Published in final edited form as:

Transl Res. 2017 February ; 180: 68–76. doi:10.1016/j.trsl.2016.08.003.

Optimizing hemoglobin thresholds for detection of iron deficiency among reproductive age women in the United States

Deepa L. Sekhar^a, Allen R. Kunselman^b, Cynthia H. Chuang^{b,c}, and Ian M. Paul^{a,b}

^aDepartment of Pediatrics, Penn State College of Medicine, Hershey, PA

^bDepartment of Public Health Sciences, Penn State College of Medicine, Hershey, PA

^cDepartment of Medicine, Penn State College of Medicine, Hershey, PA

Abstract

Iron deficiency (ID) affects 9–16% of US women with well-documented morbidity in academic performance, mood, and concentration. Current ID screening depends on detection of low hemoglobin (i.e. anemia, <12.0 g/dL). However, anemia is a late-stage indicator of ID. The study hypothesis was that using higher hemoglobin thresholds would optimize ID screening. The objective was to assess sensitivity and specificity of hemoglobin to detect ID among non-pregnant, reproductive age women 12–49 years of age, and to determine if psychometric characteristics varied by age and race. This cross-sectional study used National Health and Nutrition Examination Survey 2003–2010 data. ID was defined by Body Iron, calculated using ferritin and transferrin receptor. Logistic regression and receiver operating characteristic (ROC) curves were used to model the predictive probability of ID by hemoglobin values. ID prevalence by body iron was 11.5% (n=6,602). Using <12.0 g/dL, hemoglobin had a sensitivity of 42.9% (95% CI 39.4%, 46.4%) and specificity of 95.5% (95% CI 95.0%, 96.0%) for ID. The ROC curve was optimized at hemoglobin threshold <12.8 g/dL with sensitivity and specificity of 71.3% (95% CI 68.0%, 74.5%) and 79.3% (95% CI 78.2%, 80.3%) respectively. The probability of ID at this threshold was 13.5% (95% CI 11.3%, 15.9%). Hemoglobin better predicted ID among older (22–49 years) vs. younger (12–21 years) women (c-index 0.87 vs. 0.77, $p < 0.001$). Among non-pregnant, reproductive age women, current hemoglobin thresholds are insufficient to exclude ID. A threshold of <12.8 g/dL improves detection of ID.

Keywords

anemia; iron deficiency; hemoglobin

Corresponding author: Deepa L. Sekhar, Department of Pediatrics, Division of Academic General Pediatrics, Penn State College of Medicine, 500 University Dr, HS83, Hershey, PA 17033; Phone 1-717-531-8006; Fax 1-717-531-0869; dsekhar@hmc.psu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Iron deficiency (ID) is the most common form of nutritional deficiency in the United States (US).^{1,2} While ID affects all age groups, reproductive age women are at higher risk secondary to increased iron demands from menstrual blood loss and pregnancy. It is estimated that 9–16% of reproductive age US women are iron-deficient while 2–5% are anemic.^{1,3,4}

Anemia is a late-stage indicator of ID. In order to develop anemia, iron-deficient individuals must have significantly depleted the body's iron stores.¹ However, even non-anemic, iron-deficient women have been shown to experience significant morbidity including poor academic performance, mood lability, and concentration difficulty, which is improved with iron supplementation.^{5–10}

Recognizing the importance of detecting ID, the Centers for Disease Control and Prevention (CDC) recommends testing all non-pregnant women for ID anemia “every 5–10 years throughout their childbearing years during routine health examinations”.^{1,2} Due to lack of a single, simple, inexpensive test for ID, screening is based on detection of anemia with hemoglobin levels, which continues as routine practice despite low sensitivity and specificity for detection of ID.^{1,2,11,12} Hemoglobin is a protein within red blood cells responsible for the delivery of oxygen to body tissues.¹³ The hemoglobin protein itself contains iron, and a hemoglobin level is thus a reflection of the amount of functional iron in the body. Changes in hemoglobin levels only occur in the late stages of ID, making a decline in hemoglobin to anemic ranges a late indicator of ID.¹

Though ID is perhaps the most common etiology of anemia among United States women, anemia has many causes, and hemoglobin norms for detecting anemia were not designed solely to optimize detection of ID.¹⁰ In clinical practice, higher hemoglobin concentrations, aside from polycythemia, are often equated with better iron status. Yet, the diagnostic accuracy of using hemoglobin as a screening tool for ID is rarely discussed despite its routine use.

