Serum Ferritin and Risk of the Metabolic Syndrome in U.S. Adults

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OBJECTIVE — We examined the relationship among iron stores, the metabolic syndrome, and insulin resistance.

RESEARCH DESIGN AND METHODS — We conducted a cross-sectional study of 6,044 adults >20 years of age who participated in the Third National Health and Nutrition Examination Survey. Metabolic syndrome was defined as the presence of at least three of the following: elevated blood pressure, low HDL cholesterol, elevated serum triglycerides, elevated plasma glucose, and abdominal obesity. Insulin resistance was estimated using homeostasis model assessment (for insulin resistance), fasting insulin, and triglyceride–to–HDL cholesterol ratio.

RESULTS — After excluding individuals with likely hemochromatosis, mean serum ferritin values in premenopausal women, postmenopausal women, and men were 33.6, 93.4, and 139.9 μg/l, respectively. Metabolic syndrome was more common in those with the highest compared with the lowest levels of serum ferritin in premenopausal women (14.9 vs. 6.4%, $P = 0.002$), postmenopausal women (47.5 vs. 28.2%, $P < 0.001$), and men (27.3 vs. 13.8%, $P < 0.001$). Insulin resistance also increased across quartiles of serum ferritin for men and postmenopausal women and persisted after adjustment for age, race/ethnicity, C-reactive protein, smoking, alcohol intake, and BMI.

CONCLUSIONS — Elevated iron stores were positively associated with the prevalence of the metabolic syndrome and with insulin resistance.

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There is increasing evidence that moderately elevated body iron stores, below levels commonly found in genetic hemochromatosis, may be associated with adverse health outcomes. Elevated serum ferritin levels independently predicted incident type 2 diabetes in prospective studies in apparently healthy men and women (1,2). In cross-sectional studies, elevated ferritin levels have been associated with hypertension (3), dyslipidemia (4,5), elevated fasting insulin and blood glucose (6), and central adiposity (7). The association between elevated iron stores and the metabolic syndrome, however, has been less well explored (8).

Although the mechanisms for the potential effect of iron on the risk of metabolic syndrome are unclear, it has been hypothesized that elevated iron stores may interfere with hepatic insulin extraction leading to peripheral hyperinsulinemia (9,10). Others have suggested that iron may catalyze the formation of hydroxyl radicals, which contribute to the development of insulin resistance (11,12).

We hypothesized that the metabolic syndrome would be more common in those with moderately elevated serum ferritin levels. To test this hypothesis, we conducted a cross-sectional analysis using representative data from the general U.S. population.

RESEARCH DESIGN AND METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) was conducted by the National Center for Health Statistics between 1988 and 1994. The survey was a multistage nationwide probability sample of the civilian, noninstitutionalized U.S. population. The study design included a home interview and a detailed clinical evaluation (13).

The present analysis was restricted to NHANES III participants ≥20 years of age, who were not pregnant or nursing at the time of the examination and who were randomly assigned to receive a morning examination ($n = 7,907$). We excluded individuals who had fasted <9 h at the time of the examination ($n = 600$), who had received treatment for anemia within the last 3 months ($n = 186$), with known current hepatitis C infection ($n = 184$), who had donated blood within the last 4 months ($n = 195$), or who had probable hemochromatosis based on abnormal values of multiple iron parameters (men: serum iron >190 μg/dl, serum ferritin >300 μg/l, and transferrin saturation >60%; women: serum iron >175 μg/dl, serum ferritin >200 μg/l, and transferrin saturation >60%) ($n = 24$) (14). Because some individuals met more than one exclusion criterion, the total number eligible for the study was 6,646. Individuals missing measurements for serum ferritin, fasting insulin, or any of the components of the metabolic syndrome were further excluded in the analysis ($n = 602$). Therefore, the final analytical sample consisted of 6,044 individuals.

