The American Journal of Medicine (2007) 120, 734.e1-734.e9

ELSEVIER

THE AMERICAN JOURNAL *of* MEDICINE®

CLINICAL RESEARCH STUDY

African Americans at Risk for Increased Iron Stores or Liver Disease

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ABSTRACT

PURPOSE: We sought to determine the prevalence of elevated measures of iron status in African Americans and whether the combination of serum ferritin concentration >200 μg/L for women or >300 μg/L for men and transferrin saturation in the highest quartile represents increased likelihood of mutation of *HFE*, self-reported iron overload or self-reported liver disease.

SUBJECTS AND METHODS: A cross-sectional observational study of 27,224 African Americans ≥25 years of age recruited in a primary care setting was conducted as part of the multi-center, multi-ethnic Hemochromatosis and Iron Overload Screening (HEIRS) Study. Measurements included serum ferritin concentration, transferrin saturation, testing for *HFE* C282Y and H63D, and self-reported iron overload and liver disease.

RESULTS: Serum ferritin concentration >200 μg/L for women or >300 μg/L for men occurred in 5263 (19.3%) of African Americans, while serum ferritin concentration in this range with highest-quartile transferrin saturation (>29% women; >35% men) occurred in 1837 (6.7%). Adjusted odds of *HFE* mutation (1.76 women, 1.67 men), self-reported iron overload (1.97 women, 2.88 men), or self-reported liver disease (5.18 women, 3.73 men) were greater with elevated serum ferritin concentration and highest-quartile transferrin saturation than with nonelevated serum ferritin concentration (each $P < .05$).

CONCLUSIONS: Serum ferritin concentration >200 μg/L for women or >300 μg/L for men in combination with transferrin saturation >29% for women or >35% for men occurs in approximately 7% of adult African American primary care patients. Patients with this combination of iron test results should be evaluated for increased body iron stores or liver disease.

KEYWORDS: African Americans; Serum ferritin; Transferrin saturation; *HFE*; Liver disease; Increased iron stores

The HEIRS Study was initiated and funded by NHLBI, in conjunction with NHGRI. The study is supported by contracts N01-HC-05185 (University of Minnesota), N01-HC-05186 (Howard University), N01-HC-05188 (University of Alabama at Birmingham), N01-HC-05189 (Kaiser Permanente Center for Health Research), N01-HC-05190 (University of California, Irvine), N01-HC-05191 (London Health Sciences Centre), and N01-HC-05192 (Wake Forest University). Additional support was provided by grant UH1-HL03679-07 from NHLBI and the Office of Minority Health, and by General Clinical Research Center (GCRC) grants to Howard University (M01-RR10284), University of California, Irvine (5M01RR 00827-29) and University of Alabama at Birmingham (M01-RR00032), sponsored by the National Center for Research Resources, National Institutes of Health (NCRR/NIH).

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2006.05.049

Increased iron stores attributable to dietary and possibly heritable factors occur in approximately 10% of rural adults in sub-Saharan Africa,[1,2] but few cases of primary increases in body iron stores have been reported in African Americans.[3,4] Nonetheless, autopsy studies suggest that an increase in hepatic iron is a fairly common finding in African Americans.[5,6] Most Africans and African Americans with increased iron stores do not have *HFE* mutations that are common in whites with hemochromatosis,[5,7-9] and the prevalence of *HFE* C282Y homozygosity is approximately 14 per 100,000 among African American primary care patients.[10]

Increased iron stores may lead to multisystem organ dysfunction, contribute to the severity of viral hepatitis, or increase the risk for certain infections and malignancies.[3,11] Increased iron stores are often suspected when there is an unexplained elevation in serum ferritin concentration and transferrin saturation. Elevations in these measures of iron status are not in themselves sufficient to confirm a diagnosis of increased iron stores, for this combination is frequently seen in liver disease without iron overload. In the multicenter HEmochromatosis and IRon Overload Screening (HEIRS) Study in the US and Canada, more than 100,000 participants, of whom more than 27,000 were self-identified as African Americans, were tested for serum ferritin concentration, transferrin saturation, and *HFE* mutations, and questioned regarding health conditions including iron overload and liver disease.