The objective of this study was to determine the optimal hemoglobin threshold that maximizes the sensitivity and specificity for detecting ID among non-pregnant, reproductive age women 12–49 years of age using National Health and Nutrition Examination Survey (NHANES) 2003–2010 data. As normal hemoglobin values vary by age, adolescent/young-adult (12–21 years) and older (22–49 years) reproductive age women were also analyzed separately.^{1,2} It is anticipated this information may enhance the value of hemoglobin testing for ID in clinical care and guide the decision to pursue additional iron studies.

MATERIALS AND METHODS

Study Participants

NHANES is cross-sectional program of periodic surveys to assess the health and nutritional status of the US population.¹⁴ The nationally representative surveys combine household interviews and physical examinations conducted in mobile examination centers by the

National Center for Health Statistics, CDC. The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. Participants are selected via a stratified multistage probability with over-samplings of certain groups (e.g. African Americans, Hispanics) to produce reliable statistics.¹⁴ The project was given a “not human research” determination by the Penn State College of Medicine Institutional Review Board.

This study included all women 12 to 49 years of age with hemoglobin, ferritin, and soluble transferrin receptor laboratory values recorded in NHANES 2003–2010. Due to variation in hemoglobin by age, younger (12–21 years) and older (22–49 years) women were examined separately.^{1,2} As hemoglobin values also vary by race, blacks and non-blacks were examined separately.¹⁵ Participants were excluded for a history of blood transfusion, as this suggests their ID may have causes (e.g. trauma, malignancy) other than the ID most commonly managed in preventive care.¹⁰ Pregnant or breastfeeding participants were also excluded. Lastly, those with cancer, malignancy, chronic kidney or liver disease were excluded, but these questions were only asked for participants older than 20 years of age. As acute and chronic infection or inflammation may influence the iron indices, consistent with Cogswell et al., we also excluded participants with a white blood cell count $>10.0 \times 10^3/\mu\text{L}$ or a c-reactive protein $>0.6 \text{ mg/dL}$.⁴

Laboratory parameters

Hemoglobin concentration is a surrogate for the amount of functional iron in the body.¹ The normal hemoglobin range varies based on sex and age. For women aged 12 through 14 years, anemia is defined by a hemoglobin concentration $<11.8 \text{ g/dL}$. For women aged 15–49 years, anemia is defined by a hemoglobin concentration $<12.0 \text{ g/dL}$.^{1,2} For self-identified black women, threshold for anemia diagnosis is 1 g/dL lower as recommended by the International Nutritional Anemia Consultative Group and the World Health Organization.¹⁵ Parameters for the complete blood count, which includes hemoglobin level, were based on the Beckman Coulter method of counting and sizing. This was performed in combination with an automatic diluting and mixing device for sample processing, and a single beam photometer for hemoglobin measurement.¹⁶

ID was calculated using the body iron formula developed by Cook et al.^{4,17}

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

The formula requires laboratory values for ferritin and soluble transferrin receptor, which were included in the NHANES dataset from 2003–2010. A negative value ($<0 \text{ mg/kg}$) is indicative of ID.⁴ However, as ferritin is more commonly used in clinical care than the Body Iron calculation to assess iron stores, a second analysis defining ID as ferritin $<12 \text{ ug/L}$ was also conducted.

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.¹⁸ The Roche/Hitachi 912 nephelometric immunoassay was used in 2005–2008.^{19,20} In 2009–2010 the Roche Elecsys sandwich immunoassay was used.²¹ The Roche/Hitachi ferritin assay had previously been compared to the Cook ferritin in the calculation of body iron with no differences found between the 2 methods.⁴ Thus the 2009–2010 ferritin measurements obtained using the Roche Elecsys 170 method were converted to the Roche/Hitachi 912 scale using the following equation: Hitachi = $10^{([\log_{10}(\text{Elecsys}) - 0.049] / 0.989)}$.²¹

Soluble transferrin receptor was measured by immuno-turbidimetry using Roche kits on the Hitachi 912 clinical analyzer from 2003–2008.^{22–24} In 2009–2010 the Roche Hitachi Mod P immunoturbidimetric method was used. A crossover study was performed between the two methods, but no adjustment of the data was needed.²⁵ 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

Statistical Analyses

Because NHANES is a complex probability sample, the selected data were weighted appropriately as per NHANES study guidelines to be representative of the current US population for all analyses.²⁶ All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). In particular the procedure SURVEYLOGISTIC, which is specifically designed for complex survey analysis, was used to take into account the sampling weights and complex study design to calculate proper variances of estimates.

