Serum ferritin and risk of myocardial infarction in the elderly: the Rotterdam Study

Kerstin Klipstein-Grobusch, Johan F Koster, Diederick E Grobbee, Jan Lindemans, Heiner Boeing, Albert Hofman, and Jacqueline CM Witteman

ABSTRACT

Background: Elevated body iron stores have been suggested to be a risk factor for ischemic heart disease.

Objective: We examined whether elevated serum ferritin concentrations, other indicators of iron status, and dietary iron affected the incidence of myocardial infarction (MI) in an elderly population.

Design: A nested, case-control study of 60 patients who had their first MI and 112 age- and sex-matched control subjects embedded in the population-based cohort of the Rotterdam Study.

Results: The age- and sex-adjusted risk of MI for subjects with serum ferritin concentrations ≥200 µg/L was 1.82 (95% CI: 0.90, 3.69; P = 0.096). The odds ratio (OR) was 1.26 (95% CI: 0.98, 1.64; P = 0.078) for the highest tertile of serum ferritin and was only slightly altered in a multivariate model. Risk of MI associated with the highest tertile of ferritin was most evident in current or former smokers (OR: 1.68; 95% CI: 1.17, 2.47; P for trend = 0.008) and in subjects with hypercholesterolemia (OR: 1.43; 95% CI: 0.99, 2.11; P for trend = 0.056) or diabetes (OR: 2.41; 95% CI: 1.12, 7.67; P for trend = 0.027). No association with risk of MI was observed for tertiles of serum iron, serum transferrin, or total dietary iron. For dietary heme iron, risk of MI was significantly increased in a multivariate model in which dietary energy, fat, saturated fat, and cholesterol were adjusted for (OR: 4.01; 95% CI: 1.17, 15.87; P for trend = 0.031).


KEY WORDS Serum ferritin, iron status, myocardial infarction, ischemic heart disease, Rotterdam Study, elderly

INTRODUCTION

Free iron—a catalyst of the production of free radicals—has been implicated in ischemic myocardial damage and lipid peroxidation. Hypotheses as to how free iron may accelerate the progression of atherosclerosis or contribute to myocardial injury after an ischemic event have been generated from basic research. Direct evidence that high stored iron concentrations or high iron intakes increase the incidence of ischemic heart disease in humans, however, is limited. The strongest supporting evidence stems from a cohort study of eastern Finnish men, in whom high concentrations of serum ferritin and dietary iron were positively associated with the incidence of myocardial infarction (1). Furthermore, serum ferritin was observed to be one of the strongest indicators of the presence and progression of carotid artery disease (2, 3). Blood donation, which depletes iron stores in the donors, was associated with reduced risk of myocardial infarction (4) and cardiovascular disease (5). However, most subsequent studies investigating whether iron status or dietary iron intake are associated with increased risk of myocardial infarction or ischemic heart disease have not provided consistent results (6–14). Using a nested, case-control approach, we studied whether serum ferritin and other indicators of iron status were associated with the incidence of myocardial infarction in the population of the Rotterdam Study.

SUBJECTS AND METHODS

Study population and case ascertainment

The Rotterdam Study is a community-based, prospective cohort study of 7983 persons (response rate 78%) aged ≥55 y living in Ommoord, an urban district in Rotterdam, Netherlands. The aim of the study was to investigate the incidence of and the risk factors for chronic and disabling cardiovascular, neurodegenerative, locomotor, and ophthalmic diseases as described elsewhere (15). The study was approved by the Medical Ethics Committee of Erasmus University and written, informed consent was obtained.

1From the Department of Epidemiology and Biostatistics, the Central Clinical Chemical Laboratory, and the Department of Biochemistry, Cardiovascular Research Institute, Erasmus University Rotterdam, Netherlands; the Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Germany; and the Julius Center for Patient Oriented Research, Utrecht University Hospital, Netherlands.

2Supported by the NESTOR program for research in the elderly, Ministry of Public Health and Education and Rotterdam Medical Research Foundation, Netherlands.

3Address reprint requests to JCM Witteman, Department of Epidemiology and Biostatistics, Erasmus University Medical School, PO Box 1738, 3000 DR Rotterdam, Netherlands. E-mail: witteman@epib.fgg.eur.nl.

