Association of Ferritin Elevation and Metabolic Syndrome in Males. Results from the Aragon Workers' Health Study (AWHS)

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Context: Ferritin concentration is associated with metabolic syndrome, but the possibility of a nonlinear association has never been explored.

Objective: This study aimed to examine the relationship between serum ferritin levels and the metabolic syndrome in Spanish adult males.

Design: This was a cross-sectional analysis of baseline data from the Aragon Workers' Health Study.

Setting: Healthy workers from a factory were studied during their annual checkup.

Participants: Spanish male adults (n = 3386) between the ages of 19 and 65 years participated. We excluded participants with ferritin > 500 μg/L, ferritin < 12 μg/L, or C-reactive protein > 10 mg/L.

Main Outcome Measure: Metabolic syndrome was defined according to the 2009 consensus definition from the Joint Interim Statement of several international societies.

Results: Metabolic syndrome prevalence was 27.1%. We found a positive association between elevated iron stores, measured as serum ferritin concentration, and metabolic syndrome and its criteria. Participants within the highest serum ferritin quintile had a higher risk than those in the lowest quintile for central obesity (odds ratio [OR], 1.88; 95% confidence interval [CI], 1.46–2.42), hypertriglyceridemia (OR, 2.15; 95% CI, 1.69–2.74), and metabolic syndrome (OR, 1.92; 95% CI, 1.48–2.49). The association was nonlinear and occurred at serum ferritin concentrations > 100 μg/L (~ 33th percentile). Ferritin was also associated with insulin resistance, measured by homeostatic model assessment–insulin resistance (HOMA-IR) (*P* trend < .001).

Conclusions: Our findings suggest that serum ferritin is significantly associated with metabolic syndrome and its criteria (especially central obesity and hypertriglyceridemia), suggesting that ferritin could be an early marker of metabolic damage in the development of metabolic syndrome. **(*J Clin Endocrinol Metab* 100: 2081–2089, 2015)**

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AWHS, Aragon Workers' Health Study; BP, blood pressure; CEICA, Aragon regional government's Ethics Committee for Clinical Research; CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, HOMA-IR, homeostatic model assessment–insulin resistance; LDL, low-density lipoprotein; MSC, metabolic syndrome criterion; OR, odds ratio.

Iron is essential for multiple biological processes, among the most important being oxygen transport and inflammation. The role of iron in inflammation is related to the production of free radicals and oxidative stress. Moreover, chronic inflammation and oxidative stress are important in the pathogenesis and progress of metabolic syndrome, and iron may be involved in this process. In humans, serum ferritin concentration correlates with body iron stores, giving a more precise stores' measurement than direct quantification of iron in serum.

Cross-sectional studies have shown associations of elevated serum ferritin concentration with metabolic syndrome (1–3), hypertension, dyslipidemia, elevated fasting insulin, high blood glucose, and central adiposity (4–6). Increased serum concentrations of ferritin is also associated with insulin resistance, type 2 diabetes mellitus, and metabolic syndrome in men (7, 8). Previous studies have only studied the linear association between elevated iron stores and metabolic syndrome, and there is little information regarding the level of ferritin at which this association begins to appear, under the hypothesis that the association is nonlinear.

We performed a cross-sectional analysis of the association of serum ferritin and metabolic syndrome in Spanish adult male participants in the Aragon Workers' Health Study, using methods to detect a nonlinear relationship.

Materials and Methods

The Aragon Workers' Health Study (AWHS) is a longitudinal cohort study of cardiovascular risk factors and subclinical atherosclerosis (9) among workers at the General Motors factory in Figueruelas (Zaragoza), Spain. All workers were invited to participate, and 5456 participants had been recruited at the time of the analysis. All participants gave written informed consent, and the study was approved by the Aragon regional government's Ethics Committee for Clinical Research (CEICA). We restricted our analysis to male participants (N = 5104). Participant age range was 19–65 years. A total of 1417 participants were excluded for missing data: 436 for ferritin; 212 for criteria required for diagnosis of metabolic syndrome (waist circumference, triglycerides, high-density lipoprotein [HDL] cholesterol, blood pressure [BP], and fasting glucose); and 769 for relevant covariables (body mass index, insulin, C-reactive protein [CRP], serum iron, and information on blood donation). Participants with CRP > 10 mg/L (N = 127) were excluded because ferritin is elevated in acute inflammatory processes. We also excluded participants with serum iron > 190 μg/dL or ferritin > 500 μg/L (N = 144) because of probable hemochromatosis and those with ferritin < 12 μg/L (N = 30). The final sample size was 3386.

