Iron stores and cardiovascular disease risk factors in women of reproductive age in the United States[1–4]

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ABSTRACT

Background: The increasing proportion of iron-replete individuals in industrialized countries and the possible increased risk of cardiovascular disease (CVD) among men with high iron stores raise concerns regarding improved iron status in women of reproductive age.

Objective: This study examined the association between iron stores and a set of established CVD risk factors among nonpregnant women aged 20–49 y.

Design: Data from the third National Health and Nutrition Examination Survey (1988–1994) were used to examine the relation between race-ethnicity–specific quartiles of serum ferritin (SF) and a set of CVD risk factors [body mass index (BMI), total cholesterol, triacylglycerol, HDL cholesterol, plasma glucose, and blood pressure (BP)]. Women with a history of CVD or liver disease were excluded. We controlled for age, session of measurement, prevalent infection, recent blood donation, and treatment with iron for anemia.

Results: Mean SF values were 53.22 ± 2.08 μg/L (n = 1178), 58.93 ± 2.39 μg/L (n = 1093), and 43.33 ± 1.39 μg/L (n = 1075) among non-Hispanic white, non-Hispanic black, and Mexican American women, respectively. Iron stores were positively associated with CVD risk factors only among non-Hispanic black and Mexican American women after adjustment for confounding variables. The strongest associations were seen among Mexican American women: compared with the middle 2 quartiles, the lowest and highest quartiles of SF had lower and higher values, respectively, for BMI, total cholesterol, triacylglycerol, glucose, and diastolic BP.

Conclusion: These findings suggest that CVD risk factors, especially those related to glucose and lipid metabolism, are positively associated with iron status in women. *Am J Clin Nutr* 2002;76:1256–60.

KEY WORDS Cardiovascular disease, heart disease, women, premenopausal women, iron stores, iron status, anemia, ferritin, blood lipids, lipid metabolism, glucose metabolism, NHANES III

INTRODUCTION

In the scientific and public health communities, interest in iron overload has increased. Meanwhile, the proportion of iron-replete individuals in industrialized countries has also risen. The potential toxicity of iron derives from its ability to serve as a catalyst in oxidation-reduction reactions, and its toxicity is enhanced by the limited capacity of the human body to excrete iron (1). Animal and tissue culture studies showed that greater than physiologic amounts of iron can promote carcinogenesis or faster rates of tumor growth; studies also found evidence of iron-induced peroxidation (2, 3).

Hemochromatosis, an inherited genetic disorder in which iron absorption is impaired leading to excessive iron stores, represents the extreme case of iron overload (4). Population estimates of the hemochromatosis gene mutation were ≈0.4% for C282Y homozygosity and ≈9% for C282Y heterozygosity among subjects who were primarily of Caucasian descent (5, 6). The overall prevalence estimates in the United States are 0.26% and 5.4% for C282 homozygosity and heterozygosity, respectively, on the basis of data from phase 2 of the third National Health and Nutrition Examination Survey (NHANES III); rates were lower than expected among Mexican Americans (7).

A few epidemiologic studies in humans have examined the association between iron stores and increased risk of cardiovascular disease (CVD) (8–13). In Finnish men, for example, serum ferritin (SF) concentrations > 200 μg/L were associated with a 2.2-fold increase in the incidence of acute myocardial infarction compared with SF concentrations < 200 μg/L during a 3-y follow-up (8). However, other studies failed to confirm these findings (9–12). One plausible explanation is that elevated SF values do not reflect increased iron stores, but are rather the result of infections and other inflammatory processes associated with coronary heart disease; SF is an acute phase reactant protein (14–17). However, more recently, Tuomainen et al (13) used the ratio of serum transferrin receptors to SF and found a 2–3-fold increased risk of acute myocardial infarction among Finnish men across tertiles, even after adjusting for inflammation and alcohol intake. Another possibility is that iron stores may interact with established CVD risk factors, such as LDL cholesterol and total cholesterol concentrations, in increasing the risk of CVD (18). Thus, current epidemiologic evidence of an increased risk for chronic disease as a result of high iron stores is far from conclusive.

