Iron status of the free-living, elderly Framingham Heart Study cohort: an iron-replete population with a high prevalence of elevated iron stores

Diana J Fleming, Paul F Jacques, Katherine L Tucker, Joseph M Massaro, Ralph B D’Agostino Sr, Peter WF Wilson, and Richard J Wood

ABSTRACT

Background: Although iron deficiency occurs commonly in vulnerable groups of women of reproductive age, infants, and children, less is known about the iron nutriture of the elderly.

Objective: Our objective was to evaluate the iron status of a non-institutionalized, elderly US population, with a particular focus on 2 concerns unique to the elderly: 1) potential confounding effects of chronic disease on iron measures and 2) increased occurrence of elevated iron stores.

Design: Multiple iron measures, including serum ferritin (SF), transferrin saturation, mean cell volume, and hemoglobin, were used to evaluate the prevalence of iron deficiency (ID), iron deficiency anemia (IDA), and other measures of iron nutriture in 1016 elderly white Americans aged 67–96 y from the Framingham Heart Study. “Diseased” subjects were defined as those with possible pathologically altered iron measures due to inflammation, infection, elevated liver enzymes, hereditary hemochromatosis, or cancer. The effect of altered iron status on various prevalence estimates was assessed.

Results: The elderly subjects had a low prevalence of ID (2.7%), IDA (1.2%), and depleted iron stores (3%; SF < 12 μg/L). In contrast, 12.9% had elevated iron stores (SF > 300 μg/L in men and SF > 200 μg/L in women), of which only 1% was attributable to chronic disease. The prevalence of ID, IDA, and depleted iron stores was unaffected by the presence of chronic disease.

Conclusions: The Framingham Heart Study cohort is an iron-replete elderly population with a high prevalence of elevated iron stores in contrast with a low prevalence of iron deficiency, with insignificant effects of chronic disease on these iron status estimates. The likely liability in iron nutriture in free-living, elderly white Americans eating a Western diet is high iron stores, not iron deficiency.

KEY WORDS Iron status, elderly population, Americans, anemia of chronic disease, anemia, iron overload, iron deficiency, serum ferritin, iron supplements, hemochromatosis

INTRODUCTION

Little is known about the iron nutriture of elderly Americans, the fastest-growing segment of the population (1). Furthermore, in evaluations of the iron status of this population, there appear to be 2 concerns unique to the elderly: 1) the presence of the anemia of chronic disease (ACD) and the potential confounding effects of ACD on measures of iron status and 2) an increased occurrence of elevated iron stores.

ACD is a mild-to-moderate, often microcytic, hypochromic anemia that accompanies most acute or chronic conditions of inflammation, infection, liver disease, and malignancy. ACD is a potential confounder in assessments of iron status because it generally mimics the hematologic profile of iron deficiency anemia (IDA), with the exception of a pathologically elevated serum ferritin (SF) concentration, in contrast with decreased SF concentrations observed in uncomplicated iron deficiency (ID) (2–6). Normally, SF concentrations reflect body iron stores (7–11) but, as a positive acute-phase protein, SF increases in response to underlying disease processes (12). In the presence of ACD, SF concentrations become an unreliable indicator of storage iron because the elevation of SF is disproportionate to actual iron stores (2, 5, 6, 13). The problem of distinguishing between IDA and ACD assumes greater importance in elderly persons, who have a higher prevalence of disease than do younger persons.

1 From the Mineral Bioavailability Laboratory and the Epidemiology Program, Jean Mayer–US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston; The Framingham Heart Study, Boston University School of Medicine, Framingham, MA; Boston University School of Public Health/Framingham Heart Study, Boston; and Boston University Mathematics and Statistics Department/Framingham Heart Study, Boston.

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4 Address reprint requests to RJ Wood, Mineral Bioavailability Laboratory, JM-USDA HNRCA, 711 Washington Street, Boston, MA 02111. E-mail: rwood@hnrc.tufts.edu.

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Iron overload denotes an excess of total body iron, most of which is located in the storage compounds ferritin and hemosiderin (14). Aside from the pathologic forms of primary and secondary iron overload (15, 16), moderately elevated iron stores may be of concern because of a possible association with several chronic diseases, such as heart disease (17–19), cancer (20), and diabetes (21, 22). However, this positive relation is controversial because there are limited data for diabetes and cancer and because many studies showed no association with heart disease (23–33).