Data collection

Information on sex, age, history of blood donation, alcohol intake, and use of medication was based on clinical interview, questionnaires and self reporting. Blood pressure was estimated as the mean of three consecutive measurements made with an automatic oscillometric sphygmomanometer OMRON M10-IT (OMRON Healthcare Co. Ltd, Kyoto, Japan), after 5 minutes of sitting. The physical examination included height, weight, and waist circumference, which was measured with the participant standing, at a plane in the midpoint between the ilium and the costal border.

Laboratory measurements

Peripheral venous blood samples were collected after an 8-hour fast. All biochemistry assays were measured in serum. Ferritin was measured using the Quantex Ferritin Kit (BIOKIT, Barcelona, Spain), which is based on an antigen-antibody reaction detected by turbidimetry in an ILAB650 analyzer (Instrumentation Laboratory, Bedford, MA). Triglycerides, HDL cholesterol, total cholesterol, fasting glucose, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured in spectrophotometric assays in the ILAB650 analyzer, using the manufacturer's kits (Instrumentation Laboratory). Insulin concentration was measured by double sandwich immunoassay in frozen samples in an Access 2 Analyzer (Beckman Coulter, Inc., Fullerton, CA) using the manufacturer's ultrasensitive kit. CRP concentration was measured by turbidimetric immunoassay in a Beckman Coulter Immage Analyzer using the manufacturer's high-sensitivity kit. Low-density lipoprotein (LDL) cholesterol was estimated from the Friedewald formula, and homeostatic model assessment–insulin resistance (HOMA-IR) was calculated as glucose (mg/dL) multiplied by insulin (mU/L) divided by 405 (10). Blood extraction and anthropometric and biochemical measurements in this study are certified with the International Organization for Standardization standard ISO 9001:2008.

Metabolic syndrome criteria

Individuals were diagnosed as having metabolic syndrome according to the consensus definition in the 2009 joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, the National Heart, Lung, and Blood Institute, the American Heart Association, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity (11). Metabolic syndrome was diagnosed when subjects met at least three of the five following metabolic syndrome criteria (MSC): central obesity (waist circumference ≥ 102 cm), hypertriglyceridemia (≥ 1.7 mmol/L [≥ 150 mg/dL] or drug treatment for elevated triglycerides), low HDL cholesterol (< 1.03 mmol/L [< 40 mg/dL] or drug treatment for depressed HDL-cholesterol concentration), hypertension (systolic BP ≥ 130 mm Hg, diastolic BP ≥ 85 mm Hg, or antihypertensive drug treatment in a patient with a history of hypertension), and hyperglycemia (≥5.6 mmol/L [≥100 mg/dL] or drug treatment for elevated glucose). From

Table 1. Characteristics of the Study Population and Subpopulations With and Without Metabolic Syndrome

	Total	Without Metabolic Syndrome	With Metabolic Syndrome	*P*
N	3386	2469	917	
Age, years	48.9 (8.7)	47.6 (9.4)	52.2 (5.2)	<.001
Ferritin, μg/L	174.0 (106.4)	163.8 (101.6)	201.4 (114.2)	<.001
BMI, kg/m^2	27.6 (3.6)	26.6 (3.0)	30.3 (3.6)	<.001
Waist circumference, cm	96.9 (9.7)	94.0 (8.4)	104.8 (8.8)	<.001
Total cholesterol, mg/dL	212.0 (37.6)	209.7 (37.2)	218.2 (38.1)	<.001
Triglycerides, mg/dL	142.9 (92.1)	120.8 (71.2)	202.5 (113.1)	<.001
HDL cholesterol, mg/dL	52.7 (10.9)	54.5 (10.7)	47.8 (10.0)	<.001
LDL cholesterol, mg/dL[a]	131.4 (31.9)	131.2 (31.9)	132.0 (32.0)	.503
Systolic BP, mm Hg	126.4 (14.4)	123.7 (13.2)	133.9 (15.1)	<.001
Diastolic BP, mm Hg	83.4 (9.8)	81.1 (9.2)	89.4 (8.9)	<.001
Fasting glucose, mg/dL	98.0 (18.0)	94.2 (14.1)	108.3 (22.6)	<.001
HOMA-IR	1.7 (1.5)	1.4 (1.0)	2.6 (2.1)	<.001
AST, U/L	24.8 (10.6)	24.5 (11.6)	25.6 (7.3)	.006
ALT, U/L	27.8 (12.8)	26.0 (11.8)	32.4 (14.3)	<.001
Daily alcohol intake, g/week	65.2 (59.8)	61.9 (57.8)	74.0 (63.9)	<.001
Blood donation history, %	17.9	18.4	16.4	.162

