



# Reduced serum iron levels are associated with metabolic dysfunction and sex-specific characteristics

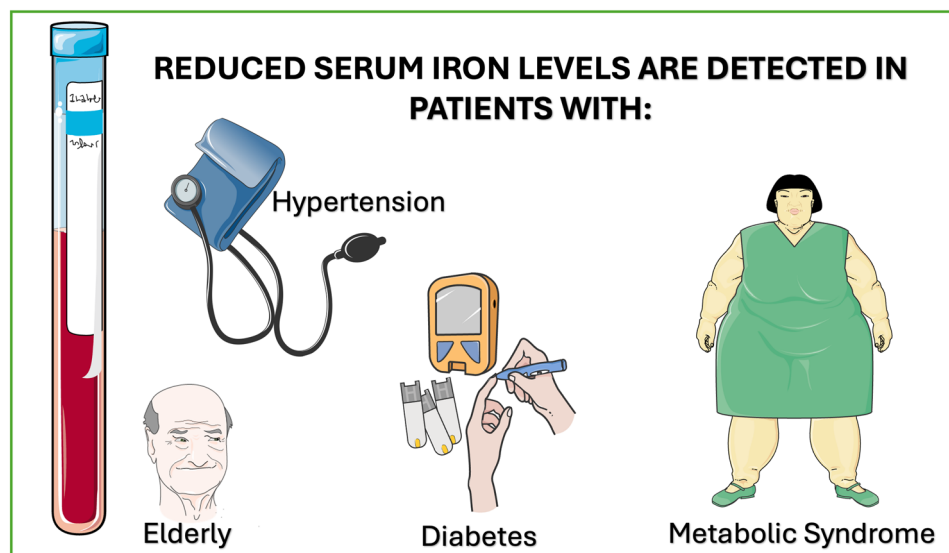
Antonio Francesco Maria Giuliano<sup>1,2</sup> · Carlo De Matteis<sup>1</sup> · Salvatore Cantatore<sup>1</sup> · Ersilia Di Buduo<sup>1</sup> · Fabio Novielli<sup>1</sup> · Elsa Berardi<sup>1</sup> · Gianfranco Antonica<sup>1</sup> · Antonio Moschetta<sup>1,3</sup> · Lucilla Crudele<sup>1,3</sup>

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## Abstract

Metabolic syndrome (MetS) is a clinical condition defined by abdominal obesity, insulin resistance, hypertension, and dyslipidaemia, associated with increased cardiovascular risk and type 2 diabetes (T2D). Emerging evidence suggests a role for iron metabolism and ferroptosis in the pathophysiology of MetS and its related complications. This study aimed to explore the association between serum iron levels and clinical, anthropometric, and biochemical parameters in a population with cardiometabolic risk factors. We ongoing treatment for such analysed data from 893 patients attending the Metabolic Disease Unit of the Interdisciplinary Medicine Department at the University of Bari “Aldo Moro”. Patients with MetS, elevated BMI, hypertension, and T2D exhibited significantly lower serum iron levels compared to healthy controls. Serum iron showed a strong inverse correlation with age ( $r = -0.09$ ,  $p = 0.0061$ ), fasting plasma glucose ( $r = -0.10$ ,  $p = .002$ ), and HbA1c ( $r = -0.18$ ,  $p < 0.0001$ ) in the overall population, while no correlations were found with Framingham Risk Score, triglycerides, waist circumference, and BMI. Conversely, when stratifying by sex, we observed that serum iron was inversely correlated with BMI ( $r = -0.12$ ,  $p = 0.008$ ) and waist circumference ( $r = -0.12$ ,  $p = 0.008$ ) in females only. Metabolic dysfunction is associated with reduced serum iron levels, with sex-specific patterns observed in relation to adiposity markers. Elucidating the interplay between iron metabolism, sex hormones, and adipose tissue biology may uncover new targets for personalized treatment strategies for metabolic diseases. Further research is warranted to clarify how modulation of iron homeostasis affects adipose tissue function, particularly in women with obesity and related metabolic disorders.