The 3 National Health and Nutrition Examination Surveys (NHANES I, II, and III) have provided the most comprehensive evaluation of the iron status of elderly Americans to date (34–36). However, none of these earlier population-based surveys provided prevalence estimates of high iron stores specifically in elderly Americans, and NHANES I and II had limitations in addressing the potential confounding of iron status measures by ACD. Therefore, in this article we describe the iron status of a well-defined, free-living, elderly US population, paying particular attention to evaluating the effects of chronic disease on iron status and reporting population prevalence estimates of high iron stores.

SUBJECTS AND METHODS

Study population

The Framingham Heart Study, initiated in 1948–1950, is a longitudinal epidemiologic study of arteriosclerotic and hypertensive cardiovascular disease (37). Because of the examination expense and follow-up constraints of longitudinal investigations, it was originally decided that the study should be set up in a single area and be limited to =6000 adults within a specific age range to ensure a sufficient number of subjects who were free of the disease of interest at entry. The industrial and trading town of Framingham, MA, was selected because 1) the population of 28000 was of sufficient size to ensure the necessary number of subjects, 2) the first community study of tuberculosis was undertaken successfully there, and 3) the town was interested in participating in the study. Therefore, the study population originally consisted of 5209 white men and women aged 30–62 y who were selected largely at random from an annual census list of all residents aged ≥20 y in Framingham. Information collected included demographics; an extensive medical history, including personal habits; a detailed physical examination; and various clinical and biochemical variables. The subjects have been followed in 2-y cycles to ascertain the development of disease and changes in clinical, biochemical, and behavioral variables. The study has been conducted in accordance with federal regulations that govern all human research.

Some 1401 surviving members of the original cohort, aged 67–96 y, participated in the 20th cycle of data collection (cycle 20) between 1988 and 1990. All materials and data used for this analysis were collected at the cycle 20 examination. For 385 subjects, there was insufficient serum available to determine either C-reactive protein (CRP), which is used as an inflammatory index (12, 38), or iron indexes, resulting in a reduction of the sample to 1016 subjects.

Biochemical variables

Nonfasting blood samples were collected by venipuncture into evacuated EDTA-containing tubes. The samples were received at the Jean Mayer–US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University 1 d after collection for determination of the clinical chemistries. Serum aliquots were stored in trace mineral–free Nunc vials (Nalge Nunc International Corporation, Naperville, IL) at −20°C.

White blood cell count (WBC), red blood cell count (RBC), mean cell volume (MCV), hemoglobin, and hematocrit were measured in whole blood specimens with a System 9000 Diff Model Automated Cell Counter (Serono-Baker Diagnostics Inc, Allentown, PA). Hemoglobin was measured by using the cyanmethemoglobin procedure. Hematocrit was calculated from the measured variables as (MCV) × (RBC)/10.

SF was measured by means of the Magic Ferritin [125I] radioimmunoassay (Ciba Corning, Norwood, MA). In our laboratory, assay of the World Health Organization (WHO) International Ferritin Standard 80/578 with the Magic Ferritin radioimmunoassay yielded mean SF values that were within 5–10% of the stated concentrations of this quality control. The Iron Panel of the International Committee for Standardization in Hematology has suggested that the rate of degradation of ferritin in specimens stored at −20°C is <0.3%/y (39). Because the Framingham cycle 20 sera were stored at −20°C for 3–5 y before we assayed for ferritin, this translates into a small practical effect (0.9–1.5%) in terms of the original values.

Serum iron (SI) and unsaturated-iron-binding capacity (UIBC) were measured colorimetrically with an in vitro reagent system (Diagnostic Chemicals Ltd, Oxford, CT) on a Cobas Fara II centrifugal analyzer (Roche, Nutley, NJ). Copper interference with the iron chelating reagent was eliminated by using thiourea (40). UIBC was measured as the total iron added to saturate the available binding sites on serum transferrin minus the excess unbound iron. Total-iron-binding capacity (TIBC) was calculated as the sum of SI and UIBC. Transferrin saturation (Tsat) was calculated from the measured variables as SI/TIBC × 100.

CRP, to be used as an inflammatory index (12, 38), was measured by using an immunoturbidimetric method using a CRP SPQ Test System Antibody Reagent Set II (INCSTAR, Stillwater, MN) on a Cobas Fara II Centrifugal Analyzer. Liver enzymes alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase were measured with an in vitro diagnostic reagent system (Roche) on a Cobas Fara II Centrifugal Analyzer.