Infectious and other inflammatory processes, hepatic disorders such as alcoholic and viral hepatitis and nonalcoholic steatohepatitis (NASH), and increased body iron stores resulting from multiple blood transfusions, *HFE* mutations, or other primary processes are all potential causes of increases in serum ferritin concentrations.[12-19] Inflammatory processes are typically characterized by reduced serum iron concentration and transferrin saturation in association with increased serum ferritin concentration.[18] On the other hand, patients with elevated iron stores or hepatic disorders tend to have transferrin saturations above the population mean in association with increased serum ferritin concentration.[19,20] We therefore reasoned that assessing serum ferritin concentration in the context of the accompanying transferrin saturation would be useful in developing certain broad categories of potential causes for serum ferritin elevation. Specifically, we hypothesized that serum ferritin concentration above the upper limit of the reference range in association with transferrin saturation in the upper population quartile would represent increased likelihood of *HFE* mutation, self-reported iron overload, or self-reported liver disease. We also hypothesized that serum ferritin concentration above the upper limit of the reference range in association with transferrin saturation in the lower population quartile would represent increased likelihood of self-reported inflammatory processes.

CLINICAL SIGNIFICANCE

- Elevated serum ferritin (>200 μg/L women, >300 μg/L men) in combination with highest quartile transferrin saturation (>29% women, >35% men) occurred in 7% of 27,224 African American primary care patients.
- This combination was associated with significantly increased odds of *HFE* mutation, self-reported iron overload, and self-reported liver disease.
- African American patients with elevated ferritin and highest quartile transferrin saturation should be screened for increased iron stores and liver disease.

STUDY PARTICIPANTS AND METHODS

Study Approval

The local Institutional Review Board of each field center approved the study protocol, which is described in detail elsewhere,[21] and written informed consent was obtained from each participant.

Selection of Study Subjects

Participants 25 years of age or older were recruited during the interval of February 2001 to March 2003 from public and private primary care offices and ambulatory clinics (Howard University, Washington, DC; University of Alabama at Birmingham; and University of California, Irvine), from a health maintenance organization (Kaiser Permanente Northwest in Portland, Oregon and Kaiser Permanente Hawaii), and from diagnostic blood collection centers (MDS Laboratories, London, Ontario, and Dynacare Laboratories, Richmond Hill, Ontario, Canada) associated with the 5 HEIRS Study field centers. These facilities serve ethnically and socioeconomically diverse primary care patients. Other adult volunteers, such as family members or friends accompanying a patient, were also eligible to participate.[21]

At the screening visit, HEIRS Study participants completed a questionnaire that included questions about race/ethnicity.[21] Of the 101,168 participants with complete transferrin saturation, serum ferritin concentration, and *HFE* mutation results, those who identified themselves only as African American or black, hereafter referred to as African Americans, were selected for this analysis. Participants who also reported Hispanic race/ethnicity or 2 or more race/ethnicity groups were not included in this analysis. The questionnaire also asked whether participants had ever been diagnosed with any or all of the following conditions: iron overload or hemochromatosis, arthritis, diabetes mellitus, liver disease or liver cancer, heart failure, and fertility problems or impotence. The options for each category were "yes," "no," or "not sure." Blood samples were obtained from participants to measure transferrin saturation and serum ferritin concentration and to analyze for *HFE* C282Y and H63D mutations.

Participants who were negative for C282Y and H63D were designated as having a wild type (wt) genotype.

Laboratory Methods

The Central Laboratory (located at University of Minnesota Medical Center, Minneapolis) performed all laboratory screening tests, except transferrin saturation testing of London Health Sciences Centre participants (performed by MDS Laboratory Services, Canada, using an identical method). Measurements included spectrophotometric serum iron and unsaturated iron-binding capacity, turbidometric immunoassay of serum ferritin concentration (Roche Diagnostics/Hitachi 911, Indianapolis, Indiana), and calculated total iron-binding capacity and transferrin saturation. Method biases were assessed 3 times a year using external proficiency testing samples provided by the College of American Pathologists Surveys (Northfield, Illinois). Internal quality control pools were included with each analytical batch at both normal and elevated transferrin saturation and serum ferritin values to assess assay drift. To monitor overall reproducibility, blind replicate samples collected from 2% of participants at each field center were analyzed at the Central Laboratory or the MDS Laboratory, as appropriate. Analytical variability was determined for transferrin saturation and serum ferritin concentration by analysis of routine internal laboratory quality control pools in each analytical batch. For transferrin saturation measurements, the batch-to-batch coefficient of variation was 3.0%, and the correlation coefficient between original and blind replicate values was 0.98. For serum ferritin measurements, the batch-to-batch coefficient of variation was 4.7%, and the correlation coefficient between original and blind replicate values was 0.99.