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Abbreviations: ALT, alanine aminotranferase; AST, aspartate aminotransferase; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment for insulin resistance; NHANES III, Third National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Prevalence of the metabolic syndrome and its components by sex and menopausal-specific quartiles of serum ferritin*

Premenopausal women (n = 1,645)	Quartile of serum ferritin				
	≤20 μg/l	21–36 μg/l	37–60 μg/l	>60 μg/l	*P* (trend)
Median ferritin in quartile	11	26	47	89	
Metabolic syndrome	6.4 ± 1.6	8.1 ± 2.1	12.2 ± 2.3	14.9 ± 2.5	0.002
Blood pressure ≥130/85 mmHg*	3.6 ± 1.0	3.1 ± 0.9	3.4 ± 0.9	4.5 ± 1.4	0.53
Plasma glucose ≥6.105 mmol/l†	5.3 ± 1.8	1.9 ± 0.8	2.9 ± 0.8	5.5 ± 1.3	0.52
HDL cholesterol <1.295 mmol/l	34.4 ± 3.8	40.4 ± 3.4	40.7 ± 4.1	41.8 ± 3.4	0.18
Serum triglycerides ≥1.695 mmol/l	13.3 ± 3.6	10.2 ± 2.5	17.6 ± 2.8	20.1 ± 2.4	0.01
Waist circumference ≥88 cm	27.0 ± 3.3	31.9 ± 3.5	37.1 ± 3.5	42.3 ± 4.9	0.02

Postmenopausal women (n = 1,424)	Quartile of serum ferritin				
	≤54 μg/l	55–95 μg/l	96–168 μg/l	>168 μg/l	*P* (trend)
Median ferritin in quartile	35	73	125	212	
Metabolic syndrome	28.2 ± 2.9	21.8 ± 3.4	34.3 ± 2.2	47.5 ± 3.9	<0.001
Blood pressure ≥130/85 mmHg*	20.2 ± 2.6	15.8 ± 2.7	21.8 ± 3.1	26.1 ± 3.3	0.04
Plasma glucose ≥6.105 mmol/l†	12.8 ± 1.8	14.9 ± 2.8	21.2 ± 2.6	33.7 ± 2.8	<0.001
HDL cholesterol <1.295 mmol/l	39.8 ± 4.5	33.8 ± 3.9	41.5 ± 3.6	44.3 ± 3.6	0.26
Serum triglycerides ≥1.695 mmol/l	30.8 ± 3.5	30.2 ± 3.1	43.7 ± 2.6	53.3 ± 3.8	<0.001
Waist circumference ≥88 cm	56.7 ± 3.0	58.1 ± 3.5	68.5 ± 3.4	70.9 ± 4.2	0.009

Men (n = 2,880)	Quartile of serum ferritin				
	≤86 μg/l	87–145 μg/l	146–231 μg/l	>231 μg/l	*P* (trend)
Median ferritin in quartile	62	113	182	318	
Metabolic syndrome	13.8 ± 2.1	16.8 ± 2.1	18.8 ± 2.7	27.3 ± 3.0	<0.001
Blood pressure ≥130/85 mmHg*	11.6 ± 2.3	13.6 ± 3.1	16.9 ± 2.7	18.4 ± 2.3	0.05
Plasma glucose ≥6.105 mmol/l†	11.9 ± 1.6	11.5 ± 1.6	14.6 ± 1.7	26.6 ± 2.7	<0.001
HDL cholesterol <1.036 mmol/l	35.5 ± 3.9	32.1 ± 3.6	34.8 ± 2.8	41.9 ± 3.9	0.13
Serum triglycerides ≥ 1.695 mmol/l	24.0 ± 3.1	33.8 ± 3.5	34.5 ± 3.6	50.7 ± 4.3	<0.001
Waist circumference ≥ 102 cm	24.0 ± 2.7	26.3 ± 3.6	29.6 ± 2.4	37.7 ± 3.1	0.02

Data are prevalence ± SE. *Includes individuals who reported current use of antihypertensive medications regardless of blood pressure values. †Includes individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values.