Received June 23, 1998.

Accepted for publication November 26, 1998.
from all participants. The follow-up for ischemic heart disease started after the baseline survey in 1990. Until April 1996 (mean: 4 y), follow-up information was available for 94% of the cohort. With respect to the vital status of participants, information was obtained at regular intervals from the municipal health service in Rotterdam. Information on fatal and nonfatal endpoints was obtained from the general practitioners (GPs) working in the study district of Ommoord. All possible events reported by the GPs were verified by research physicians from the Rotterdam Study through records of the participating GPs and medical specialists. Causes and circumstances of death were obtained from the GP and from hospital-discharge records in cases of admittance or referral, shortly after death was reported by the municipal health service or the GP. Classification of fatal and nonfatal events was based on the International Classification of Diseases (ICD), 10th revision (16). In the present analysis, cases of first myocardial infarction (ICD-10:I21-I24) were used. All events were classified independently by 2 research physicians. If there was disagreement about case status, a consensus was reached in a special session. Finally, all these events were verified by a cardiovascular disease expert. In case of discrepancies, the judgment by this expert was considered definite.

A nested, case-control approach was used to examine the association between serum ferritin and risk of fatal and nonfatal myocardial infarction. For every subject with a first myocardial infarction during follow-up (n = 202), a control subject without a cardiac endpoint was selected. Age strata (5-y interval) and sex were used as matching variables. Frozen serum samples, stored at −20°C for determination of serum ferritin, were available for 255 subjects (111 case subjects with myocardial infarction and 144 control subjects). Blood samples were not available for all cases and control subjects allocated to this study because multiple blood samples were used in the Rotterdam Study. Subjects with C-reactive protein concentrations > 6 mg/L, with missing C-reactive protein data, or an erythrocyte sedimentation rate > 20 mm/h (n = 25 cases and 15 control subjects), indicating the presence of inflammation or infection that could potentially lead to elevated ferritin concentrations, were excluded from analysis. After exclusion of subjects with a verified history of myocardial infarction, 172 subjects [60 cases (35 nonfatal and 25 fatal) and 112 control subjects] remained for analysis of serum ferritin and risk of myocardial infarction.

Baseline measurements

Information on current health status, medical history, drug use, education, income, and smoking behavior was obtained with use of a computerized questionnaire during a home interview. Height and weight were measured and body mass index [wt (in kg)/ht² (in m)] was calculated as a measure of obesity. Sitting blood pressure was measured on the right upper arm with a random-zero sphygmomanometer. The average of 2 measurements was used in the analysis. A venipuncture was performed and hematologic indexes were obtained by standard clinical laboratory procedures. Serum total and HDL-cholesterol concentrations were determined at baseline by using an automated enzymatic procedure. Serum samples were collected from the case and control subjects simultaneously at baseline and frozen at −20°C until used to determine concentrations of ferritin, iron, transferrin, ceruloplasmin, and C-reactive protein. Sera from case and control subjects were analyzed in the same run. Serum ferritin concentrations were determined by enzyme-linked immunosorbent assay (Boehringer Mannheim, Mannheim, Germany). The CVs were 2.8%, 4.0%, and 10.4% for ferritin concentrations of 389, 139, and 27 μg/L, respectively. Serum transferrin and C-reactive protein were measured by kinetic nephelometry with a Beckman-Array system (Munich, Germany) and serum iron was determined by photometry with an EPOS Chemistry Analyzer (Boehringer Mannheim). CVs were 4%, 2%, 4.6%, and 3.8% for transferrin, iron, ceruloplasmin, and C-reactive protein, respectively.

Dietary assessment

The semiquantitative food-frequency questionnaire (SFFQ) completed during baseline aimed at assessing habitual food intake during the past year and included 170 food items in 13 food groups and questions about dietary habits, supplementation, and prescribed diets. SFFQ data were converted to nutrient intake by using the computerized Dutch food-composition table (17). Heme iron was estimated to account for 40% of the total iron intake from meat, poultry, and fish (18). Data for β-carotene and tocopherol were updated by using an additional database from the Netherlands Institute of Public Health and Environmental Protection (YCJ Volleburgt, EJM Feskens, unpublished observations, 1993). Nutrient intakes from nutritional supplements were not considered because brand labels, doses, and durations were not recorded with sufficient accuracy. The validity of the SFFQ assessed in a subsample of 80 men and women aged 55–75 y. Nutrient intakes estimated from the SFFQ were compared with estimated nutrient intakes from 15 d of food records collected over 1 y (19). The ability of the SFFQ to adequately rank subjects according to their dietary intake was shown by Pearson’s correlation coefficients (0.5–0.9 for crude data) and a high degree of classification into the same or adjacent quintile (75.8% for crude data). The Pearson’s correlation coefficient between food records and the SFFQ for iron intake was 0.67.