Disease criteria for evaluating the effects of chronic disease on iron status

To evaluate the possible confounding effects of ACD due to inflammation, infection, and liver disease on iron variables, we established the following disease criteria. Inflammation was defined as a CRP ≥ 6 mg/L, the detection limit of our laboratory method (n = 71; 7.0%). Infection was defined as a WBC above or below the reference range (>10.6 or <3.9 × 109/L for men and >11.0 or <3.5 × 109/L for women; n = 46; 4.6%); the prevalence of infection was calculated excluding 12 subjects who did not have WBC recorded. Possible liver disease was defined as an abnormal elevation of any 1 of the following 3 liver enzymes: alanine aminotransferase > 2 times the upper limit of normal (>1.23 μkat/L, or >74 U/L; n = 10; 1.0%), aspartate aminotransferase > 2 times the upper limit of normal (>1.13 μkat/L, or >68 U/L; n = 9; 0.9%), or alkaline phosphatase > 1.5 times the upper limit of normal (>2.58 μkat/L, or >154.5 U/L; n = 28; 2.8%). Because some subjects met more than one criterion for abnormally elevated liver enzymes, 39 subjects (3.8%) composed the group with possible liver disease. All disease criteria were intended to be suggestive, not diagnostic.
TABLE 1
Cutoff criteria for abnormal iron status measures and prevalence of abnormal values for all and by sex

<table>
<thead>
<tr>
<th>Iron status measures</th>
<th>Cutoff</th>
<th>Total (n = 1016)</th>
<th>Men (n = 411)</th>
<th>Women (n = 605)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF (μg/L)</td>
<td>&lt;12</td>
<td>34 (3.4%)</td>
<td>10 (2.4%)</td>
<td>24 (4.0%)</td>
</tr>
<tr>
<td>Tsat (%)</td>
<td>&lt;15</td>
<td>116 (11.4%)</td>
<td>37 (9.0%)</td>
<td>79 (13.1%)</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>&lt;80</td>
<td>19 (1.9%)</td>
<td>10 (2.5%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Hb (g/L) Men, &lt;124;</td>
<td>88 (8.7%)</td>
<td>25 (6.1%)</td>
<td>63 (10.5%)</td>
<td></td>
</tr>
<tr>
<td>women, &lt;118</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct</td>
<td>Men, &lt;0.39;</td>
<td>168 (16.7%)</td>
<td>65 (16.0%)</td>
<td>103 (17.2%)</td>
</tr>
<tr>
<td>women, &lt;0.36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1SF, serum ferritin; Tsat, transferrin saturation; MCV, mean cell volume; Hb, hemoglobin; Hct, hematocrit. Prevalence estimates are based on nonmissing data. Four men and 6 women were each missing values for MCV, Hb, and Hct.

Blood concentrations of ferritin can be pathologically elevated in conditions of iron overload. The most common inherited form is hereditary hemochromatosis, an autosomal recessive disorder characterized by increased iron absorption, which affects ≈1 in 300 in populations of northern European descent (15). We attempted to identify subjects with the highest probability of being homozygous for hemochromatosis as having each of the following 3 abnormal iron indexes, inclusive: SF > 300 μg/L, SI > 32 μmol/L (>180 μg/dL), and Tsat > 0.50 (or 50%) (41, 42). Three individuals met these criteria. Some 13.4% (n = 136) of the population had ≥1 of the 4 disease conditions mentioned above (inflammation, infection, liver disease, and hereditary hemochromatosis), whereas 1.0% (n = 10) had 2 conditions and 0.1% (n = 1) had 3 conditions. Blood measures of iron status can also be pathologically altered in conditions of malignancy (ACD) (12, 38). We identified subjects with active cancer at examination 20 (n = 53; 5%).

To evaluate the effects of chronic disease on various prevalence estimates of iron status, we formed a “diseased” group composed of all subjects who met ≥1 of the 4 above-mentioned disease criteria and subjects with active cancer. An additional female subject with an SF concentration of 934 μg/L was included because she had an unusually elevated hemoglobin concentration (203 g/L, or 20.3 g/dL) and hematocrit (0.59, or 59%) and an abnormally elevated RBC (6.7 × 10¹²/L, or 6.7 × 10⁹/mm³). She may have had polycythemia vera, a neoplastic stem cell disorder of unknown cause, that is typically characterized by an elevated hemoglobin and hematocrit with or without an abnormal RBC (43). Because some subjects met more than one of the disease or cancer criteria, the diseased group included 182 subjects. The rest of the population (n = 834) is referred to as the normal group, although we appreciate the fact that any elderly population is probably not absolutely free of disease.