## Graphical abstract



**Keywords** Metabolic syndrome · Cardiovascular risk · Liver steatosis · Obesity · Ferroptosis · Gender medicine

## Introduction

Iron plays a pivotal role in numerous physiological processes, including oxygen transport, mitochondrial function, and cellular metabolism. Ferroptosis, a form of programmed cell death driven by iron overload, glutathione-dependent antioxidant system failure, and lipid peroxidation, has been proposed as a cellular mechanism linking iron dysregulation to adverse cardiovascular outcomes [1]. Several studies have highlighted the contribution of tissue iron overload to the generation of reactive oxygen species (ROS), lipid peroxidation, and lipid accumulation in multiple organs [2]. Consequently, ferroptosis has been implicated in pancreatic  $\beta$ -cell dysfunction, contributing to the development of type 2 diabetes (T2D) [3], as well as in the pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD) [4]. These metabolic disorders are often co-present within the clinical entity known as metabolic syndrome (MetS), which arises from a complex interplay of abdominal obesity, insulin resistance, hypertension, and dyslipidaemia [5]. This constellation of metabolic abnormalities significantly increases the risk for T2D and various cardiovascular diseases (CVDs). Recent epidemiological data indicate that MetS affects approximately 25–33% of the global adult population [6, 7], posing a substantial burden on healthcare systems, patient quality of life, and socioeconomic structures [8]. A variety of environmental, genetic, societal, and dietary factors contribute to the onset, progression, and management of MetS. Current research efforts are increasingly focused on elucidating the metabolic pathways and identifying biomarkers involved in its pathogenesis [9]. In this context, circulating iron parameters—including ferritin, transferrin, and hepcidin—have been investigated for their association with MetS and CVD. Although serum ferritin levels have been found increased in patients with MASLD and liver steatosis, chronic inflammation, obesity, and dyslipidaemia [10], little is known on iron serum levels in subjects with cardiometabolic risk conditions.

For instance, iron deficiency is frequently observed in patients with heart failure and is associated with worse clinical outcomes, including higher rates of hospitalization and mortality [11]. Randomized trials have demonstrated that correction of iron deficiency can improve symptoms and reduce adverse cardiovascular events in these patients [12, 13]. Conversely, iron overload may contribute to vascular injury and atherogenesis by promoting endothelial dysfunction and plaque instability through enhanced ROS production [14]. Moreover, genetic studies suggest that

polymorphisms affecting systemic iron regulation are associated with coronary artery disease risk, underscoring the complex and bidirectional role of iron homeostasis in cardiovascular health [15].

Thus, in this observational study, we primarily aimed to investigate the association between serum iron levels and the prevalence of MetS in a large cohort of patients with cardiometabolic risk factors. Furthermore, we also explored the correlation between iron levels and the clinical entities contributing to cardiometabolic risk, with a focus on potential sex-specific differences.

## Materials and methods

### Study participants

Written informed consent for the use of clinical data was obtained from all participants in the study. The study was approved by the Ethics Committee (n.311, MSC/PBMC/2015) of the Azienda Ospedaliero-Universitaria Policlinico di Bari (Bari, Italy) in accordance with the requirements of the Declaration of Helsinki. The initial study population enrolled patients whose clinical and biochemical parameters were collected in the electronic health register of the Metabolic Disease Department in Interdisciplinary Medicine—Internal Division “Cesare Frugoni” of the “Aldo Moro” University of Bari, Policlinico (Bari, Italy) from 2017 to June 2024. A total of 2,767 observations were initially considered; we then excluded 1,222 observations because data about iron, serum ferritin, and blood count values were not available. We further excluded 647 evaluations consisting of re-evaluations for the same patients, patients with genetic hemochromatosis, and subjects having iron-supplementation therapy. Additionally, five subjects were removed from the final cohort, since their iron levels were considered outliers according to Grubbs’ outlier test. Finally, we performed statistical analysis on a population of 893 patients with a quite similar distribution of two sexes (48% males, 52% females) (Supplementary Fig. 1).

### Clinical and biochemical assessment

Physical examination, anthropometric measures, biochemical assessment, and abdomen ultrasound were performed. Morning blood samples were obtained after 12 h of fasting from the antecubital veins of patients. After blood clotting and centrifugation, serum was processed for analysis of biochemical