Logistic regression was used to fit models assessing the association between hemoglobin and ID. From the logistic regression models, the predicted probability of ID and ROC curves were generated.²⁷ The ROC curve is created by varying the diagnostic threshold of hemoglobin. The diagnostic threshold indicative of ID susceptibility for hemoglobin was selected based on the Youden index, which is defined by the formula: sensitivity + specificity – 1. The maximal Youden index identifies the optimal threshold when sensitivity and specificity are considered of equal importance, and this maximal value is the “knee” of the ROC curve.²⁸

The concordance index (c-index), also referred to as the area under the curve (AUC), is reported for the ROC curves. The c-index, a measure of predictive ability, is the proportion of all pairs of females with different outcomes (ID vs. no ID) in which the females with the higher predicted probability of ID was indeed the 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 $0.7 < \text{c-index} < 0.8$ and “excellent discrimination” if $0.8 < \text{c-index} < 0.9$.²⁹ Area under the ROC curves were compared between the younger and older female groups using a chi-square test.²⁷

RESULTS

Characteristics of the sample population

There were 13,015 women aged 12 to 49 years who participated in NHANES 2003–2010. This represented 18.7% of the NHANES 2003–2010 participants. After applying the exclusion criteria, the sample included 7,658 women. Many women had multiple exclusions (e.g. liver disease and elevated white blood cell count), resulting in 94 different combinations of groups for exclusion. Collapsing exclusion criteria, Fig 1 provides an overview of these exclusions. There were 6,602 women with the necessary hemoglobin and body iron laboratory data included in the analysis. This sample includes 2,985 (45.2%) younger women aged 12–21 years and 3,617 (54.8%) older women aged 22–49 years. The overall prevalence of ID was 11.5% and anemia was 5.9% (Table I).

The ROC curve for all reproductive age women had an AUC of 0.83 (95% CI 0.82, 0.85; Fig 2a). From the ROC curve, as the hemoglobin threshold increases the sensitivity increases; however, the specificity declines. The ROC curve indicates using values <12.0 g/dL for “abnormal” hemoglobin (as is the recommended threshold for women 15–49 years) had a sensitivity of 42.9% (95% CI 39.4%, 46.4%) and specificity of 95.5% (95% CI 95.0%, 96.0%) for ID. The ROC curve was optimized at a hemoglobin threshold of <12.8 g/dL with sensitivity and specificity for detection of ID of 71.3% (95% CI 68.0%, 74.5%) and 79.3% (95% CI 78.2%, 80.3%) respectively. The probability of having ID at this threshold was 13.5% (95% CI 11.3%, 15.9%; Fig 2b).

Age Stratified Analyses

The analyses were then stratified by age, young women 12–21 years and older women 22–49 years. The ROC curve for women aged 12–21 years of age had an AUC of 0.77 (95% CI 0.74, 0.80; Fig 3a). A value of 11.8 g/dL is commonly used as the diagnostic threshold for normal hemoglobin in women 12–14 years of age, so this was examined on the ROC curve. Using a threshold of <11.8 g/dL yields a sensitivity of 27.8% (95% CI 22.9%, 32.7%) and specificity of 97.1% (95% CI 96.5%, 97.7%) among those 12–21 years old. Using a threshold of <12.0 g/dL yields a sensitivity of 34.7% (95% CI 29.5%, 39.9%) and specificity of 95.0% (95% CI 94.2%, 95.9%). The ROC curve was optimized at a hemoglobin threshold of <12.8 g/dL with sensitivity and specificity of 64.4 (95% CI 59.1%, 69.6%) and 77.4% (95% CI 75.8%, 79.0%) respectively. The probability of having ID at this threshold was 13.0% (95% CI 10.7%, 15.8%; Fig 3b).

The ROC curve for older women aged 22–49 years of age had an AUC of 0.87 (95% CI 0.86, 0.89; Fig 4a). For older women, a hemoglobin threshold <12.0 g/dL resulted in sensitivity of 48.9% (95% CI 44.2%, 53.5%) and specificity of 95.9% (95% CI 95.2%, 96.6%). The ROC curve was optimized at a hemoglobin threshold of <12.7 g/dL with sensitivity and specificity 74.0% (95% CI 69.9%, 78.1%) and 83.5% (95% CI 82.2%, 84.8%) respectively. The probability of having ID at this threshold was 15.4% (95% CI 12.6%, 18.7%; Fig 4b). Furthermore, the AUC of 0.87 in the older women was significantly larger than the AUC of 0.77 observed for the younger women ($p < 0.001$).