Data from NHANES III were collected by household interview followed by a detailed physical examination conducted at a mobile examination center or at the participant's home. Information on age, race/ethnicity, education, smoking history, alcohol intake, and use of antihypertensive and diabetes medications was collected during the interview. Menopausal status was defined as self-reported cessation of menstruation or hysterectomy. The average of all available blood pressure readings taken during the home interview and physical examination (up to six) was used in the analysis. Waist circumference was measured by a trained technician to the nearest 0.1 cm in a horizontal plane at the level of the high point of the iliac crest at minimal respiration. BMI was calculated as weight in kilograms divided by the square of height in meters. Alcohol intake was categorized as never, zero to

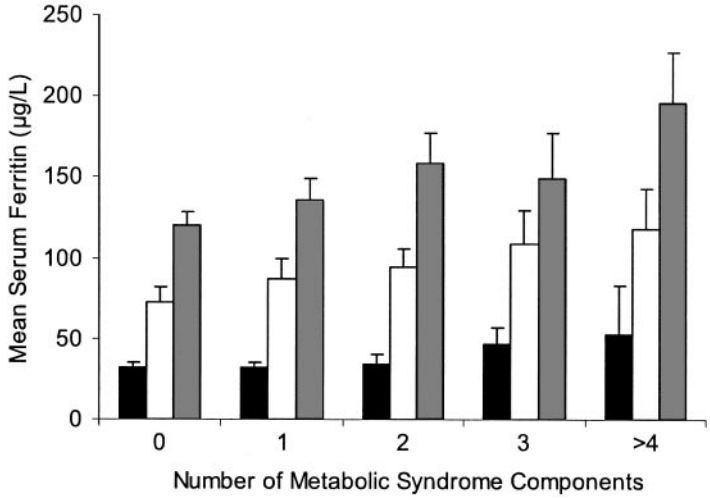

Figure 1—*Mean serum ferritin levels by the number of metabolic syndrome components. Geometric mean values of serum ferritin are shown for premenopausal women (black bar), postmenopausal women (white bar), and men (gray bar). Error bars represent upper 95% CI. The trend of increasing mean ferritin values across categories of metabolic syndrome components was significant for all three groups* ($P < 0.05$).

Table 2—*Adjusted* odd ratios (95% CI) of the metabolic syndrome and its components by sex and menopausal-specific quartiles of serum ferritin*

Premenopausal women (n = 1,645)	Quartile of serum ferritin				
	≤20 μg/l	21–36 μg/l	37–60 μg/l	>60 μg/l	*P* (trend)
Median ferritin in quartile	11	26	47	89	
Metabolic syndrome	1.0	1.5 (0.7–3.5)	2.6 (1.2–5.7)	2.4 (1.1–5.2)	0.03
Blood pressure ≥130/85 mmHg†	1.0	1.3 (0.6–2.6)	1.0 (0.4–2.9)	0.9 (0.3–2.3)	0.37
Plasma glucose ≥6.105 mmol/l‡	1.0	0.4 (0.2–1.3)	0.7 (0.3–2.0)	0.8 (0.3–2.4)	0.99
HDL cholesterol <1.295 mmol/l	1.0	1.2 (0.7–2.0)	1.1 (0.6–2.1)	1.2 (0.8–1.8)	0.57
Serum triglycerides ≥1.695 mmol/l	1.0	0.8 (0.2–0.9)	1.8 (0.5–2.8)	1.5 (0.7–2.7)	0.07
Waist circumference ≥88 cm	1.0	3.7 (1.3–8.1)	1.6 (1.4–6.9)	2.8 (1.6–5.9)	0.14

Postmenopausal women (n = 1,424)	Quartile of serum ferritin				
	≤54 μg/l	55–95 μg/l	96–168 μg/l	>168 μg/l	*P* (trend)
Median ferritin in quartile	35	73	125	212	
Metabolic syndrome	1.0	0.8 (0.4–1.3)	1.4 (0.7–2.0)	2.7 (1.7–4.1)	<0.001
Blood pressure ≥130/85 mmHg†	1.0	0.4 (0.2–1.0)	0.8 (0.3–1.7)	1.0 (0.5–2.1)	0.21
Plasma glucose ≥6.105 mmol/l‡	1.0	1.4 (0.8–2.6)	2.0 (1.2–3.5)	3.6 (2.4–5.5)	<0.001
HDL cholesterol <1.295 mmol/l	1.0	0.8 (0.5–1.3)	1.1 (0.6–2.0)	1.1 (0.7–2.0)	0.57
Serum triglycerides ≥1.695 mmol/l	1.0	1.1 (0.7–1.8)	2.0 (1.1–3.1)	3.2 (1.6–4.6)	0.001
Waist circumference ≥88 cm	1.0	0.8 (0.4–1.4)	1.5 (0.8–2.5)	1.2 (0.5–2.0)	0.33