Data analysis

Associations between serum ferritin and risk factors for ischemic heart disease were investigated by using Pearson’s correlation coefficients; those for categorical variables were investigated by using the chi-square test. Analysis of variance was used to test for differences in baseline characteristics between cases and control subjects. All analyses were adjusted for age and sex. Serum ferritin was censored as being < or ≥200 μg/L and the risk of myocardial infarction was investigated by multivariate logistic regression. Estimation of CIs was based on the likelihood ratio. To evaluate whether there was a graded association between serum ferritin concentrations and risk of myocardial infarction, analyses were performed for tertiles of serum ferritin. Analyses were initially adjusted for age and sex and subsequently for body mass index, pack-years of smoking (ie, the number of packs of cigarettes smoked per day times the number of years smoked), equivalent household income (5 categories), and alcohol intake (5 categories). To evaluate whether smoking status, hypertension, hypercholesterolemia, or diabetes modified the association between serum ferritin and myocardial infarction, stratified analyses were conducted. In addition, the association between risk of myocardial infarction and other measures of iron status (serum iron and transferrin) and dietary iron intake (total iron and heme iron) was evaluated. For dietary intakes of total and heme iron, the multivariate model was fur-
Serum ferritin concentrations in the case-control population ranged from 10 to 1221 μg/L and averaged 47, 119, and 309 μg/L per tertile. Median concentrations of serum ferritin were 129 μg/L for men and 101 μg/L for women. Serum ferritin was significantly inversely associated with serum transferrin ($r = -0.28$, $P = 0.002$) and was directly associated with serum iron and alcohol intake. A weak association ($r = 0.14$, $P = 0.17$) was noted for serum ferritin and heme iron intake. The distribution of serum ferritin for cases and control subjects indicated a shift toward higher serum ferritin concentrations in patients with myocardial infarction (Figure 1). Correspondingly, more patients with myocardial infarction (33.3%) than control subjects (21.4%) had concentrations above the cutoff of 200 μg ferritin/L. Cases and control subjects differed significantly in heme iron intake (Table 1).

When adjusted for age and sex, subjects with a serum ferritin concentration ≥200 μg/L tended to have a risk of 1.82 (95% CI: 0.90, 3.69; $P = 0.096$) for myocardial infarction compared with those with serum ferritin concentrations <200 μg/L. Further adjustment for body mass index, pack-years of smoking, income, and alcohol intake only marginally altered the risk of myocardial infarction (OR: 1.81; 95% CI: 0.88, 3.74; $P = 0.108$). To evaluate whether there was a graded association between serum ferritin concentrations and risk of myocardial infarction, serum ferritin tertiles were examined. Age- and sex-adjusted ORs for the highest compared with the lowest tertile were 1.26 (95% CI: 0.98, 1.64; $P$ for trend = 0.070) and 1.28 (95% CI: 0.98, 1.67; $P$ for trend = 0.066), respectively, in the multivariate adjusted model (Table 2). Inclusion of subjects with an elevated C-reactive protein or erythrocyte sedimentation rate gave smaller estimates for subjects with ferritin concentrations ≥200 μg/L (age- and sex-adjusted OR: 1.46; 95% CI: 0.75, 2.80), indicating misclassification of iron status when subjects with signs of inflammation were not excluded from the analyses. No association with risk of myocardial infarction was observed for tertiles of serum iron, serum transferrin, or total dietary iron (Table 2).

