Ferritin and Transferrin Are Associated With Metabolic Syndrome Abnormalities and Their Change Over Time in a General Population

Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR)

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OBJECTIVE — The aim of this work was to study cross-sectional and longitudinal relations between iron stocks (ferritin) and the iron transport protein (transferrin) with the metabolic syndrome and its abnormalities.

RESEARCH DESIGN AND METHODS — A total of 469 men and 278 premenopausal and 197 postmenopausal women from the French Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort, aged 30–65 years, were followed over 6 years.

RESULTS — Higher concentrations of both ferritin and transferrin were associated with the International Diabetes Federation (IDF) and the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III original and revised definitions of the metabolic syndrome at baseline: for the IDF definition of the metabolic syndrome, the standardized, age-adjusted odds ratios (95% CI) for log(ferritin) were 1.49 (1.14–1.94) for men, 2.10 (1.27–3.48) for premenopausal women, and 1.80 (1.21–2.68) for postmenopausal women; for transferrin they were, respectively, 1.94 (1.53–2.47), 2.22 (1.32–3.75), and 2.14 (1.47–3.10). After 6 years of follow-up, the change in the presence of the metabolic syndrome was associated with higher baseline values in all three groups: log(ferritin), 1.46 (1.13–1.89), 1.28 (0.85–1.94), and 1.62 (1.10–2.38); and transferrin, 1.41 (1.10–1.81), 1.63 (1.05–2.52), and 1.51 (1.02–2.22). Among syndrome components, hypertriglyceridemia at 6 years was the component most strongly associated with baseline ferritin and transferrin. The odds of an incident IDF-defined metabolic syndrome after 6 years was more than fourfold higher when ferritin and transferrin values were both above the group-specific top tertile, in comparison with participants with both parameters below these thresholds.

CONCLUSIONS — This is the first prospective study associating ferritin and transferrin with the metabolic syndrome and its components. When both markers of the iron metabolism are elevated, the incidence of the metabolic syndrome is increased in men and both pre- and postmenopausal women.

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In 1981, Sullivan (1) formulated hypotheses that attributed the sex difference in heart disease risk to differences in iron stores. Hereditary hemochromatosis, a disorder leading to a chronic iron overload syndrome, has been associated with cardiovascular disease and incident diabetes (2,3). Further, in hypercholesterolemic rabbits, iron deposits in atherosclerotic lesions occurred secondary to iron overload (4). Some, but not all, prospective studies have shown that moderately high levels of body iron stores are a risk factor for cardiovascular disease, including atherosclerosis (5–9), although a meta-analysis of 12 prospective studies concluded that there was no evidence for a strong relation between iron status and coronary heart disease (9). Only one of three studies has shown blood donation to be cardioprotective (10–12).

The implication of iron overload in diabetes was evoked by a small case-control study in Finnish men (13) and confirmed in two population studies, one of which was prospective and showed relations between iron stores and diabetes (14,15). Further, high ferritin levels have been associated with the metabolic syndrome and measures of insulin resistance (16–21). A syndrome of liver iron overload was proposed by Moirand et al. (22),

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Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome; GGT, γ-glutamyl transferase; HOMA, homeostasis model assessment; HOMA-%β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IDF, International Diabetes Federation; NCEP-ATP III, National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III.

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

following an observation that there was a higher prevalence of metabolic disorders among patients with high ferritin, normal transferrin saturation, and normal transferrin without genetic hemochromatosis than among patients with genetic hemochromatosis; both groups had similar ferritin levels. The liver iron overload syndrome shares features with the metabolic or insulin resistance syndrome. The mechanisms of such an association have not been identified, and it has been hypothesized that the hyperinsulinemia of the metabolic syndrome could be related to an accumulation of iron in the liver (23).

Although ferritin is an indicator of cellular iron stores in healthy subjects, it provides little information on iron turnover in the body. Transferrin is a "shuttle protein" (24), mainly synthesized in the liver, and its principal role is to transport ionic iron to the liver, spleen, and bone marrow (25). Transferrin levels rise with iron deficiency and fall with iron stores.

Ferritin and transferrin were shown to independently predict hyperglycemia in a 3-year follow-up of our French cohort, Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) (26). We investigated, in the same cohort over a 6-year follow-up period, the relations between these two iron metabolism markers and the metabolic syndrome and its constituent abnormalities.

RESEARCH DESIGN AND METHODS

— A total of 5,212 men and women, aged 30–65 years, participated in the DESIR cohort, a longitudinal study aiming to clarify the development of the insulin resistance syndrome (27). Participants were recruited in 10 health examination centers from volunteers insured by the French Social Security system, which offers periodic health examinations free of charge. The protocol was approved by the ethics committee of Bicêtre Hospital, and participants provided informed consent.

