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Identifying factors predicting iron deficiency in United States adolescent females using the ferritin and the body iron models

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Abstract

Background & Aims—Iron deficiency is the most prevalent nutritional deficiency in the United States affecting 9–16% of female adolescents. With the primary purpose of detecting iron deficiency, primary care screening consists of a hemoglobin or hematocrit laboratory test. This method is simple and inexpensive, but tests for anemia, and is neither sensitive nor specific for iron deficiency. Alternate methods for diagnosing iron deficiency using the ferritin and body iron models are not widely utilized. The study objective was to compare iron deficiency risk factors among adolescent females defined by the ferritin and body iron models to better characterize those who may benefit from iron deficiency testing as opposed to the current anemia-based screen.

Methods—This cross-sectional study of female adolescents aged 12–21 years utilized National Health and Nutrition Examination Survey 2003–2006 data. Anemia was defined by standard hemoglobin cutoffs. The ferritin model defines iron deficiency through transferrin saturation, ferritin and erythrocyte protoporphyrin laboratory testing. Body iron calculates iron status with a formula involving transferrin receptor and ferritin. Bivariate and multivariable analyses examined associations between questionnaire responses and iron deficiency defined by each model.

Results—Among 1765 participants, 2.7% were anemic. Iron deficiency prevalence was 13.1% and 9.1% by the ferritin and body iron models, respectively. Based on the model, anemia-based screening had a sensitivity of 15.6–18.8% for iron deficiency. Multivariable associations for ferritin model iron deficiency included age, race/ethnicity, activity level and

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medroxyprogresterone acetate injection. Age and food insecurity were significant using the body iron model.

Conclusions—Universal anemia-based screening misses the majority of iron-deficient adolescent females. The common risk factor identified here, adolescent age, may both inform preventive care guidelines on age-based screenings and prospective studies of adolescent iron deficiency risk factors.

Keywords

iron deficiency; anemia; adolescent females; screening; adolescent health; primary care

Introduction

Iron deficiency (ID)[1] is the most common form of nutritional deficiency in the United States [US; 1,2]. It is estimated that 9–16% of US female adolescents are iron deficient while 2–5% are anemic [1,3,4]. Due to lack of a simple, inexpensive test for ID, primary care screening is based on testing for anemia, which has low sensitivity and specificity for detection of ID [2,5,6]. This is unfortunate, as even non-anemic iron deficient adolescents experience significant morbidity, which is easily corrected with iron supplementation [7–9].

Risk assessment tools can select individuals requiring more extensive laboratory evaluation. To develop such a tool for adolescent ID screening, risk factors must be identified with data from that population. Most studies of risk factors for ID and anemia group adolescents with older reproductive age women, typically defined between 12–49 years of age [1,10–12]. However, the care of adolescent females cannot be approached similarly to older women.

A challenge in developing an ID risk assessment tool is that current ID laboratory testing relies on multiple markers that, combined, determine iron status [6]. The ferritin model, which uses serum ferritin, erythrocyte protoporphyrin, and transferrin saturation to define ID, was used from the mid-1980's to 2006 to determine ID among the US population [4,6,13,14]. In 2003 Cook et al. presented the body iron model in response to the need for a reliable method to both assess and quantify iron status [6,15]. Similar to the ferritin model, the body iron model does not provide a single, simple test for ID for use in the office setting, but uses a formula with ferritin and soluble transferrin receptor. A comparison of the prevalence of ID defined by the 2 models found fair to good agreement, but the body iron model produces lower estimates of ID prevalence with better prediction of anemia and less inaccuracy from inflammation [4].

Evaluation of both ID models and associated risk factors through the lens of their utility for the development of a pediatric screening tool would fill a gap in current ID screening. Therefore, the objective of this study was to compare ID risk factors among adolescent females as defined by the ferritin and body iron models with the National Health and Nutrition Examination Survey (NHANES)[2] dataset. Our hypothesis was that the two models

[1]Iron deficiency (ID)
[2]National Health and Nutrition Examination Survey (NHANES)

would share enough overlapping risk factors to create a clinical prediction tool to select adolescents at high risk of ID for more costly laboratory tests or even empiric iron therapy. This implementation science-based study has the potential to replace the current low-sensitivity anemia-based screen (hemoglobin) used daily in US pediatric primary care to test adolescents for ID.