Men (n = 2,880)	Quartile of serum ferritin				
	≤86 μg/l	87–145 μg/l	146–231 μg/l	>231 μg/l	*P* (trend)
Median ferritin in quartile	62	113	182	318	
Metabolic syndrome	1.0	1.3 (0.8–2.4)	1.6 (0.8–3.2)	1.6 (0.9–2.7)	0.11
Blood pressure ≥130/85 mmHg†	1.0	1.2 (0.7–2.0)	1.5 (0.8–2.9)	1.0 (0.6–1.9)	0.89
Plasma glucose ≥6.105 mmol/l ‡	1.0	1.1 (0.7–1.9)	1.5 (0.9–2.5)	2.2 (1.4–3.6)	0.001
HDL cholesterol <1.036 mmol/l	1.0	0.8 (0.5–1.3)	0.9 (0.6–1.4)	1.1 (0.7–1.9)	0.31
Serum triglycerides ≥1.695 mmol/l	1.0	1.6 (1.0–2.6)	1.7 (1.0–2.6)	2.7 (1.6–4.6)	0.004
Waist circumference ≥102 cm	1.0	1.2 (0.5–2.9)	1.5 (0.8–2.8)	0.8 (0.5–1.3)	0.27

*Adjusted for age, race/ethnicity, CRP, smoking, alcohol intake, and BMI. †Includes individuals who reported current use of antihypertensive medications regardless of blood pressure values. ‡Includes individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values.

two alcoholic drinks per day, and more than two alcoholic drinks per day based on self-reported average over the past 12 months. Smoking was categorized as current, former, and never.

NHANES laboratory procedures and quality control have been published previously (15). Serum ferritin was measured on fasting blood samples using a single-incubation two-site immunoradiometric assay (Bio-Rad Laboratories, Hercules, CA). The interassay coefficients of variation ranged from 4 to 6%. Plasma glucose was measured using a modified hexokinase enzymatic reference method (COBAS MIRA; Roche Diagnostics Laboratory Systems, Indianapolis, IN). Serum insulin was measured using the Pharmacia Insulin radioimmunoassay kit (Pharmacia Diagnostics, Uppsala, Sweden). Serum triglycerides and HDL cholesterol were measured enzymatically (Boehringer Mannheim Diagnostics, Indianapolis, IN). Alanine aminotranferase (ALT) and aspartate aminotransferase (AST) were assayed using the α-ketoglutarate reaction. Serum C-reactive protein (CRP) concentration was determined using latex-enhanced nephelometry with a limit of detection of 0.21 mg/dl.

The metabolic syndrome was defined as the presence of three or more of the following criteria set forth by the National Cholesterol Education Program Adult Treatment Panel III guidelines (16): *1*) elevated blood pressure (average systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg) or current blood pressure medication use, *2*) low HDL cholesterol (<1.036 mmol/l in men and <1.295 mmol/l in women), *3*) elevated serum triglycerides (≥1.695 mmol/l), *4*) elevated fasting plasma glucose (≥6.105 mmol/l) or current antidiabetes medication use, and *5*) abdominal obesity (waist circumference ≥102 cm in men and ≥88 cm in women). Diabetes was defined as a fasting plasma glucose value >7.0 mmol/l or current use of antidiabetes medication.

Insulin resistance was determined using the homeostasis model assessment (HOMA) estimate of insulin resistance (HOMA-IR = fasting insulin [μU/ml] × fasting glucose [mmol/l]/22.5) (17), fasting insulin level, and the ratio of triglyceride to HDL cholesterol.