Ferritin, transferrin, and C-reactive protein (CRP) were measured at baseline in 650 men and 650 women, randomly selected from among individuals examined at 3 years. We excluded participants with a baseline CRP >10 mg/l (43 individuals), because inflammation may increase serum ferritin, and those with "very low" ferritin, which might be due to anemia (<16 μg/l in men and <15 μg/l in women: 63 individuals), and "very high" ferritin, which might be due to hemochromatosis (>400 μg/l in men and >300 μg/l in women: 90 individuals) (28–31). Analyses are of participants with measures at baseline and at the 6-year follow-up of fasting glucose, insulin, triglycerides, HDL cholesterol, CRP, systolic and diastolic blood pressures, and waist circumference. The population studied included 469 men and 475 women.

Measures

Blood pressure was taken in a supine position after 5 min of rest; waist circumference (the smallest circumference between the lower rib and the iliac crests), weight, and height were measured in lightly clad participants, and the BMI was calculated. As part of the clinical examination, physicians noted the menopausal status of the women after discussion with them; hormone levels were not measured. Alcohol intake was determined from a self-questionnaire in which questions on wine, beer, cider, and spirits were asked; the number of grams of alcohol per day was then calculated. Drug treatment for hypertension, dyslipidemia, and diabetes was coded from information provided on this questionnaire

All biochemical measurements were from one of four health center examination laboratories at the Institut inter-Régionale pour la Santé, Blois, Chartres, or Orleans. Total cholesterol, HDL cholesterol, triglycerides, alanine aminotransferase (ALT), and γ glutamyl transferase (GGT) were assayed by a Technicon DAX24 automatic analyzer (Bayer Diagnostics, Puteaux, France) or a Kone Automate (Konelab, Evry, France). Fasting plasma glucose was measured by the glucose oxidase method using a Technicon RA100 (Bayer Diagnostics) or a Specific or Delta analyzer (Konelab). ALT and GGT were assayed by enzymatic methods, using a Technicon DAX24 automatic analyzer or a Specific or Delta analyzer. Interlaboratory variability was assessed monthly on normal and pathological values for each biological variable; the coefficients of variation for laboratories were <6% over the inclusion period. Insulin was centrally assayed on serum by a specific microenzyme immunoassay with an IMX chemistry analyzer (Abbott, Rungis, France). CRP levels were centrally assessed by an immunonephelometric method (Dade Behring Marburg); for serum ferritin and transferrin, Immunolatex spheres and nephelometry with a BNII nephelometer were used (Behring, Rueil Malmaison, France).

The outcome variables studied are the metabolic syndrome abnormalities defined according to the International Diabetes Federation (IDF) criteria (32); we used three syndrome definitions: the IDF definition and the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III (NCEP-ATP III) original and revised definitions (32–34). The IDF metabolic syndrome components are abdominal adiposity, waist circumference ≥94/80 cm (men/women); hyperglycemia, fasting plasma glucose ≥5.6 mmol/l or treatment for hyperglycemia; high blood pressure, systolic/diastolic blood pressure ≥130/85 mmHg or treatment for hypertension; hypo-HDL cholesterolemia, HDL cholesterol <1.03/1.29 mmol/l (men/women) or treatment for lipids; and hypertriglyceridemia, triglycerides ≥1.69 mmol/l or treatment for lipids. The IDF metabolic syndrome is present if individuals have abdominal adiposity and two or more of the other components (32). The original NCEP-ATP III metabolic syndrome is defined by the presence of three or more abnormalities: abdominal adiposity, waist circumference >102/88 cm (men/women); hyperglycemia, fasting plasma glucose ≥6.1 mmol/l; high blood pressure, systolic/diastolic blood pressure ≥130/85 mmHg; hypo-HDL cholesterolemia, HDL cholesterol <1.03/1.29 mmol/l (men/women); and hypertriglyceridemia, triglycerides ≥1.69 mmol/l (33). The revised NCEP-ATP III metabolic syndrome criteria include treatment for glucose, lipids, and hypertension in the corresponding abnormalities, with hyperglycemia defined as fasting plasma glucose ≥5.6 mmol/l (34). Hyperinsulinemia was defined when the insulin concentration was above the upper quartile for each group, and homeostasis model assessment (HOMA)2 was used to measure insulin resistance (HOMA2-IR) and β-cell function (HOMA2-%β) (35) with quartile cut points.

Statistical methods

Analyses are by sex and for women according to menopausal status. Because of skewed distributions, ferritin levels were log transformed. Characteristics of the population studied are described by means ± SD, geometric means, and percentages and are compared between