### RESULTS

Serum ferritin concentrations in the case-control population ranged from 10 to 1221 μg/L and averaged 47, 119, and 309 μg/L per tertile. Median concentrations of serum ferritin were 129 μg/L for men and 101 μg/L for women. Serum ferritin was significantly inversely associated with serum transferrin ($r = -0.28$, $P = 0.002$) and was directly associated with serum iron and alcohol intake. A weak association ($r = 0.14$, $P = 0.17$) was noted for serum ferritin and heme iron intake. The distribution of serum ferritin for cases and control subjects indicated a shift toward higher serum ferritin concentrations in patients with myocardial infarction (Figure 1). Correspondingly, more patients with myocardial infarction (33.3%) than control subjects (21.4%) had concentrations above the cutoff of 200 μg ferritin/L. Cases and control subjects differed significantly in heme iron intake (Table 1).

When adjusted for age and sex, subjects with a serum ferritin concentration ≥200 μg/L tended to have a risk of 1.82 (95% CI: 0.90, 3.69; $P = 0.096$) for myocardial infarction compared with those with serum ferritin concentrations <200 μg/L. Further adjustment for body mass index, pack-years of smoking, income, and alcohol intake only marginally altered the risk of myocardial infarction (OR: 1.81; 95% CI: 0.88, 3.74; $P = 0.108$). To evaluate whether there was a graded association between serum ferritin concentrations and risk of myocardial infarction, serum ferritin tertiles were examined. Age- and sex-adjusted ORs for the highest compared with the lowest tertile were 1.26 (95% CI: 0.98, 1.64; $P$ for trend = 0.070) and 1.28 (95% CI: 0.98, 1.67; $P$ for trend = 0.066), respectively, in the multivariate adjusted model (Table 2). Inclusion of subjects with an elevated C-reactive protein or erythrocyte sedimentation rate gave smaller estimates for subjects with ferritin concentrations ≥200 μg/L (age- and sex-adjusted OR: 1.46; 95% CI: 0.75, 2.80), indicating misclassification of iron status when subjects with signs of inflammation were not excluded from the analyses. No association with risk of myocardial infarction was observed for tertiles of serum iron, serum transferrin, or total dietary iron (Table 2). For dietary heme iron, a significantly increased risk of myocardial infarction was observed for the highest compared with the lowest tertile of heme iron intake in an age- and sex-adjusted model (OR: 2.79; 95% CI: 1.01, 8.13; $P$ for trend = 0.047). Multivariate adjust-

### TABLE 1

Baseline characteristics of case subjects with myocardial infarction and control subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case subjects</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 60)</td>
<td>(n = 112)</td>
<td></td>
</tr>
<tr>
<td>Men (%)</td>
<td>44.6</td>
<td>45.0</td>
</tr>
<tr>
<td>Age (y)</td>
<td>75.9 ± 8.5$^d$</td>
<td>76.4 ± 7.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.2 ± 2.8</td>
<td>26.0 ± 3.5</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.93 ± 0.09</td>
<td>0.92 ± 0.08</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75 ± 12</td>
<td>74 ± 12</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>148 ± 21</td>
<td>143 ± 23</td>
</tr>
<tr>
<td>Ferritin (μg/L)</td>
<td>183 ± 168</td>
<td>144 ± 142</td>
</tr>
<tr>
<td>Transferrin (g/L)</td>
<td>2.52 ± 0.45</td>
<td>2.59 ± 0.42</td>
</tr>
<tr>
<td>Serum iron (μmol/L)</td>
<td>16.4 ± 5.0</td>
<td>16.9 ± 5.2</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>6.80 ± 1.22</td>
<td>6.53 ± 1.33</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/L)</td>
<td>1.26 ± 0.28</td>
<td>1.27 ± 0.32</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>10.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Hypertension (%)$^d$</td>
<td>36.7</td>
<td>32.1</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)$^d$</td>
<td>55.0</td>
<td>44.6</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20.3</td>
<td>20.6</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>18.3</td>
<td>16.1</td>
</tr>
<tr>
<td>High alcohol intake$^d$</td>
<td>3.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Dietary iron (mg/d)$^d$</td>
<td>12.1 ± 2.7</td>
<td>12.5 ± 3.5</td>
</tr>
<tr>
<td>Dietary heme iron (mg/d)$^d$</td>
<td>1.14 ± 0.46</td>
<td>0.95 ± 0.36</td>
</tr>
</tbody>
</table>

$^a$ SD.

