Body iron stores and their determinants in healthy postmenopausal US women¹⁻³

Jian-Meng Liu, Susan E Hankinson, Meir J Stampfer, Nader Rifai, Walter C Willett, and Jing Ma

ABSTRACT

Background: Data on the determinants of body iron stores in middle-aged women are sparse.

Objective: We prospectively evaluated nondietary and dietary determinants of iron stores.

Design: Using blood samples collected in 1989–1990, we measured plasma ferritin concentrations in 620 healthy postmenopausal women aged 44–69 y who participated in the Nurses' Health Study. Food-frequency questionnaires completed in 1980, 1984, and 1986 were used to calculate average dietary intakes. Generalized linear regression and multiple logistic regression models were used to assess the association between plasma ferritin and its determinants.

Results: Among these postmenopausal women, the median plasma ferritin concentration was 73.8 ng/mL (interquartile range: 41.6–125.8 ng/mL), 2.7% were iron depleted (ferritin concentration < 12 ng/mL), and 9.8% had an elevated ferritin concentration (> 200 ng/mL). Age, time since menopause, time since the last postmenopausal hormone (PMH) use, body mass index, iron supplement use, and alcohol and heme-iron intakes were positively associated with ferritin concentrations, whereas PMH use, physical activity, aspirin use, and gastrointestinal ulcer were inversely related. The association between heme-iron intake and ferritin was most apparent among the women who consumed > 30 g alcohol/d.

Conclusions: Our prospective data confirm that in postmenopausal women, intakes of heme iron, supplemental iron, and alcohol are dietary determinants of plasma ferritin, and age, PMH use, body mass index, physical activity, aspirin use, and gastrointestinal ulcer are nondietary determinants.

KEY WORDS Iron, ferritin, alcohol, postmenopausal women, Nurses' Health Study

INTRODUCTION

Iron is essential for oxygen transport, electron transfer reactions, gene regulation, and regulation of cell growth and differentiation. Excessive iron, however, can damage tissues by catalyzing the conversion of hydrogen peroxide to free radical ions that attack cellular membranes, proteins, and DNA (1, 2). Elevated concentrations of plasma ferritin, a commonly accepted marker of body iron stores (3), have been linked in some studies to increased risks of ischemic heart disease (4–11), colorectal cancer (12, 13), and some other chronic diseases (14–17), although these associations remain controversial.

In searching for the physiologic and pathologic role of iron, it is important to understand the dietary and nondietary determinants of body iron stores. Body iron stores accumulate by the absorption of dietary iron (heme and nonheme iron). Experimental studies using controlled meals showed that the absorption of heme iron is more complete and less regulated than that of nonheme iron (18). Absorption of nonheme iron is more likely to be influenced by various dietary enhancers (eg, vitamin C, alcohol, and meat) and inhibitors (eg, phytate, calcium, and coffee). However, the association between long-term intakes of these dietary variables and body iron stores has not been fully evaluated among free-living persons, especially middle-aged women.

In addition to diet, body iron stores also vary by sex, physiologic demands such as growth and pregnancy (19–23), loss of iron due to natural or hormone-induced menstruation (24), gastrointestinal ulcer (25), and physical activity (26). A positive association between body mass index (BMI; in kg/m²) and body iron stores has been reported (23, 27, 28). These nondietary variables should be taken into consideration when evaluating the association between dietary intakes and body iron stores in observational studies. Six cross-sectional studies examined the relation between dietary iron intake and plasma ferritin concentrations (29–34). These studies were either small (n < 128) (31, 33, 34), encompassed a very large age range (32), combined men and women together (29, 35), or did not extensively take other nondietary variables into consideration (29–35). Only one small study (48 men and 77 women) prospectively examined the relations between plasma ferritin and iron intake (35), and this study found a significant association between supplemental iron intake, but not dietary heme- or

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nonheme-iron intake, and iron stores. The Nurses’ Health Study (NHS) provides an opportunity to prospectively examine the association of dietary and nondietary variables with body iron stores in middle-aged postmenopausal US women.

