

Serum ferritin and risk of myocardial infarction in the elderly: the Rotterdam Study¹⁻³

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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 $\mu\text{g/L}$ 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).

Conclusion: In the presence of other risk factors, serum ferritin may adversely affect ischemic heart disease risk in the elderly. *Am J Clin Nutr* 1999;69:1231-6.

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

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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 $>6\text{ mg/L}$, with missing C-reactive protein data, or an erythrocyte sedimentation rate $>20\text{ mm/h}$ ($n = 25$ 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 $\mu\text{g/L}$, 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 Volleburt, 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 categorized as being $<$ or $\geq 200\text{ }\mu\text{g/L}$ 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-



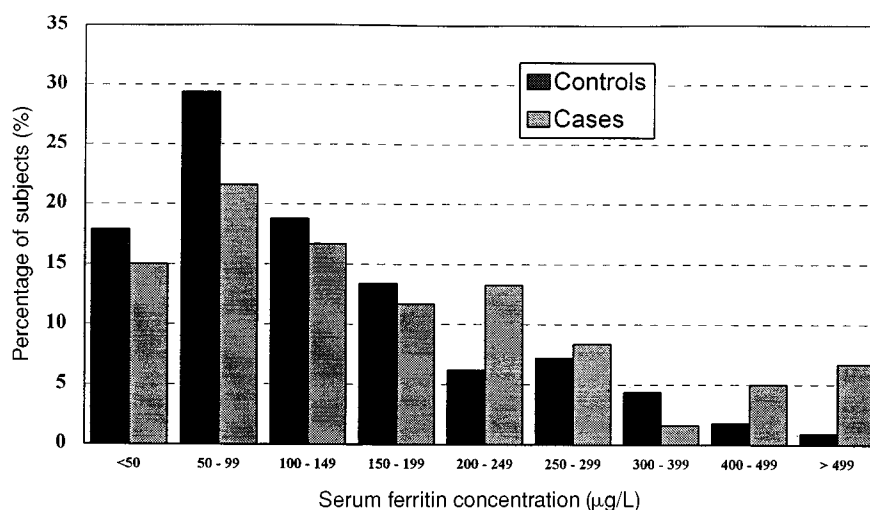


FIGURE 1. Serum ferritin concentrations in cases and control subjects with myocardial infarction.

ther adjusted for categories of energy, fat, saturated fat, and cholesterol. Associations are expressed as odds ratios (ORs) with 95% CIs. Two-sided *P* values were calculated. Statistical analyses were performed by using SAS statistical software (version 6.11; SAS Institute, Cary, NC).

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 mg/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 misclas-

sification 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

Variables	Case subjects (n = 60)	Control subjects (n = 112)
Men (%)	44.6	45.0
Age (y)	75.9 ± 8.5 ¹	76.4 ± 8.9
Body mass index (kg/m ²)	26.2 ± 2.8	26.0 ± 3.5
Waist-to-hip ratio	0.93 ± 0.09	0.92 ± 0.08
Diastolic blood pressure (mm Hg)	75 ± 12	74 ± 12
Systolic blood pressure (mm Hg)	148 ± 21	143 ± 23
Ferritin (µg/L)	183 ± 168	144 ± 142
Transferrin (g/L)	2.52 ± 0.45	2.59 ± 0.42
Serum iron (µmol/L)	16.4 ± 5.0	16.9 ± 5.2
Serum cholesterol (mmol/L)	6.80 ± 1.22	6.53 ± 1.33
Serum HDL cholesterol (mmol/L)	1.26 ± 0.28	1.27 ± 0.32
Obesity (%)	10.0	13.4
Hypertension (%) ²	36.7	32.1
Hypercholesterolemia (%) ³	55.0	44.6
Diabetes (%)	20.3	20.6
Current smokers (%)	18.3	16.1
High alcohol intake ⁴	3.3	5.4
Dietary iron (mg/d) ⁵	12.1 ± 2.7	12.5 ± 3.5
Dietary heme iron (mg/d) ⁵	1.14 ± 0.46 ⁶	0.95 ± 0.36

¹ $\bar{x} \pm SD$.

²Defined as a systolic blood pressure > 160 mm Hg, a diastolic blood pressure > 95 mm HG, or use of antihypertensive medication.

³Serum cholesterol > 6.5 mmol/L.

⁴Alcohol intake > 20 g/d for women and > 30 g/d for men.

⁵Dietary data available for 37 case subjects with myocardial infarction and 66 control subjects.

⁶Significantly different from control subjects, $P = 0.016$.

TABLE 2

Odds ratios and 95% CIs for myocardial infarction (MI) according to tertiles of indicators of iron status