markers of lipid and glucose metabolism. All biochemical measurements were centralized and performed in the ISO 9001 certified laboratories of the University Hospital of Bari. Specifically, blood count, haemoglobin and iron blood concentration, and serum ferritin were measured. Measurements of total and HDL cholesterol, fasting plasma glucose (FPG), and triglycerides were obtained through enzymatic colorimetric assay (Siemens, Erlangen, Germany). Glycosylated haemoglobin (HbA1c) was assessed in human whole blood using ion-exchange high-performance liquid chromatography (HPLC) on the Bio-Rad Variant II Haemoglobin A1c Program (BIO-RAD Laboratories Srl, Milan, Italy). Iron and ferritin measurements were carried out on fully automated clinical analysers and serum ferritin by immunoassays, whereas serum iron was measured using a colorimetric reaction. After an overnight fasting, patients underwent an abdominal ultrasound scanning with a 3.5–5 MHz convex probe (Esaote My Lab 70 Gold ultrasound system). B-mode ultrasound was used for assessment of fatty liver. Mild steatosis was defined by diffusely increased hepatic echogenicity, but periportal and diaphragmatic echogenicity was still appreciable. Moderate steatosis was represented by a diffusely increased hepatic echogenicity obscuring periportal echogenicity, but diaphragmatic echogenicity was still appreciable. Severe steatosis was diagnosed when hepatic echogenicity was diffusely increased, obscuring periportal as well as diaphragmatic echogenicity. MetS was diagnosed according to the NCEP ATP III definition; visceral obesity was defined for waist circumference (WC) values equal to or above 88 cm in women and 102 cm in men. More isolated metabolic criteria were considered: impaired glycaemic and lipid control and arterial hypertension. Average systolic and diastolic blood pressures (BPs) were recorded for each patient in three different measurements using a manual sphygmomanometer. Hypertension was diagnosed for systolic BP  $\geq 130$  mmHg, diastolic BP  $\geq 85$  mmHg, and/or treatment with antihypertensive agents. Impaired glycemic control was diagnosed for FPG  $> 110$  mg/dL, impaired lipid control was diagnosed for HDL cholesterol  $< 40$  mg/dL in males and  $< 50$  mg/dL in females, and for triglycerides  $> 150$  mg/dL, or ongoing treatment for such impairments. For T2D, the criteria were HbA1c  $\geq 48$  mmol/mol, FPG  $\geq 126$  mg/dL, or glycaemia  $> 200$  mg/dl at 2 h during oral glucose test tolerance and/or treatment for diabetes. BMI (body mass index) was computed as weight (kg) divided by the height (m) squared, and BMI values (kg/m<sup>2</sup>) 25.0–29.9 and over 30.0 were considered as overweight and obesity conditions, respectively. The Framingham Risk Score was used to calculate the 10-year risk for cardiovascular events. MASLD diagnosis was based on the presence of liver steatosis identified by ultrasound and at least one of the five criteria for MetS, also considering BMI  $\geq 25$  kg/sqm to assess overweight or obesity as an alternative to increased WC. Ultrasound assessment of internal carotid arteries was used to detect atherosclerotic disease, permitting the evaluation of

both the macroscopic appearance of plaques and flow characteristics in the carotid artery.

## Data analysis

Grubbs' outlier test was used to detect outliers. Descriptive statistical analyses of the study sample were performed, and results were expressed as mean  $\pm$  standard deviation (SD) for continuous variables and percentages for categorical ones. Data distribution was assessed using the Kolmogorov–Smirnov test. As the data were found to be normally distributed, parametric tests were used for the subsequent statistical analyses. Comparisons of clinical variables between two groups were conducted with Student's *T* test, while ANOVA was performed to assess differences among three or more groups. All reported *p*-values (*p*) were based on two-sided tests and compared to a significance level of 5%. The significance level for all statistical tests was set a priori at  $\alpha = 0.05$ . The magnitude of the differences was assessed by calculating Cohen's *d* for the Student's *T* test and partial eta-squared ( $\eta_p^2$ ) for ANOVA. Data were represented by using box plots showing the median (second quartile), first, and third quartiles, and whiskers representing minimum and maximum values. Correlations between iron levels and bio-humoral and clinical parameters were analysed and estimated using Pearson's correlation coefficient (*r*). Correlations were shown in heatmaps with *R* values and respective *p*-values. Receiver operating characteristic (ROC) curve was performed to identify the association between lower iron serum levels and MetS. The area under the curve (AUC) was plotted to distinguish between clinical groups and Youden's Index, or equivalently, the highest sensitivity + specificity was used to determine the optimal cutoff of each variable for the prediction of MetS. Analysis of covariance (ANCOVA) was used to compare group means while adjusting for the influence of continuous covariates. Potentially confounding variables in the assessment of the causal effect were accounted for in a multivariable logistic regression and were selected a priori based on their established roles as risk factors for metabolic disease and their potential influence on iron metabolism, as documented in existing literature. All analyses were performed using the NCSS 2023 Statistical Software (2023, NCSS, LLC, Kaysville, Utah, USA) and GraphPad Prism, version 10 (GraphPad Software; San Diego, CA, USA).