Table 1—*Baseline characteristics of men and women studied: DESIR*

		Women		*P* values	
	Men	Premenopausal	Postmenopausal	Men and women	Pre- and postmenopausal women
n	469	278	197		
Age (years)	47 ± 10	41 ± 7	57 ± 5	0.3	<0.0001
Ferritin (μg/l)	178 ± 90	56.4 ± 40.8	91.7 ± 54.3	<0.0001	<0.0001
Geometric mean (μg/l)	152	45.9	76.5	<0.0001	<0.000
Transferrin (g/l)	2.27 ± 0.30	2.33 ± 0.36	2.30 ± 0.36	0.1	0.2
CRP (mg/l)	1.61 ± 1.43	1.75 ± 1.60	1.88 ± 1.57	0.05	0.1
Waist circumference (cm)	89 ± 9	75 ± 9	80 ± 10	<0.0001	<0.0001
BMI (kg/m²)	25.4 ± 3.2	23.3 ± 3.6	24.7 ± 3.7	<0.0001	<0.0001
Systolic blood pressure (mmHg)	132 ± 15	122 ± 15	132 ± 16	<0.0001	<0.0001
Diastolic blood pressure (mmHg)	82 ± 10	76 ± 10	79 ± 9	<0.0001	<0.0001
Total cholesterol (mmol/l)	5.76 ± 0.92	5.42 ± 0.86	6.01 ± 0.97	0.1	<0.0001
HDL cholesterol (mmol/l)	1.50 ± 0.37	1.76 ± 0.42	1.87 ± 0.46	<0.0001	0.009
Triglycerides (mmol/l)	1.18 ± 0.63	0.94 ± 0.53	0.99 ± 0.48	<0.0001	0.02
Plasma glucose (mmol/l)	5.54 ± 0.60	5.07 ± 0.70	5.26 ± 1.08	<0.0001	0.004
Serum insulin (pmol/l)	47.5 ± 28.2	42.8 ± 22.2	42.3 ± 21.9	0.01	0.9
HOMA2-IR	1.05 ± 0.63	0.92 ± 0.49	0.93 ± 0.49	<0.0001	0.8
HOMA2-%β	78 ± 29	87 ± 31	81 ± 25	<0.001	0.009
Alcohol consumption (g/day)	23 ± 22	6.7 ± 10.3	8.6 ± 12.1	<0.0001	0.7
ALT (U/l)	29.7 ± 16.7	17.9 ± 7.4	21.7 ± 9.1	<0.0001	<0.0001
GGT (U/l)	39.7 ± 39.5	20.5 ± 15.8	23.0 ± 15.0	<0.0001	0.007
Participants with medication for					
Hypertension	48 (10.2)	18 (6.5)	36 (18.3)	0.6	<0.0001
Dyslipidemia	41 (8.7)	4 (1.4)	24 (12.2)	0.09	<0.0001
Hyperglycemia	7 (1.5)	1 (0.4)	1 (0.5)	0.9	0.9

Data are *n*, means ± SD, or *n* (%).

groups by Wilcoxon or χ^2 tests. Associations between parameters were evaluated by Spearman correlation coefficients. Analyses were performed with SAS (version 9.1.3; SAS Institute, Cary, NC).

Age-adjusted logistic regression models were used to study the presence of the IDF-defined metabolic syndrome abnormalities, the IDF and NCEP-ATP III original and revised metabolic syndrome criteria, hyperinsulinemia, insulin resistance, and β-cell function according to the two iron parameters, log(ferritin) and transferrin, both studied as continuous variables at inclusion and at the 6-year follow-up. The 6-year models were adjusted for the presence of the corresponding abnormality at inclusion; thus, the models essentially tested whether the iron parameters were associated with the change in syndrome components during the 6-year period. To increase the power of our analyses, data from men and women were pooled, and the same relations were studied after adjustments for the three groups. All associations are expressed as the odds ratio (OR) for a 1 SD increase in the baseline log(ferritin) and transferrin, using the respective group SDs. This enables a comparison of the strength of the association for the two iron markers with the various outcomes studied. The incidence of the IDF-defined metabolic syndrome was studied at the 6-year follow-up among 371 men and 256 pre- and 150 postmenopausal women without metabolic syndrome at entry, for combinations of high and low levels of the iron parameters: the upper one-third and the lower two-thirds of the sex-specific ferritin and transferrin distributions, with tertiles 208, 58, and 109 μg/l for ferritin and 2.37, 2.45, and 2.42 g/l for transferrin in men, premenopausal women, and postmenopausal women, respectively.

RESULTS — At baseline, the population was middle-aged: men 47 years, premenopausal women 41 years, and postmenopausal women 57 years (Table 1). The average ferritin concentration in men (178 μg/l) was nearly two times higher than in postmenopausal women (92 μg/l) and threefold higher than in premenopausal women. In contrast, mean transferrin concentrations were similar in the three groups (2.3 g/l).

Ferritin and transferrin were negatively correlated, but this correlation was only statistically significant in premenopausal women ($r = -0.30$) (Table 2). CRP was not correlated with ferritin but was correlated with transferrin in both pre- and postmenopausal women. Waist circumference, triglycerides, insulin, and HOMA-IR were significantly correlated with ferritin and with transferrin in all three groups. Higher values of hepatic markers, ALT and GGT, were significantly correlated with both ferritin and transferrin (exceptions were transferrin with ALT in premenopausal women and with GGT in postmenopausal women).