Race stratified analysis

ROC curves were similarly generated for black and nonblack women. Using a threshold of <11.0 g/dL (1 g/dL lower as stated above¹⁵) to define anemia for black women resulted in sensitivity of 37.4% (95% CI 31.4%, 43.5%) and specificity of 98.7% (95% CI 98.0, 99.3%). The ROC curve was optimized at a hemoglobin threshold of <12.5 g/dL with sensitivity of 80.7% (95% CI 75.7%, 85.6%) and specificity of 73.3% (95% CI 71.0%, 75.7%). The probability of having ID at this threshold was 13.2% (95% CI 10.0%, 17.2%). The AUC for black women was 0.85 (95% CI 0.82, 0.88). Analyzing non-blacks separately the ROC curve was optimized at hemoglobin <13.0 g/dL with sensitivity of 69.9% (95% CI 66.0%, 73.9%) and specificity of 79.3% (95% CI 78.1%, 80.5%). The probability of having ID at this threshold was 11.3% (95% CI 9.2%, 13.9%). The AUC for non-black women was 0.83 (95% CI 0.81, 0.85).

Ferritin to define ID

A second analysis using ferritin <12 ug/L to define ID produced similar results to the use of Body Iron (Table II). The overall prevalence of ID when defined by ferritin <12 ug/L was 14.0%. For all women 12–49 years the ROC curve was optimized at a hemoglobin of <12.8 g/dL with sensitivity of 63.9% (95% CI 60.8%, 67.0%) and specificity of 79.5% (95% CI 78.5%, 80.6%). For young women 12–21 years the ROC curve was optimized at a slightly higher hemoglobin threshold of <13.0 g/dL with sensitivity of 63.5% (95% CI 58.9%, 68.1%) and specificity of 71.3% (95% CI 69.5%, 73.0%). For nonblack women the ROC curve was also optimized at a slightly higher hemoglobin threshold of <13.1 g/dL with sensitivity of 65.3% (95% CI 61.6%, 68.9%) and specificity of 77.5% (95% CI 76.2%, 78.7%).

DISCUSSION

The ROC curves generated in this analysis of 2003–2010 NHANES data confirm that the current hemoglobin thresholds for an “abnormal” or anemic value have poor sensitivity for ID. The optimal hemoglobin threshold to prompt further iron testing has not been considered. While hemoglobin testing in clinical medicine has a scope beyond detection of ID, it is frequently used for this purpose in the context of preventive care. The study results suggest that redefining “abnormal” to <12.8 g/dL is a more appropriate threshold when screening reproductive age women for ID. If age and race are considered the optimal threshold changes slightly, <12.7 g/dL for older women, <12.5 g/dL for black women, and <13.0 g/dL for nonblack women. Similar results were obtained when ID was defined by a ferritin <12 ug/L.

Anemia is defined as a value $<5^{\text{th}}$ percentile of the distribution of hemoglobin concentration in a healthy population based on age and sex.^{1,3} Prior publications using an older ID model (two of three positive test results including low mean cell volume, high erythrocyte protoporphyrin, or low transferrin saturation) similarly demonstrate current hemoglobin thresholds have low sensitivity (37%) for ID among reproductive age women (specificity of 93%).¹ The impact of varying hemoglobin thresholds in various clinical situations has been debated in the literature on transfusion criteria for septic shock, premature infants, and

morbidity in military combat.^{30–32} Similarly, the pros and cons of changing the hemoglobin threshold to improve ID screening are also worth consideration.

While the ROC curves for all reproductive age women are optimized at a hemoglobin of 12.8 g/dL, use of this new threshold will increase the number of women sent for additional laboratory studies to exclude ID. Undetected ID has been associated with negative effects on academic performance, mood, and concentration with improvements in symptoms following iron supplementation.^{5–7} The long-term cost of a missed diagnosis of ID versus the increased cost of additional iron studies (ferritin, transferrin receptor) has not been examined. The probability of ID in women with a hemoglobin <12.8 g/dL is 13.5% or 1 in 8. In contrast, approximately 30% of women with a hemoglobin <12.0 g/dL will have ID. Thus, the optimal threshold may lie in between. Next steps may include a cost-effectiveness model varying the hemoglobin threshold.