Methods

Data source

NHANES is a program of studies to assess the health and nutritional status of the US population [16]. The survey combines household interviews and physical examinations conducted in mobile examination centers by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC)[3]. NHANES includes demographic, socioeconomic, dietary, and health-related questions. Participants are selected via a stratified multistage probability design. NHANES over-samples certain groups (e.g. African Americans, Hispanics) to produce reliable statistics [16].

From the mid-1980s until 2003–2004 the ferritin model was used to estimate the iron status of the US population [4]. Beginning with the 2003–2004 NHANES survey, the body iron model was adopted [4,6,13,14]. Laboratory values for both models were measured in females 12 to 21 years-old in the 2003–2004 and 2005–2006 NHANES surveys after which point the ferritin model parameters were phased out [4,13]. Thus, these years were selected to directly compare risk factors between the two models.

Ferritin Model

The ferritin model defines ID as an abnormal value for at least 2 of 3 indicators among serum ferritin, erythrocyte protoporphyrin, and transferrin saturation [Table 1; 4,11,17].

Body Iron Model

Body iron is measured using a formula developed by Cook et al. [4,15]:

$$\text{Body iron}(\text{mg/kg}) = -\frac{[\log 10(\text{soluble transferrin receptor}[\text{mg/L}] \times 1000/\text{ferritin}[\text{ug/L}]) - 2.8229]}{0.1207}$$

In this case a negative value (<0 mg/kg) is indicative of ID [4].

Ferritin

Two methods were used to measure ferritin in 2003–2004. The National Center for Environmental Health analyzed all 2003 samples with a BioRad assay and all 2004 samples with a Roche/Hitachi assay [18]. Prior to the release of the 2003 data, piecewise linear regression equations were applied to adjust the 2003 ferritin data to be comparable to the 2004 ferritin data. The Roche/Hitachi assay was used in 2005–2006 [18].

[3]Centers for Disease Control and Prevention (CDC)

Soluble transferrin receptor

Soluble transferrin receptor was measured by immuno-turbidimetry using Roche kits on the Hitachi 912 clinical analyzer. This method was consistent across the sampled study years [18,19]. As per Cogswell, et al. the Roche soluble transferrin reception values were converted to the equivalent in the Flowers assay used in developing the body iron model [4].

Anemia definition

Hemoglobin is a measure of the concentration of iron-containing protein in circulating red blood cells. It is used in the clinical setting as a surrogate for the amount of functional iron in the body [1]. Anemic adolescent females were defined by CDC standard cutoffs for hemoglobin based on sex and age. For adolescent females aged 12 through 14 years, anemia is defined by a hemoglobin concentration <11.8 g/dL. For adolescent females ≥ 15 years of age, anemia is defined by a hemoglobin concentration <12.0 g/dL [1,2]. For self-identified black adolescents, the threshold for anemia diagnosis is 1 g/dL lower as recommended by the International Nutritional Anemia Consultative Group and the World Health Organization [20].

Inclusions/Exclusions

All females 12 to 21 years of age with laboratory data enabling us to determine ID status using both the ferritin and body iron model definitions were included.

Participants were excluded if they reported a history of blood transfusion or were pregnant or breastfeeding at the time of participation. Those with cancer, malignancy, chronic kidney or liver disease also were excluded, but these questions were only asked for participants ≥20 years of age.

As acute and chronic infection or inflammation may influence the iron indices, consistent with Cogswell et al., we excluded participants with a white blood cell count >10.0 × 10^3/uL or a c-reactive protein >0.6 mg/dL [4]. One participant had a missing white blood cell value, but a c-reactive protein level of 0.08 mg/dL and was included.