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In addition, most studies have been conducted in men, who typically have higher iron stores than women. For physiological reasons, women of reproductive age are at greater risk of iron deficiency and are therefore more likely to be adversely affected by policies that would reduce the dietary availability of iron, such as withdrawal of fortification of foods with iron or multivitamin and mineral supplements. On the other hand, if high iron stores are causally associated with increased CVD risk, a reduction in iron intakes would be warranted. The objective of this study was therefore to use nationally representative data from NHANES III to examine whether iron stores are positively associated with CVD risk factors in different race-ethnicity groups of women of reproductive age.

SUBJECTS AND METHODS

Data collection

NHANES III was conducted by the National Center for Health Statistics; details of the procedures used for data collection and laboratory analysis were published previously (19). Ethical approval was obtained and written consent was received from all participants. Briefly, the data were collected via household interviews and physical examinations in mobile examination centers. Participants were asked about their history of specific conditions such as stroke and CVD and treatment for diabetes and hypertension. They were asked to recall whether they had ever experienced severe chest pain for half an hour and whether their doctor had ever informed them that they had a heart attack, stroke, or congestive heart failure. Anthropometric and blood pressure measurements were obtained by following standardized protocols during the physical examination (20).

Blood lipid and glucose concentrations were measured in a venous blood sample by using standard techniques. Serum total cholesterol, HDL cholesterol, and triacylglycerol concentrations were determined at Johns Hopkins University Hospital Lipoprotein Analytic Laboratory by using spectrophotometry (21). Blood glucose was determined at the Diabetes Reference Laboratory, Columbia School of Medicine, University of Missouri by using the glucose-hexokinase method (21). SF concentration was measured with the Quantimune Ferritin IRMA kit (Bio-Rad Laboratories, Hercules, CA) (21). Blood tests were also used to evaluate subjects for liver disease. If any of the following 3 biochemical indexes were elevated, the subject was considered to have possible liver disease: alanine aminotransferase (EC 2.6.1.2) >74 μmol/L or >1.23 μkat/L, aspartate aminotransferase (EC 2.6.1.10) >68 μmol/L or >1.13 μkat/L, or alkaline phosphatase (EC 3.1.3.1) >1.5 times normal. These enzyme concentrations were assayed at the White Sands Research Center by using spectrophotometric methods. C-reactive protein concentrations were determined by using latex-enhanced nephelometry at the University of Washington (21).

Study sample

NHANES III represents the total civilian noninstitutionalized population 2 mo of age or older in the United States. A stratified multistage probability design was used to select participants. The sample for the study described in this article consisted of nonpregnant women of reproductive age (20–49 y) from the 3 largest race-ethnicity groups: non-Hispanic white (NHW), non-Hispanic black (NHB), and Mexican American (MA). Women were excluded if they were missing data on SF or any of 7 established CVD risk factors: body mass index (BMI), serum triacylglycerol, total cholesterol, HDL cholesterol, blood glucose, diastolic blood pressure (DBP), and systolic blood pressure (SBP). To minimize the potential for confounding of the primary relation of interest (SF and CVD risk factors), women with any of the following conditions were also excluded: possible liver disease, history of ischemic heart disease or stroke, current use of insulin, and use of oral medications for hypertension or diabetes. Women who had not fasted for ≥ 6 h at the time of blood collection were also excluded.

Data collection was approved by the National Institutes of Health. The secondary data analysis was approved by the Human Investigations Committee at Emory University.

Variable definition

The 25th and 75th percentile values of SF within each race-ethnicity group were used as threshold values to define 3 categories of iron stores: low ($<$25th percentile), medium (25th to 75th percentile), and high ($>$75th percentile). Ethnicity was self-reported. The CVD risk factors of interest were analyzed as continuous variables, and the triacylglycerol and glucose distributions were log transformed before analysis. Age was expressed in years as a continuous variable. The session of measurement was coded as either morning or afternoon and evening. Subjects reported whether they had been treated with iron for anemia in the past 3 mo or had donated blood in the past 3 mo; their answers were coded as yes, no, or missing. The presence of infection was determined on the basis of either elevated concentrations of C-reactive protein (>6 mg/L) or an abnormal white blood cell count (>11.0 or $<3.5 \times 10^9$/L). Women with missing data for infection, blood donation, and treatment with iron for anemia were included in the models as a separate stratum.