Abbreviation: BMI, body mass index.

Data are shown as means (SD) for clinical, physical, and biochemical parameters. For blood donation history, percentage of donors. *P* values were calculated from simple unadjusted *t* tests.

[a] n = 3313 due to missing values.

here on, we denote these variables with the suffix MSC (metabolic syndrome criterion) to distinguish them from general clinical situations with the same name.

Statistical analysis

Participants were divided into quintiles of ferritin concentration based on the sample distribution. Transaminases (ALT and AST) were categorized according to reference values (normal: < 40 U/L; high normal: 40–100 U/L; high: > 100 U/L). HOMA-IR was log transformed. Adjusted mean differences between the lowest ferritin concentration quintile and each of the other quintiles were calculated using multivariable linear regression. For dichotomous variables, interquintile odds ratios (ORs) were calculated by multivariable logistic regression. Models were adjusted for age (continuous), history of blood donation (as a dichotomous variable), transaminase activity (categorized as above) and daily alcohol intake (continuous) (Model 1). Models were further adjusted for continuous metabolic syndrome parameters (waist circumference, systolic BP, diastolic BP, fasting glucose, triglycerides, and HDL cholesterol) omitting some of them in case they would introduce colinearity (Model 2).

To further explore the shape of the relationship between ferritin levels and metabolic syndrome, we used restricted cubic splines with knots at ferritin concentration percentiles 5, 27.5, 50, 72.5, and 95 in a logistic model adjusted in the same way as Model 1. The changes observed in slope were confirmed with a linear spline with knots at 100 and 300 μg/L (percentiles 27.7 and 86.3). To assess the potential importance of inflammation as confounder of the relationship between ferritin and metabolic syndrome, we performed a sensitivity analysis adjusting our models for CRP. All statistical analyses were performed with STATA (version 11.1; StataCorp, College Station, TX).

Results

Baseline characteristics

Metabolic syndrome prevalence in this sample of working males was 27.1%. Mean ferritin concentration (SD) was 201.4 (114.2) μg/L among study participants with metabolic syndrome and 163.8 (101.6) μg/L among those without it. Participants with metabolic syndrome were more likely to be older (Table 1).

Association between serum ferritin concentration and metabolic syndrome

Ferritin concentration increased together with age, body mass index, waist circumference, total cholesterol, triglycerides, systolic and diastolic BP, serum glucose, and log-HOMA-IR, and decreased with increasing HDL cholesterol (Table 2). The association was statistically significant after adjusting for age, transaminase activity, history of blood donation, and alcohol intake (Model 1).

To investigate an independent association of ferritin with particular metabolic syndrome traits, we adjusted each continuous metabolic syndrome variable for the other metabolic syndrome variables (Model 2). Comparing the highest ferritin quintile (> 261 μg/L) to the lowest (< 83 μg/L), the adjusted differences (95% confidence interval [CI]) were statistically significant for waist circumference [3.01 (2.06–3.95) cm] and for triglycerides [27.84 (17.97–37.70) mg/dL] (Table 3).