Statistical Analyses

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC). In particular the procedures SURVEYMEANS, SURVEYFREQ, and SURVEYLOGISTIC were used. These procedures are designed for complex survey analysis and take into account the sampling weights and complex study design to calculate proper variances of estimates. Data are reported as raw frequencies and appropriately weighted percentages and percentiles. First, bivariate analyses using logistic regression assessed the association of potential predictors selected from the NHANES questionnaires and dietary recall (e.g., age, race, country of birth, general health status, nutritional intake, etc.) with the outcomes of interest (i.e., ferritin ID and body ID). Over one-hundred independent variables were initially selected as possible predictors of adolescent female ID based on a literature review and clinical expertise (Supplemental Table 1). Note the NHANES questionnaire refers to medroxyprogesterone acetate injection (Depo-Provera, Pfizer, Inc.) by its better known trade name.

Body mass index (BMI) for age percentile was examined to age 20 and for those 20–21 years of age using CDC adult BMI classifications. Participants were then categorized as underweight, normal weight, overweight and obese [21]. Many potential risk factors had questions with more than 2 response levels; and given our data, lead to many levels having small cell counts. To provide an adequate number of participants per level of a question, we collapsed the data over multiple levels for analytical purposes. Food frequency questionnaire items were dichotomized into never vs. ever consuming the item in question. In asking participants to compare their activity level to others the same age, responses were dichotomized into about the same/more vs. less. Food security questions were dichotomized to compare full food security or never worrying about food to any degree of food insecurity.

Age was dichotomized at <16 years versus ≥16 years as most adolescent females will attain menarche by 16 years [22]. Absence of menarche by 16 years qualifies as primary amenorrhea. Years since menarche was dichotomized at <3 versus ≥3 years as most adolescents have regular menses three years after menarche [22].

Of the variables remaining from the bivariate analyses (Table 2), potential predictors were retained for a multivariable model based on adequate sample size and the strongest association with the outcome of interest, i.e., ID ($p \leq 0.10$). These variables were used as a candidate pool of predictors to construct a multivariable logistic regression model using backward variable selection with the criteria for a variable to remain in the multivariable model set to $\alpha=0.05$. Age and years since menarche were anticipated to be collinear. Age is easier to use in the clinical setting as it does not require the adolescent to recall age at menarche and then calculate years since menarche, so the decision was made to retain age and drop years since menarche in the candidate pool for the multivariable model.

For the multivariable model the concordance index (c-index)[4], also referred to as the area under the curve, is reported. The c-index, a measure of predictive ability, is the proportion of all pairs of adolescent females with different outcomes (ID vs. no ID) in which the adolescent female with the higher predicted probability of ID was indeed the adolescent female who had ID. A c-index value of 0.50 indicates completely random predictions, while a value of 1 indicates perfect predictions. For the c-index, Hosmer and Lemeshow refer to “acceptable discrimination” if $0.7 \leq$ c-index < 0.8 and “excellent discrimination” if $0.8 \leq$ c-index < 0.9 [23].

Results

Demographics

A sample of 1765 adolescent females aged 12 to 21 years participating in NHANES 2003–2006 with the necessary laboratory data to define ID using both the ferritin model and the body iron model were included in this analysis. This sample represents 6.3% of all NHANES study participants (unweighted N=28,127) and 65.4% of all adolescent women (unweighted N=2700) in the selected years. Among the sample, 65.8% were self-described white, 14.6% black, 9.7% Mexican, 4.2% Hispanic and 5.7% other. Almost all participants

[4]Concordance index (c-index)

(91.4%) reported their place of birth as the US. Median age was 15.7 years (interquartile range [Q1–Q3]: 13.4–17.9 years) and median time since menarche was 3.5 years (Q1–Q3: 1.5–5.5 years).

Anemia and ID Prevalence

Among the 1765 participants, 2.7% were anemic. In contrast, the prevalence of ID was 13.1% by the ferritin model and 9.1% by the body iron model. Of those participants that met the criteria for ID by the ferritin model, 15.6% were anemic. Of those participants that met the criteria for ID by the body iron model, 18.8% were anemic. Among participants not meeting ID criteria by the ferritin or body iron models 0.8% and 1.1% were anemic, respectively.

The sensitivity and specificity of hemoglobin for adolescent female ID using the ferritin model as the gold standard was 15.6%, 95% CI (9.4–21.8%) and 99.2%, 95% CI (98.7–99.8%) respectively. The sensitivity and specificity of hemoglobin for adolescent female ID using the body iron model as the gold standard was 18.8%, 95% CI (10.9–26.8%) and 98.9%, 95% CI (98.2–99.6%) respectively.