$^d$ Defined as a systolic blood pressure > 160 mm Hg, a diastolic blood pressure > 95 mm Hg, or use of antihypertensive medication.

$^d$ Serum cholesterol > 6.5 mmol/L.

$^d$ Alcohol intake > 20 g/d for women and > 30 g/d for men.

$^d$ Dietary data available for 37 case subjects with myocardial infarction and 66 control subjects.

$^d$ Significantly different from control subjects, $P = 0.016$. 

![FIGURE 1. Serum ferritin concentrations in cases and control subjects with myocardial infarction.](image-url)
ment, including dietary variables that could potentially confound the association between heme iron and myocardial infarction resulted in an OR of 4.01 (95% CI: 1.17, 15.97; P for trend = 0.031). Further adjustment by dietary antioxidants (β-carotene, vitamin C, and vitamin E) did not materially alter the risk estimate.

Stratification by smoking status, hypercholesterolemia, and diabetes showed modification of the association between serum ferritin and myocardial infarction (Table 3). Risk of myocardial infarction was more pronounced in hypercholesterolemia (OR: 1.43; 95% CI: 0.99, 2.11; P for trend = 0.056 for the highest compared with the lowest tertile of serum ferritin) and diabetes (OR: 2.50; 95% CI: 1.15, 8.05; P for trend = 0.020). Both current and former smoking considerably increased the risk of myocardial infarction in association with elevated serum ferritin concentrations.

**DISCUSSION**

In this study of an elderly Dutch population, elevated serum ferritin concentrations were associated with increased risk of myocardial infarction. It was most pronounced in current and former smokers and in those with diabetes. Serum iron, transferrin, and dietary total iron were not associated with myocardial infarction. High heme iron intake, however, was significantly associated with increased myocardial infarction risk.

Studies investigating whether iron status can be considered a cardiovascular risk factor presented conflicting results, as reviewed recently (20, 21). This was not unexpected because none of the indicators of iron status evaluated—hemoglobin, hematocrit, serum iron, transferrin, transferrin saturation, total iron binding capacity, or ferritin—accurately reflects body iron (22). Because serum ferritin concentrations are directly proportional to