## Results

### Study population characterization

The mean age of the subjects was  $58.7 \pm 14.6$  years. Overall, subjects displayed increased BMI (64%) and abdominal

obesity (54%) according to diagnostic criteria for MetS that was diagnosed in 449 subjects (54%). Dysmetabolic conditions such as atherosclerosis, arterial hypertension, liver steatosis, and T2D were also largely represented in our population study. According to Framingham Risk Score (mean  $18.8 \pm 16.8$ ), our population had an intermediate risk of developing coronary heart disease within 10 years. Mean iron ( $83.7 \pm 29.4$  mcg/dL) and serum ferritin ( $98.9 \pm 90.9$  ng/mL) levels were both normal. While mean FPG and HbA1c depicted a condition of pre-diabetes, lipid panel did not show noteworthy alteration. The details are shown in Table 1.

We compared iron concentration in two sexes (Fig. 1a), finding that iron levels were significantly higher ( $p=0.0012$ , Cohen's  $d=0.74$ ) in males ( $87.1 \pm 30.6$ ) than in females ( $80.6 \pm 27.9$ ). We also studied correlation between age and iron values (Fig. 1b), finding a significant ( $p=0.0061$ ) inverse correlation ( $r=-0.09$ ). Moreover, since women generally experience increased iron levels due to cessation of menstruation, we divided our female population into two groups according to age under and above 55 years, finding no significant difference between younger and older women ( $82.1 \pm 31.3$  vs  $79.7 \pm 25.6$ ,  $p=0.3960$ ).

### Iron level correlation with cardiovascular risk

Aiming to investigate whether iron level could be involved in determining an increased cardiovascular risk (CVR), we firstly studied its correlations with Framingham Risk Score. We performed Pearson correlation in the overall population (Fig. 2a), finding no significant correlation between iron levels and CVR ( $p=0.0899$ ). Considering known CVR differences between males and females, we then performed different correlation studies in the two sexes (Fig. 2b–c). Such studies confirmed that no significant correlation between Framingham Risk Score and iron levels could be identified in our population.

### Iron level comparison in patients with and without cardiometabolic risk factors

To investigate whether iron level differs in subjects with specific clinical and dysmetabolic conditions, we firstly compared iron levels in patients with and without cardiometabolic risk factors. We did not find any difference when comparing patients with and without increased WC, although a trend could be identified ( $82.0 \pm 28.1$  vs  $85.3 \pm 29.9$ ,  $p=0.1761$ , Cohen's  $d=0.23$ ) (Fig. 3a), while a significant decrease was found considering different classes of BMI (ANOVA  $p=0.0145$ ,  $\eta^2p=0.07$ ). Specifically, iron levels were significantly lower in subjects with obesity ( $78.8 \pm 28.6$ ) compared to overweight subjects ( $86.4 \pm 27.0$ ) ( $p=0.0017$ , Cohen's  $d=0.71$ ) (Fig. 3b). We then investigated iron level differences in patients with and