In men and in postmenopausal women, the metabolic syndrome was more frequent than in premenopausal women for the IDF-defined syndrome: 21, 24, and 8%, respectively (Table 3). However, the standardized ORs associated with the syndrome were not dissimilar among these three groups: for the IDF-defined syndrome, ORs at baseline for log(ferritin) were 1.49, 1.80, and 2.10

Table 2—*Spearman correlation coefficients of baseline characteristics with ferritin and transferrin, according to sex and menopausal status: DESIR*

	Men		Premenopausal women		Postmenocpausal women	
	Ferritin	Transferrin	Ferritin	Transferrin	Ferritin	Transferrin
n	469		278		197	
Ferritin	—	−0.05	—	−0.30*	—	−0.05
Age	0.01	0.03	0.16†	−0.13‡	0.19†	0.06
CRP	0.04	0.05	0.05	0.24*	0.13	0.17‡
Waist	0.21*	0.21*	0.15‡	0.14‡	0.25*	0.19‡
BMI	0.24*	0.19*	0.12‡	0.07	0.19†	0.17‡
Systolic blood pressure	0.10‡	0.06	0.11	0.08	0.15‡	-0.00
Diastolic blood pressure	0.13†	0.16*	0.08	0.08	0.09	-0.07
HDL cholesterol	−0.09	−0.02	−0.04	−0.11	−0.15‡	0.01
Triglycerides	0.16*	0.16*	0.12‡	0.35*	0.27*	0.18‡
Glucose	0.14†	0.04	0.25*	−0.08	0.21†	0.20†
Insulin	0.24*	0.16†	0.17†	0.19†	0.26*	0.18†
HOMA2-IR	0.24*	0.16*	0.19†	0.18†	0.27*	0.19†
HOMA2-%β	0.17†	0.15*	0.02	0.24*	0.11	0.05
Alcohol	0.06	0.11‡	0.15‡	0.09	0.11	0.01
ALT	0.20*	0.24*	0.13‡	0.01	0.22†	0.20†
GGT	0.19*	0.24*	0.24*	0.13‡	0.27*	0.11

*$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$.

and for transferrin were 1.94, 2.14, and 2.22, respectively, and all were statistically significant. At the 6-year follow-up, the corresponding ORs were lower: 1.46, 1.62, and 1.28 for log(ferritin) and 1.41, 1.51, and 1.63, for transferrin, respectively. These relations were statistically significant ($P < 0.05$), with the exception of ferritin in premenopausal women.

Both baseline ferritin and transferrin concentrations were associated with many of the metabolic syndrome abnormalities, with hyperinsulinemia, and with HOMA-IR and HOMA-%β, both cross-sectionally and after 6 years of follow-up, although these relations were not always statistically significant (Table 3). The most consistent relations were with hypertriglyceridemia, hyperinsulinemia, and the metabolic syndrome by any definition, with slightly stronger relations at baseline than at follow-up. These relations remained after further adjustment for alcohol intake, CRP, ALT, and GGT (data not shown). There were fewer significant relations in women, partly due to the fact that numbers in both the pre- and postmenopausal groups were smaller.

Concentrations of both ferritin and transferrin above the group-specific higher tertiles were associated with a significantly higher incidence of the IDF-defined syndrome in men and postmenopausal women (both $P < 0.004$), and there was a trend for a higher incidence in premenopausal women ($P = 0.08$) (Fig. 1). In these younger women, only 10% had an incident metabolic syndrome compared with 17% in men and 21% in postmenopausal women. In the pooled data, the ORs associated with high values of the iron parameters, separately or together, were significantly higher than in the 45% of our population with both parameters below the upper tertile.

CONCLUSIONS — Higher levels of ferritin and transferrin at baseline were associated with the metabolic syndrome anomalies, hyperinsulinemia, high HOMA-IR, and low HOMA-%β and with an increased prevalence of the metabolic syndrome. They were also associated, over the 6-year follow-up, with a worsening profile.

Although our cross-sectional results on ferritin are similar to those found in the literature (16–21), we have been able to analyze this relation longitudinally and, further, to show that transferrin is also associated with the metabolic syndrome. In the subgroup of individuals with ferritin and transferrin both above the upper tertile, there was a four times higher odds of incident IDF-defined metabolic syndrome compared with those with both iron parameters below the upper tertile.

In our previous analysis (26) we studied only two outcomes: fasting insulin and glucose concentrations, and we found the same results here both at baseline and longitudinally; in the present analysis, with the exclusion criteria for CRP and ferritin, the population studied is smaller, but the follow-up is longer. In accordance with the results from the National Health and Nutrition Examination Survey (19) but in contrast to the results of Sheu et al. (18) in a Chinese population, the ferritin level was found to be associated with the metabolic syndrome and hyperinsulinemia in both men and postmenopausal women, and this relationship also held for predicting change over 6 years, although with a lower OR. We also found that this association was independent of CRP and liver enzymes.

Our study is limited by the small sample size, particularly for pre- and postmenopausal women. Not all individuals had data available at 6 years, but they had similar mean values for all parameters, except for men, who had significantly higher baseline CRP, glucose, insulin, and triglycerides and lower HDL cholesterol, and postmenopausal women, who had a higher mean triglyceride concentration. Consequently, the metabolic syndrome would be more frequent in those lost to follow-up, and very likely the incidence would also have been higher, leading to a lowering of power in the analysis.