HFE C282Y and H63D were detected by a modification of the Invader assay (Third Wave Technologies, Inc., Madison, Wisconsin), which increases the allele-specific fluorescent signal by including 12 cycles of locus-specific polymerase chain reaction before the cleavase reaction. Buffy coats from whole-blood EDTA samples were spotted onto FTA paper (Fitzco, Inc., Maple Plain, Minnesota), and a 1.5-mm punch was used for testing. Analyses of blind replicate participant samples to detect C282Y and H63D were concordant in 99.8% and 99.2% of participants, respectively. In 2% of samples selected randomly, repetition of analyses using a different genotyping method (PCR-RFLP) yielded concordant results in 99.8% of C282Y determinations and 99.9% of H63D determinations. Specimens for which inconsistent results were obtained were analyzed further, as indicated, to resolve uncertainty about respective *HFE* genotypes before the corresponding participant data were subjected to final analysis.

Statistical Analysis

The HEIRS Study prospectively defined elevated serum ferritin concentration as >300 ug/L for men and >200 ug/L for women.[21] The hypothesis that categorizing iron status further by transferrin saturation quartiles would identify subgroups at greater risk for *HFE* mutations, self-reported iron overload, or self-reported liver disease versus self-reported inflammatory conditions was developed after collection of the screening data. Differences in self-reported disease and the presence of *HFE* mutations with respect to subgroups for serum ferritin concentrations were assessed using multiple logistic regression models adjusting for sex and age. Each subgroup with elevated serum ferritin concentration based on transferrin saturation quartile was compared with the nonelevated serum ferritin concentration group using a separate model. $P < .05$ was considered statistically significant. Means are reported ± SD; medians are reported with interquartile ranges. Odds ratio estimates (adjusted for sex and age) are reported with corresponding 95% confidence intervals (CIs). To estimate the population risk (percent) of elevated measures of iron status not attributable to mutation of *HFE*, self-reported iron overload or self-reported liver disease, we divided the proportion with the elevated measure in those with none of the 3 conditions by the proportion with the elevated measure among all participants[22]; the estimates were calculated in those participants with complete self-report information. SAS statistical software (version 8.2, SAS Institute Inc., Cary, NC) was used for all regression analyses.

RESULTS

Study Participants

Of the 101,168 participants >25 years of age screened in the HEIRS Study, 27,224 were African Americans. Demographic and clinical characteristics are summarized in Table 1. Participants were recruited from 5 field centers in the United States and Canada. Two field centers, Howard University in Washington, DC and the University of Alabama at Birmingham, Birmingham, AL enrolled 97% of the African American participants. Self-reported arthritis was noted in 30.0% of participants (95% CI, 29.5-30.6), diabetes mellitus in 17.5% (95% CI, 17.0-18.0), heart failure in 5.3% (95% CI, 5.0-5.5), sexual dysfunction or fertility problems in 3.3% (95% CI, 3.1-3.5), liver disease in 2.0% (95% CI, 1.8-2.1), and iron overload or hemochromatosis in 1.1% (95% CI, 1.0-1.3). Ninety-two percent (95% CI, 91.6-92.2) of the participants were negative for *HFE* mutations.