Bivariate analyses

The bivariate analyses demonstrate overlap in some of the potential predictors of adolescent female ID as defined by the two models (Table 2). Specifically, age ≥16 years, non-white race, treatment for anemia in the past 3 months, and food insecurity with worries about running out of food were associated with ID by both models.

Multivariable logistic regression

In the multivariable analysis, sample size was limited by the independent variable with the smallest number of responses which was n=1347 for the ferritin model and n=1001 for the body iron model. For the ferritin model, age ≥16 years, non-white race, self-reported activity level about the same/more than peers and use of medroxyprogesterone acetate injection were significant predictors of adolescent female ID (Table 3). In the multivariable model for body iron, age ≥16 years and food insecurity emerged as significant predictors of adolescent female ID (Table 3). Thus, age ≥16 years was the only overlapping risk factor between the two models. The multivariable model c-indices were 0.61 and 0.67 for the ferritin model and body iron model, respectively.

Discussion

This analysis of a nationally representative cohort of female adolescents aged 12 to 21 years confirms that current anemia-based screening, with a sensitivity of only 15.6–18.8%, greatly underestimates ID and is inadequate as a widely used screening tool. Survey-based risk factors for adolescent ID showed some variability by the model used to define its presence and the prevalence of ID. However, adolescent age was a significant predictor of ID in both the ferritin model and the body iron model, and may be used to inform age-based screening guidelines as well as prospective studies of adolescent ID risk factors.

An adolescent-specific ID risk assessment tool is needed as identifying a single, simple and reliable test for ID remains a problem in clinical practice [1,6]. Multiple laboratory markers of ID have been studied including erythrocyte protoporphyrin, zinc protoporphyrin, serum ferritin, serum transferrin receptor, reticulocyte hemoglobin and hepcidin [1,6,14,24–30]. Each marker has its own limitations. While combining several indices improves the sensitivity for detection of ID, from the clinician's perspective, none of these tests are available for point-of-care testing, and all are more complex to interpret when compared with a hemoglobin level [1,6].

Unfortunately anemia is a late-stage indicator of ID, and reliance on hemoglobin testing for anemia misses non-anemic, iron deficient adolescent females [1]. Our results indicate anemia-based screening has an unacceptably low sensitivity of 15.6–18.8% for detection of iron deficient adolescent females. These undetected adolescents are likely to experience the known morbidities of ID, including negative effects on cognition and scholastic achievement, which may impact future academic and workplace success, but are easily correctable with iron supplementation [7–9].

As new models of ID evolve, it makes sense to ensure that beyond agreement for population-based statistics, there is applicability for the clinician assessing the individual patient. An accurate adolescent-specific ID clinical prediction tool would select adolescent females at highest risk for ID for more costly laboratory testing, thus targeting those most likely to benefit from iron therapy. Such prediction tools have successfully been applied in other areas of medicine [e.g. Centor criteria for streptococcal pharyngitis; 31,32].

The factors significantly associated with ID in each model warrant further discussion. In the ferritin model, age ≥16 years emerged as a risk factor for ID. By 16 years-old adolescent females should have begun menstruation, a risk factor for blood and iron loss, which is why this cut point was chosen to dichotomize age [22]. Non-white race is associated with ID anemia, thus it is not unexpected that it is also associated with ID [20,33]. Increased physical activity also has been associated with ID anemia [2]. Lastly, use of medroxyprogesterone acetate injection is anticipated to be protective as women on this form of birth control often become amenorrheic [34].

In the body iron model age ≥16 years was also a risk factor for ID, for the same reasons as discussed above. Participants who were sometimes or often worried about running out of food also demonstrated an increased risk of ID. Eicher-Miller et al. used the ferritin model and examined NHANES data from 1999–2004 noting an increased odds of ID anemia among 12–15 year-old adolescents in food insecure households [35].