**SUBJECTS AND METHODS**

**Study population**

The NHS was established in 1976, when 121,700 female registered nurses who were between the ages of 30 and 55 y and who were from 11 states returned an initial questionnaire reporting medical histories and baseline health-related exposures. Details of the design and follow-up of this cohort were described previously (36, 37). Updated information has been obtained by questionnaires every 2 y. Dietary data were assessed with the use of a semiquantitative food-frequency questionnaire (FFQ) in 1980, 1984, and 1986. For all subsequent questionnaire cycles in this subcohort, >90% of the subjects were followed up. Between 1989 and 1990, blood samples were collected from 32,826 women. Approximately 97% of the samples were returned within 24 h of blood collection; immediately centrifuged (20 min, 2000 × g, 4 °C); divided into aliquots of plasma, red blood cells, anduffy coat fractions; and stored in the vapor phase of liquid nitrogen freezers.

The study population for these analyses was drawn from 873 healthy control subjects who were free of cardiovascular disease, cancer, and chronic kidney failure; were 44–69 y of age in 1990; and participated in case-control studies of cardiovascular disease and cancer that were nested in the NHS blood cohort. We excluded premenopausal women and women with missing data for plasma ferritin, postmenopausal hormone (PMH) use, or uncertain menopausal status in 1990, which left 620 postmenopausal women in the analyses. The Partners HealthCare System Institutional Review Board approved this study.

**Assessment of nondietary variables**

Nondietary variables were assessed by biennial questionnaires completed between 1976 and 1988; age, menopausal status, and PMH use were assessed in 1990. The women were asked about their current (at the time of the questionnaire response) and previous PMH use. Mean values for BMI were computed from the 1980-1988 questionnaires, and mean values for physical activity (h/wk) were computed from the 1980, 1982, 1986, and 1988 questionnaires (38). Data on average regular aspirin use were derived from the 1984 and 1988 questionnaires, which included a question about the number of days each month that aspirin was taken. Anyone with a prior report of peptic ulcer or ulcerative colitis before 1988 was considered to have a history of gastrointestinal ulcer.

**Assessment of dietary variables**

We examined the following dietary variables in relation to plasma ferritin: iron (heme, nonheme, and supplemental) intakes and intakes of potential enhancers or inhibitors (alcohol, phytate, calcium, vitamin C, coffee, and red meat) of iron absorption. In 1980 we assessed dietary intakes with a 61-item FFQ. In 1984 the questionnaire was expanded to 116 food items, and similar questionnaires were used to update information on diet in 1986. A common unit or portion size was specified for each food. The participants were asked how often, on average, they had consumed that amount during the previous year. The 9 responses ranged from “never” to “≥6 times/ d.” Red meat intake, a major contributor of heme-iron intake, was calculated as the sum of the intakes of beef, pork, and lamb (main dish or mixed dish); hamburgers; hot dogs; bacon; and other processed meats. The intake of nutrients was computed by multiplying the frequency of consumption of each unit of food by its nutrient content and then summing these products over all the food items. Food-composition values were obtained from the Harvard University Food Composition Database, which is derived from US Department of Agriculture sources (39), and from manufacturer information. Questions about beer, wine, and liquor intakes were included in each of the FFQs to permit calculation of alcohol intake (40). In 1986 the validity of the FFQ was assessed in a sample of 92 NHS participants living in the Boston area. Nutrient intake from the FFQ was compared with two 1-wk diet records spaced ~6 mo apart. The correlation coefficient for energy-adjusted total dietary iron intake was 0.60 after adjustment for within-person variability in daily intake (41).

To reduce within-person variability and obtain the best estimate of long-term dietary intakes, we used the average intakes from the 1980, 1984, and 1986 questionnaires. Except for the intakes of supplemental iron (including the contribution from multivitamins), alcohol, and coffee and the total intake of red meat (servings/d), all nutrient intakes were energy adjusted.

**Laboratory analysis**

Plasma samples were shipped on dry ice to the Core Laboratory of the Children’s Hospital, where ferritin concentrations were measured with the use of a sandwich immunoassay method (Heterogenous Sandwich Magnetic Separation Assay; Bayer, Tarrytown, NY) on the Technicon Immuno 1 system (Bayer). Aliquots from a pool of quality-control plasma were inserted randomly, and the mean CV for plasma ferritin concentration in these quality-control specimens was 9.7%. In a substudy of 40 participants, the Spearman correlation coefficient for ferritin concentrations measured in plasma samples collected at baseline and 5 y later was 0.64.