We also calculated the ORs for metabolic syndrome and each of its criteria across ferritin quintiles through

Table 2. Raw Means and Adjusted Differences (95% CI) between the Lowest (First) Ferritin Quintile and the Other Four Quintiles for Physiological Parameters Related to Metabolic Syndrome

	Quintile of Ferritin Concentration (Interval in μg/L)					
Variable	1st (< 83)	2nd (83–127)	3rd (128–180)	4th (181–261)	5th (>261)	*P* Trend
N	681	680	672	677	676	
Age, y	49.0	47.7	48.5	48.8	50.3	
Ferritin, μg/L	51.4	104.8	152.6	217.6	344.7	
BMI, kg/m^2	27.01	27.08	27.42	27.72	28.69	
Difference	0.00	0.34	0.62	0.77	1.52	<.001
Reference		(−0.02–0.70)	(0.25–0.98)	(0.40–1.13)	(1.15–1.89)	
Waist circumference, cm	95.24	95.46	96.51	97.42	99.87	
Difference	0.00	0.86	1.63	2.11	3.86	<.001
Reference		(−0.10–1.83)	(0.65–2.61)	(1.12–3.09)	(2.86–4.85)	
Total cholesterol, mg/dL	208.22	209.22	211.88	214.00	216.66	
Difference	0.00	3.19	5.15	6.44	7.17	<.001
Reference		(−0.68–7.06)	(1.23–9.07)	(2.50–10.38)	(3.19–11.14)	
Triglycerides, mg/dL	124.70	128.69	140.17	155.07	166.26	
Difference	0.00	3.81	14.07	26.51	34.65	<.001
Reference		(−5.85–13.48)	(4.27–23.87)	(16.66–36.37)	(24.73–44.58)	
HDL cholesterol, mg/dL	53.78	53.18	52.78	51.44	52.29	
Difference	0.00	−0.45	−0.78	−2.04	−1.33	.002
Reference		(−1.62–0.73)	(−1.97–0.42)	(−3.24–−0.84)	(−2.53–−0.12)	
LDL cholesterol, mg/dL[a]	129.97	130.51	131.83	132.38	132.48	
Difference	0.00	2.62	3.45	3.39	2.08	.226
Reference		(−0.72–5.95)	(0.06–6.85)	(−0.02–6.81)	(−1.37–5.53)	
Systolic BP, mm Hg	124.95	125.70	126.57	126.76	128.17	
Difference	0.00	1.04	1.55	1.41	2.03	.013
Reference		(−0.47–2.55)	(0.03–3.08)	(−0.12–2.95)	(0.48–3.58)	
Diastolic BP, mm Hg	82.24	82.60	83.36	83.65	85.03	
Difference	0.00	0.77	1.20	1.17	1.84	<.001
Reference		(−0.21–1.75)	(0.20–2.19)	(0.16–2.17)	(0.83–2.85)	
Fasting glucose, mg/dL	96.54	96.80	98.26	98.18	100.37	
Difference	0.00	0.40	1.31	0.77	2.09	.040
Reference		(−1.48–2.28)	(−0.60–3.21)	(−1.14–2.69)	(0.15–4.02)	
Log-HOMA-IR	0.22	0.25	0.28	0.37	0.48	
Difference	0.00	0.03	0.05	0.11	0.19	<.001
Reference		(−0.04–0.10)	(−0.02–0.12)	(0.04–0.17)	(0.12–0.26)	

Abbreviation: BMI, body mass index.

The first line in each cell shows the raw mean. The second and third lines show the adjusted differences and their 95% CI calculated from a linear model adjusted for age, history of blood donation, transaminases, and alcohol intake (Model 1). *P* trend values are calculated from a model introducing ferritin quintiles because an ordinal variable.

[a] n = 3313 due to missing values.

a logistic model adjusted in the same way as Model 1. The adjusted OR (95% CI) for metabolic syndrome comparing individuals in the highest serum ferritin quintile with those in the lowest was 1.92 (1.48–2.49) (Table 4). The multivariable model showed a significantly graded relationship between serum ferritin concentration and individual metabolic syndrome criteria (Table 4). The risk of all individual metabolic syndrome criteria increased with increasing serum ferritin quintile; however, the statistical significance of the HDL cholesterol criterion was at the limit (Table 4). The cubic spline model showed a tendency toward flatness in the lower third of the ferritin distribution, whereas a steep increase was observed at higher levels (Figures 1 and 2). Based on observations in the cubic spline model, we decided to apply a linear spline function, with knots at 100 and 300 μg/L serum ferritin. The odds slope for metabolic syndrome changed significantly at 100 μg/L ($P = .048$). The association at ferritin concentrations below 100 μg/L was not statistically significant ($P =$