Comparing younger and older women, the ROC curves were optimized at hemoglobin of 12.8 g/dL and 12.7 g/dL respectively. While this difference is unlikely to be clinically significant, it is notable that the AUC was significantly better for older as compared to younger women. This is likely related to the higher prevalence of ID anemia among older women, but comparatively lower prevalence of ID without anemia in this age group. Similarly, when black and non-black women are examined separately, the optimal hemoglobin threshold changes. The cost and clinical significance of this difference of 12.5 g/dL vs. 13.0 g/dL will need to be considered.

Limitations

NHANES is intended to be representative of the US population, thus the hemoglobin thresholds identified in this analysis should be applicable to the general US population. Several different models exist to define ID. The body iron model by Cook et al. was adopted by NHANES starting in 2003 to define the iron status of the US population. Prior to this, models using 2 out of 3 abnormal iron-related laboratory values were used.^{1,3} However, in both cases current hemoglobin thresholds consistently demonstrate poor sensitivity for detection of ID. It may be that changing the ID model results in slightly different hemoglobin thresholds than identified in this analysis. Hemoglobin concentration may also vary by altitude and smoking status, which were not factored into this analysis.¹ Altitude was not a part of the NHANES questionnaire. Subjective responses on exposure to tobacco products did not give a clear indication of the regularity and duration of tobacco use to factor into the analysis, specifically among younger participants. Blood conditions such as sickle cell anemia and thalassemia were also not able to be considered with the available data. Additionally, while age and racial/ethnic variations in values for ferritin and transferrin receptor introduce a potential source of error, unlike hemoglobin,¹⁵ we did not find standard published adjustments for the abnormal cut-points for these parameters by age and race which could be readily incorporated into the analysis.

CONCLUSION

The study results confirm the poor sensitivity of current hemoglobin thresholds for identification of ID among reproductive age women. Using a higher threshold when

identification of ID is the goal (<12.8 g/dL) will improve the detection of ID in this population.

Acknowledgments

Dr. Sekhar's research is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under BIRCWH award number K12HD055882, "Career Development Program in Women's Health Research at Penn State." The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflicts of interest: All authors have read the journal's policy on disclosure of potential conflicts of interest. A.R.K. discloses stock ownership in a pharmaceutical company, Merck & Co. This had no bearing on the research involved in the submitted manuscript.

All authors have read the journal's authorship statement and the manuscript has been reviewed and approved by all named authors.

Abbreviations

ID	Iron deficiency
US	United States
CDC	Centers for Disease Control and Prevention
NHANES	National Health and Nutrition Examination Survey
ROC	receiver operating characteristic
AUC	area under the curve

References

- Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. MMWR Recomm Rep. 1998; 47(RR-3):1–29.
- Holt, K. Wooldridge, N. Story, M., Sofka, D., editors. Bright Futures Nutrition. 3. American Academy of Pediatrics; 2011. Iron-Deficiency anemia.
- Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. JAMA. 1997; 277(12):973–976. [PubMed: 9091669]
- Cogswell ME, Looker AC, Pfeiffer CM, et al. 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(5):1334–1342. [PubMed: 19357218]
- 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(9033):992–996. [PubMed: 8855856]
- 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]
- Murray-Kolb LE, Beard JL. Iron treatment normalizes cognitive functioning in young women. Am J Clin Nutr. 2007; 85(3):778–787. [PubMed: 17344500]
- Blanton CA, Green MW, Kretsch MJ. Body iron is associated with cognitive executive planning function in college women. Br J Nutr. 2013; 109(5):906–913. [PubMed: 22676919]
- Murray-Kolb LE. Iron status and neuropsychological consequences in women of reproductive age: what do we know and where are we headed? J Nutr. 2011; 141(4):747S–755S. [PubMed: 21346109]