**Statistical analysis**

To make direct comparisons with previous studies (42, 43), we defined depleted iron stores as a ferritin concentration < 12 ng/mL and elevated ferritin as a ferritin concentration ≥ 200 ng/mL. Prevalence estimates of depleted iron stores and elevated ferritin were provided with exact binomial 95% CI. Fisher’s exact test was used to test for the significance of differences in prevalence. Spearman correlation coefficients were calculated between plasma ferritin and study variables. We used generalized linear regression models to calculate least-squares geometric mean plasma ferritin concentrations by categories of different dietary and nondietary variables. We used 3 categories for age (< 60, 60–64, and 65–69 y), BMI (< 25, 25–29.9, and ≥ 30), physical activity (< 3.5, 3.5–6.9, and ≥ 7.0 h of moderate to vigorous activity/wk), and regular aspirin use (0, 1–14, and 15–30 d/mon) and used quintiles for dietary intakes. We tested for an interaction between the intakes of alcohol and heme in association with ferritin concentrations by including the product term of the 2 variables in the
linear regression model. Multiple logistic regression was used to obtain odds ratios as estimates of the relative risk of elevated ferritin. Linear trends for all variables except PMH use were tested by assigning the median value of each category as the score; for PMH use, values of 1, 2, and 3 were assigned instead.

Three subgroup analyses were performed to analyze the effect of age, time since menopause, and time since last PMH use, and type of hormone on ferritin concentrations. All analyses were performed by using SAS (version 8.2; SAS Institute Inc., Cary, NC) on a Unix operating system. All P values were two-sided, and statistical significance, including that for interactions, was set at P = 0.05.

RESULTS

The study included 620 postmenopausal women with a mean age of 61.6 y (range: 44–69 y). The median intakes of dietary nonheme and heme iron were 10.2 mg/d (25th–75th percentile range: 8.4–12.8 mg/d) and 1.3 mg/d (25th–75th percentile range: 1.0–1.6 mg/d), respectively. The median plasma ferritin concentration was 73.8 ng/mL (25th–75th percentile range: 41.6–125.8 ng/mL), 2.7% (95% CI: 1.6%, 4.4%) of the subjects were iron depleted (ferritin concentration < 12 ng/mL), and 9.8% (95% CI: 7.6%, 12.5%) of the subjects had an elevated ferritin concentration (> 200 ng/mL).

Geometric mean plasma ferritin concentrations according to categories of selected nondietary and dietary factors among the postmenopausal women are shown in Table 1. For nondietary factors, age [crude Spearman correlation coefficient (r) = 0.20, P < 0.01] and BMI (r = 0.16, P < 0.01) were positively related to ferritin concentrations, whereas PMH use (r = −0.17, P < 0.01), aspirin use (r = −0.10, P < 0.01), and chronic gastrointestinal ulcer (r = −0.11, P < 0.01) were inversely associated with ferritin concentrations. The correlation between physical activity and ferritin was not significant (r = −0.05).

We examined the associations between the average intakes of selected foods or nutrients during the past 10 y (FFQs in 1980, 1984, and 1986) and plasma ferritin concentrations in 1990 (Table 1 and Table 2). Intakes of heme iron (r = 0.15), supplemental iron (r = 0.12), alcohol (r = 0.14), and red meat (r = 0.11) (P < 0.01 for all 4 variables) were positively correlated with ferritin after adjustment for nondietary variables, whereas phytate intake was inversely related (r = −0.09, P < 0.05). Dietary intakes of nonheme iron, calcium, vitamin C, and coffee were not correlated with ferritin concentrations (Table 2).

We further added both nondietary and dietary variables in a multivariate generalized linear model to evaluate their independent associations with ferritin (Table 1). The results for the nondietary factors were essentially unchanged. For the dietary factors, intakes of heme iron, alcohol, and supplemental iron remained significant, whereas phytate intake became nonsignificant. Because red meat is a major contributor of dietary heme iron (r = 0.6, P < 0.01), it was not included in the model.