Serum Biochemical Measures of Iron Status

Results for serum ferritin concentration and transferrin saturation values are summarized in Tables 2 and 3. The median serum ferritin concentration was 2.5-fold higher in men than in women, and the median transferrin saturation was 1.3-fold higher. Overall, 5263 (19.3%) of African Americans had serum ferritin levels above 200 μg/L for women and 300 μg/L for men, with 1837 (6.7%; 95% CI, 6.5%-7.1%) having serum ferritin concentration in this range in combination with transferrin saturation in the highest quartile (>29% in women and >35% in men). In contrast, the combination of serum ferritin concentration above

Table 1 Demographic and Clinical Features of 27,224 African American Study Participants*

	Women (n = 17,341)	Men (n = 9883)
Age in years (mean ± SD) (n = 9881 men, 17,334 women)	49 ± 14	49 ± 14
Field Center at which recruited (no. and %)		
Howard University, Washington, DC	10,576 (61.0%)	6054 (61.3%)
Kaiser Permanente, Portland, Oregon	188 (1.1%)	139 (1.4%)
University of Alabama, Birmingham	6273 (36.2%)	3453 (34.9%)
University of California, Irvine	192 (1.1%)	155 (1.6%)
University of Western Ontario, London	112 (0.7%)	82 (0.8%)
Self-reported disease (no. and %)		
Arthritis (n = 9234 men, 16,161 women)	5506 (34.1%)	2116 (22.9%)
Diabetes mellitus (9267 men, 16,168 women)	2857 (17.7%)	1590 (17.2%)
Heart disease (9218 men, 16,134 women)	784 (4.9%)	549 (6.0%)
Sexual dysfunction or infertility (9105 men, 16,016 women)	467 (2.9%)	361 (4.0%)
Liver disease (9209 men, 16,112 women)	270 (1.7%)	229 (2.5%)
Iron overload/hemochromatosis (9039 men, 15,864 women)	182 (1.1%)	95 (1.1%)
HFE mutations (no. and %)		
Wild type/wild type	15,934 (91.89%)	9084 (91.92%)
H63D/wild type	970 (5.59%)	560 (5.67%)
C282Y/wild type	394 (2.27%)	212 (2.12%)
C282Y/H53D	21 (0.12%)	15 (0.15%)
H63D/H63D	21 (0.12%)	9 (0.09%)
C282Y/C282Y	1 (0.01%)	3 (0.03%)

*The sample size is 27,224 except where noted.

200 μg/L for women and 300 μg/L for men and transferrin saturation in the lowest quartile (<17% in women and <23% in men) occurred in 792 (2.9%). There was a tendency to higher serum ferritin concentrations and transferrin saturations in the participants with *HFE* mutations compared with the wild type participants (Table 3).

Prevalence of *HFE* Mutations in Serum Ferritin Subgroups Based on Transferrin Saturation Quartiles

Mutations of *HFE* (C282Y/C282Y, C282Y/H63D, H63D/H63D, C282Y/wild type or H63D/wild type) were found in 13.7% of women with elevated serum ferritin concentration in combination with highest-quartile transferrin saturation compared with 7.9% of women and 7.6% of men without serum ferritin concentration elevation (Table 4). The adjusted odds ratio for having mutation of *HFE* in patients with elevated serum ferritin concentration and highest-quartile transferrin saturation compared to those with nonelevated serum ferritin concentration was 1.76 (95% CI, 1.45-2.13) for women and 1.67 (95% CI, 1.32-2.10) for men.

Prevalence of Self-Reported Disease in Serum Ferritin Subgroups Based on Transferrin Saturation Quartiles

Among both women and men, the adjusted odds of having self reported arthritis (1.36, 95% CI, 1.03, 1.80 for women; 1.32, 95% CI, 1.07, 1.64 for men) or diabetes mellitus (2.34, 95% CI, 1.77, 3.09 for women; 1.99, 95% CI, 1.61, 2.46 for men) were significantly higher with the combination of elevated serum ferritin concentration and transferrin saturation in the lowest quartile when compared to the group with nonelevated serum ferritin concentration (Tables 5, 6). In

Table 2 Measures of Iron Status in 27,224 African American Study Participants

	Women (n = 17,341)	Men (n = 9883)
Serum ferritin in μg/L (median and IQ range)	75 (35-146)	186 (110-309)
Serum ferritin >200 μg/L women, >300 μg/L men (no. and %)	2688 (15.5%)	2575 (26.1%)
Transferrin saturation in % (median and IQ range)	22 (16-29)	28 (22-35)
Transferrin saturation in % by approximate quartile		
1st Quartile	<3-16	<3-22
2nd Quartile	17-22	23-28
3rd Quartile	23-29	29-35
4th Quartile	30-100	36-100
Serum ferritin >200 μg/L women, >300 μg/L men by Approximate transferrin saturation quartile (no. and column %)		
1st TS quartile	258 (9.6%)	534 (20.7%)
2nd TS quartile	554 (20.6%)	634 (24.6%)
3rd TS quartile	842 (31.3%)	604 (23.5%)
4th TS quartile	1034 (38.5%)	803 (31.2%)