Table 3. Adjusted Differences (95% CI) between the Lowest, (1st) Ferritin Quintile, and the Other Four Quintiles for Continuous Variables Used in the Definition of Metabolic Syndrome, Adjusted for the Other Variables Associated with the Syndrome

	Quintile of Ferritin Concentration (Interval in μg/L)					
Variable	**1st (<83)**	**2nd (83–127)**	**3rd (128–180)**	**4th (181–261)**	**5th (>261)**	***P* Trend**
Waist circumference, cm[a]	0.00 (Reference)	0.61 (−0.30–1.52)	1.15 (0.22–2.08)	1.40 (0.47–2.33)	3.01 (2.06–3.95)	<.001
Triglycerides, mg/dL[b]	0.00 (Reference)	2.09 (−7.44–11.61)	10.88 (1.21–20.55)	22.78 (13.05–32.50)	27.84 (17.97–37.70)	<.001
HDL cholesterol, mg/dL[b]	0.00 (Reference)	−0.23 (−1.37–0.92)	−0.34 (−1.50–0.83)	−1.49 (−2.67–−0.32)	−0.29 (−1.48–0.90)	.174
Systolic BP, mm Hg[c]	0.00 (Reference)	0.82 (−0.66–2.30)	1.02 (−0.48–2.52)	0.81 (−0.70–2.33)	0.82 (−0.71–2.36)	.368
Diastolic BP, mm Hg[c]	0.00 (Reference)	0.53 (−0.41–1.48)	0.65 (−0.31–1.61)	0.48 (−0.49–1.44)	0.57 (−0.41–1.55)	.349
Fasting glucose, mg/dL[a]	0.00 (Reference)	0.06 (−1.79–1.91)	0.71 (−1.17–2.60)	−0.00 (−1.90–1.90)	0.98 (−0.95–2.91)	.392

Cells show the adjusted differences and their 95% CI calculated from a linear model adjusted for age, history of blood donation, transaminases, and alcohol intake for all the variables.

[a] Further adjusted for the rest of the parameters.

[b] Further adjusted for waist circumference, systolic BP, diastolic BP, and fasting glucose.

[c] Further adjusted for waist circumference, triglycerides, HDL cholesterol, and fasting glucose (Model 2). *P* trend values are calculated from a model introducing ferritin quintiles as an ordinal variable.

.525), whereas at ferritin values between 100 and 300 μg/L the odds of metabolic syndrome increased at a rate of 1.23 per 50 μg/L of ferritin ($P < .001$) (Supplemental Figure and Table). Adjustment of our models for CRP did not substantially change the associations found.

Discussion

In this study of male Spanish workers, we found a positive association between elevated iron stores and metabolic syndrome. Our results show that central obesity and hypertri-

Table 4. Adjusted OR (95% CI) for the Association of Serum Ferritin with Metabolic Syndrome and Defining Criteria, Comparing the Lowest (1st) Ferritin Quintile with the Other Four Quintiles

	Quintile of Ferritin Concentration (Interval in μg/L)					
	1st (<83)	**2nd (83–127)**	**3rd (128–180)**	**4th (181–261)**	**5th (>261)**	***P* Trend**
Central obesity MSC[a]	1.00 (Reference)	1.12 (0.87–1.45)	1.23 (0.95–1.59)	1.37 (1.06–1.77)	1.88 (1.46–2.42)	<.001
Hypertriglyceridemia MSC[a]	1.00 (Reference)	1.09 (0.85–1.40)	1.23 (0.96–1.58)	1.86 (1.46–2.37)	2.15 (1.69–2.74)	<.001
Low HDL cholesterol MSC[a]	1.00 (Reference)	0.90 (0.66–1.22)	0.90 (0.67–1.23)	1.20 (0.90–1.61)	1.18 (0.88–1.58)	.054
Hypertension MSC	1.00 (Reference)	1.12 (0.89–1.41)	1.22 (0.96–1.54)	1.22 (0.97–1.55)	1.41 (1.11–1.79)	.004
Hyperglycemia MSC	1.00 (Reference)	1.10 (0.87–1.40)	1.12 (0.88–1.42)	1.29 (1.01–1.64)	1.49 (1.17–1.89)	<.001
Metabolic syndrome[a]	1.00 (Reference)	0.91 (0.69–1.20)	1.11 (0.84–1.45)	1.52 (1.17–1.98)	1.92 (1.48–2.49)	<.001

Cells show the adjusted ORs and their 95% CIs calculated from a logistic model adjusted for age, history of blood donation, transaminases, and alcohol intake (Model 1). *P* trend values are calculated from a model introducing ferritin quintiles as an ordinal variable.