The frequency of the metabolic syndrome increased with both serum transferrin and ferritin, cross-sectionally and with change after 6 years, adding credibility to the hypothesis that iron metabolism

Table 3—*Frequencies and age-adjusted ORs (95% CI) for the metabolic syndrome abnormalities and the metabolic syndrome according to standardized values of log(ferritin) and transferrin, at entry* and at 6 years follow-up†: DESIR*

	% with abnormalities		Log(ferritin)		Transferrin	
	Inclusion	6 years	Inclusion	6 years	Inclusion	6 years
Men (n = 469)						
Abdominal obesity	32	39	1.48 (1.18–1.85)	1.44 (1.11–1.87)	1.62 (1.31–1.99)	1.14 (0.89–1.46)
High blood pressure	67	70	1.14 (0.94–1.39)	1.38 (1.10–1.73)	1.08 (0.88–1.32)	1.43 (1.12–1.81)
Hypo-HDL cholesterolemia	14	20	1.53 (1.12–2.08)	1.22 (0.91–1.63)	1.72 (1.31–2.25)	1.48 (1.13–1.94)
Hypertriglyceridemia	24	31	1.47 (1.15–1.88)	1.35 (1.06–1.71)	2.04 (1.62–2.58)	1.50 (1.19–1.89)
Hyperglycemia	48	44	1.24 (1.02–1.50)	1.21 (0.99–1.48)	1.02 (0.84–1.22)	1.33 (1.09–1.63)
Metabolic syndrome						
IDF	21	28	1.49 (1.14–1.94)	1.46 (1.13–1.89)	1.94 (1.53–2.47)	1.41 (1.10–1.81)
NCEP original	7.3	9.0	2.16 (1.34–3.49)	1.73 (1.13–2.64)	1.09 (0.77–1.55)	1.48 (1.07–2.08)
NCEP revised	20	28	1.62 (1.22–2.14)	1.42 (1.09–1.84)	1.78 (1.39–2.27)	1.54 (1.20–1.97)
Hyperinsulinemia	25	33	1.66 (1.30–2.13)	1.34 (1.06–1.69)	1.52 (1.22–1.88)	1.48 (1.19–1.85)
High HOMA-IR	25	32	1.69 (1.31–2.18)	1.34 (1.06–1.69)	1.58 (1.27–1.96)	1.47 (1.08–1.84)
Low HOMA-%β	25	32	1.35 (1.07–1.70)	1.10 (0.88–1.38)	1.46 (1.18–1.81)	1.32 (1.06–1.65)
Premenopausal women (n = 278)						
Abdominal obesity	25	39	1.54 (1.13–2.09)	1.82 (1.29–2.56)	1.79 (1.30–2.46)	1.50 (1.06–2.14)
High blood pressure	34	36	1.28 (0.96–1.69)	1.12 (0.82–1.54)	1.25 (0.94–1.66)	1.33 (0.98–1.82)
Hypo-HDL cholesterolemia	9	14	1.81 (1.17–2.80)	0.99 (0.67–1.47)	1.59 (1.03–2.46)	1.35 (0.93–1.96)
Hypertriglyceridemia	10	14	1.99 (1.29–3.07)	1.24 (0.83–1.86)	2.50 (1.61–3.88)	1.24 (0.82–1.87)
Hyperglycemia	17	16	1.58 (1.13–2.21)	1.23 (0.84–1.80)	0.89 (0.62–1.28)	1.41 (0.96–2.08)
Metabolic syndrome						
IDF	7.9	15	2.10 (1.27–3.48)	1.28 (0.85–1.94)	2.22 (1.32–3.75)	1.63 (1.05–2.52)
NCEP original	4.0	4.7	1.72 (0.89–3.35)	1.26 (0.65–2.45)	2.88 (1.50–5.51)	0.76 (0.39–1.45)
NCEP revised	6.5	11	2.27 (1.26–4.09)	1.66 (1.03–2.68)	3.36 (1.78–6.32)	1.19 (0.71–1.99)
