Ferritin and transferrin are associated with metabolic syndrome abnormalities and their change over time in a general population. The D.E.S.I.R. Study

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OBJECTIVE—To study cross-sectional and longitudinal relations between iron stocks (ferritin) and the iron transport protein (transferrin) with the metabolic syndrome and its abnormalities.

METHODS—469 men, 278 pre- and 197 post-menopausal women from the French D.E.S.I.R. cohort, aged 30-65 years, were followed over six years.

RESULTS—Higher concentrations of both ferritin and transferrin were associated with the IDF, ~~and~~ NCEP-ATP III original and revised metabolic syndromes at baseline: for the IDF 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 pre-menopausal women, 1.80 (1.21-2.68) for post-menopausal women; for transferrin they were respectively: 1.94 (1.53-2.47), 2.22 (1.32-3.75), 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 log(ferritin) in all three groups: 1.46 (1.13-1.89), 1.28 (0.85-1.94), 1.62 (1.10-2.38), and transferrin: 1.41 (1.10-1.81), 1.63 (1.05-2.52), 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 four-fold higher when ferritin and transferrin 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 post-menopausal women.

Key words: ferritin, transferrin, waist, triglycerides, glucose, insulin, metabolic syndrome,

Abreviations ALT: alanine aminotransferase; CI: confidence interval; CRP: C-reactive protein; D.E.S.I.R: Data from an Epidemiological Study on the Insulin Resistance syndrome; IDF: International Diabetes Federation; GGT: gamma glutamyl transferase; NCEP-ATP III: National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults - Adult Treatment Panel III; OR: odds ratio; SD: standard deviation

Sullivan formulated in 1981, hypotheses that attributed the sex difference in heart disease risk to differences in iron stores (1). Hereditary haemochromatosis, 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 found blood donation to be cardio-protective (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), following an observation that there was a higher prevalence of metabolic disorders among patients with high ferritin, normal transferrin saturation, normal transferrin but without genetic haemochromatosis than among patients with genetic haemochromatosis; 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).

While ferritin is an indicator of cellular iron stores in healthy subjects, it provides little information on iron turn-over in the body. Transferrin is a “shuttle protein” (24), mainly synthesized in the liver and its ~~main~~ 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 have been shown to independently predict hyperglycemia in a three year follow up of our French cohort: Data for an Epidemiological Study on the Insulin Resistance Syndrome (D.E.S.I.R.) (26). We investigate, 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

Study population

A total of 5212 men and women, aged 30-65 years, participated in the cohort study: D.E.S.I.R. (Data from an Epidemiological Study on the Insulin Resistance Syndrome), a longitudinal study that aims to clarify the development of the insulin resistance syndrome (27). Participants were recruited in ten 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 signed an 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 three years. We excluded participants with a baseline CRP >10mg/l (43 individuals), because inflammation may increase serum ferritin and those with “very low” ferritin, which might be due to anemia: <16µg/l in men, <15µg/l in women (63 individuals), and “very high” ferritin, which might be due to haemochromatosis: >400µg/l in men and >300µg/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 minutes of rest and 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 calculated. As part of the clinical examination, ~~the~~ 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 where 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 centre examination laboratories at IRSA, Blois, Chartres or Orleans. Total cholesterol, HDL-cholesterol, triglycerides, alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) were assayed by a DAX 24 (Bayer Diagnostics, Puteaux, France) or a KONE (Evry, France). Fasting plasma glucose was measured by the glucose-oxidase method, using a Technicon RA100 (Bayer Diagnostics, Puteaux, France) or a Specific or a Delta (Konelab, Evry, France). ALT and GGT were assayed by enzymatic methods, using a Technicon DAX24 automatic analyzer (Bayer Diagnostics, Puteaux, France) or a Specific or a Delta (Konelab, Evry, France). Inter-laboratory variability was assessed monthly on normal and pathological values for each biologic variable, the coefficients of variation for laboratories were lower than 6% over the inclusion period. Insulin was centrally assayed on serum by a specific micro-enzyme immunoassay with an IMX (Abbott, Rungis, France). CRP levels were centrally assessed by immunonephelemetric method (Dade Behring Marburg), serum ferritin and transferrin used Immunolatex spheres and nephelometry with a BNII nepholemeter (Behring, Rueil Malmaison, France).