[a] n = 3382 in these models all observations (4) with very high AST were decreased because they were all positive for the tested criterion.

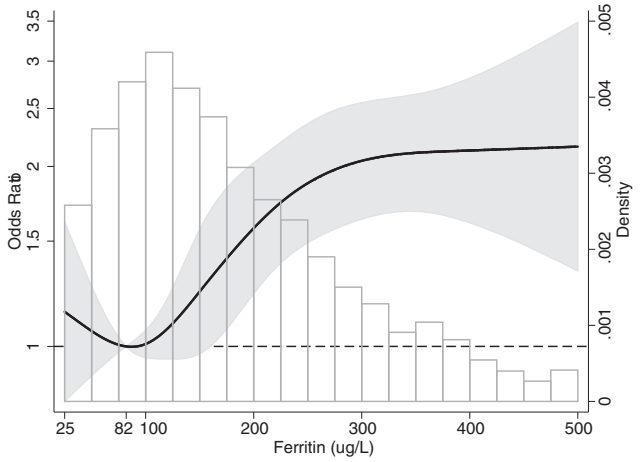

Figure 1. Adjusted ORs (95% CIs) for the association of metabolic syndrome with ferritin concentration. Ferritin was modeled as restricted cubic splines with knots at the percentiles 5, 27.5, 50, 72.5, and 95 of its distribution. The multivariable logistic regression model was adjusted for age, history of blood donation, transaminases, and alcohol intake (Model 1). The odds for metabolic syndrome at the 20th percentile (82 μg/L) of the ferritin distribution were used as a reference. The histogram shows the distribution of ferritin concentrations in the study sample.

glyceridemia are the main independent criteria associated with elevated ferritin, and also show that the association has a potential threshold, with an important association with metabolic syndrome detected when serum ferritin levels are between 100 and 300 μg/L.

There has been considerable interest in the possibility that excess iron stores contribute to the pathogenesis of metabolic syndrome. Elevated serum ferritin levels have been linked to different health conditions, such as hypertension (4), central obesity (12), higher values of serum triglycerides, and lower levels of HDL cholesterol (5, 6). Iron overload is a predictor of abnormal glucose metabolism, obesity, and insulin resistance (7, 13, 14). Iron accumulates in human adipose tissue, and iron metabolism is associated with insulin pathways there (15). Furthermore, adipocyte iron overload decreases adiponectin gene expression in association with insulin resistance in mice (16), and blood donation decreases glycosylated hemoglobin and improves insulin resistance in subjects with high ferritin and diabetes (17).

Most previous cross-sectional studies reported associations between iron stores and metabolic syndrome. Jehn et al (2) reported an association in men between ferritin and metabolic syndrome criteria, especially hyperglycemia MSC and hypertriglyceridemia MSC. Yoo et al (18) found an association with hyperglycemia MSC only in men and with triglycerides MSC and low HDL cholesterol MSC only in women. Lee et al (19) found an association between increased ferritin and hyperglycemia MSC and hypertriglyceridemia MSC only in men. Our results show similar associations with hypertension MSC, central obesity MSC, hypertriglyceridemia MSC and hyperglycemia MSC, with steeper associations at serum ferritin levels above 100 μg/L. This association was independent of age, blood donation history, transaminases, and alcohol intake. Ferritin was also associated with insulin resistance (measured as HOMA-IR).

Longitudinal studies related ferritin concentration prospectively to the incidence of metabolic syndrome in French men and women (20). Similarly, a 5-year follow-up study in Korean men found a strong and significant association of ferritin with the development of metabolic syndrome (21). These studies and our findings suggest that high serum ferritin levels or iron metabolism may play a causal role in the development of metabolic syndrome; however, elevated serum ferritin could be cause or consequence of metabolic syndrome, given that iron interferes with insulin action in the liver and insulin stimulates iron uptake by adipocytes and hepatocytes (22).