Hyperinsulinemia	25	30	1.70 (1.26–2.20)	1.22 (0.90–1.65)	1.62 (1.20–2.19)	1.58 (1.16–2.15)
High HOMA-IR	25	29	1.74 (1.28–2.35)	1.30 (0.95–1.78)	1.58 (1.17–2.15)	1.56 (1.14–2.14)
Low HOMA-%β	25	32	1.42 (1.05–1.93)	1.26 (0.93–1.71)	2.00 (1.47–2.73)	1.39 (1.02–1.88)
Postmenopausal women (n = 197)						
Abdominal obesity	46	58	1.55 (1.13–2.11)	1.12 (0.79–1.59)	1.53 (1.12–2.08)	1.15 (0.80–1.65)
High blood pressure	64	71	1.12 (0.82–1.53)	1.41 (0.98–2.04)	0.87 (0.64–1.19)	0.72 (0.51–1.02)
Hypo-HDL cholesterolemia	18	31	1.86 (1.20–2.89)	1.28 (0.87–1.88)	2.32 (1.55–3.47)	1.31 (0.89–1.94)
Hypertriglyceridemia	18	33	1.61 (1.04–2.49)	2.19 (1.46–3.27)	2.74 (1.79–4.20)	1.24 (0.84–1.84)
Hyperglycemia	24	23	1.45 (1.02–2.06)	1.43 (0.97–2.11)	1.32 (0.95–1.83)	1.32 (0.93–1.88)
Metabolic syndrome						
IDF	24	35	1.80 (1.21–2.68)	1.62 (1.10–2.38)	2.14 (1.47–3.10)	1.51 (1.02–2.22)
NCEP original	8.6	12	1.74 (0.96–2.72)	1.77 (1.00–3.13)	1.37 (0.84–2.23)	1.20 (0.74–1.93)
NCEP revised	21	34	1.88 (1.22–2.88)	1.62 (1.08–2.43)	2.10 (1.42–3.09)	1.07 (0.71–1.61)
Hyperinsulinemia	26	34	2.23 (1.52–3.27)	1.34 (0.93–1.92)	1.20 (0.86–1.67)	1.22 (0.87–1.71)
High HOMA-IR	25	32	2.16 (1.46–3.17)	1.30 (0.90–1.87)	1.19 (0.85–1.66)	1.26 (0.89–1.77)
Low HOMA-%β	25	34	1.37 (0.97–1.94)	1.16 (0.83–1.62)	1.04 (0.75–1.44)	1.23 (0.89–1.70)
All individuals (n = 944)						
Abdominal obesity	33	43	1.52 (1.30–1.77)	1.44 (1.21–1.72)	1.62 (1.39–1.88)	1.20 (1.01–1.43)
High blood pressure	57	60	1.19 (1.03–1.36)	1.30 (1.11–1.53)	1.06 (0.92–1.22)	1.22 (1.04–1.44)
Hypo-HDL cholesterolemia	13	20	1.67 (1.34–2.07)	1.17 (0.97–1.43)	1.82 (1.50–2.21)	1.42 (1.18–1.72)
Hypertriglyceridemia	19	26	1.60 (1.32–1.94)	1.50 (1.25–1.79)	2.24 (1.86–2.69)	1.39 (1.17–1.66)
Hyperglycemia	34	31	1.36 (1.17–1.58)	1.27 (1.08–1.49)	1.03 (0.89–1.19)	1.34 (1.14–1.57)
Metabolic syndrome						
IDF	18	26	1.70 (1.39–2.08)	1.47 (1.22–1.78)	2.01 (1.67–2.43)	1.46 (1.22–1.76)
NCEP original	6.6	8.4	1.85 (1.37–2.51)	1.70 (1.27–2.28)	1.37 (1.07–1.77)	1.27 (1.00–1.63)
NCEP revised	16	25	1.78 (1.43–2.20)	1.52 (1.25–1.85)	1.99 (1.63–2.42)	1.37 (1.13–1.66)
Hyperinsulinemia	25	32	1.78 (1.50–2.10)	1.30 (1.10–1.53)	1.46 (1.26–1.70)	1.46 (1.25–1.71)
High HOMA-IR	25	31	1.80 (1.52–2.14)	1.32 (1.11–1.56)	1.48 (1.27–1.73)	1.45 (1.23–1.70)
Low HOMA-%β	25	32	1.34 (1.14–1.57)	1.14 (0.97–1.34)	1.48 (1.27–1.73)	1.32 (1.13–1.54)

