)**
Pica present	21% * (3)	10% (4)	4% (3)
p vs. Iron Replete	0.009	0.166	
RLS present	43% (6)	10% (4)	11% (9)
p vs. Iron Replete	0.002	0.854	

RLS=Restless Legs Syndrome

* Data shown as percent (number) of donors in each iron status column who reported pica or RLS.

Table 7

Association of Iron Status with Pica and RLS in Men in the Low Hemoglobin Group

	Iron Status		
	Fe Deficient (Ferritin < 18 mcg/L) (n=87)	**Fe Depleted (Ferritin 18–29 mcg/L) (n=13)**	**Fe Replete (Ferritin > 29 mcg/L) (n=63)**
Pica present	8% * (7)	0% (0)	8% (5)
p vs. Iron Replete	0.981	0.300	
RLS present	21% (18)	0% (0)	6% (4)
p vs. Iron Replete	0.014	0.357	

RLS=Restless Legs Syndrome

* Data shown as percent (number) of donors in each iron status column who reported pica or RLS.

Table 8

Association of Iron Status with Pica and RLS in Men in the Control Group

	Iron Status		
	Fe Deficient (Ferritin < 18 mcg/L) (n=54)	**Fe Depleted (Ferritin 18–29 mcg/L) (n=47)**	**Fe Replete (Ferritin > 29 mcg/L) (n=155)**
Pica present	0%* (0)	2% (1)	1% (1)
p vs. Iron Replete	0.556	0.371	
RLS present	7% (4)	9% (4)	10% (16)
p vs. Iron Replete	0.533	0.717	

RLS=Restless Legs Syndrome

* Data shown as percent (number) of donors in each iron status column who reported pica or RLS.