Statistical analysis

The relations between iron stores and the CVD risk factors were examined within each race-ethnicity group. Tests for linear trend were performed to compare unadjusted mean values for the CVD risk factors across the 3 categories of iron stores. General linear regression models were then used to examine the associations between individual CVD risk factors as the outcome and the categories of iron stores (low, medium, and high, with medium as the reference group). We adjusted for age, session, presence of infection, treatment with iron for anemia, and blood donation.

Because the CVD risk factors of interest represent a cluster of indicators that collectively predict risk and may be correlated, we used multivariate analysis of variance in which the entire set of CVD risk factors was considered as the dependent variable (22). A single P value was used to interpret the significance of the association between the set of CVD risk factors and SF concentration. This approach may be superior to consideration of each risk factor separately, because it adjusts for multiple comparisons and accounts for collinearity between the dependent variables. Because 2 comparisons were done (high versus medium and low versus medium SF), a Bonferroni correction was applied and $P < 0.025$ was considered statistically significant. In addition to race-ethnicity–specific models, a single model for the entire sample (ie, all race-ethnicity groups combined) was used to examine the overall relation between SF and CVD risk factors, along with main effects and interactions between SF and race-ethnicity groups. All statistical analyses were weighted appropriately and SUDAAN (release 5.5) was used to derive parameter estimates that took into account the complex sample design (23).

TABLE 1
Selected characteristics of non-Hispanic white, non-Hispanic black, and Mexican American women of reproductive age (20–49 y) from NHANES III, 1988–1994[1]

	Non-Hispanic whites (n = 1178)	Non-Hispanic blacks (n = 1093)	Mexican Americans (n = 1075)
CVD risk factors			
BMI (kg/m^2)[2]	24.98 ± 0.21[a]	28.07 ± 0.29[b]	27.49 ± 0.23[b]
Serum triacylglycerol (mmol/L)[2]	1.14 ± 0.03[a]	0.97 ± 0.02[a]	1.41 ± 0.03[b]
Serum total cholesterol (mmol/L)	4.88 ± 0.03	4.83 ± 0.03	4.88 ± 0.04
Serum HDL cholesterol (mmol/L)[2]	1.44 ± 0.02[a]	1.46 ± 0.01[a]	1.31 ± 0.01[b]
Plasma glucose (mmol/L)[2]	4.96 ± 0.02[a]	4.99 ± 0.03[a]	5.13 ± 0.04[b]
Diastolic BP (mm Hg)[2]	70.29 ± 0.26[a]	71.89 ± 0.34[b]	69.56 ± 0.51[a]
Systolic BP (mm Hg)[2]	110.5 ± 0.4[a]	113.44 ± 0.43[b]	111.19 ± 0.47[a]
Iron status			
Serum ferritin (μg/L)[2]	53.22 ± 2.08[a]	58.93 ± 2.39[a]	43.33 ± 1.39[b]
Other variables			
Blood donation (%)[2]	8.81 ± 1.01[a]	6.32 ± 0.85[b]	3.85 ± 0.65[c]
Anemia treatment (%)[2,3]	2.85 ± 0.51[a]	5.88 ± 0.83[b]	2.01 ± 0.53[a]
Infection (%)[3]	9.35 ± 0.96	13.08 ± 1.23	12.59 ± 1.22
Age (y)[2]	34.15 ± 0.26[a]	32.62 ± 0.23[b]	32.18 ± 0.29[b]
Morning session (%)	51.89 ± 1.87	55.03 ± 2.08	55.51 ± 1.60

[1] $\bar{x}$ ± SE. NHANES III, third National Health and Nutrition Examination Survey; CVD, cardiovascular disease; BP, blood pressure.
[2] $P < 0.05$ for overall comparisons by race-ethnicity groups; values in the same row with different superscript letters are significantly different, $P < 0.017$ (Bonferroni adjusted value for multiple comparisons between race-ethnicity groups).
[3] For this variable, 1–2% of values were missing.

RESULTS

Of 4579 nonpregnant women belonging to the 3 race-ethnicity groups, 4267 had data available for SF and all the CVD risk factors of interest. Of this sample, ≈12% (n = 538) were subsequently excluded because of the presence of liver disease, history of CVD, or use of insulin or oral medications for diabetes or hypertension. An additional 383 women were excluded because they had not fasted for ≥6 h before blood sample collection. The final analytic sample (n = 3346) included 1178 NHW, 1093 NHB, and 1075 MA women. The sample of women who had been excluded (n = 1233) from the analytic sample was older and had a higher proportion of NHB women (18.3% compared with 12.5%). The prevalence of infections was also higher among those who were excluded (18.5 ± 0.8%) compared with those who were not (10.0 ± 2.8%), and the excluded group had significantly higher values for SF and all the CVD risk factors of interest ($P < 0.05$).