Table 3 Indirect Measures of Iron Status by Sex and *HFE* C282Y and H63D Genotype in African Americans

HFE C282Y and H63D Genotype	n	Age (Years) Mean ± SD	Serum Ferritin (μg/L) Mean ± SD	Serum Ferritin (μg/L) Median (Interquartile Range)	Transferrin Saturation (%) Mean ± SD	Transferrin Saturation (%) Median (Interquartile Range)
All participants	27,224					
All Women	17,341	49 ± 14	118 ± 178	75 (35-146)	23 ± 11	22 (16-29)
All Men	9883	49 ± 14	249 ± 280	186 (110-309)	29 ± 12	28 (22-35)
Wild type/wild type	25,018					
Women	15,934	49 ± 14	117 ± 180	74 (35-144)	23 ± 11	22 (16-29)
Men	9084	49 ± 14	244 ± 282	184 (110-306)	29 ± 11	27 (22-35)
H63D/wild type	1530					
Women	970	50 ± 15	113 ± 135	75 (38-46)	25 ± 11	25 (18-31)
Men	560	50 ± 15	266 ± 257	198 (113-339)	32 ± 12	30 (24-38)
C282Y/wild type	606					
Women	394	50 ± 15	145 ± 185	97 (39-191)	28 ± 13	27 (19-34)
Men	212	51 ± 14	280 ± 255	204 (126-357)	35 ± 13	33 (25-42)
H63D/H63D	30					
Women	21	60 ± 16	146 ± 124	85 (52-241)	33 ± 13	28 (23-38)
Men	9	54 ± 15	194 ± 101	173 (159-193)	30 ± 12	28 (21-37)
C282Y/H63D	36					
Women	21	52 ± 17	155 ± 194	103 (50-168)	36 ± 12	35 (30-45)
Men	15	50 ± 19	233 ± 129	211 (131-363)	45 ± 15	44 (31-55)
C282Y/C282Y	4					
Women	1	65	303	303	30	30
Men	3	45 ± 25	397 ± 400	297 (57-838)	95 ± 7	99 (87-99)

"Wild type" indicates the absence of an *HFE* C282Y or H63D mutation.

contrast, the adjusted odds of self-reported liver disease (5.18, 95% CI, 3.80-7.08 for women; 3.73, 95% CI, 2.66-5.24 for men) or iron overload (1.97, 95% CI, 1.20-3.23 for women; 2.88, 95% CI, 1.71-4.86 for men) were significantly higher with the combination of elevated serum ferritin concentration and transferrin saturation in the highest quartile when compared to the group with nonelevated serum ferritin concentration. Among women, but not men, the adjusted odds of having self-reported heart failure were significantly higher with elevated serum ferritin concentration and transferrin saturation in the lowest quartile than with nonelevated serum ferritin concentration. Among both women and men, the odds of having self-reported arthritis, diabetes mellitus, or liver disease also were significantly higher with elevated serum ferritin concentration and transferrin saturation in the middle quartiles (17%-29% for women and 23%-35% for men) than with nonelevated serum ferritin concentration.

Table 4 Prevalence of *HFE* Mutations in Subgroups of Patients Based on Serum Ferritin Concentration and Transferrin Saturation (The Comparison Group Consists of Patients with Serum Ferritin Concentration ≤200 μg/L for Women and ≤300 μg/L for Men)