10. Friedman AJ, Chen Z, Ford P, et al. Iron deficiency anemia in women across the life span. *J Womens Health*. 2012; 21(12):1282–1289.
11. Hagan, JF, Shaw, JS., Duncan, PM., editors. *Bright Futures: Guidelines for Health Supervision for Infants, Children, and Adolescents*. 3. Elk Grove Village, IL: American Academy of Pediatrics; 2008.
12. Lynch SR. Why nutritional iron deficiency persists as a worldwide problem. *J Nutr*. 2011; 141(4): 763S–768S. [PubMed: 21367937]
13. Billett, HH. Hemoglobin and Hematocrit. In: Walker, HK, Hall, WD., Hurst, JW., editors. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3. Vol. Chapter 151. Boston, MA: Butterworths; 1990. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK259/> [Accessed February 1, 2016]
14. NCHS. National Health and Nutrition Examination Survey. [Accessed February 1, 2016] About the National Health and Nutrition Examination Survey. Updated February 3, 2014. Available at http://www.cdc.gov/nchs/nhanes/about_nhanes.htm
15. Nestel, P. [Accessed February 1, 2016] Adjusting Hemoglobin Values in Program Surveys. 2002. Available at http://pdf.usaid.gov/pdf_docs/PNACQ927.pdf
16. NHANES. [Accessed February 1, 2016] 2009–2010 Data documentation, codebook, and frequencies. Complete blood count with 5-part differential - whole blood (CBC_F). Description of Laboratory Methodology. Updated January 2012. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/CBC_F.htm#Description_of_Laboratory_Methodology
17. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. *Blood*. 2003; 101(9): 3359–3364. [PubMed: 12521995]
18. NHANES. [Accessed February 1, 2016] 2003–2004 Data Documentation, Codebook, and Frequencies. Ferritin and transferrin receptor (L06TFR_C). Analytic Notes. Updated December 2007. Available at http://www.cdc.gov/nchs/nhanes/nhanes2003-2004/L06TFR_C.htm#Analytic_Notes
19. NHANES. [Accessed February 1, 2016] 2005–2006 Data Documentation, Codebook, and Frequencies. Ferritin (FERTIN_D). Description of Laboratory Methodology. Published April 2008. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/FERTIN_D.htm#Description_of_Laboratory_Methodology
20. NHANES. [Accessed February 1, 2016] 2007–2008 Data Documentation, Codebook, and Frequencies. Ferritin (FERTIN_E). Description of Laboratory Methodology. Published September 2009. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/FERTIN_E.htm#Description_of_Laboratory_Methodology
21. NHANES. [Accessed February 1, 2016] 2009–2010 Data Documentation, Codebook, and Frequencies. Ferritin (FERTIN_F). Analytic Notes. Published February 2012. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/FERTIN_F.htm#Analytic_Notes
22. NHANES. [Accessed February 1, 2016] 2003–2004 Data Documentation, Codebook, and Frequencies. Ferritin and transferrin receptor (L06TFR_C). Description of Laboratory Methodology. Updated December 2007. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2003-2004/L06TFR_C.htm#Description_of_Laboratory_Methodology
23. NHANES. [Accessed February 1, 2016] 2005 – 2006 Data Documentation, Codebook, and Frequencies. Transferrin Receptor (TFR_D). Description of Laboratory Methodology. Published April 2008. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2005-2006/TFR_D.htm#Description_of_Laboratory_Methodology
24. NHANES. [Accessed February 1, 2016] 2007–2008 Data Documentation, Codebook, and Frequencies. Transferrin Receptor (TFR_E). Description of Laboratory Methodology. Published September 2009. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2007-2008/TFR_E.htm#Description_of_Laboratory_Methodology
25. NHANES. [Accessed February 1, 2016] 2009–2010 Data Documentation, Codebook, and Frequencies. Transferrin Receptor (TFR_F). Published February 2012. Available at http://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/TFR_F.htm#Analytic_Notes
26. NHANES. [Accessed January 27, 2016] Survey Methods and Analytic Guidelines. Updated May 2, 2014. Available at http://www.cdc.gov/nchs/nhanes/survey_methods.htm

27. Gonen, M. Analyzing Receiver Operating Characteristic Curves with SAS®. Cary, NC: SAS Institute Inc; 2007.
28. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950; 3(1):32–35. [PubMed: 15405679]
29. Hosmer, D., Lemeshow, S. *Applied Logistic Regression*. 2. New York: Wiley; 2000.
30. Kirpalani H, Whyte RK, Andersen C, et al. The premature infants in needs of transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birthweight infants. *J Pediatr*. 2006; 149(3):301–307. [PubMed: 16939737]
31. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold or transfusion in septic shock. *N Engl J Med*. 2014; 371(15):1381–1391. [PubMed: 25270275]
32. Mora AG, Ervin AT, Ganem VJ, Bebartá VS. Aeromedical evacuation of combat patients by military critical care air transport teams with a lower hemoglobin threshold approach is safe. *J Trauma Acute Care Surg*. 2014; 77(5):724–728. [PubMed: 25494424]

Fig 1.