Cutoff criteria for abnormal values of iron status measures

Cutoff criteria for iron status measures used in this analysis are shown in Table 1. Although there is some evidence suggesting a higher threshold of SF for depleted iron stores in the elderly (11, 44–48), we chose the generally accepted cutoff of SF < 12 μg/L that is used in both NHANES II (34) and NHANES III (36). The 0.15 (15%) threshold for an abnormal Tsat used in NHANES III was lower than the more familiar 0.16 (16%) used in NHANES II. This was due to a change in method that corrected for copper interference, causing a systematic lowering of SI values resulting in a lowering of Tsat (36). Because our SI thresholds, WHO criteria were used (49).

Definitions of anemia, iron deficiency, iron deficiency anemia, and high iron stores

Anemia

Traditional assessment of iron status has rested on the prevalence of anemia on the basis of either hemoglobin or hematocrit concentrations. Anemia is commonly estimated by the percentage of individuals with hemoglobin concentrations below a cutoff value defined as 2 SDs below the mean of a healthy reference population (50–52). In our analyses, prevalence estimates of anemia are based on this definition using NHANES III cutoff criteria for an abnormal hemoglobin concentration [men: <124 g/L (12.4 g/dL); women: <118 g/L (11.8 g/dL)] (36). We also calculated the prevalence of anemia on the basis of abnormal hematocrit values using WHO cutoff criteria (men: <39; women: <36). However, it is widely appreciated that using hemoglobin values alone overestimates the prevalence of ID because there are other causes of anemia besides lack of iron (16, 53–55) and there is a large overlap in the frequency distribution of hemoglobin values in anemic and healthy subjects, resulting in frequent misclassification of subjects (52, 56–58). Moreover, this approach may be particularly unsuitable in elderly populations because of the presence of ACD.

Iron deficiency and iron deficiency anemia

Therefore, we also assessed a lack of iron in our population by using multiple iron measures that reflect different stages of iron depletion (59). ID was defined as an abnormal value from 2 or 3 laboratory tests of iron status other than hemoglobin (SF, Tsat, and MCV) and refers to impaired iron status with or without anemia. IDA was defined as ID plus a low hemoglobin value (using the NHANES III criteria discussed above). Even though ID is more likely to be the cause of anemia with a multiple-measures approach, these definitions provide suggestive evidence of impaired iron status, not a definitive diagnosis.

High iron stores

The reference range of SF values is commonly considered to be ≈15–300 μg/L (58), suggesting >300 μg/L as indicative of abnormally high iron stores for both sexes. Because sex has a marked effect on body iron stores (60), and because the elderly men in our study had a significantly higher geometric mean SF concentration than did the women and their 95th-percentile value for SF was 120 μg/L higher than the women’s (Table 2), we chose sex-specific cutoff criteria for defining high iron stores: SF > 300 μg/L in men and >200 μg/L in women.

Statistical analysis

All statistical procedures were performed using SAS for WINDOWS, version 6.12 (61). Prevalence estimates of ID and IDA based on a multiple-measures model of iron status assessment (described above) were determined by using indicator variables designed to represent 1) abnormal values for ≥2 of 3 indicators
of ID (SF, Tsat, and MCV) and 2) subjects with ID plus a low hemoglobin concentration, indicating IDA. Four men and 6 women were missing values for MCV, hemoglobin, and hematocrit. Prevalence estimates of iron status involving these iron indexes are based on nonmissing data.

Because the distribution of SF values was positively skewed, a natural logarithmic transformation was applied to the measurements before the statistical analyses were performed. Therefore, we present geometric mean SFs. Student’s *t* test was used to compare means between men and women. Because the distribution of SF values was positively skewed, an arithmetic mean SF ± SD was not appropriate for statistical comparison because of the skewed distribution of SF, but the values for men and women were 161.2 ± 82.4 (134.3, 198.1) and 109.7 ± 54.4 (84.9, 134.7), respectively.

**RESULTS**

**Description of the sample**

Our elderly study population consisted of 411 men (40%) and 605 women. The mean (±SD) age was 76.3 ± 5.0 y and ranged from 67 to 96 y. Seven percent (*n* = 68) of the study population were aged 67–69 y, 67% (*n* = 679) were aged 70–79 y, 23% (*n* = 238) were aged 80–89 y, and 3% (*n* = 31) were aged ≥90 y.