**Table 1** Study population characterization

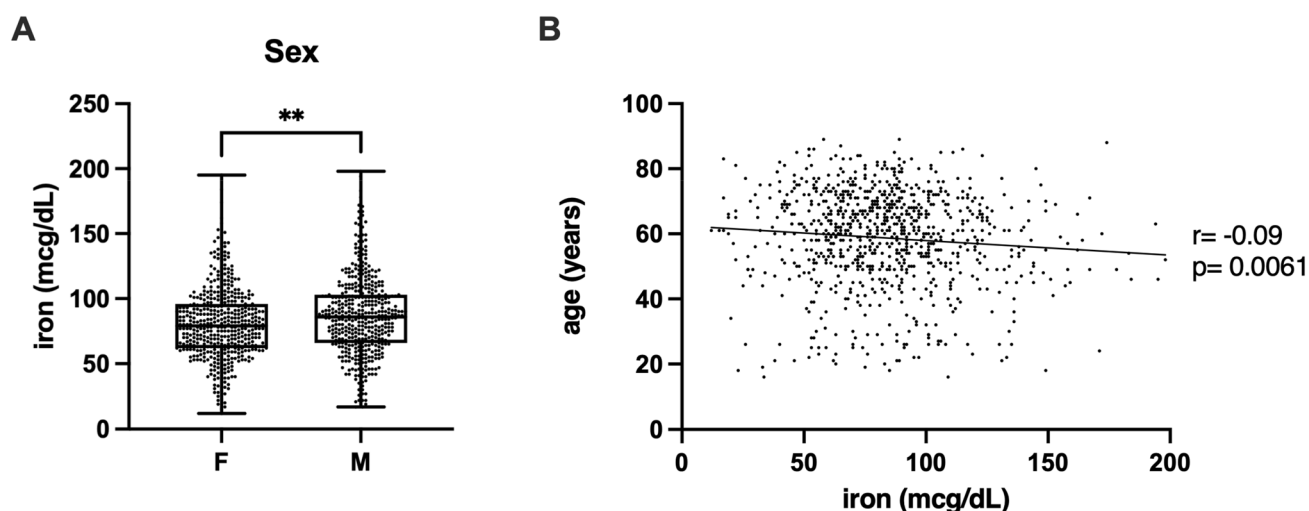
|                                              |                        |
|----------------------------------------------|------------------------|
| Sample number (m;f)                          | 893 (427;466)          |
| Age (years)                                  | $58.7 \pm 14.6$ (39)   |
| BMI ( $\text{kg}/\text{m}^2$ )               | $27.2 \pm 5.3$ (14.8)  |
| Waist circumference (cm)                     | $97.2 \pm 14.5$ (43)   |
| Iron (mcg/dL)                                | $83.7 \pm 29.4$ (59)   |
| Serum ferritin (ng/mL)                       | $98.9 \pm 90.9$ (285)  |
| Erythrocytes ( $\times 10^6/\text{mL}$ )     | $4.8 \pm 0.5$ (2.4)    |
| Haemoglobin (g/dL)                           | $13.9 \pm 1.4$ (6.5)   |
| Platelet count ( $\times 10^3/\mu\text{L}$ ) | $253.3 \pm 65.1$ (128) |
| Glucose (mg/dL)                              | $99.4 \pm 25.9$ (101)  |
| HbA1c (mmol/mol)                             | $40.2 \pm 10.1$ (14.3) |
| Total cholesterol (mg/dL)                    | $180.4 \pm 41.6$ (140) |
| HDL cholesterol (mg/dL)                      | $54.3 \pm 14.5$ (72)   |
| LDL cholesterol (mg/dL)                      | $106.4 \pm 36.1$ (149) |
| Triglycerides (mg/dL)                        | $113.7 \pm 60.8$ (186) |
| CRP                                          | $5.2 \pm 12.5$ (200)   |
| ERS                                          | $19.8 \pm 16.7$ (135)  |
| Framingham risk score                        | $18.9 \pm (33.5)$      |
| Smokers (n;%)                                | 286 (32)               |
| Abdominal obesity (n;%)                      | 475 (54)               |
| Overweight (BMI = 25–29.9) (n;%)             | 331 (38)               |
| General obesity (BMI > 29.9) (n;%)           | 224 (26)               |
| Metabolic syndrome (n;%)                     | 449 (50)               |
| Atherosclerosis (n;%)                        | 365 (58)               |
| Arterial hypertension (n;%)                  | 569 (66)               |
| Liver steatosis (n;%)                        | 510 (61)               |
| Type 2 diabetes (n;%)                        | 346 (39)               |

Data are presented as mean  $\pm$  SD with range (in round brackets) for continuous variables, and in number and percentages for categorical ones

m males, f females, CRP C-reactive protein, ESR erythrocyte sedimentation rate

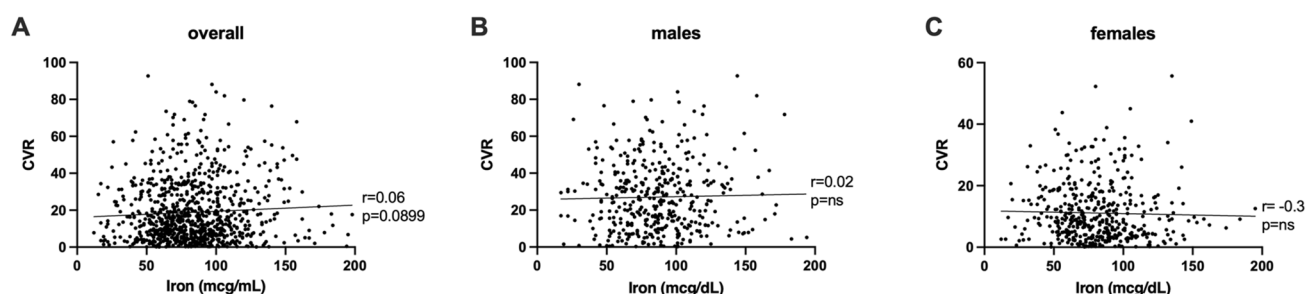
without Mets (Fig. 3c), finding significant decreased levels in metabolic patients ( $86.8 \pm 31.2$  vs.  $80.6 \pm 27.0$ ,  $p=0.0017$ , Cohen's  $d=0.63$ ).