Several study limitations should be acknowledged. Study nonresponse bias was adjusted by sample weights, but not all adolescents aged 12–21 years had the necessary laboratory values and survey responses to be included in the analysis. This was a national survey not solely focused on ID, so the study was limited by the available NHANES questions to consider as candidate risk factors for ID. Other items, such as weight-related questions included due to the association of restrictive diets and ID [2], were excluded due to small sample sizes as these questions were only asked for participants age 16 years and above. The

prevalence of ID anemia may be an overestimate as participants may have been anemic for other reasons, though the reported prevalence is consistent with previously published work [1,3]. Reporting odds ratios rather than relative risks may overestimate the risk for cross-sectional data such as NHANES. It is a challenge to obtain relative risks while accounting for the multiple weights (i.e., cluster, strata, and sampling weights) used in complex survey designs. Specifically, the SURVEYLOGISTIC procedure in SAS software used to analyze the complex survey data does not have the log link function necessary to fit a log-binomial model that would provide estimates of relative risk. Thus, the possibility exists that the independent variables identified as significant in the final multivariable models may represent the 5% of false positives. Lastly, the cross sectional nature of NHANES does not permit a longitudinal assessment of iron status among the participants.

Conclusions

Anemia-based screening is widely utilized in primary care, but fails to detect the majority of iron deficient adolescent females. Currently, universal laboratory testing for adolescent ID is impractical in the clinical setting. Identification of adolescent age as a common risk factor between the ferritin and body iron models may inform age-based recommendations on ID screening as well as prospective studies on optimizing adolescent ID screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. MMWR Morb Mortal Wkly Rep. 1998; 47(RR-3):1–29. [PubMed: 9450721]
2. Holt, K.; Wooldridge, N.; Story, M.; Sofka, D., editors. Bright Futures Nutrition. American Academy of Pediatrics. 3rd ed.. 2011. Iron-Deficiency anemia; p. 175-181.
3. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. JAMA. 1997; 277:973–976. [PubMed: 9091669]
4. Cogswell ME, Looker AC, Pfeiffer CM, Cook JD, Lacher DA, Beard JL, Lynch SR, Grummer-Strawn LM. Assessment of iron deficiency in US preschool children and nonpregnant females of childbearing age: National Health and Nutrition Examination Survey 2003–2006. Am J Clin Nutr. 2009; 89:1334–1342. [PubMed: 19357218]
5. Hagan, JF.; Shaw, JS.; Duncan, PM., editors. 3rd ed.. Elk Grove Village, IL: American Academy of Pediatrics; 2008. Bright Futures: Guidelines for Health Supervision for Infants, Children, and Adolescents.
6. Lynch SR. Why nutritional iron deficiency persists as a worldwide problem. J Nutr. 2011; 141:763S–768S. [PubMed: 21367937]

7. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. Lancet. 1996; 348:992–996. [PubMed: 8855856]
8. Devaki PB, Chandra RK, Geisser P. Effects of oral iron(III) hydroxide polymaltose complex supplementation on hemoglobin increase, cognitive function, affective behavior and scholastic performance of adolescents with varying iron status: a single centre prospective placebo controlled study. Arzneimittelforschung. 2009; 59(6):303–310. [PubMed: 19634512]
9. Murray-Kolb LE, Beard JL. Iron treatment normalizes cognitive functioning in young women. Am J Clin Nutr. 2007; 85:778–787. [PubMed: 17344500]
10. Parker J, Branum A, Axelrad D, Cohen J. Adjusting National Health and Nutrition Examination Survey sample weights for women of childbearing age. National Center for Health Statistics. Vital Health Stat. 2013; 2:1–20.
11. Centers for Disease Control and Prevention. Iron deficiency--United States, 1999–2000. MMWR Morb Mortal Wkly Rep. 2002; 51:897–899. [PubMed: 12418542]
12. Oregon Evidence-based Practice Center. Evidence syntheses, No. 40. Rockville, MD: Agency for Healthcare Research and Quality (US); 2006. Screening for Iron Deficiency Anemia in Childhood and Pregnancy: Update of the 1996 U.S. Preventive Task Force Review.
13. Cusick SE, Looker AC, Cogswell ME, Pfeiffer CM, Grummer-Strawn L. Iron-status indicators. Pediatrics. 2008; 121:651–652. [PubMed: 18310220]
14. Mei Z, Pfeiffer CM, Looker AC, Flores-Ayala RC, Lacher DA, Mirel LB, Grummer-Strawn LM. Serum soluble transferrin receptor concentrations in US preschool children and non-pregnant women of childbearing age from the National Health and Nutrition Examination Survey 2003–2010. Clin Chim Acta. 2012; 413:1479–1484. [PubMed: 22705806]
15. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood. 2003; 101:3359–3364. [PubMed: 12521995]
16. National Center for Health Statistics. [accessed 31 March 2014] About the National Health and Nutrition Examination Survey. Version current 3 February 2014. Internet: www.cdc.gov/nchs/nhanes/about_nhanes.htm
17. Expert Scientific Working Group. Summary of a report on assessment of the iron nutritional status of the United States population. Am J Clin Nutr. 1985; 42:1318–1330. [PubMed: 4072962]
18. National Health and Nutrition Examination Survey. [accessed 26 March 2014] 2003–2004 Data Documentation, Codebook, and Frequencies. Laboratory component. Ferritin and Transferrin Receptor. Version current December 2007. Internet: http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/L06TFR_C.htm#Analytic_Notes
19. National Health and Nutrition Examination Survey. [accessed 22 May 2014] 2005–2006 Data Documentation, Codebook, and Frequencies. Laboratory component. Transferrin Receptor. Version current April 2008. Internet: http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/TFR_D.htm#Description_of_Laboratory_Methodology.
20. Nestel, P. [accessed 10 December 2013] Adjusting Hemoglobin Values in Program Surveys. International Nutritional Anemia Consultative Group. 2002. Internet: http://pdf.usaid.gov/pdf_docs/PNACQ927.pdf.
21. Centers for Disease Control and Prevention. [accessed 5 March 2014] Body Mass Index. Version current 6 December 2014. Internet: http://www.cdc.gov/healthyweight/assessing/bmi/
22. Diaz A, Laufer MR, Breech LL. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. Pediatrics. 2006; 118:2245–2250. [PubMed: 17079600]
23. Hosmer, DW.; Lemeshow, S. Applied Logistic Regression. 2nd ed.. New York: John Wiley & Sons, Inc.; 2000.
24. Vazquez Lopez MA, Carracedo A, Lendinez F, Munoz FJ, Lopez J, Munoz A. The usefulness of serum transferrin receptor for discriminating iron deficiency without anemia in children. Haematologica. 2006; 91:264–265. [PubMed: 16461317]
25. Takala TI, Suominen P, Lehtonen-Veromaa M, Möttönen T, Viikari J, Rajamäki A, Irjala K. Increased serum soluble transferrin receptor concentration detects subclinical iron deficiency in healthy adolescent girls. Clin Chem Lab Med. 2003; 41:203–208. [PubMed: 12667008]

26. Malope BI, MacPhail AP, Alberts M, Hiss DC. The ratio of serum transferrin receptor and serum ferritin in the diagnosis of iron status. Br J Haematol. 2001; 115:84–89. [PubMed: 11722416]
27. Wharton BA. Iron deficiency in children: detection and prevention. Br J Haematol. 1999; 106:270–280. [PubMed: 10460583]
28. Beard J. Annex 3 Indicators of the iron status of populations: free erythrocyte protoporphyrin and zinc protoporphyrin; serum and plasma iron, total iron binding capacity and transferrin saturation; and serum transferrin receptor. Assessing the Iron Status of populations. World Health Organization (2nd ed.). 2004:77–93.
29. Suominen P, Virtanen A, Lehtonen-Veromaa M, Heinonen OJ, Salmi TT, Alanen M, Möttönen T, Rajamäki A, Irjala K. Regression-based reference limits for serum transferrin receptor in children 6 months to 16 years of age. Clin Chem. 2001; 47:935–937. [PubMed: 11325899]
30. Friedrich MJ. Marker for iron-deficiency anemia? JAMA. 2014; 311(23):2372.
31. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA. 2004; 291:1587–1595. [PubMed: 15069046]
32. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? JAMA. 2000; 284:2912–2918. [PubMed: 11147989]
33. Frith-Terhune AL, Cogswell ME, Khan LK, Will JC, Ramakrishnan U. Iron deficiency anemia: higher prevalence in Mexican American than in non-Hispanic white females in the third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr. 2000; 72:963–968. [PubMed: 11010938]
34. Apgar BS, Greenberg G. Using progestins in clinical practice. Am Fam Physician. 2000; 62:1839–1846. 1849–1850. [PubMed: 11057840]
35. Eicher-Miller HA, Mason AC, Weaver CM, McCabe GP, Boushey CJ. Food insecurity is associated with iron deficiency anemia in US adolescents. Am J Clin Nutr. 2009; 90:1358–1371. [PubMed: 19776137]