The outcome variables studied are the metabolic syndrome abnormalities defined according to the International Diabetes Federation (IDF) criteria (32), and we used three

syndrome definitions: IDF, 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 syndromes (32-34). The IDF syndrome components are: abdominal adiposity, waist circumference ≥94/80cm men/women; hyperglycemia, fasting plasma glucose ≥5.6mmol/l or treatment for hyperglycemia; high blood pressure, systolic/diastolic blood pressure ≥130/85mmHg or treatment for hypertension; hypo HDL-cholesterolemia, HDL-cholesterol <1.03/1.29mmol/l men/women or treatment for lipids; hypertriglyceridemia, triglycerides ≥1.69mmol/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 NCEP-ATP III syndrome is defined by the presence of three or more abnormalities: abdominal adiposity, waist circumference >102/88cm men/women; hyperglycemia, fasting plasma glucose ≥6.1 mmol/l; high blood pressure, systolic/diastolic blood pressure ≥130/8mmHg; hypo-HDL cholesterolemia, HDL-cholesterol <1.03/1.29mmol/l men/women; hypertriglyceridemia, triglycerides ≥1.69mmol/l (33). The revised NCEP-ATP III syndrome includes treatment for glucose, lipids and hypertension in the corresponding abnormalities, and hyperglycemia is a fasting plasma glucose ≥5.6mmol/l (34). Hyperinsulinemia was defined when the insulin concentration was above the upper quartile for each group, and insulin resistance (HOMA2-IR) and β -cell function (HOMA2-%β), evaluated by the HOMA2 model (35), used quartile cut-points.

Statistical methods

Analyses are by gender and for women according to menopausal status. Because of skewed distributions, ferritin levels were log-transformed. Characteristics of the studied population are described by means (SD), geometric means, percentages and compared between groups by Wilcoxon or χ^2 tests. Associations between parameters were evaluated by Spearman correlation coefficients.

Age-adjusted logistic regression models were used to study the presence of the IDF defined metabolic syndrome abnormalities, the IDF, NCEP original and revised metabolic syndromes, hyperinsulinaemia, insulin resistance and β-cell function according to the two iron parameters at baseline: 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 tested essentially 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 studied, after also adjusting for the three groups. All associations were expressed as the odds ratio (OR) for a one standard deviation increase in the baseline log(ferritin) and transferrin, using the respective group standard deviations. This enables the 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, 256 pre- and 150 post-menopausal women without the 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, 109 µg/l for ferritin and 2.37, 2.45, 2.42 g/l for transferrin in men, pre- and post-menopausal women respectively.

Analyses used: SAS Version 9.1.3 (SAS Institute Inc. Cary, NC USA).

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

Ferritin and transferrin were negatively correlated, but this was only statistically significant in pre-menopausal women ($r = -0.30$) (Table 2). CRP was not correlated with ferritin, but was correlated with transferrin in both pre and post-menopausal 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 pre-menopausal women and with GGT in post-menopausal women).

In men and in post-menopausal women the syndrome was more frequent than in pre-menopausal women, for the IDF syndrome: 21%, 24% and 8% respectively (Table 3). However, the standardized odds ratios associated with the syndrome were not dissimilar between these three groups: for the IDF syndrome at baseline for log(ferritin) 1.49, 1.80, 2.10, respectively, and for transferrin 1.94, 2.14, 2.22 and all were statistically significant. At the six year follow-up, the corresponding odds ratios were lower: 1.46, 1.62, 1.28 for log(ferritin) and 1.41, 1.51, 1.63, for transferrin, respectively. These relations were statistically significant ($p < 0.05$), with the exception of ferritin in pre-menopausal women.