Since we found significant difference when comparing iron levels in patients according to the absence or presence of different number of criteria to diagnose MetS (Fig. 3d,  $p=0.009$ ,  $\eta^2p=0.09$ ), we investigated if iron levels could be associated with specific MetS clinical features. Thus, we compared subjects with and without atherosclerosis (Fig. 3e), finding no significant difference in ( $p=0.0539$ , Cohen's  $d=0.38$ ) iron levels in patients with atherosclerotic plaque ( $81.4 \pm 29.2$ ) compared to subjects without any vessel alteration ( $86.1 \pm 30.1$ ), while such difference was significant when dividing our study population according to arterial hypertension diagnosis ( $86.4 \pm 30.5$  vs.  $82.3 \pm 28.8$ ,  $p=0.0484$ , Cohen's  $d=0.42$ ) (Fig. 3f). Also, differences between subjects with and without liver steatosis (Fig. 3g) were not significant ( $83.8 \pm 31.7$  vs  $84.9 \pm 33.2$ ,  $p=0.5837$ ,



**Fig. 1** Iron levels according to sex and age. (A) Student's T test was performed to assess differences between the two groups.  $p < 0.05$  was considered significant. The box plots show the median (second quar-

tile), first, and third quartile, and whiskers represent minimum and maximum values.  $**p < 0.01$ . (B) Pearson's correlations ( $r$ ) and the corresponding  $p$ -values ( $p$ ) are reported



**Fig. 2** Iron level correlations with cardiovascular risk (CVR) assessed by the Framingham Risk Score. Pearson's correlations ( $r$ ) and the corresponding  $p$ -values ( $p$ ) are reported

Cohen's  $d = 0.11$ ). Conversely, the strongest significant difference ( $p < 0.0001$ , Cohen's  $d = 0.89$ ) was found when comparing patients with and without diabetes (Fig. 2h). Indeed, diabetic patients displayed significantly lower iron levels ( $78.5 \pm 26.7$ ) compared to subjects without diabetes ( $87.1 \pm 30.3$ ).

To assess for multicollinearity prior to the multivariate analysis, we tested the correlation between serum iron and serum ferritin, finding a non-significant association ( $r = 0.05$ ,  $p = 0.1181$ ). Therefore, both variables were retained in the following analyses. Thus, we investigated the role of confounding factors in determining the association of low iron levels with MetS. Through ROC curve (sensitivity 75%, specificity 42%,  $p = 0.0013$ ), the iron level cutoff of 94 mcg/dL to diagnose MetS was calculated. Thus, we performed a logistic regression to analyse the risk for MetS in patients with lower iron levels.

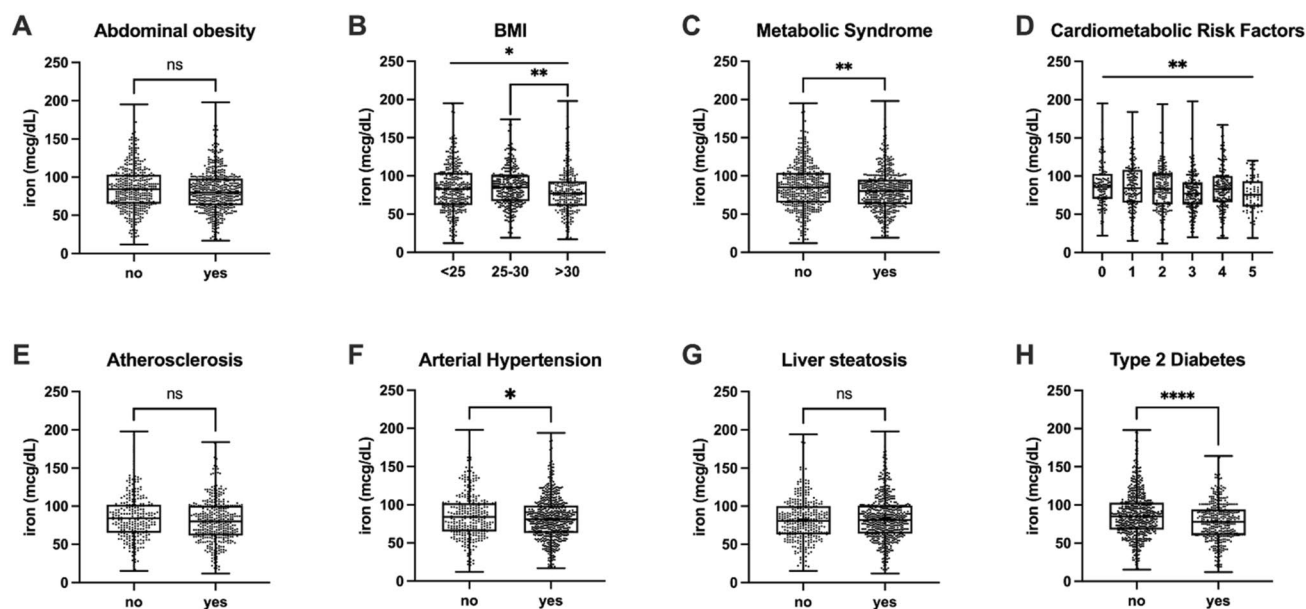
We observed that such relationship was still significant following the adjustment for covariates like age, sex,