All analyses were performed separately for men, premenopausal women, and postmenopausal women, including calculation of specific quartiles of serum ferritin. Serum ferritin values were right skewed and were log transformed. Odds

Table 3—*Geometric mean (95% CI) values of estimated insulin resistance by sex and menopausal-specific quartiles of serum ferritin in nondiabetic U.S. adults*

Premenopausal women (n = 1,612)	Quartile of serum ferritin				
	≤20 μg/l	21–36 μg/l	37–60 μg/l	>60 μg/l	*P* (trend)
Median ferritin in quartile	11	26	47	89	
HOMA-IR	1.9 (1.7–2.1)	1.7 (1.6–1.8)	1.9 (1.8–2.1)	1.9 (1.8–2.2)	0.14
Fasting insulin (pmol/l)	49.9 (46.0–54.1)	45.8 (42.6–49.8)	52.4 (48.8–56.3)	51.8 (47.3–56.7)	0.16
Triglyceride-to-HDL ratio	0.71 (0.62–0.81)	0.72 (0.66–0.80)	0.75 (0.67–0.83)	0.82 (0.73–0.92)	0.06
Postmenopausal women (n = 1,234)	Quartile of serum ferritin				
	≤54 μg/l	55–95 μg/l	96–168 μg/l	>168 μg/l	*P* (trend)
Median ferritin in quartile	35	73	125	212	
HOMA-IR	2.0 (1.9–2.2)	1.9 (1.7–2.1)	2.3 (2.2–2.6)	2.5 (2.3–2.8)	<0.001
Fasting insulin (pmol/l)	51.3 (47.8–55.1)	49.0 (44.9–53.5)	58.0 (54.2–62.2)	62.3 (57.0–68.2)	<0.001
Triglyceride-to-HDL ratio	1.03 (0.92–1.16)	0.87 (0.79–0.96)	1.07 (0.98–1.16)	1.28 (1.11–1.48)	0.001
Men (n = 2,618)	Quartile of serum ferritin				
	≤86 μg/l	87–145 μg/l	146–231 μg/l	>231 μg/l	*P* (trend)
Median ferritin in quartile	62	113	182	318	
HOMA-IR	1.9 (1.7–2.0)	2.0 (1.9–2.2)	2.1 (2.0–2.3)	2.5 (2.3–2.6)	<0.001
Fasting insulin (pmol/l)	47.8 (44.2–51.6)	51.8 (48.3–55.6)	52.8 (49.1–56.8)	60.2 (56.9–63.7)	<0.001
Triglyceride-to-HDL ratio	1.05 (0.95–1.17)	1.11 (0.99–1.26)	1.21 (1.11–1.33)	1.41 (1.28–1.62)	<0.001

Data are means (95% CI).

ratios for the prevalence of the metabolic syndrome and its components were calculated for quartiles of serum ferritin using logistic regression. Tests for trend across quartiles were computed by including a variable with the median value for each quartile as a continuous variable in the logistic regression models. All models were adjusted for age, race/ethnicity, BMI, CRP, smoking, and alcohol intake. Statistical analyses were performed using STATA (version 8.1; College Station, TX) "svy" commands to account for complex survey design and included sampling weights to provide nationally representative prevalence estimates.

RESULTS — Mean levels of serum ferritin were significantly lower in premenopausal women 33.6 μg/l (95% CI 31.5–35.8) compared with postmenopausal women 93.4 μg/l (87.9–99.2) and lower in postmenopausal women compared with men 139.9 μg/l (133.6–146.6). The prevalence of the metabolic syndrome was 10.2% in premenopausal women, 27.8% in postmenopausal women, and 17.5% in men.

In all three groups, the highest prevalence of the metabolic syndrome occurred in the highest quartile of serum ferritin (Table 1). The prevalence of elevated blood pressure, elevated plasma glucose, elevated triglycerides, and abdominal adiposity all increased significantly with increasing serum ferritin in men and postmenopausal women. In premenopausal women, the prevalence of elevated triglycerides and abdominal adiposity also increased with increasing serum ferritin. For all three groups, the greater the number of metabolic syndrome components present, the greater the serum ferritin level (Fig. 1).

After adjusting for age, race/ethnicity, BMI, smoking status, alcohol consumption, and CRP, serum ferritin remained positively associated with prevalence of the metabolic syndrome in all three groups (Table 2). Further adjustment for triceps skinfold thickness, as an additional marker of adiposity, did not change the results. The metabolic syndrome was more common in the highest compared with the lowest quartile of serum ferritin in premenopausal women (OR 2.4 [95% CI 1.1–5.2]), in postmenopausal women (2.7 [1.7–4.1]), and in men (1.6 [0.9–2.7]) (Table 2). Ferritin was also positively associated with elevated triglycerides and elevated glucose levels in postmenopausal women and in men. These results remained unchanged if individuals taking antihypertensives or hypoglycemic medications are excluded from the analysis. The association between serum ferritin and abdominal adiposity observed in univariate analyses was attenuated when BMI was included in multivariate models.