Table 1

Thresholds for laboratory tests of iron status indicative of iron deficiency in the ferritin model

	Abnormal values		
Age	**Serum ferritin (ug/L)**	**Transferrin saturation (%)**	**Erythrocyte protoporphyrin (ug/dL of red blood cells)**
12–15 years-old	<16.5	<14%	>70
≥16–21 years-old	<16.5	<15%	>70

Table 2

Bivariate analysis of risk factors for iron deficiency by the ferritin model versus the body iron model[a]

Risk Factor	Ferritin Model		Body Iron Model	
	OR (95% CI)[b]	*P* value	OR (95% CI)	*P* value
Age ≥ 16 years	1.48 (1.04, 2.11)	0.03	1.93 (1.19, 3.11)	0.007
Years since menarche ≥ 3	1.51 (0.89, 2.55)	0.13	2.36 (1.33, 4.19)	0.003
Non-white race	1.88 (1.31, 2.70)	0.001	1.61 (1.01, 2.56)	0.04
Born outside of the United States	1.92 (1.05, 3.50)	0.03	1.60 (0.80, 3.19)	0.19
Treatment for anemia in the past 3 months	2.91 (1.17, 7.22)	0.02	2.12 (0.98, 4.57)	0.06
Self-report of physical activity compared with peers (about the same/more vs. less)	2.19 (1.31, 3.68)	0.003	1.62 (0.84, 3.10)	0.15
Past pregnancy	1.85 (0.78, 4.39)	0.17	2.46 (1.00, 6.10)	0.05
Household worried run out of food (sometimes/often true vs. never true)	1.55 (1.03, 2.32)	0.04	1.84 (1.11, 3.06)	0.02
Household food security (marginal/low/very low vs. full)	1.44 (1.00, 2.08)	0.05	1.45 (0.89, 2.37)	0.14
Drink coffee	1.38 (0.79, 2.42)	0.25	2.06 (1.11, 3.81)	0.02
Spanish language of interview	3.10 (1.70, 5.67)	<0.001	1.87 (0.69, 5.04)	0.22
Medroxyprogesterone acetate injection	0.44 (0.22, 0.88)	0.02	0.60 (0.25, 1.47)	0.26
Family income < $20,000/year	1.61 (1.09, 2.38)	0.02	1.43 (0.93, 2.17)	0.11
Eat any type of chicken or turkey >1 time per week	1.32 (0.87, 2.00)	0.19	1.69 (0.99, 2.90)	0.06

[a] Unweighted N=1765.

[b] OR=odds ratio, CI=confidence interval

Table 3

Multivariable analysis of factors predicting iron deficiency in the ferritin model and the body iron model[a]

Risk factor	OR (95% CI)[b]	*P* value
Ferritin Model		
Age ≥ 16 years	1.69 (1.13, 2.53)	0.01
Non-white race	1.98 (1.24, 3.14)	0.004
Self-report of physical activity compared with peers (about the same/more vs. less)	2.30 (1.24, 4.26)	0.008
Medroxyprogesterone acetate injection	0.36 (0.17, 0.76)	0.008
Body Iron Model		
Age ≥ 16 years	3.54 (1.73, 7.24)	0.001
Household worried run out of food (sometimes/often true vs. never true)	2.55 (1.33, 4.88)	0.005

[a] Analyses conducted using multivariable logistic regression. Unweighted N and C-index are 1347 and 0.61and 1001 and 0.67.

[b] OR=odds ratio, CI=confidence interval