smoking, physical activity, serum ferritin levels, ESR, and CRP as markers of inflammation (Fig. 4). Compared to individuals with higher iron levels, those with lower values had significantly higher OR of being classified as having MetS (OR = 1.8;  $p < 0.001$ ).

### Iron level correlations with bio-humoral parameters in the two sexes

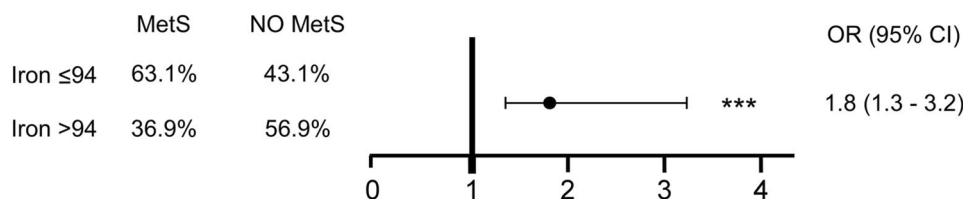
To deepen the iron putative role in determining CVD and metabolic syndrome-associated diseases, we then performed a correlation study between iron levels and bio-humoral parameters considered as diagnostic criteria. We found that in the overall population (Fig. 5), iron levels were significantly and inversely correlated with FPG ( $r = -0.1$ ,  $p = 0.002$ ) and HbA1c ( $r = -0.18$ ,  $p < 0.0001$ ), suggesting an involvement of iron levels in glucose metabolism. We then considered lipidic profile, finding that iron levels were significantly correlated with total cholesterol ( $r = 0.17$ ,





**Fig. 3** Comparison of iron level in patients with and without dysmetabolic conditions. Student' *T* test was performed to assess differences between two groups. ANOVA was performed to assess differences among three or more groups.  $p < 0.05$  was considered significant. The

box plots show the median (second quartile), first, and third quartile, and whiskers represent minimum and maximum values. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\*\* $p < 0.0001$ ; ns = not significant



**Fig. 4** Multivariate analyses for low iron levels and metabolic syndrome (MetS). Logistic regression was performed to investigate the association after adjusting for age, sex, smoking, physical activity, inflammatory markers ESR and CRP, and serum ferritin. \*\*\* $p < 0.001$