**Characteristics of iron status measurements**

The distribution of laboratory iron variables for all subjects and by sex is presented in Table 2 along with the reference ranges for the laboratory in which the assays were performed. The mean concentration of all iron measurements for both men and women fell within the reference range. The elderly men had significantly higher geometric mean SF (*P* < 0.001) and significantly higher mean SI, Tsat, hemoglobin, hematocrit (*P* < 0.001), and MCV (*P* = 0.017) values than did the elderly women.

The distribution of SF values in our elderly population is shown in Figure 1. Although 3.3% of the subjects had depleted iron stores (SF < 12 µg/L), 3 times that amount (9.2%) had elevated iron stores (SF > 300 µg/L); most subjects (59%) had SF concentrations in the range of 46–200 µg/L. There was a significantly (*P* = 0.001) greater proportion of men than women in the 2 highest SF categories (201–300 and >300 µg/L SF).

**Prevalence estimates of anemia**

The prevalences of impaired iron status based solely on hemoglobin concentrations or hematocrit are shown in Table 1. Nine percent of the subjects were classified as being anemic on the basis of low hemoglobin values assessed by NHANES III criteria (men: 6.1%; women: 10.5%). On the basis of low hematocrit alone, 16.7% were classified as being anemic (men: 16.0%; women: 17.2%).

**Prevalence estimates of iron deficiency and iron deficiency anemia: multiple-measures model**

On the basis of having abnormal values for ≥2 of 3 laboratory tests of iron status (SF, Tsat, and MCV), only 2.7% of all

**TABLE 2**

<table>
<thead>
<tr>
<th>Laboratory variable</th>
<th>Range</th>
<th>Median ± SD (5th and 95th percentile)</th>
<th>Median ± SD (5th and 95th percentile)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF (µg/L)</td>
<td>10–300</td>
<td>110.7 (100.8, 121.6) i</td>
<td>73.7 (68.2, 79.6) i</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SI (µg/dL)</td>
<td>40–160</td>
<td>95.1 ± 38.8 (90, 164)</td>
<td>81.2 ± 30.1 (80, 134)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIBC (µg/dL)</td>
<td>227–400</td>
<td>338.7 ± 54.4 (332, 437)</td>
<td>343.4 ± 53.1 (339, 431)</td>
<td>0.168</td>
</tr>
<tr>
<td>Tsat (%)</td>
<td>16–55</td>
<td>24.8 ± 11.9 (27, 42)</td>
<td>23.8 ± 9.2 (23, 40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCV (IL)</td>
<td>82–102</td>
<td>91.3 ± 5.5 (91, 84)</td>
<td>90.5 ± 5 (91, 82)</td>
<td>0.017</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>Men, 13.0–18.9; women, 11.5–16.0</td>
<td>14.6 ± 1.5 (14.7, 16.8)</td>
<td>13.4 ± 1.4 (13.4, 15.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hct</td>
<td>Men, 0.40–0.54; women, 0.36–0.49</td>
<td>42.7 ± 4.3 (42.8, 49.1)</td>
<td>39.4 ± 4.2 (39.4, 46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 Normal ranges for the Nutrition Evaluation Laboratory at the Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging at Tufts University. SF, serum ferritin; SI, serum iron; TIBC, total iron-binding capacity; Tsat, transferrin saturation; MCV, mean cell volume; Hb, hemoglobin; Hct, hematocrit.

2 Student’s *t* test was used to compare means between men and women.

3 Geometric mean (with 95% CI). Arithmetic mean ± SD (5th and 95th percentile).

4 Men, 0.40–0.54; 42.7–14.6; 134.3 and 109.7; 84.9. Women, 0.36–0.49; 90.5–13.4; 339.4. *n* = 407 men and 599 women.

* *Significant difference between men and women, *P* < 0.05.

**FIGURE 1.** Distribution of serum ferritin concentrations in elderly men and women from The Framingham Heart Study cohort. Error bars are the SEs of a proportion. *Significant difference between men and women, *P* < 0.05.
Of the women had an SF concentration <12 g/L, which is indicative of depleted iron stores. This sex difference was not significant. In contrast with the relatively low prevalence of depleted iron stores in our elderly sample, the prevalence of high iron stores was much greater. With the sex-specific cutoffs of SF > 300 g/L for both men and women, Milman et al (62) found an overall prevalence of high iron stores of 13% in a small sample of 85-y-old healthy Danes, whereas 8.7% of men and 3.7% of women in another free-living population of 469 Danes aged 70 y had high iron stores (63). In another healthy, free-living population of 1332 Danish men aged 40–70 y, Milman et al (64) observed the prevalence of elevated iron stores to be 20.8% and 15.2% in the 60- and 70-y-olds, respectively. In the

![Figure 2](image-url) Prevalence of high iron stores in elderly men and women from the Framingham Heart Study cohort at various serum ferritin cutoffs. Error bars are the SEs of a proportion. *Significant difference between men and women, P < 0.05.