Ferritin, an intracellular protein, is an established biomarker of body iron stores (23). Iron and its homeostasis are associated with the inflammatory response (24). In hemochromatosis, liver injury is associated with impaired insulin sensitivity in the liver and pancreatic dysfunction (25–27). In animal models, iron participates in the formation of hydroxyl radicals, and an excess of iron might lead to cell oxidative stress, which can decrease insulin secretory capacity (28). Several studies have demonstrated that hepatic iron overload induces liver damage through the production of malonyldialdehyde in the lipid peroxidation in nonalcoholic fatty liver disease. This metabolite can activate hepatic stellate cells, the major contributors to fibrogenesis (29, 30). Our observations show that above a certain threshold, increases in ferritin are associated with metabolic impairment, suggesting that the metabolic disorder in hemochromatosis might be part of a progressive continuum starting at lower iron levels. The only continuous metabolic syndrome variables independently associated with ferritin were waist circumference and triglycerides. Ferritin is associated with triglycerides even in the absence of metabolic syndrome (31), and triglycerides decrease after therapeutic phlebotomy, independently of basal blood glucose (32). These observations suggest that obesity might be an additional factor inducing functional hepatic changes associated with an increase in iron and hepatic triglyceride deposits. Individuals in advanced stages of obesity and metabolic syndrome develop nonalcoholic fatty liver disease, which may further elevate transaminase levels (29, 30). Ferritin is also elevated in acute and chronic hepatitis as a consequence of liver damage (33, 34). We adjusted our analysis for transaminases to avoid confusion with other causes of hepatic damage. Our data suggest that ferritin has potential as an early