---

**TABLE 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tertiles</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (Lowest)</td>
<td>2</td>
<td>3 (Highest)</td>
<td></td>
<td>P for trend</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case subjects with MI (n)</td>
<td>17</td>
<td>17</td>
<td>26</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Control subjects (n)</td>
<td>41</td>
<td>40</td>
<td>31</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Concentration (µg/L)</td>
<td>&lt;77</td>
<td>77–171</td>
<td>&gt;171</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.00</td>
<td>1.01 (0.67, 1.51)</td>
<td>1.26 (0.98, 1.64)</td>
<td></td>
<td>0.070</td>
</tr>
<tr>
<td>Multivariate adjusted²</td>
<td>1.00</td>
<td>1.08 (0.71, 1.64)</td>
<td>1.28 (0.98, 1.67)</td>
<td></td>
<td>0.066</td>
</tr>
<tr>
<td>Serum iron</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case subjects with MI (n)</td>
<td>23</td>
<td>16</td>
<td>21</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Control subjects (n)</td>
<td>35</td>
<td>42</td>
<td>35</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Concentration (µmol/L)</td>
<td>&lt;14.1</td>
<td>14.1–18.9</td>
<td>&gt;18.9</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.00</td>
<td>0.75 (0.50, 1.11)</td>
<td>0.95 (0.72, 1.24)</td>
<td></td>
<td>0.699</td>
</tr>
<tr>
<td>Multivariate adjusted²</td>
<td>1.00</td>
<td>0.77 (0.51, 1.15)</td>
<td>0.97 (0.73, 1.28)</td>
<td></td>
<td>0.788</td>
</tr>
<tr>
<td>Serum transferrin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case subjects with MI (n)</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Control subjects (n)</td>
<td>49</td>
<td>31</td>
<td>32</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Concentration (g/L)</td>
<td>&lt;2.5</td>
<td>2.5–2.7</td>
<td>&gt;2.7</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.00</td>
<td>1.12 (0.77, 1.63)</td>
<td>0.97 (0.75, 1.26)</td>
<td></td>
<td>0.624</td>
</tr>
<tr>
<td>Multivariate adjusted²</td>
<td>1.00</td>
<td>1.15 (0.78, 1.68)</td>
<td>0.96 (0.73, 1.25)</td>
<td></td>
<td>0.642</td>
</tr>
<tr>
<td>Dietary iron³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case subjects with MI (n)</td>
<td>12</td>
<td>14</td>
<td>11</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Control subjects (n)</td>
<td>23</td>
<td>20</td>
<td>23</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Intake (mg/d)</td>
<td>&lt;11.1</td>
<td>11.1–13.1</td>
<td>&gt;13.1</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.00</td>
<td>1.73 (0.61, 5.09)</td>
<td>1.33 (0.43, 4.26)</td>
<td></td>
<td>0.641</td>
</tr>
<tr>
<td>Multivariate adjusted²</td>
<td>1.00</td>
<td>1.49 (0.50, 4.62)</td>
<td>1.35 (0.41, 4.62)</td>
<td></td>
<td>0.606</td>
</tr>
<tr>
<td>Multivariate adjusted⁴</td>
<td>1.00</td>
<td>2.12 (0.57, 8.45)</td>
<td>3.02 (0.50, 20.52)</td>
<td></td>
<td>0.274</td>
</tr>
<tr>
<td>Dietary heme iron³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case subjects with MI (n)</td>
<td>9</td>
<td>12</td>
<td>16</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Control subjects (n)</td>
<td>26</td>
<td>22</td>
<td>18</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Intake (mg/d)</td>
<td>&lt;0.86</td>
<td>0.86–1.10</td>
<td>&gt;1.10</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.00</td>
<td>1.68 (0.59, 4.96)</td>
<td>2.79 (1.01, 8.13)</td>
<td></td>
<td>0.047</td>
</tr>
<tr>
<td>Multivariate adjusted²</td>
<td>1.00</td>
<td>1.66 (0.56, 5.08)</td>
<td>2.75 (0.92, 8.64)</td>
<td></td>
<td>0.069</td>
</tr>
<tr>
<td>Multivariate adjusted⁴</td>
<td>1.00</td>
<td>1.85 (0.61, 5.91)</td>
<td>4.01 (1.17, 15.87)</td>
<td></td>
<td>0.031</td>
</tr>
</tbody>
</table>

¹Reference category.

²Adjusted for age, sex, body mass index, pack-years of smoking, equivalent household income (5 categories), and alcohol intake (5 categories).

³Dietary data available for 37 case subjects with myocardial infarction and 66 control subjects.

⁴Adjusted for age, sex, body mass index, pack-years of smoking, equivalent household income (5 categories), alcohol intake (5 categories), and categories of dietary energy, total fat, saturated fat, and cholesterol.
in intracellular ferritin concentrations, it is considered to be the best
clinical measure of body iron stores (22) and the most feasible to
use in epidemiologic studies (23). However, so far only a few stud-
ies evaluated serum ferritin concentrations to examine whether
body iron stores are associated with cardiovascular disease. Serum
ferritin concentrations are known to increase in response to
inflammation. To circumvent a confounding effect of inflamma-
tion on serum ferritin concentrations, we excluded from analysis
subjects with C-reactive protein concentrations > 6 mg/L or, if data
for C-reactive protein were missing, erythrocyte sedimentation
rates > 20 mm/h.