Because excess alcohol intake may enhance iron absorption, we further assessed whether the association between heme-iron intake and ferritin concentrations varied by alcohol intake. After other nondietary and dietary factors were controlled for, the positive association between heme-iron intake and ferritin was much stronger among the women who had an alcohol

![Table 1](https://academic.oup.com/ajcn/article-abstract/78/6/1160/4677528)
TABLE 2
Spearman partial correlation coefficients between plasma ferritin (ng/mL) and dietary variables after adjustment for nondietary variables among 620 postmenopausal women.

<table>
<thead>
<tr>
<th>Dietary variable</th>
<th>Ferritin</th>
<th>Heme iron</th>
<th>Nonheme iron</th>
<th>Supplemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy (kcal/d)</td>
<td>−0.04</td>
<td>−0.04</td>
<td>0.01</td>
<td>−0.05</td>
</tr>
<tr>
<td>Heme iron (mg/d)</td>
<td>0.15&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.03</td>
<td>−0.03</td>
<td>−0.04</td>
</tr>
<tr>
<td>Nonheme iron (mg/d)</td>
<td>0.02</td>
<td>−0.03</td>
<td>−0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Supplemental iron (mg/d)</td>
<td>0.12&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.04</td>
<td>0.06</td>
<td>−0.04</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>0.14&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.05</td>
<td>−0.04</td>
<td>−0.05</td>
</tr>
<tr>
<td>Phytate (mg/d)</td>
<td>−0.09&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.31&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.43&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.07</td>
</tr>
<tr>
<td>Calcium (mg/d)</td>
<td>−0.06</td>
<td>−0.37&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.15&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.25&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitamin C (mg/d)</td>
<td>0.04</td>
<td>−0.14&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.10&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Coffee (servings/d)</td>
<td>−0.06</td>
<td>−0.02</td>
<td>−0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Total red meat (servings/d)</td>
<td>0.11&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.60&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.07</td>
<td>−0.10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Notes: Adjusted for postmenopausal hormone use (current, past, and never), gastrointestinal ulcer (yes or no), age (y), BMI (kg/m<sup>2</sup>), physical activity (h/wk), and aspirin use (d/mo).

<sup>2</sup> P < 0.01.
<sup>4</sup> P < 0.05.

intake > 30 g/d than among those who never drank or were moderate drinkers (P for interaction = 0.01). Multivariate-adjusted geometric mean plasma ferritin concentrations by categories of heme-iron and alcohol intake are shown in Table 3.

Multiple logistic regressions were used to evaluate predictors of elevated ferritin (Table 4). Age > 60 y and BMI > 25 were the 2 strongest nondietary predictors of elevated ferritin, whereas the women who currently took hormones or who took aspirin ≥ 15 d/mo in the past were less likely to have elevated ferritin. Among the dietary variables, heme-iron intake was the major predictor of elevated ferritin; the relative risks in quintiles 1–5 were 1.0 (reference), 1.0, 1.3, 1.9, and 3.9 (95% CI: 1.3, 11.5), respectively (P for trend = 0.01). Supplemental iron intake tended to be associated with elevated ferritin, but the trend was less apparent probably because of the small numbers in some of the categories. In addition, the risk of elevated ferritin in the women who consumed > 30 g alcohol/d was 4-fold (95% CI: 1.3, 13.6) that of those who consumed 0.1–5.0 g alcohol/d (P for trend = 0.01).

Because natural or hormone-induced menstruation causes iron loss, we further investigated the effect on plasma ferritin concentrations of time since menopause among the women who had never taken hormones after menopause, time since the last hormone use among the women who had taken hormones in the past, and type of hormones taken among the current hormone users (Table 5). Both longer times since menopause and longer times since the last hormone use were associated with higher plasma ferritin concentrations (P for trend ≤ 0.05). Current users of oral conjugated estrogen plus progestin had significantly lower plasma ferritin concentrations than did current users of estrogen only (P < 0.01).

The association between age, which was categorized into 6 groups (<56, 56–58, 59–61, 62–64, 65–67, and 68–69 y), and ferritin was further examined among the women who had never taken hormones after menopause. Multivariate-adjusted geometric mean plasma ferritin concentrations are shown by age in Figure 1. Ferritin concentrations increased gradually with age in years until the early 60s and reached a plateau afterwards.