Mean values for SF, the CVD risk factors of interest, age, and prevalence of confounding factors (session, infection, treatment with iron for anemia, and recent blood donation) are shown by race-ethnicity groups in **Table 1**. MA women had significantly higher triacylglycerol and glucose concentrations and lower HDL cholesterol and SF values than did NHB and NHW women ($P < 0.001$). NHB women had higher blood pressure than did NHW and MA women ($P < 0.001$). NHW women were older and less obese than were MA and NHB women and also had the highest prevalence of recent blood donation ($P < 0.001$). The proportion of women receiving iron as treatment for anemia was low overall but was highest among NHB women.

TABLE 2
Distribution of selected risk factors for cardiovascular disease by quartile of serum ferritin among non-Hispanic white, non-Hispanic black, and Mexican American women of reproductive age (20–49 y)

Serum ferritin quartile (μg/L)	BMI	Triacylglycerol	Total cholesterol	HDL cholesterol	Glucose	Diastolic blood pressure	Systolic blood pressure
	kg/m^2	*mmol/L*	*mmol/L*	*mmol/L*	*mmol/L*	*mm Hg*	*mm Hg*
Non-Hispanic whites (n = 1178)							
Low (<22)	24.54 ± 0.43	1.022 ± 0.031	4.718 ± 0.047	1.432 ± 0.027	4.952 ± 0.032	70.05 ± 0.54	110.96 ± 1.00
Medium (22–66)[1]	24.70 ± 0.23	1.109 ± 0.039	4.856 ± 0.047	1.462 ± 0.017	4.923 ± 0.024	69.98 ± 0.34	109.75 ± 0.47
High (>66)[2]	26.02 ± 0.39	1.313 ± 0.057	5.105 ± 0.056	1.399 ± 0.034	5.039 ± 0.059	71.16 ± 0.48	111.50 ± 0.66
Non-Hispanic blacks (n = 1093)							
Low (<18)	27.10 ± 0.52	0.871 ± 0.036	4.738 ± 0.063	1.488 ± 0.022	4.943 ± 0.030	72.04 ± 0.87	115.02 ± 1.15
Medium (18–77)[1]	28.10 ± 0.43	0.925 ± 0.021	4.817 ± 0.045	1.452 ± 0.020	4.963 ± 0.040	71.59 ± 0.46	112.87 ± 0.64
High (>77)[2]	28.95 ± 0.45	1.140 ± 0.054	4.959 ± 0.054	1.433 ± 0.027	5.083 ± 0.070	72.35 ± 0.65	112.89 ± 0.88
Mexican Americans (n = 1075)							
Low (<15)	26.56 ± 0.37	1.224 ± 0.029	4.680 ± 0.069	1.354 ± 0.022	5.044 ± 0.040	68.72 ± 0.67	111.19 ± 0.91
Medium (15–59)[1]	27.04 ± 0.30	1.383 ± 0.046	4.873 ± 0.048	1.312 ± 0.020	5.067 ± 0.043	68.78 ± 0.58	110.33 ± 0.51
High (>59)[2]	29.41 ± 0.46	1.661 ± 0.111	5.058 ± 0.090	1.278 ± 0.029	5.364 ± 0.103	72.05 ± 0.72	112.98 ± 1.06

[1] Second and third quartiles combined.
[2] $P < 0.025$ (Bonferroni adjusted value for multiple comparisons) compared with medium serum ferritin by using multivariate analysis of variance in which the entire set of cardiovascular disease risk factors was considered as the dependent variable with 8 degrees of freedom.