*Logistic model for each abnormality at entry included age, log(ferritin), and transferrin as explanatory variables; models for all individuals were adjusted for group.
†Logistic model for each abnormality at the 6-year examination included age, log(ferritin), transferrin, and the corresponding abnormality at entry as explanatory variables; models for all individuals were adjusted for group.

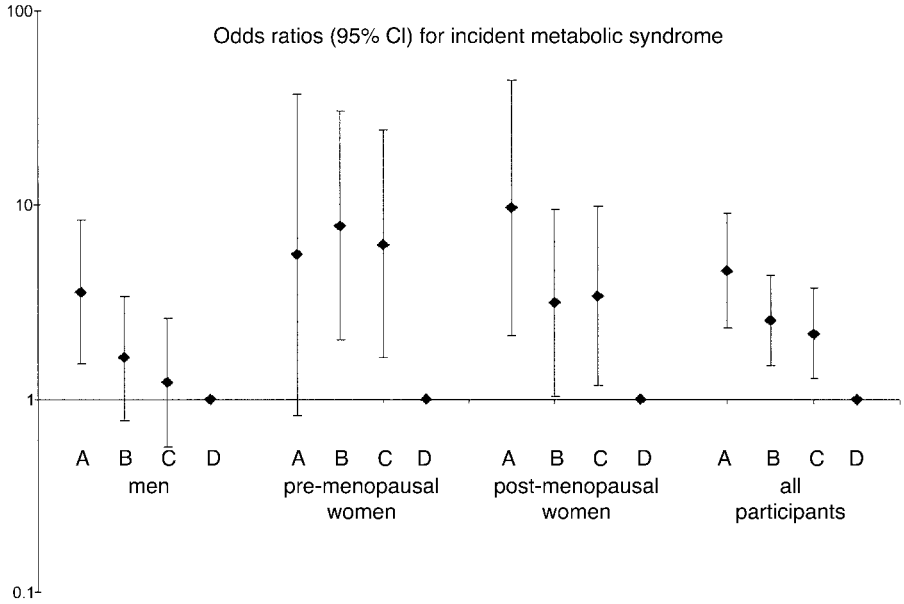

Figure 1—*Age-adjusted ORs (95% CI) for the 6-year incidence of the IDF-defined metabolic syndrome according to high ferritin and transferrin levels (both above the upper tertiles) (A), lower ferritin and high transferrin levels (B), high ferritin and lower transferrin levels (C), and lower ferritin and lower transferrin levels (D). High and low levels were defined according to the three groups: men, premenopausal women, and postmenopausal women (DESIR).*

might participate in the etiology of insulin resistance. Transferrin has been shown to be a major determinant of lipolytic activity in adipocytes by a pro-oxidative mechanism (36) and thus may be involved in enhanced free fatty acid metabolism in the development of insulin resistance and its associated abnormalities. Transferrin has also been shown to be an insulin agonist, and this effect is likely to extend to skeletal muscle (37,38). Moreover, an insulin resistance phenotype has been associated with liver iron overload, and it is characterized by normal transferrin saturation, normal transferrin, and high ferritin in patients without genetic hemochromatosis (22). The consistent association of ferritin and transferrin with both hypertriglyceridemia and hyperinsulinemia in the present study are in accord with these hypotheses. The mechanism proposed by Ferrannini (23), that hyperinsulinemia may be directly responsible for the accumulation of iron in the liver, appears to be less in agreement with our findings that baseline ferritin and transferrin levels were predictive of the metabolic syndrome and hyperinsulinemia changes during follow-up.

Whatever the complex mechanisms that underlie these associations, the present data indicate that not only iron stores but also iron transport is involved in the development of the metabolic syndrome and very likely of insulin resistance. Similar analyses should be performed in other populations, as they may have important implications for screening and prevention of type 2 diabetes and its complications.

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APPENDIX

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References

1. Sullivan JL: Iron and the sex difference in heart disease risk. *Lancet* 1:1293–1294, 1981
2. Fuchs J, Podda M, Packer L, Kaufmann R: Morbidity risk in HFE associated hereditary hemochromatosis C282Y heterozygotes. *Toxicology* 180:169–181, 2002
3. Moczulski DK, Grzeszczak W, Gawlik B: Role of hemochromatosis C282Y and H63D mutations in HFE gene in development of type 2 diabetes and diabetic nephropathy. *Diabetes Care* 24:1187–1191, 2001
4. Araujo JA, Romano EL, Brito BE, Parthe V, Romano M, Bracho M, Montano RF, Cardier J: Iron overload augments the development of atherosclerotic lesions in rabbits. *Arterioscler Thromb Vasc Biol* 15: 1172–1180, 1995
5. Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R: High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation* 86:803–811, 1992
6. Kiechl S, Willeit J, Egger G, Poewe W, Oberhollenzer F: Body iron stores and the risk of carotid atherosclerosis: prospective results from the Bruneck study. *Circulation* 96:3300–3307, 1997
7. Tuomainen TP, Punnonen K, Nyyssönen K, Salonen JT: Association between body iron stores and the risk of acute myocardial infarction in men. *Circulation* 97: 1461–1466, 1998
8. Reunanen A, Takkunen H, Knekt P, Seppanen R, Aromaa A: Body iron stores, dietary iron intake and coronary heart disease mortality. *J Intern Med* 238:223–230, 1995
9. Danesh J, Appleby P: Coronary heart disease and iron status: meta-analyses of prospective studies. *Circulation* 99:852–854, 1999
10. Salonen JT, Tuomainen TP, Salonen R, Lakka TA, Nyyssonen K: Donation of blood is associated with reduced risk of myocardial infarction: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Epidemiol* 148:445–451, 1998
11. Meyers DG, Strickland D, Maloley PA, Seburg JK, Wilson JE, McManus BF: Possible association of a reduction in cardiovascular events with blood dona-