TABLE 3
Multivariate-adjusted plasma ferritin concentrations by categories of heme-iron and alcohol intake among 620 postmenopausal women.

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Low (&lt;1.1 mg/d)</th>
<th>Middle (1.1–1.3 mg/d)</th>
<th>High (≥1.4 mg/d)</th>
<th>P for trend†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric $\bar{x}$ (mg/mL)</td>
<td>52.1</td>
<td>77.0</td>
<td>69.3</td>
<td></td>
</tr>
<tr>
<td>$\bar{x} \pm SE$ (mg/mL)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3.95 ± 0.14</td>
<td>4.34 ± 0.14</td>
<td>4.24 ± 0.15</td>
<td>0.12</td>
</tr>
<tr>
<td>n</td>
<td>49</td>
<td>47</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>0.1–30.0 g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric $\bar{x}$ (mg/mL)</td>
<td>64.5</td>
<td>71.0</td>
<td>76.5</td>
<td></td>
</tr>
<tr>
<td>$\bar{x} \pm SE$ (mg/mL)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.17 ± 0.11</td>
<td>4.26 ± 0.11</td>
<td>4.34 ± 0.11</td>
<td>0.06</td>
</tr>
<tr>
<td>n</td>
<td>150</td>
<td>146</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>≥ 30.1 g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric $\bar{x}$ (mg/mL)</td>
<td>71.7</td>
<td>120.6</td>
<td>165.1</td>
<td></td>
</tr>
<tr>
<td>$\bar{x} \pm SE$ (mg/mL)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4.27 ± 0.27</td>
<td>4.79 ± 0.24</td>
<td>5.11 ± 0.31</td>
<td>0.06</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>13</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Multivariate linear regression stratified according to alcohol consumption. Tests for linear trend were calculated by assigning the median value of each category of heme-iron intake as the score.

† For a natural logarithm of ferritin concentration.
### TABLE 4
Multivariate-adjusted relative risks (RRs) of elevated ferritin (> 200 ng/mL) according to categories of nondietary and dietary factors among 620 postmenopausal women^1^

<table>
<thead>
<tr>
<th>Variable</th>
<th>n^2</th>
<th>RR (95% CI)^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal hormone use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>16/256</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Past</td>
<td>19/113</td>
<td>2.57 (1.14, 5.84)</td>
</tr>
<tr>
<td>Never</td>
<td>26/190</td>
<td>2.96 (1.33, 6.55)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>6/193</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>60–64</td>
<td>27/186</td>
<td>4.89 (1.82, 13.11)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>26/180</td>
<td>5.13 (1.89, 13.91)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25.0</td>
<td>22/349</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>29/160</td>
<td>3.47 (1.72, 7.03)</td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>10/50</td>
<td>4.93 (1.87, 13.03)</td>
</tr>
<tr>
<td>P for trend</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Physical activity (h/wk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.5</td>
<td>41/379</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>3.5–6.9</td>
<td>18/147</td>
<td>0.80 (0.39, 1.65)</td>
</tr>
<tr>
<td>≥ 7.0</td>
<td>2/33</td>
<td>0.68 (0.14, 3.42)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Aspirin use (d/mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9/110</td>
<td>0.43 (0.17, 1.06)</td>
</tr>
<tr>
<td>1–14</td>
<td>45/373</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>15–30</td>
<td>7/76</td>
<td>0.37 (0.14, 0.99)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>57/504</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>4/55</td>
<td>0.53 (0.15, 1.93)</td>
</tr>
<tr>
<td>Heme iron (mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.96</td>
<td>9/117</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>0.96–1.15</td>
<td>10/114</td>
<td>1.04 (0.35, 3.08)</td>
</tr>
<tr>
<td>1.16–1.32</td>
<td>9/101</td>
<td>1.29 (0.44, 3.77)</td>
</tr>
<tr>
<td>1.33–1.55</td>
<td>17/114</td>
<td>1.93 (0.71, 5.24)</td>
</tr>
<tr>
<td>≥ 1.56</td>
<td>16/113</td>
<td>3.93 (1.34, 11.54)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Nonheme iron (mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8.3</td>
<td>13/115</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>8.3–9.1</td>
<td>8/110</td>
<td>0.68 (0.23, 2.00)</td>
</tr>
<tr>
<td>9.1–10.0</td>
<td>9/117</td>
<td>0.66 (0.23, 1.91)</td>
</tr>
<tr>
<td>10.1–11.5</td>
<td>17/111</td>
<td>1.36 (0.52, 3.59)</td>
</tr>
<tr>
<td>≥ 11.6</td>
<td>14/106</td>
<td>0.99 (0.34, 2.86)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Supplemenial iron (mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>34/375</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>0.1–1.5</td>
<td>2/47</td>
<td>0.43 (0.09, 2.01)</td>
</tr>
<tr>
<td>5.5–11.1</td>
<td>11/44</td>
<td>2.26 (0.87, 5.87)</td>
</tr>
<tr>
<td>11.2–21.4</td>
<td>5/50</td>
<td>1.19 (0.35, 4.00)</td>
</tr>
<tr>
<td>≥ 21.5</td>
<td>9/43</td>
<td>2.61 (0.93, 7.32)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11/124</td>
<td>0.80 (0.34, 1.89)</td>
</tr>
<tr>
<td>0.1–1.5</td>
<td>23/215</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>5.1–15.0</td>
<td>13/140</td>
<td>1.20 (0.53, 2.71)</td>
</tr>
<tr>
<td>15.1–30.0</td>
<td>6/57</td>
<td>0.94 (0.32, 2.80)</td>
</tr>
<tr>
<td>≥ 30.1</td>
<td>8/23</td>
<td>4.24 (1.32, 13.61)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