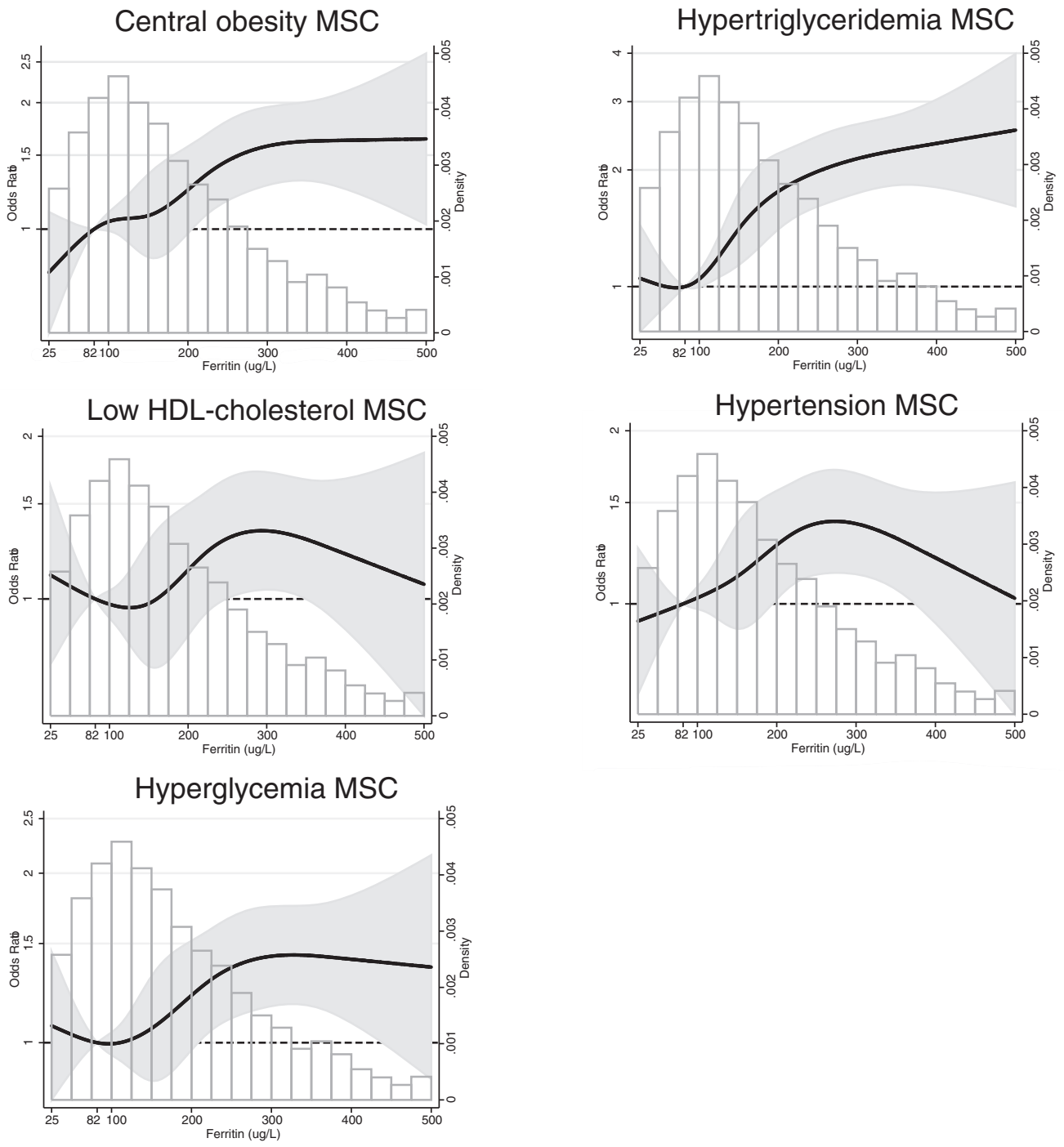

Figure 2. Adjusted ORs (95% CIs) for the association of metabolic syndrome criteria with ferritin concentration. Ferritin was modeled as restricted cubic splines with knots at the percentiles 5, 27.5, 50, 72.5, and 95 of its distribution. The multivariable logistic regression model was adjusted for age, history of blood donation, transaminases, and alcohol intake (Model 1). The odds for metabolic syndrome at the 20th percentile (82 μg/L) of the ferritin distribution were used as a reference. The histogram shows the distribution of ferritin concentrations in the study sample.

marker of parenchymal damage in obesity and metabolic syndrome.

If we accept that iron predisposes metabolic syndrome, future confirmation of the 100 ug/L threshold may help to identify patients who would benefit from interventions that target iron. This would require the development of therapies able to modulate body iron at this near-normal level. Even in cases where iron is elevated as a consequence of liver damage brought about by intense metabolic-syndrome related injury, the restriction of the association to the higher ferritin range may hint that the presence of this elevation signals a more intense damage derived from the metabolic disturbances, and this could inform decisions about whether to increase the intensity of therapy for met-

abolic syndrome in those particular subjects. Considering that two thirds of our sample had ferritin above 100 μg/L, these results suggest the need for studies to better define the optimal tissue iron level among the broad range of normal values, and the feasibility of manipulating body iron.

Ferritin is an acute phase reactant, among others like CRP. In our analysis, we excluded participants with high CRP, thus discarding those with acute phase responses. Nonetheless, metabolic syndrome and obesity are associated with the development of chronic, low-level inflammation. Indeed, levels of CRP are mildly elevated in metabolic syndrome (35). Adipose tissue releases proinflammatory mediators (36) that induce hepatic production of CRP (37). However, our sensitivity analysis adjusting for CRP indicated that this inflammation pathway has only a minor influence on the described associations.

Strengths of this study include the use of data from a cohort that has been studied using strict procedures, both in the collection of data and biological samples, which meet the criteria for quality certification. Limitations include not having performed identification of a genetic cause underlying high ferritin concentrations and the restriction of the study to men. In addition, the study has a cross-sectional design making it impossible to infer causation. Differences in age, transaminase levels, and alcohol intake between those with metabolic syndrome and without it could act as potential confounders for the association. However, adjustment of our analysis for these variables provided differences and ORs that show associations independent of age, hepatic cytolysis, and alcohol intake. We designed the linear spline knots based solely on visual inspection of the restricted cubic spline. We produced our inferences and adjusted our methods to account for these limitations.

Our results show that serum ferritin is associated with metabolic syndrome, with independent association shown for the diagnostic criteria central obesity MSC and hypertriglyceridemia MSC. The association with the risk of metabolic syndrome is seen only above a ferritin concentration of approximately 100 μg/L (percentile 27.7). Future studies should be considered to demonstrate the potential of serum ferritin as an early marker of the metabolic damage associated with the development of metabolic syndrome. Serum ferritin might be a particularly valuable marker when levels are between 100 and 300 μg/L.

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