Table 3

| Iron status measures | Diseased group | Normal group | P
|----------------------|----------------|--------------|---
| SF (µg/L)            | 93 (80,108)    | 86 (80,91)   | 0.309
| SI (µg/dL)           | 78.6 ± 5.2     | 85.5 ± 6.1   | 0.003
| TIBC (µg/dL)         | 331.3 ± 4.3    | 343.7 ± 1.8  | 0.005
| Tsat (%)             | 24.0 ± 1.0     | 26.1 ± 0.34  | 0.054
| MCV (fL)             | 90.6 ± 0.52    | 90.8 ± 0.17  | 0.737
| Hb (g/dL)            | 13.6 ± 0.14    | 14.0 ± 0.05  | 0.006
| Hct                  | 0.398 ± 0.0040 | 0.410 ± 0.0015 | 0.006

^7SE. SF, serum ferritin; SI, serum iron; TIBC, total iron-binding capacity; Tsat, transferrin saturation; MCV, mean cell volume; Hb, hemoglobin; Hct, hematocrit.

Subjects with possibly pathologically altered iron measures due to inflammation, infection, liver disease, cancer, or hereditary hemochromatosis.

P values from Student’s t test comparing means between groups.

Geometric ± (95% CI). Arithmetic ± SE of disease and normal groups: 150.4 ± 11.1 and 126.2 ± 3.9, respectively.

When we attempted to determine the influence of chronic disease on prevalence estimates of iron status, we found that the prevalence of ID and IDA based on our multiple-measures model of iron status assessment were 2.5% and 0.8%, respectively, when the diseased group was excluded from the analyses, compared with 2.7% and 1.2% when the diseased group was included, suggesting that chronic disease had little effect on population prevalence estimates of ID and IDA. Similarly, there was an insignificant effect (1%) of disease on the population prevalence estimates of high iron stores. Using sex-specific cutoffs for elevated iron stores, prevalence in the total population was 12.9%, whereas the prevalence in the population with the diseased group excluded was 11.9%.

A summary of the iron status of the elderly Framingham Heart Study cohort is provided in Figure 4.

**DISCUSSION**

To our knowledge, this is the first study of the iron status of a large, free-living, elderly US population to report prevalence estimates of elevated iron stores while attempting to comprehensively account for the possible confounding effects of chronic disease on these estimates, as well as on the prevalence of ID and IDA.

Not surprisingly, we found that ID and IDA are not common among the free-living, elderly, white Framingham Heart Study cohort. We found that the disparity in low iron status typically seen between younger men and women is markedly absent in the elderly.

**High iron stores**

Because the concern for the possible adverse health effects of high storage iron is a recent one, prevalence data in elderly populations are scarce and involve mostly non-US subjects. Using an SF cutoff of 300 µg/L for both men and women, Milman et al (62) found an overall prevalence of high iron stores of 13% in a small sample of 85-y-old healthy Danes, whereas 8.7% of men and 3.7% of women in another free-living population of 469 Danes aged 70 y had high iron stores (63). In another healthy, free-living population of 1332 Danish men aged 40–70 y, Milman et al (64) observed the prevalence of elevated iron stores to be 20.8% and 15.2% in the 60- and 70-y-olds, respectively. In the

**TABLE 3**

Comparison of mean values of iron status measures in the diseased group and the normal group

<table>
<thead>
<tr>
<th>Iron status measures</th>
<th>Diseased group (n = 182)</th>
<th>Normal group (n = 834)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF (µg/L)</td>
<td>93 (80,108)</td>
<td>86 (80,91)</td>
<td>0.309</td>
</tr>
<tr>
<td>SI (µg/dL)</td>
<td>78.6 ± 5.2</td>
<td>85.5 ± 6.1</td>
<td>0.003</td>
</tr>
<tr>
<td>TIBC (µg/dL)</td>
<td>331.3 ± 4.3</td>
<td>343.7 ± 1.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Tsat (%)</td>
<td>24.0 ± 1.0</td>
<td>26.1 ± 0.34</td>
<td>0.054</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>90.6 ± 0.52</td>
<td>90.8 ± 0.17</td>
<td>0.737</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>13.6 ± 0.14</td>
<td>14.0 ± 0.05</td>
<td>0.006</td>
</tr>
<tr>
<td>Hct</td>
<td>0.398 ± 0.0040</td>
<td>0.410 ± 0.0015</td>
<td>0.006</td>
</tr>
</tbody>
</table>

^7SE. SF, serum ferritin; SI, serum iron; TIBC, total iron-binding capacity; Tsat, transferrin saturation; MCV, mean cell volume; Hb, hemoglobin; Hct, hematocrit.