Phenotype		Women (n = 17,341)			Men (n = 9883)		
Serum Ferritin Concentration*	Transferrin Saturation in % (Quartile)	n	Prevalence of *HFE* Mutations† (No. and %)	Adjusted Odds Ratio (95% CI)‡	n	Prevalence of *HFE* Mutations† (No. and %)	Adjusted Odds Ratio (95% CI)‡
>200 μg/L women; >300 μg/L men	<3-16 F, <3-22 M (Q1)	258	12 (4.7%)	0.54§ (0.30-0.98)	524	38 (7.1%)	0.93 (0.66-1.30)
	17-29 F, 23-35 M (Q2 & Q3)	1396	95 (6.8%)	0.79§ (0.64-0.99)	1238	110 (8.9%)	1.18 (0.96-1.47)
	30-100 F, 36-100 M (Q4)	1034	142 (13.7%)	1.76* (1.45-2.13)	803	97 (12.1%)	1.67* (1.32-2.10)
Below above cutoffs	All	14,653	1158 (7.9%)	1	7308	554 (7.6%)	1

CI = confidence interval.

*$P < .0001$.

†All *HFE* mutations (C282Y/C282Y, C282Y/H63D, C282Y/+, H63D/H63D, H63D/+).

‡The effect of each subgroup for elevated serum ferritin concentration was compared with the nonelevated serum ferritin concentration group using multiple logistic regression models adjusted for age.

§$.0001 < P < .05$.

Table 5 Prevalence of Self-Reported Condition in Subgroups of 17,341 African American Women Based on Serum Ferritin Concentration and Transferrin Saturation (The Comparison Group Consists of Patients with Serum Ferritin Concentration ≤200 μg/L)

Phenotype				Self-Reported Arthritis		Self-Reported Diabetes Mellitus	
Serum ferritin	Transferrin Saturation in % (Quartile)	n	%	Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†
>200 μg/L	<3-16 (Q1)	258	1.5	113/240 (47.1%)	1.36‡ (1.03-1.80)	85/239 (35.6%)	2.34* (1.77-3.09)
	17-29 (Q2 & Q3)	1396	8.1	660/1306 (50.5%)	1.35* (1.19-1.52)	414/1315 (31.5%)	1.78* (1.56-2.03)
	30-100 (Q4)	1034	6.0	442/965 (45.8%)	1.10 (0.95-1.27)	221/960 (23.0%)	1.13 (0.96-1.33)
≤200 μg/L	All	14,653	84.5	4291/13,650 (31.4%)	1	2137/13,654 (15.7%)	1

CI = confidence interval.

For self-reported conditions, the denominators for prevalence estimates are different from the n for the transferrin saturation quartiles because not all participants completed this part of the questionnaire.

*P <.0001.

†The effect of each subgroup for elevated serum ferritin concentration was compared with the nonelevated serum ferritin concentration group using multiple logistic regression models adjusted for age.

‡.0001 < P < .05.

Attributable Risk for Combinations of Serum Ferritin Concentration and Transferrin Saturation above Certain Cutoff Levels

The combination of serum ferritin concentration above 200 μg/L in women or 300 μg/L in men and transferrin saturation above 29% in women or 35% in men, which applied to 6.7% of our population, could be attributed to mutation of *HFE,* self-reported iron overload, or self-reported liver disease in 10.6% (95% CI, 8.5-12.7) of patients with the combination. The combination of serum ferritin concentration above 500 μg/L in women or 600 μg/L in men and transferrin saturation above 29% in women or 35% in men, which applied to 1.7% of our population, could be attributed to mutation of *HFE,* self-reported iron overload or self-reported liver disease in 18.4% (95% CI, 13.6-23.2) of patients with the combination.

DISCUSSION

Based on the prospective definition of the HEIRS Study, we found serum ferritin concentration above 200 μg/L for women or 300 μg/L for men in 19.3% of more than 27,000 African Americans investigated in a multicenter primary care setting. Although the definition of what constitutes an elevated serum ferritin concentration in African Americans is open to discussion, participants with the combination of elevated serum ferritin concentration as defined by the HEIRS Study and transferrin saturations in the highest quartile to a significant extent more often had *HFE* mutations and self-reported histories of iron overload or liver disease than those with nonelevated serum ferritin concentrations. Conversely, African American participants with the combination of elevated serum ferritin concentration and transferrin saturation in the lowest quartile gave histories of arthritis, diabetes mellitus and, for women only, heart