^1^ Tests for linear trend for all variables except postmenopausal hormone use were calculated by assigning the median value of each category as the score; for postmenopausal hormone use, values of 1, 2, and 3 were assigned instead.

^2^ Number of subjects with an elevated ferritin concentration/number of subjects with a normal ferritin concentration (≤ 200 ng/mL).

^3^ Logistic regression model included 6 nondietary factors, heme iron, nonheme iron, supplemental iron, alcohol, phytate, calcium, vitamin C, and coffee; the RRs for phytate, calcium, vitamin C, and coffee did not differ significantly across the categories and thus are not listed in the table.

(P for trend < 0.01). Adjusted geometric mean ferritin concentrations were significantly higher among the women aged ≥ 62 y (median: 86.8 ng/mL; 95% CI: 62.3, 121.0 ng/mL) than among those aged < 62 y (median: 58.5 ng/mL; 95% CI: 41.6, 82.2 ng/mL) (P < 0.01).

### DISCUSSION

In our study of healthy postmenopausal women, plasma ferritin concentrations increased with age until approximately 60 y and then reached a plateau; this result agrees with the results of previous work (19–23, 29, 44). Ferritin concentrations were lower than those (92–156 ng/mL) previously reported in men aged 45–74 y (8, 30), which suggests that even after menopause, women may not reach the levels of body iron stores that are found in men. Both the prevalence of iron depletion (2.7%) and that of elevated ferritin (9.8%) in our study (mean age: 62 y) were somewhat lower than those (4.0% and 12.2%, respectively) reported in the Framingham Heart Study (mean age: 77 y), perhaps because of differences in age (29, 42).

Among the women who had never taken hormones after menopause, ferritin concentrations increased with time since menopause. The PMH users in our study had significantly lower ferritin concentrations than did the nonusers presumably because of hormone-induced bleeding, and this result was consistent with that of a previous small study of 54 women (24). In 1990, 37% of the current PMH users in our study took estrogen plus progestin, which typically induces menstruation. Furthermore, ~40% of women who begin continuous regimens of combined estrogen and progestin will bleed during the first 4–6 mo of treatment (45). This was consistent with our subgroup analysis that ferritin concentrations were significantly lower in the women who were currently taking both estrogen and progestin than in those who were taking estrogen only.

Although age, PMH use, aspirin use (25), BMI (23, 27, 28), and physical activity (26) are individually associated with body iron stores, few studies simultaneously examined these factors in relation to plasma ferritin concentrations, especially among postmenopausal women. Occult blood loss induced by aspirin or gastrointestinal ulcer may reduce body iron stores, which is consistent with our data. A similar finding was observed for aspirin use in an elderly population (25). Physical activity may also increase gastrointestinal blood loss and red blood cell turnover, thereby lowering plasma ferritin concentrations (46).