Subjects with possibly pathologically altered iron measures due to inflammation, infection, liver disease, cancer, or hereditary hemochromatosis.

^P values from Student’s t test comparing means between groups.

^Geometric ± (95% CI). Arithmetic ± SE of disease and normal groups: 150.4 ± 11.1 and 126.2 ± 3.9, respectively.
Therefore, could not determine the possible effect of the various iron measures due to inflammation, infection, liver disease, cancer, or hereditary hemochromatosis ($n = 182$) and the normal group (the rest of the population; $n = 834$). Prevalence estimates of anemia are based on nonmissing data. Four men and 6 women were missing hemoglobin values. Error bars are the SEs of a proportion. *Significant difference in prevalence between groups, $P < 0.05$. Depleted iron stores: serum ferritin < 12 μg/L. Anemia: hemoglobin < 124 g/L in men and < 118 g/L in women. High iron stores: serum ferritin > 300 μg/L in men and > 200 μg/L in women.

Framingham cohort, using this same cutoff for both sexes, we found the overall prevalence of high iron stores to be 9.2%: men had a prevalence of 13.9% and women had a prevalence of 6.0%. On the basis of sex-specific cutoffs as in our study, higher prevalence estimates of iron overload were reported in healthy Parisian elderly ($65$): the overall prevalence was 20%, (men: 22.3%; women: 16.6%). Our overall prevalence of elevated iron stores based on sex-specific cutoffs was 12.9%, with no significant difference between men and women. Garry et al ($66$) found the prevalence of elevated iron stores to be 35% in men and 15% in women in a healthy, free-living US elderly population when an SF of >200 μg/L was used for both sexes. Using this cutoff, we observed the prevalence of high iron stores to be 28.0% in men and 12.2% in women.

It is difficult to compare the prevalence estimates of high iron stores in our study with those from other studies because of a lack of validation of the SF assay against a known standard and a lack of control for disease-related confounding of SF values. The prevalence estimates presented in this article largely reflect the true values because 1) the Magic Ferritin radioimmunoassay used to generate our SF concentrations yielded mean SF values within 5–10% of the concentrations of the WHO International Ferritin Standard 80/578 quality control, 2) we attempted to control for elevated SF due to disease, and 3) Framingham cycle 20 sera were stored at −20°C for only 3–5 y before assay, allowing for little degradation of the protein ($39$).

We did not determine any genotypes in our population and, therefore, could not determine the possible effect of the various $HFE$ heterozygous genotypes on the prevalence of elevated iron stores in our elderly subjects. It is recognized that such genotypic variations can influence iron stores ($67$) and the risk of developing ID ($68, 69$). However, we did identify 3 individuals as having a high probability of being homozygous for hereditary hemochromatosis on the basis of laboratory evidence. This is consistent with the expected $HFE$ gene frequency of ≈1/300 ($15$).

**Effect of chronic disease on iron status**

With the higher prevalence of chronic disease in the elderly, possible confounding effects of disease on iron status assessment are a compelling concern. In this elderly Framingham cohort we attempted a comprehensive definition of chronic disease by using several different biochemical indexes, combining subjects with abnormal values into a diseased group, and including subjects with active cancer. When we compared single iron status measures between the diseased group and the rest of the study population, we observed significant differences for several indicators, including a 2.6-fold higher prevalence of anemia and a 1.5-fold higher prevalence of elevated iron stores in the diseased group than in the normal group, suggesting an important effect of chronic disease on iron status measures in this elderly group. We speculate that the significantly greater proportion of anemic subjects in the diseased group than in the normal group reflects the higher prevalence of ACD in the diseased group.