Table 6 Prevalence of Self-Reported Condition in Subgroups of 9883 African American Men Based on Serum Ferritin Concentration and Transferrin Saturation (The Comparison Group Consists of Patients with Serum Ferritin Concentration ≤300 μg/L)

Phenotype				Self-Reported Arthritis		Self-Reported Diabetes	
Serum ferritin Concentration*	Transferrin Saturation in % (Quartile)	n	%	Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†
>300 μg/L	<3-22 (Q1)	524	5.4	147/504 (29.2%)	1.32‡ (1.07-1.64)	140/509 (27.5%)	1.99* (1.61-2.46)
	23-35 (Q2 & Q3)	1238	12.5	304/1174 (25.9%)	1.17‡ (1.01-1.36)	277/1178 (23.5%)	1.66* (1.42-1.93)
	36-100 (Q4)	803	8.1	172/747 (23.0%)	0.99 (0.82-1.20)	133/749 (17.8%)	1.14 (0.93-1.40)
≤300 μg/L	All	7308	74.0	1493/6809 (21.9%)	1	1040/6831 (15.2%)	1

For self-reported conditions, the denominators for prevalence estimates are different from the n for the transferrin saturation quartiles because not all participants completed this part of the questionnaire.

*P <.0001.

†The effect of each subgroup for elevated serum ferritin concentration was compared with the nonelevated serum ferritin concentration group using multiple logistic regression models adjusted for age. CI denotes confidence interval.

‡.0001 < P <.05.

Table 5 Continued

Self-Reported Heart Failure		Self-Reported Infertility		Self-Reported Liver Disease		Self-Reported Iron Overload or Hemochromatosis	
Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†
29/239 (12.1%)	2.21*(1.47-3.31)	6/235 (2.6%)	1.00 (0.44-2.28)	3/238 (1.3%)	0.99 (0.31-3.12)	4/231 (1.7%)	1.62 (0.59-4.42)
91/1302 (7.0%)	1.03 (0.81-1.30)	39/1297 (3.0%)	1.25 (0.89-1.76)	32/1310 (2.4%)	1.95‡ (1.32-2.87)	18/1284 (1.4%)	1.26 (0.76-2.09)
57/960 (5.9%)	0.89 (0.66-1.18)	18/951 (1.9%)	0.80 (0.49-1.29)	58/960 (6.0%)	5.18* (3.80-7.08)	19/930 (2.0%)	1.97‡(1.20-3.23)
607/13,633 (4.5%)	1	404/13,533 (3.0%)	1	177/13,604 (1.3%)	1	141/13419(1.1%)	1

failure significantly more often than those with nonelevated serum ferritin concentration. Although arthritis, diabetes mellitus, and heart failure are sometimes associated with certain iron overload conditions or increased indirect measures of iron status,[23-26] considerable research points to strong associations of these conditions with inflammation.[27-30]

The combination of elevated serum ferritin concentration and transferrin saturation in the highest quartile occurred in 6.7% of the participants, while the combination of elevated serum ferritin concentration and transferrin saturation in the lowest quartile occurred in 2.9%. This observation suggests that more participants with serum ferritin elevation had abnormalities related to increased iron stores or liver disease than to inflammation. Based on population risk estimates, approximately 11% of the cases of elevated serum ferritin concentration in combination with highest quartile transferrin saturation could be attributed to mutation of *HFE*, self-reported iron overload, or self-reported liver disease. Because self-reporting may considerably underestimate true prevalence of disease,[31-33] it seems likely that 11% is a conservative estimate. In addition to *HFE* mutations, potential causes for increased body iron stores in African Americans include multiple blood transfusions in patients with sickle cell disease and other hematologic disorders[34,35] and non-*HFE* primary iron-loading conditions,[10,36] some perhaps not yet identified. Potential causes of hepatic dysfunction in African Americans include hepatitis C infection,[37] nonalcoholic steatosis and hepatitis (NASH),[32,38] and heavy alcohol consumption.[39,40]

Limitations to our study include these considerations: The values for serum biochemical measures of iron status reported here represent single random determinations not confirmed by repeat testing. Other than testing for *HFE* mutations and concomitant transferrin saturation and interviewing patients for histories of certain diseases, possible explanations for an elevated serum ferritin concentration were not investigated in this screening cohort in the HEIRS Study.