Flow diagram representing application of exclusion criteria to derive the sample population of non-pregnant reproductive age women for the analysis. NHANES – National Health and Nutrition Examination Survey.

Fig 2.

Receiver operating characteristic curve for the use of (a) hemoglobin in diagnosing iron deficiency among 12–49 year-old non-pregnant reproductive age women and (b) the probability (solid line; 95% CI dashed lines) an individual has iron deficiency based on hemoglobin level.

Fig 3. Receiver operating characteristic curve for the use of (a) hemoglobin in diagnosing iron deficiency among 12–21 year-old non-pregnant reproductive age women and (b) the probability (solid line; 95% CI dashed lines) an individual has iron deficiency based on hemoglobin level.

Fig 4. Receiver operating characteristic curve for the use of (a) hemoglobin in diagnosing iron deficiency among 22–49 year-old non-pregnant reproductive age women and (b) the probability (solid line; 95% CI dashed lines) an individual has iron deficiency based on hemoglobin level.

Table I

Characteristics of younger (12–21 years) and older (22–49 years) women

Characteristic	Younger N=2985* n (%)	Older N=3617* n (%)	Combined N=6602* n (%)
Anemia and Body Iron Deficiency			
Anemic and Body Iron Deficient	70 (2.3)	198 (5.5)	268 (4.1)
Anemic and Not Body Iron Deficient	46 (1.5)	72 (2.0)	118 (1.8)
Body Iron Deficient and Not Anemic	250 (8.4)	244 (6.7)	494 (7.5)
No Anemia or Body Iron Deficiency	2619 (87.7)	3103 (85.8)	5722 (86.7)
Race/Ethnicity			
White	962 (32.2)	1777 (49.1)	2739 (41.5)
Mexican/Hispanic	1010 (33.8)	942 (26.0)	1952 (29.6)
Black	856 (28.7)	722 (20.0)	1578 (23.9)
Other	157 (5.3)	176 (4.9)	333 (5.0)

* Sample sizes listed are based on having a hemoglobin level recorded and information to determine body iron deficiency status. Sample sizes of the sample characteristics may be smaller due to missing data.

Sensitivity and specificity of various hemoglobin thresholds to detect iron deficiency (ID; defined as ferritin <12 ug/L) among reproductive age women stratified by age and race

Table II

	Hemoglobin (g/dL)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	ID Probability (%) (95% CI)	AUC (%) (95% CI)
All women	<12.0	37.0 (33.9, 40.1)	95.7 (95.1, 96.2)	36.8 (32.0, 41.8)	-
12-49 years	<12.8 *	63.9 (60.8, 67.0)	79.5 (78.5, 80.6)	17.4 (14.9, 20.3)	0.80 (0.78, 0.81)
Young women	<11.8	22.4 (18.4, 26.4)	97.2 (96.6, 97.8)	39.8 (32.9, 47.1)	-
	<12.0	27.9 (23.6, 32.2)	95.1 (94.3, 95.9)	34.7 (28.7, 41.3)	-
12-21 years	<13.0 *	63.5 (58.9, 68.1)	71.3 (69.5, 73.0)	15.3 (12.5, 18.6)	0.74 (0.71, 0.77)
Older women	<12	44.6 (40.2, 48.9)	96.1 (95.4, 96.8)	37.3 (31.6, 43.5)	-
	<12.7 *	67.5 (63.4, 71.6)	83.6 (82.3, 84.9)	18.9 (15.8, 22.5)	0.83 (0.82, 0.86)
22-49 years					
Black women	<11.0	34.0 (28.2, 39.7)	98.5 (97.8, 99.1)	59.2 (51.7, 66.2)	-
	<12.5 *	76.7 (71.6, 81.8)	73.3 (70.9, 75.7)	14.8 (12.3, 17.7)	0.83 (0.80, 0.85)
12-49 years					
Non-Black women	<12.0	28.7 (25.3, 32.1)	97.7 (97.3, 98.2)	40.8 (34.2, 47.7)	-
	<13.1 *	65.3 (61.6, 68.9)	77.5 (76.2, 78.7)	13.7 (11.3, 16.5)	0.80 (0.78, 0.82)
12-49 years					

Abbreviations: Area under the curve (AUC)

* optimal hemoglobin by receiver operating characteristic curve