However, the critical question of interest is: to what extent are population prevalence estimates of iron status affected by chronic disease? Because the depletion of iron stores is specific for loss of iron and generally unaffected by chronic disease ($54, 70$), it is not surprising that there was no significant difference between the normal and diseased groups in the proportion of subjects with depleted iron stores (SF < 12 μg/L). Furthermore, population prevalence estimates of ID and IDA for the diseased and nondiseased groups were almost identical. This observation

![FIGURE 3. Comparison of the prevalence of various iron conditions between the diseased group (those with possibly pathologically altered iron measures due to inflammation, infection, liver disease, cancer, or hereditary hemochromatosis; $n = 182$) and the normal group (the rest of the population; $n = 834$). Prevalence estimates of anemia are based on nonmissing data. Four men and 6 women were missing hemoglobin values. Error bars are the SEs of a proportion. *Significant difference in prevalence between groups, $P < 0.05$. Depleted iron stores: serum ferritin < 12 μg/L. Anemia: hemoglobin < 124 g/L in men and < 118 g/L in women. High iron stores: serum ferritin > 300 μg/L in men and > 200 μg/L in women.

![FIGURE 4. Summary of the iron status of the elderly Framingham Heart Study cohort. Prevalence of iron deficiency, iron deficiency anemia, depleted iron stores, and high iron stores by sex. Prevalence estimates are based on nonmissing data. Four men and 6 women were each missing values for mean cell volume, hemoglobin, and hematocrit. Error bars are the SEs of a proportion. There was no significant difference in prevalence between men and women for each iron condition ($P < 0.05$). ID: an abnormal result of ≥2 of 3 laboratory tests of iron status (serum ferritin, transferrin saturation, and mean cell volume). IDA: having ID plus a low hemoglobin concentration (men: hemoglobin < 124 g/L; women: hemoglobin < 118 g/L). Depleted iron stores: serum ferritin < 12 μg/L. High iron stores: serum ferritin > 300 μg/L in men and > 200 μg/L in women.](https://example.com/iron-status-graph)
suggests that the increased diagnostic specificity of a multiple-measures approach for estimating ID and IDA probably compensates for any confounding of prevalence estimates by chronic disease. Similarly, we conclude that disease effects on population prevalence estimates of elevated iron stores are small because the prevalence dropped by only 1% after the removal of the diseased group from the population.

Study limitations

There were several possible limitations to our analyses, which may have resulted in either an underestimation of ID or an overestimation of the prevalence of high iron stores on the basis of SF concentrations. First, it is well known that blood donation alters blood measures of iron status. This is unlikely to have affected our results in this elderly sample (aged 67–96 y) because US blood banks, until very recently, have generally mandated a maximum donor age of 65 y (71, 72). Second, it is also well known that the use of estrogen or progesterone may cause breakthrough bleeding in postmenopausal women and thus be a potential confounder of iron status in elderly female subjects. We consider this to be of small practical significance in overall status assessment because only 26 of 605 women, (0.04, or 4%) reported current estrogen use at cycle 20. Fewer than 1% of the women reported current or past use of progesterone. Third, the use of nonfasting blood may have been a problem. Serum iron exhibits a marked diurnal variation; the highest concentrations are observed in the morning and the lowest concentrations in the evening. In our study, blood was drawn in the afternoon after lunch. Meals have been shown to have variable effects on SI concentrations as well, resulting in no change, an increase, or a decrease (73–78). Consequently, it is difficult to know the effect of the use of nonfasting blood on our SI values and thus on our prevalence estimates of ID. However, we consider this to be of small practical significance for overall status assessment given the distributions of SF and hemoglobin, both of which are generally unaffected by diurnal variation, in our elderly subjects. Fourth, the principal caveat to a multiple-measures assessment approach is that its enhanced specificity will be at the expense of sensitivity, resulting in an underestimation of true prevalence of ID. However, this is also of small practical significance for overall status assessment because the distributions of SF and hemoglobin indicate an iron-replete elderly population. Last, we defined inflammation as a CRP ≥ 6 mg/L because that was the detection limit of our laboratory method. However, ultrasensitive assays with detection limits as low as 0.05 mg CRP/L were developed recently. Investigations of the effect of mild underlying inflammatory conditions on SF are needed.

Conclusion

Free-living, elderly white Americans eating a Western diet are an iron-replete group with the liability in iron nutriture more likely being chronic positive iron balance and elevated total body iron than iron deficiency. The cause of high iron stores in the elderly is unknown but, on the basis of our data, it is not likely attributable to disease. The role of diet needs further investigation. However, given the adequacy of this population’s iron status, our present findings suggest that the use of unprescribed iron supplements in free-living, elderly white Americans is probably unnecessary and could be detrimental given the reported adverse association between elevated iron stores and the risk of some chronic diseases (17–22).

REFERENCES