Both baseline ferritin and transferrin concentrations were associated with many of the metabolic syndrome abnormalities, with hyperinsulinemia, 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 hyper-triglyceridemia, hyperinsulinemia and the metabolic syndrome by any definition, with slightly stronger relations at baseline than at follow-up. These relations remained after further

adjustment on 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 pos-menopausal 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 post-menopausal women (both $p < 0.004$), and there was a trend for a higher incidence in pre-menopausal women ($p = 0.08$) (Fig. 1). In these younger women there were only 10% who had an incident metabolic syndrome, in comparison to 17% in the men and 21% in the post-menopausal women. In the-pooled data, the odds ratios 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.

DISCUSSION— 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 syndromes. They were also associated, over the 6-year follow-up, with a worsening profile.

While 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 sub-group of individuals with ferritin and transferrin both above the upper tertile, there was a four times higher odds of incident IDF-defined metabolic syndrome, in comparison 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 find 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 NHANES (19) but

in contrast to Sheu et al. in a Chinese population (18), the ferritin level was found to be associated with the metabolic syndrome and hyperinsulinemia in both men and post-menopausal women and this relationship also held for predicting change over 6 years, although with a lower odds ratio. We also found that this association was independent of CRP and liver enzymes.

Our study is limited by the small sample size, particularly in pre- and post-menopausal women. Not all individuals had data available at 6 years, but they had similar mean values for all parameters, excepting men who had a significantly higher baseline CRP, glucose, insulin, triglycerides and a lower HDL-cholesterol, and post-menopausal women who had a higher mean triglycerides 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 the iron metabolism 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 an 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 haemochromatosis (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, which 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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Table 1—***Baseline characteristics (mean (SD), n (%)) of men and women studied The D.E.S.I.R. Study.***

	Men	Women		*P*-values	
		Pre-menopausal	Post-menopausal	Men & Women	Pre- & Post menopausal 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 BP (mmHg)	132 (15)	122 (15)	132 (16)	<0.0001	<0.0001
Diastolic BP (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/d)	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
Number (%) of 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

Table 2—*Spearman correlation coefficients of baseline characteristics with ferritin and transferrin, according to gender and menopausal status. The D.E.S.I.R. study*

	Men n=469		Pre-menopausal women n=278		Post-menopausal women n=197	
	Ferritin	Transferrin	Ferritin	Transferrin	Ferritin	Transferrin
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 BP	0.10*	0.06	0.11	0.08	0.15*	-0.00
Diastolic BP	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

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3—***Frequencies and age-adjusted odds ratios (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**. The D.E.S.I.R. Study***

MEN	% with abnormalities		Log(ferritin)		Transferrin	
n = 469	Inclusion	6 years	Inclusion	6 years	Inclusion	6 years
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)**	1.1 (0.88-1.38)	**1.46 (1.18-1.81)**	**1.32 (1.06-1.65)**

PRE-MENOPAUSAL	% with abnormalities		Log(ferritin)		Transferrin	
WOMEN n = 278	Inclusion	6 years	Inclusion	6 years	Inclusion	6 years
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)**

POST-MENOPAUSAL	% with abnormalities		Log(ferritin)		Transferrin	
WOMEN n =197	Inclusion	6 years	Inclusion	6 years	Inclusion	6 years
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)** [a]	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	% with abnormalities		Log(ferritin)		Transferrin	
n=944	Inclusion	6 years	Inclusion	6 years	Inclusion	6 years
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 Legend

Figure—Age-adjusted odds ratios (95% confidence interval) for the 6-year incidence of the IDF-defined metabolic syndrome according to: A. high ferritin and transferrin levels (both above the upper tertiles); B. lower ferritin, high transferrin; C. high ferritin, lower transferrin; D. lower ferritin, lower transferrin; high and low levels were defined according to the three groups: men, pre-menopausal women, menopausal women. The D.E.S.I.R. Study