TABLE 3
Comparison of adjusted estimates (±SE) of selected cardiovascular disease risk factors by quartile of serum ferritin among non-Hispanic white, non-Hispanic black, and Mexican American women of reproductive age (20–49 y)

Serum ferritin quartile (μg/L)	BMI	Triacylglycerol[1]	Total cholesterol	HDL cholesterol	Glucose[1]	Diastolic blood pressure	Systolic blood pressure
	kg/m²	*mmol/L*	*mmol/L*	*mmol/L*	*mmol/L*	*mm Hg*	*mm Hg*
Non-Hispanic whites (n = 1178)							
Model 1[2]							
Low (<22)	−0.36 ± 0.41	−0.001 ± 0.000	−0.188 ± 0.076	−0.034 ± 0.027	0.000 ± 0.000	−0.46 ± 0.46	0.54 ± 0.97
Medium (22–66)	—	—	—	—	—	—	—
High (>66)	0.97 ± 0.48	0.002 ± 0.001	0.168 ± 0.070	−0.071 ± 0.037	0.001 ± 0.000	0.27 ± 0.64	0.60 ± 0.70
Model 2[3]							
Low (<22)	−0.40 ± 0.39	0.000 ± 0.000	−0.194 ± 0.077	−0.036 ± 0.028	0.000 ± 0.000	−0.45 ± 0.47	0.61 ± 0.95
Medium (22–66)	—	—	—	—	—	—	—
High (>66)	0.81 ± 0.47	0.001 ± 0.000	0.159 ± 0.071	−0.064 ± 0.035	0.001 ± 0.000	0.20 ± 0.62	0.38 ± 0.65
Non-Hispanic blacks (n = 1083)							
Model 1[2]							
Low (<18)[4]	−1.23 ± 0.59	−0.001 ± 0.000	−0.109 ± 0.065	0.038 ± 0.028	0.000 ± 0.000	−0.08 ± 0.89	1.39 ± 1.17
Medium (18–77)	—	—	—	—	—	—	—
High (>77)[4]	0.27 ± 0.63	0.002 ± 0.000	0.060 ± 0.072	−0.013 ± 0.031	0.001 ± 0.001	−0.71 ± 0.75	−2.07 ± 1.2
Model 2[3]							
Low (<18)	−0.67 ± 0.54	−0.001 ± 0.000	−0.106 ± 0.067	0.025 ± 0.028	0.000 ± 0.000	−0.14 ± 0.92	1.73 ± 1.19
Medium (18–77)	—	—	—	—	—	—	—
High (>77)[4]	0.15 ± 0.63	0.002 ± 0.000	0.062 ± 0.071	−0.009 ± 0.032	0.001 ± 0.001	−0.74 ± 0.75	−2.19 ± 1.19
Mexican Americans (n = 1075)							
Model 1[2]							
Low (<15)[4]	−0.60 ± 0.52	−0.001 ± 0.000	−0.199 ± 0.079	0.043 ± 0.027	0.000 ± 0.000	−0.49 ± 0.56	0.30 ± 0.89
Medium (15–59)	—	—	—	—	—	—	—
High (>59)[4]	2.02 ± 0.36	0.001 ± 0.001	0.128 ± 0.087	−0.030 ± 0.033	0.002 ± 0.001	2.47 ± 0.68	1.65 ± 1.05
Model 2[3]							
Low (<15)[4]	−0.70 ± 0.52	−0.001 ± 0.000	−0.199 ± 0.079	0.043 ± 0.027	0.000 ± 0.000	−0.52 ± 0.56	0.30 ± 0.89
Medium (15–59)	—	—	—	—	—	—	—
High (>59)[4]	1.74 ± 0.36	0.001 ± 0.001	0.125 ± 0.090	−0.028 ± 0.034	0.002 ± 0.001	2.44 ± 0.69	1.42 ± 1.06

[1] Values were log transformed.
[2] Adjusted for age and session of measurement.
[3] Adjusted for age, session of measurement, prevalent infection, recent blood donation, and recent treatment for anemia.
[4] $P < 0.025$ (Bonferroni adjusted value for multiple comparisons) compared with medium serum ferritin (second and third quartiles combined) by multivariate analysis of variance in which the entire set of cardiovascular disease risk factors was considered as the dependent variable with 8 degrees of freedom. Parameter estimates were generated by using SUDAAN and one dependent variable at a time.