Previous evidence of an association between increased risk of
myocardial infarction and elevated serum ferritin concentrations
came from the Kuopio Ischaemic Heart Disease Risk Factor
Study, which followed 1931 men for an average of 3 y (1). Men
with serum ferritin concentrations ≥200 µg/L had a 2.2-fold
(95% CI: 1.2, 4.0; P < 0.01) higher risk of myocardial infarction
than did men with lower serum ferritin concentrations after
adjustment for other risk factors. This association was stronger in
men with serum LDL concentrations ≥5.0 mmol/L (≥193 mg/dL).
Extended follow-up after a mean follow-up period of 5 y con-
firmed these previous findings (24). In 847 Austrian men and
women aged 40–79 y, Kiechl et al (2) examined the relation
between sonographically assessed carotid atherosclerosis and
body iron stores. Ferritin was observed to be one of the strongest
indicators of the presence of carotid artery disease (OR: 1.54 per
100 µg/L serum ferritin; P < 0.001) in men and women aged
40–59 y. Again, a synergistic effect between hypercholesterolemia
and serum ferritin concentrations was observed. Five-year follow-
up showed that serum ferritin was also a strong risk predictor of
overall progression of atherosclerosis and of incident cardio-
vascular disease and death. Risk of atherosclerosis and cardiovas-
ular disease was modified by serum LDL cholesterol. Changes in
iron stores during the follow-up period modified the risk of ath-
erosclerosis: a reduction was beneficial and further iron accumu-
lation was not (3). Further studies relating serum ferritin concen-
trations to carotid intima media thickness (25), presence of ather-
osclerosis (26), myocardial infarction (6, 7), or ischemic heart
disease (8, 27) did not support an association between body iron
stores and risk of cardiovascular disease. However, studies of the
effect of blood donation or phlebotomy, resulting in a consid-
erable decrease in serum ferritin concentrations, on cardiovascular
disease risk support the finding of a decreased risk. Meyers et al
(5), who compared cardiovascular event rates between whole-
blood donors and nondonors, showed that blood donation was
associated with a reduced risk of cardiovascular events (crude
OR: 0.50; 95% CI: 0.38, 0.66) after 5–8 y of follow-up. The ben-
efit of donation was confined to nonsmoking males (adjusted OR:
0.67; 95% CI: 0.45, 0.99), limited to blood donation in the most
recent 3 y, and was greater in nonsmoking men with serum LDL-
cholesterol concentrations > 4.14 mmol/L (160 mg/dL). Among
2682 Finnish men, blood donation was prospectively associated
with a reduction in risk of myocardial infarction of 86% (4).
However, likely self-selection by healthier persons to be blood
donors should be considered. Examination of the effect of phle-
botomy on the oxidation resistance of serum lipoproteins in 14
men with elevated serum ferritin concentrations showed signifi-
cantly decreased maximal oxidation and increased lag time to
start of oxidation (28).

We observed risk of myocardial infarction to be confined to
current and former smokers and to be more pronounced in sub-
jects with diabetes or serum cholesterol concentrations > 6.5 mmol/L
(Table 3). The effects of iron stores on atherogenesis were more
pronounced in smokers (3) and synergistic effects between serum
ferritin and serum cholesterol or LDL cholesterol have been
reported as discussed above (1–3). These findings indicate that
high serum ferritin may increase the risk of ischemic heart dis-
ease in the presence of other risk factors that increase the forma-
tion of free radicals, thus accelerating atherogenesis via stimula-
tion of LDL oxidation (29, 30). Basic research has provided
strong evidence that LDL oxidation plays an important role in
the pathogenesis of atherosclerosis and cardiovascular disease. Oxid-
dized LDL causes lipid accumulation in macrophages and foam cell formation (31, 32) and has been shown to be cytotoxic to many cell types and chemoattract for monocyte macrophages. Lipid peroxidation of LDL can be enhanced by metal-catalyzed reactions, resulting in highly reactive hydroxyl radicals. Superoxide anions produced by oxidative stress and reducing agents have been found to be capable of mobilizing iron from ferritin (29, 30).

In the present study we observed dietary heme iron to be associated with increased risk of myocardial infarction. Increased risk of nonfatal myocardial infarction or fatal ischemic heart disease with heme iron intake was also reported in the Health Professionals’ Study (33). Observations among Seventh-day Adventists in whom meat consumption ≥6 times/wk was associated with increased risk of fatal ischemic heart disease (34) are furthermore supportive of a possible role of heme iron in ischemic heart disease. Results suggestive of a role of heme iron in lipid peroxidation also came from a nested, case-control study showing a positive association between blood hemoglobin concentration and the titer of autoantibodies against malondialdehyde-modified LDL (35) and from the ability of hemin to efficiently promote LDL oxidation in vitro (36).

In conclusion, we observed elevated serum ferritin concentrations to be associated with increased risk of myocardial infarction in our elderly population. An increased risk was most evident in current or former smokers and in subjects with diabetes, suggesting that ferritin may adversely affect ischemic heart disease risk in the presence of other risk factors. It may be possible that these factors in interaction with elevated body iron stores may accelerate atherogenesis by stimulating the oxidation of LDLS.

REFERENCES