In our study, the women who had daily physical activity had significantly lower plasma ferritin concentrations than did those who were less active, and this result is consistent with findings from a small intervention study (26, 46). Parity may influence iron stores, especially among premenopausal women, but we found no association between ferritin and parity in postmenopausal women.

Relative to the normal-weight women (BMI < 25) in our study, the overweight women (BMI of 25–29.9) and the obese women (BMI ≥ 30.0) were > 3 times and 5 times as likely, respectively, to have elevated ferritin after adjustment for dietary and nondietary variables. This strong association is consistent with the results of previous studies (23, 27, 28). BMI has been associated with C-reactive protein (47). Plasma ferritin, like C-reactive protein, is an inflammatory marker. Thus, the positive association between BMI and plasma ferritin could...
be at least partly due to inflammation, which is linked to insulin resistance.

In the present study, the average intakes of heme iron (mainly from red meat) and supplemental iron assessed by using 3 validated, semiquantitative FFQs were positively associated with plasma ferritin concentrations. In several, but not all (35), cross-sectional studies, plasma ferritin was positively associated with dietary nonheme-iron intake and ferritin, which was consistent with the results of previous studies (29, 35).

Consumption of $>30$ g alcohol/d was associated with markedly elevated ferritin concentrations, which was consistent with the results of previous studies (48–51), and the positive association between heme iron and ferritin was most apparent among the women who drank $>30$ g alcohol/d. Excess alcohol intake may increase iron absorption by enhancing gastric acid secretion and iron solubilization. Alcohol-induced chronic liver damage and inflammation could also elevate ferritin concentrations (48, 50, 52).

Intakes of phytate and calcium may inhibit nonheme-iron absorption, whereas a high intake of vitamin C may enhance absorption (53). The positive associations between nonheme-iron intake and intakes of phytate, calcium, and vitamin C and between supplemental iron intake and intakes of calcium and vitamin C suggest that these dietary factors probably come from similar sources. On the other hand, inverse associations were observed between heme-iron intake and intakes of phytate ($r = -0.31$), calcium ($r = -0.37$), and vitamin C ($r = -0.14$), which probably reflects different sources of these dietary factors. The null associations between plasma ferritin and intakes of calcium and vitamin C and the weak inverse crude association between plasma ferritin and phytate intake, which was significantly attenuated in the multivariate model that included both nondietary and dietary variables, suggest that these dietary factors have little influence on body iron stores in postmenopausal women.

Imperfect assessment of diet in our analysis may have led to underestimations of the true associations between intakes and ferritin concentrations. However, the average intakes assessed by using an FFQ 3 times over a period of 10 y would account for dietary changes and thus reduce measurement error. Indeed,
our study provides evidence for the validity of iron intakes assessed by our FFQ. Although the relatively homogeneous population in our study (98% were white female US nurses) makes the observed associations less likely to be confounded by race and socioeconomic status, our findings may not be directly applicable to other races and socioeconomic groups. We did not collect information about blood donation and hereditary hemochromatosis, which can significantly influence body iron stores (54). Finally, although our study participants were free of chronic diseases such as cardiovascular disease, cancer, and kidney failure, we did not have information on markers of inflammation and therefore did not control for them in our analyses.

In summary, our prospective data confirmed that intakes of heme iron, supplemental iron, and alcohol are major dietary determinants of plasma ferritin concentrations, whereas age, PMH use, BMI, physical activity, aspirin use, and gastrointestinal ulcer are nondietary determinants. In addition, we found that a high alcohol intake strengthens the association between heme-iron intake and ferritin. These dietary and nondietary variables should be considered when evaluating the association between body iron stores and diseases.

We are indebted to the participants in the NHS for their continuing and outstanding level of cooperation. J-ML, JM, and MJS designed the study, analyzed the data, and wrote the manuscript; SEH, NR, and WCW provided advice, consultation, or interpretation. None of the authors had any conflicts of financial or personal interest in any company or organization sponsoring this study.

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