Because serum ferritin is an acute-phase reactant (18), we repeated our analyses after excluding individuals with a white blood cell count above or below the reference range (>11.7 or <3.0 × 10^9 cells/l) (n = 136), CRP >1.0 mg/dl (n = 474), or elevation of one or more of the following liver enzymes: ALT greater than two times the upper limit of normal (>80 units/l for men and >62 units/l for women) or AST greater than two times the upper limit of normal (>74 U/l for men or >62 units/l for women) (n = 32) (15). Similar results were observed after these individuals were excluded. For example, the adjusted odds ratios of metabolic syndrome comparing the highest with lowest quartile of serum ferritin for premenopausal women, postmenopausal women,

Table 4—*Adjusted* ratio (95% CI) of mean insulin resistance parameters for increasing quartiles of serum ferritin in nondiabetic U.S. adults*

	Quartile of serum ferritin				
Premenopausal women (n = 1,612)	≤20 μg/l	21–36 μg/l	37–60 μg/l	>60 μg/l	*P* (trend)
Median ferritin in quartile	11	26	47	89	
HOMA-IR	1 (reference)	0.91 (0.83–0.99)	1.03 (0.89–1.06)	0.97 (0.87–1.03)	0.98
Fasting insulin (pmol/l)	1 (reference)	0.92 (0.86–1.03)	1.02 (0.90–1.06)	0.96 (0.88–1.03)	0.99
Triglyceride-to-HDL ratio	1 (reference)	1.03 (0.90–1.19)	1.05 (0.89–1.23)	1.09 (0.96–1.23)	0.12
	Quartile of serum ferritin				
Postmenopausal women (n = 1,234)	≤54 μg/l	55–95 μg/l	96–168 μg/l	>168 μg/l	*P* (trend)
Median ferritin in quartile	35	73	125	212	
HOMA-IR	1 (reference)	0.95 (0.88–1.02)	1.13 (1.04–1.23)	1.21 (1.12–1.30)	<0.001
Fasting insulin (pmol/l)	1 (reference)	0.96 (0.89–1.02)	1.10 (1.03–1.19)	1.19 (1.09–1.26)	<0.001
Triglyceride-to-HDL ratio	1 (reference)	0.89 (0.79–0.99)	1.03 (0.89–1.19)	1.27 (1.10–1.48)	<0.001
	Quartile of serum ferritin				
Men (n = 2,618)	≤86 μg/l	87–145 μg/l	146–231 μg/l	>231 μg/l	*P* (trend)
Median ferritin in quartile	62	113	182	318	
HOMA-IR	1 (reference)	1.01 (0.93–1.09)	1.04 (0.97–1.13)	1.09 (1.00–1.18)	0.04
Fasting insulin (pmol/l)	1 (reference)	1.01 (0.94–1.08)	1.02 (0.95–1.09)	1.05 (0.99–1.13)	0.08
Triglyceride-to-HDL ratio	1 (reference)	1.01 (0.88–1.16)	1.08 (0.97–1.21)	1.21 (1.05–1.40)	<0.001

*Adjusted for age, race/ethnicity, CRP, smoking, alcohol intake, and BMI. The table represents the ratio of the geometric mean of IR parameters in a given quartile of serum ferritin with respect to the first quartile. For instance, premenopausal women in the second quartile of serum ferritin had HOMA-IR 9% lower than premenopausal women in the first quartile (ratio of means 0.91).

and men were 1.5 (95% CI 0.9–2.6), 2.3 (0.8–7.0), and 2.0 (1.2–3.4), respectively.