Table 6 Continued

Self-Reported Heart Failure		Self-Reported Infertility/ Impotence		Self-Reported Liver Disease		Self-Reported Iron Overload or Hemochromatosis	
Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†	Prevalence (%)	Adjusted Odds Ratio (95% CI)†
38/504 (7.5%)	1.18 (0.83-1.67)	21/496 (4.2%)	0.95 (0.60-1.51)	15/506 (3.0%)	1.60 (0.93-2.75)	2/490 (0.4%)	0.43 (0.11-1.78)
67/1166 (5.8%)	0.92 (0.70-1.20)	49/1156 (4.2%)	1.00 (0.73-1.37)	39/1165 (3.4%)	1.82‡ (1.26-2.62)	14/1151 (1.2%)	1.32 (0.74-2.38)
42/743 (5.7%)	0.90 (0.65-1.25)	23/729 (3.2%)	0.74 (0.48-1.14)	49/739 (6.6%)	3.73* (2.66-5.24)	19/733 (2.6%)	2.88* (1.71–4.86)
402/6805 (5.9%)	1	268/6724 (4.0%)	1	126/6799 (1.9%)	1	60/6665 (0.9%)	1

We conclude that approximately 7% of African American primary care patients have the combination of serum ferritin concentration above 200 μg/L in women or 300 μg/L in men, and transferrin saturation above 29% in women or 35% in men, and that such individuals should be evaluated for increased body iron stores or liver disease.

ACKNOWLEDGMENTS

Participating "HEIRS Study" Investigators and Institutions:

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Birmingham, AL—University of Alabama at Birmingham:
Dr. Ronald T. Acton (Principal Investigator), Dr. James C. Barton (Co-Principal Investigator), Ms. Deborah Dixon, Dr. Susan Ferguson, Dr. Richard Jones, Dr. Jerry McKnight, Dr. Charles A. Rivers, Dr. Diane Tucker and Ms. Janice C. Ware.

Irvine, CA—University of California, Irvine:
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London, Ontario, Canada—London Health Sciences Center:
Dr. Paul C. Adams (Principal Investigator), Ms. Erin Bloch, Dr. Subrata Chakrabarti, Ms. Arlene Fleischhauer, Ms. Helen Harrison, Ms. Kelly Jia, Ms. Sheila Larson, Dr. Edward Lin, Ms. Melissa Lopez, Ms. Lien Nguyen, Ms. Corry Pepper, Dr. Tara Power, Dr. Mark Speechley, Dr. Donald Sun and Ms. Diane Woelfle.

Portland, OR and Honolulu, HI—Kaiser Permanente Center for Health Research, Northwest and Hawaii, and Oregon Health and Science University:
Dr. Emily L. Harris (Principal Investigator), Dr. Mikel Aickin, Dr. Elaine Baker, Ms. Marjorie Erwin, Ms. Joan Holup, Ms. Carol Lloyd, Dr. Nancy Press, Dr. Richard D. Press, Dr. Jacob Reiss, Dr. Cheryl Ritenbaugh, Ms. Aileen Uchida, Dr. Thomas Vogt and Dr. Dwight Yim.

Washington, DC—Howard University:
Dr. Victor R. Gordeuk (Principal Investigator), Dr. Fitzroy W. Dawkins (Co-Principal Investigator), Ms. Margaret Fadojutimi-Akinsiku, Dr. Oswaldo Castro, Dr. Debra White-Coleman, Dr. Melvin Gerald, Ms. Barbara W. Harrison, Dr. Ometha Lewis-Jack, Dr. Robert F. Murray, Dr. Shelley McDonald-Pinkett, Ms. Angela Rock, Dr. Juan Romagoza and Dr. Robert Williams.

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NHLBI Project Office

Bethesda, MD—Ms. Phyliss Sholinsky (Project Officer), Dr. Ebony Bookman, Dr. Henry Chang, Dr. Richard Fabsitz, Dr. Cashell Jaquish, Dr. Teri Manolio and Ms. Lisa O'Neill.

NHGRI Project Office

Bethesda, MD—Ms. Elizabeth Thomson.

Dr. Jean MacCluer, Southwest Foundation for Biomedical Research, also contributed to the design of this study.

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