Variable	Tertiles			P for trend
	1 (Lowest) ¹	2	3 (Highest)	
Serum ferritin				
Case subjects with MI (<i>n</i>)	17	17	26	—
Control subjects (<i>n</i>)	41	40	31	—
Concentration (μg/L)	<77	77–171	>171	—
Odds ratio (95% CI)				
Adjusted for age and sex	1.00	1.01 (0.67, 1.51)	1.26 (0.98, 1.64)	0.070
Multivariate adjusted ²	1.00	1.08 (0.71, 1.64)	1.28 (0.98, 1.67)	0.066
Serum iron				
Case subjects with MI (<i>n</i>)	23	16	21	—
Control subjects (<i>n</i>)	35	42	35	—
Concentration (μmol/L)	<14.1	14.1–18.9	>18.9	—
Odds ratio (95% CI)				
Adjusted for age and sex	1.00	0.75 (0.50, 1.11)	0.95 (0.72, 1.24)	0.699
Multivariate adjusted ²	1.00	0.77 (0.51, 1.15)	0.97 (0.73, 1.28)	0.788
Serum transferrin				
Case subjects with MI (<i>n</i>)	25	20	15	—
Control subjects (<i>n</i>)	49	31	32	—
Concentration (g/L)	<2.5	2.5–2.7	>2.7	—
Odds ratio (95% CI)				
Adjusted for age and sex	1.00	1.12 (0.77, 1.63)	0.97 (0.75, 1.26)	0.909
Multivariate adjusted ²	1.00	1.15 (0.78, 1.68)	0.96 (0.73, 1.25)	0.624
Dietary iron³				
Case subjects with MI (<i>n</i>)	12	14	11	—
Control subjects (<i>n</i>)	23	20	23	—
Intake (mg/d)	<11.1	11.1–13.1	>13.1	—
Odds ratio (95% CI)				
Adjusted for age and sex	1.00	1.73 (0.61, 5.09)	1.33 (0.43, 4.26)	0.641
Multivariate adjusted ²	1.00	1.49 (0.50, 4.62)	1.35 (0.41, 4.62)	0.606
Multivariate adjusted ⁴	1.00	2.12 (0.57, 8.45)	3.02 (0.50, 20.52)	0.274
Dietary heme iron³				
Case subjects with MI (<i>n</i>)	9	12	16	—
Control subjects (<i>n</i>)	26	22	18	—
Intake (mg/d)	<0.86	0.86–1.10	>1.10	—
Odds ratio (95% CI)				
Adjusted for age and sex	1.00	1.68 (0.59, 4.96)	2.79 (1.01, 8.13)	0.047
Multivariate adjusted ²	1.00	1.66 (0.56, 5.08)	2.75 (0.92, 8.64)	0.069
Multivariate adjusted ⁴	1.00	1.85 (0.61, 5.91)	4.01 (1.17, 15.87)	0.031

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.

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, 15.87; *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 3

Odds ratio and 95% CIs for myocardial infarction (MI) for tertiles of serum ferritin¹

Variable	Tertiles			P for trend
	1 (Lowest) ²	2	3 (Highest)	
Serum ferritin ($\mu\text{g/L}$)	<77	77–171	>171	
Smoking status ³				
Current ($n = 11$ MI, 18 C)	1.00	0.39 (0.07, 1.66)	2.62 (1.12, 9.10)	0.047
Former ($n = 29$ MI, 46 C)	1.00	1.63 (0.88, 3.13)	1.56 (1.01, 2.48)	0.046
Nonsmoker ($n = 20$ MI, 48 C)	1.00	0.80 (0.36, 1.70)	1.00 (0.65, 1.54)	0.975
Hypertension ⁴				
Present ($n = 18$ MI, 44 C)	1.00	0.96 (0.55, 1.66)	1.23 (0.88, 1.74)	0.219
Not present ($n = 42$ MI, 68 C)	1.00	1.02 (0.46, 2.31)	1.26 (0.76, 2.12)	0.353
Hypercholesterolemia ⁵				
Present ($n = 33$ MI, 50 C)	1.00	1.17 (0.65, 2.10)	1.43 (0.99, 2.11)	0.056
Not present ($n = 27$ MI, 62 C)	1.00	1.03 (0.56, 1.90)	1.17 (0.80, 1.74)	0.410
Diabetes				
Present ($n = 12$ MI, 22 C)	1.00	3.35 (0.91, 19.92)	2.41 (1.12, 7.67)	0.027
Not present ($n = 47$ MI, 85 C)	1.00	0.95 (0.60, 1.49)	1.11 (0.81, 1.50)	0.541

¹Adjusted for age, sex, body mass index, pack-years of smoking, equivalent household income (5 categories), and alcohol intake (5 categories). C, control subjects.

²Reference category.

³Adjusted for age, sex, body mass index, equivalent household income (5 categories), and alcohol intake (5 categories).

⁴Defined as a systolic blood pressure >140 mm Hg, or a diastolic blood pressure >90 mm Hg, or use of antihypertensive medication.

⁵Serum cholesterol >6.5 mmol/L.

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 studies 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 inflammation 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 $\geq 200 \mu\text{g/L}$ 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 $\geq 5.0 \text{ mmol/L}$ ($\geq 193 \text{ mg/dL}$). Extended follow-up after a mean follow-up period of 5 y confirmed 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 $\mu\text{g/L}$ 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 cardiovascular disease and death. Risk of atherosclerosis and cardiovascular disease was modified by serum LDL cholesterol. Changes in iron stores during the follow-up period modified the risk of atherosclerosis: a reduction was beneficial and further iron accumulation was not (3). Further studies relating serum ferritin concen-

trations to carotid intima media thickness (25), presence of atherosclerosis (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 considerable 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 benefit 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 phlebotomy on the oxidation resistance of serum lipoproteins in 14 men with elevated serum ferritin concentrations showed significantly 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 subjects 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 disease in the presence of other risk factors that increase the formation of free radicals, thus accelerating atherogenesis via stimulation 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. Oxi-

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 chemotactic 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 heme 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. 

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