Insulin resistance

Mean values of estimated insulin resistance were calculated by quartile of serum ferritin (Table 3). This analysis was restricted to individuals without diabetes. We did not observe any consistent association between HOMA-IR or fasting insulin with serum ferritin in premenopausal women. We did observe a trend of increasing insulin resistance (HOMA-IR, fasting insulin, and triglyceride-to-HDL ratio) with increasing serum ferritin in both postmenopausal women and men. In Table 4, we present the multivariate-adjusted ratio of insulin resistance measures for the second, third, and fourth quartiles of serum ferritin compared with the first. Similar to the unadjusted analyses, the ratio of insulin resistance values increased with increasing quartiles of serum ferritin in men and postmenopausal women. For example, levels of the triglyceride-to-HDL ratio were 21% higher in the highest quartile of serum ferritin compared with the lowest quartile of serum ferritin for men. In postmenopausal women, the observed association between insulin resistance and ferritin appeared to follow a j-shaped pattern in which values were slightly elevated in the first quartile, lower in the second quartile, and then increased in the third and fourth quartiles.

CONCLUSIONS — In this study, we observed a positive association between elevated iron stores, measured by serum ferritin levels, and the prevalence of the metabolic syndrome. Ferritin levels also correlated with individual components of the metabolic syndrome, particularly serum triglycerides and plasma glucose, as well as markers of insulin resistance.

Several cross-sectional studies have previously examined the association between iron stores and individual metabolic cardiovascular risk factors, including hypertension (3), dyslipidemia (4,5), elevated fasting insulin and blood glucose (6), and central adiposity (7). Our results are consistent with the previous literature and extend these observations to include the metabolic syndrome. The explanation for the observed j-shaped association between ferritin levels and markers of insulin resistance in postmenopausal women is unknown. It is possible that a carbohydrate-rich, protein-poor diet, which may lead to iron deficiency, may also contribute to insulin resistance (19).

Several lines of evidence support the association between elevated iron stores and insulin resistance. Type 2 diabetes is commonly observed in patients with hemochromatosis, a group with demonstrated iron overload (20). Second, serum ferritin levels correlated with various measures of insulin sensitivity in several different populations, including individuals without diabetes (6,21), individuals with diabetes (22), women with gestational diabetes (23), and patients with thalassemia (24). Third, a small intervention study of phlebotomy in patients with type 2 diabetes resulted in improved insulin sensitivity (22). Finally, two prospective studies have shown an association between elevated iron stores and incident diabetes (1,2). These studies were conducted in Finnish men (1) and U.S. nurses (2), and both provide evidence that elevated ferritin levels precede the development of diabetes.

It is unclear whether elevated iron stores may simply be another marker of insulin resistance or whether elevated

iron stores may contribute to the pathogenesis of altered metabolic states. Iron is a transition metal capable of causing oxidative tissue damage by catalyzing the formation of free radicals (12). Iron overload may contribute to insulin resistance through mechanisms related to both reduced extraction of insulin and impaired insulin secretion (25). Results of oral glucose tolerance tests in patients with hemochromatosis have suggested that hepatic iron overload results in impaired insulin extraction (10). Others have suggested that iron deposition in pancreatic β-cells may also impair insulin secretion in more advanced states of iron overload (25).

Serum ferritin is a widely used marker of iron status in epidemiological studies (20) and accurately reflects differences in body iron stores by age and sex (26). However, serum ferritin is an acute-phase reactant and may be artificially elevated in the presence of inflammation (18). We attempted to minimize this potential source of confounding by adjusting for CRP and by excluding those individuals with suspected inflammation, infection, and liver disease in sensitivity analyses; however, we cannot rule out residual confounding by other inflammatory conditions. Similarly, we cannot rule out residual confounding by unmeasured factors that may be related both to the prevalence of the metabolic syndrome and to ferritin levels. A further limitation of this study is the cross-sectional design, which prevents us from making inferences about the directionality of the associations. Although there is increasing evidence to suggest that iron may influence glucose metabolism, it is possible that glucose metabolism may also influence body iron stores. Insulin, possibly through the activation of hypoxia-inducible factor-1α, may stimulate the production of erythropoietin, thus increasing the efficiency of iron absorption (27).

In summary, moderately elevated iron levels were associated with an increased prevalence of the metabolic syndrome and markers of insulin resistance. These associations were evident at moderately elevated iron levels, below levels associated with hemochromatosis. Given the high prevalence of elevated iron stores, especially in older ages, prospective studies are needed to determine whether moderately elevated iron stores precede the development of insulin resistance and contribute to the increased risk associated with it.

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