tion. *Heart* 78:188–193, 1997
12. Ascherio A, Rimm EB, Giovannucci E, Willett WC, Stampfer MJ: Blood donations and risk of coronary heart disease in men. *Circulation* 103:52–57, 2001
13. Salonen JT, Tuomainen TP, Nyyssonen K, Lakka HM, Punnonen K: Relation between iron stores and non-insulin dependent diabetes in men: case-control study. *BMJ* 317:727–730, 1998
14. Ford ES, Cogswell ME: Diabetes and serum ferritin concentration among U.S. adults. *Diabetes Care* 22:1978–1983, 1999
15. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB: Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *JAMA* 291:711–717, 2004
16. Tuomainen TP, Nyyssonen K, Salonen R, Tervahauta A, Korpela H, Lakka T, Kaplan GA, Salonen JT: Body iron stores are associated with serum insulin and blood glucose concentrations: population study in 1,013 eastern Finnish men. *Diabetes Care* 20:426–428, 1997
17. Fernandez-Real JM, Ricart-Engel W, Arroyo E, Balanca R, Casamitjana-Abella R, Cabrero D, Fernandez-Castaner M, Soler J: Serum ferritin as a component of the insulin resistance syndrome. *Diabetes Care* 21:62–68, 1998
18. Sheu WH, Chen YT, Lee WJ, Wang CW, Lin LY: A relationship between serum ferritin and the insulin resistance syndrome is present in non-diabetic women but not in non-diabetic men. *Clin Endocrinol* 58: 380–385, 2003
19. Jehn M, Clark JM, Guallar E: Serum ferritin and risk of the metabolic syndrome in U.S. adults. *Diabetes Care* 27:2422–2428, 2004
20. Wrede CE, Buettner R, Bollheimer LC, Scholmerich J, Palitzsch KD, Hellerbrand C: Association between serum ferritin and the insulin resistance syndrome in a representative population. *Eur J Endocrinol* 154:333–340, 2006
21. Gonzalez AS, Guerrero DB, Soto MB, Diaz SP, Martinez-Olmos M, Vidal O: Metabolic syndrome, insulin resistance and the inflammation markers C-reactive protein and ferritin. *Eur J Clin Nutr* 60:802–809, 2006
22. Moirand R, Mortaji AM, Loreal O, Paillard F, Brissot P, Deugnier Y: A new syndrome of liver iron overload with normal transferrin saturation. *Lancet* 349:95–97, 1997
23. Ferrannini E: Insulin resistance, iron, and the liver. *Lancet* 355:2181–2182, 2000
24. Huebers HA, Huebers E, Csiba E, Rummel W, Finch CA: The significance of transferrin for intestinal iron absorption. *Blood* 61:283–290, 1983
25. Andrews NC, Levy JE: Iron is hot: an update on the pathophysiology of hemochromatosis. *Blood* 92:1845–1851, 1998
26. Fumeron F, Pean F, Driss F, Balkau B, Tichet J, Marre M, Grandchamp B, DESIR Study Group: Ferritin and transferrin are both predictive of the onset of hyperglycemia in men and women over 3 years: the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study. *Diabetes Care* 29:2090–2094, 2006
27. Balkau B, Eschwège E, Tichet J, Marre M: Proposed criteria for the diagnosis of diabetes: evidence from a French epidemiological study (D.E.S.I.R.). *Diabetes Metab* 23:428–434, 1997
28. Mainous AG 3rd, Wells BJ, Everett CJ, Gill JM, King DE: Association of ferritin and lipids with C-reactive protein. *Am J Cardiol* 93:559–562, 2004
29. Milman N, Ovesen L, Byg K, Graudal N: Iron status in Danes updated 1994. I. Prevalence of iron deficiency and iron overload in 1332 men aged 40–70 years: influence of blood donation, alcohol intake, and iron supplementation. *Ann Hematol* 78:393–400, 1999
30. Milman N, Byg KE, Ovesen L, Kirchhoff M, Jürgensen KS: Iron status in Danish women 1984–1994: a cohort comparison of changes in iron stores and the prevalence of iron deficiency and iron overload. *Eur J Haematology* 71:51–61, 2003
31. Galan P, Yoon HC, Preziosi P, Viteri F, Valeix P, Fieux B, Briançon S, Malvy D, Roussel AM, Favier A, Hercberg S: Determining factors in the iron status of adult women in the SU.VI.MAX study: SUpplementation en VItamines et Mineraux AntioXydants. *Eur J Clin Nutr* 52:383–388, 1998
32. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group: The metabolic syndrome—a new worldwide definition. *Lancet* 366:1059–1062, 2005
33. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
34. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute: Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112:2735–2752, 2005
35. Wallace TM, Levy JC, Matthews DR: Use and abuse of HOMA modeling. *Diabetes Care* 27:1487–1495, 2004
36. Rumberger JM, Peters T, Burrington C, Green A: Transferrin and iron contribute to the lipolytic effect of serum in isolated adipocytes. *Diabetes* 53:2535–2541, 2004
37. Vargas L, Kawada ME, Bazaes S, Karplus PA, Faerman CH: Insulin antagonism: a novel role for human serum transferrin. *Horm Metab Res* 30:113–117, 1998
38. Green A, Basile R, Rumberger JM: Transferrin and iron induce insulin resistance of glucose transport in adipocytes. *Metabolism* 55:1042–1045, 2006