The 25th and 75th percentile values for SF (which were used to define low, medium, and high iron stores) were 22 and 66 μg/L for NHW, 18 and 77 μg/L for NHB, and 15 and 59 μg/L for MA women, respectively. Unadjusted mean values for the selected CVD risk factors in the different quartiles of SF values are shown in **Table 2**. The adjusted race-ethnicity–specific estimates for the various CVD risk factors comparing women in the lowest and highest quartiles of SF to those in the middle 2 quartiles are shown in **Table 3** for the 2 models. In the first model, we controlled for age and session only. In the second model, we also controlled for infections, blood donation, and treatment with iron for anemia.

The unadjusted analysis (Table 2) indicated that in each of the 3 race-ethnicity groups, CVD risk was significantly higher in the highest quartile of SF values compared with the middle 2 quartiles combined (the entire set of CVD risk factors was considered as the dependent variable; $P < 0.025$ with the Bonferroni adjustment for multiple comparisons). In the highest SF quartile of the NHW group, certain CVD risk factors were especially high; this was true for BMI, serum triacylglycerol, total cholesterol, and glucose. However, these effects disappeared after adjustment for age and session and further adjustment for confounding by infections, recent blood donation, and treatment with iron for anemia (Table 3). Significant associations between the set of CVD risk factors and iron status were found for both the NHB and MA groups, even after adjustment for confounding. For NHB women, CVD risk was significantly higher in the highest quartile of SF compared with the middle 2 quartiles ($P < 0.025$ with the Bonferroni adjustment for multiple comparisons). The strongest associations were observed among MA women: compared with women in the middle 2 quartiles of SF, women in the highest and lowest quartiles of SF values had correspondingly higher and lower CVD risk factors, especially BMI, triacylglycerol, total cholesterol, glucose, and diastolic BP, after adjustment for age and session. These relations remained unaltered after adjusting for infections, treatment with iron for anemia, and blood donation and were statistically significant in the overall multivariate analysis of variance model for both the lowest and highest quartiles ($P < 0.025$ with the Bonferroni adjustment for multiple comparisons).

Age, session, and infections were significantly associated with the CVD risk factors in all 3 race-ethnicity groups, whereas blood donation and treatment with iron for anemia were associated with the outcomes for NHW women only. Examination of the relations with a single model that combined all 3 race-ethnicity groups confirmed the above results.

DISCUSSION

Our results suggest an association between iron stores and CVD risk factors in women of reproductive age. Although the cross-sectional

design of NHANES III precludes inferences of causality, it is not likely that the observed associations were confounded by factors such as infections, time of day, and fasting status, all of which were controlled for in the analysis. The choice of SF as a valid indicator of iron stores is a potential concern (14–17). However, we found that in our study population, SF was strongly correlated ($r > 0.9$) with a composite indicator of total body iron stores that combines hemoglobin, serum transferrin, and ferritin (24). Finally, another strength of the study design is that the study sample consisted of relatively healthy women of reproductive age; we excluded women with a history of CVD and women who were taking medications for diabetes or hypertension.

Few studies have examined the relation between iron stores and CVD risk factors in women of reproductive age. Milman and Kirchoff (25) found positive associations between SF and both BMI and serum triacylglycerol but no associations with serum total cholesterol, HDL cholesterol, or blood pressure among healthy white Danish women aged 40–60 y who were not blood donors (25). In a much smaller sample of 159 healthy Nordic women (113 premenopausal and 46 postmenopausal), Berge et al (26) also reported significant associations between SF and serum total, LDL, and HDL cholesterol after adjusting for age. Interestingly, neither SF nor serum lipids were associated with female sex hormones.

The stronger association in MA women is intriguing because this group has the poorest iron status but increased prevalence of some CVD risk factors. Although serum cholesterol concentrations and blood pressure were similar among the 3 race-ethnicity groups in our sample, MA women had significantly higher concentrations of triacylglycerol and glucose and lower HDL cholesterol concentrations compared with NHW and NHB women. This raises important public health questions, because this subgroup was shown to be at increased risk of both iron deficiency and obesity in the United States (27, 28). More research is definitely needed to better understand the nature of this association before appropriate interventions can be developed. Dietary intakes do not explain the difference in the prevalence of iron deficiency between MA and NHW women, suggesting that the etiology of iron deficiency may depend on other factors (29). Prospective studies, especially intervention studies that ensure adequate iron status, are needed to compare 2 possible scenarios: *1*) improved iron status increases the risk of CVD, or *2*) women with a higher risk of CVD have higher iron stores, with both factors resulting from the same underlying cause.

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