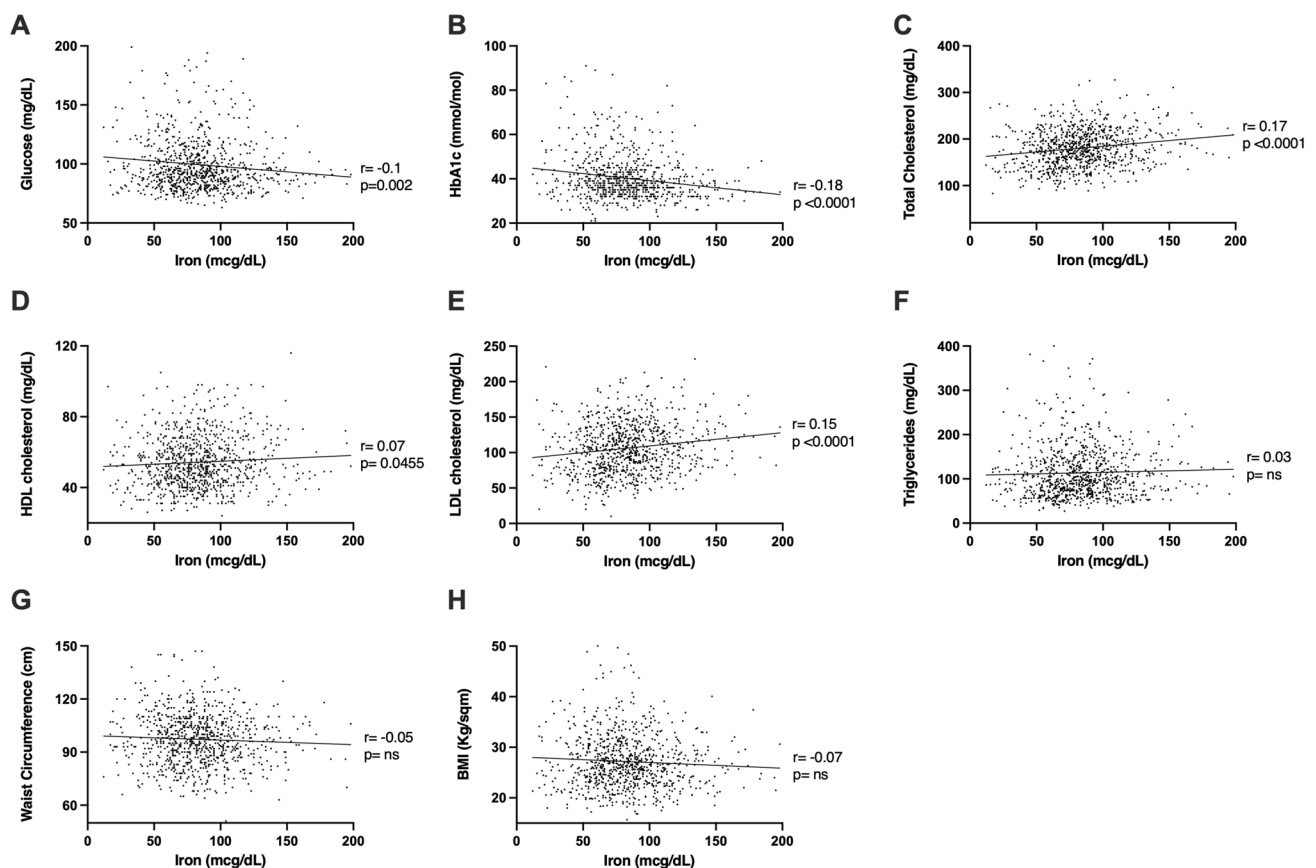
$p < 0.0001$ ), HDL-cholesterol ( $r = 0.07$ ,  $p = 0.0455$ ), and LDL-cholesterol ( $r = 0.15$ ,  $p < 0.0001$ ), while triglycerides did not display a statistically significant correlation ( $p = 0.3246$ ). Then, we performed a correlation analysis also for anthropometric measures, finding that neither BMI ( $p = 0.0662$ ) nor WC ( $p = 0.1243$ ) was significantly correlated with iron values. After adjusting for serum ferritin, such correlations were confirmed, and WC was found to be inversely correlated with iron levels (Supplementary Table 1). We also performed serum ferritin correlation analysis with bio-humoral and clinical parameters, showing that it positively and significantly correlated with WC, BMI, triglycerides, and LDL cholesterol (Supplementary Fig. 2).

Finally, we analysed iron correlations separately in the two sexes (Fig. 6). While iron correlations with glycaemic and lipidic parameters were confirmed, some intriguing differences were discovered between males and females regarding anthropometric parameters. Specifically, differently from

the overall population, in women an inverse significant correlation was present for both WC ( $r = -0.12$ ,  $p = 0.008$ ) and BMI ( $r = -0.12$ ,  $p = 0.008$ ).

## Discussion

Over the past decade, growing evidence has investigated the role of iron metabolism in modulating cardiovascular risk. In the present study, we specifically deepened the role of iron serum levels as marker of acquired metabolic disease. We observed no significant correlation between serum iron levels and the Framingham Risk Score, one of the most widely validated tools for predicting cardiovascular risk. However, a more detailed analysis revealed that abnormal iron levels were significantly associated with specific cardiometabolic risk factors. Lower serum iron levels were observed in patients with elevated BMI, MetS, arterial hypertension,



**Fig. 5** Iron level correlations with bio-humoral and clinical parameters in the study population. Pearson's correlations ( $r$ ) and corresponding  $p$ -values ( $p$ ) are reported

and T2D. These findings suggest that iron metabolism may contribute to the pathophysiological mechanisms underlying the clinical components of MetS. This association is likely mediated through iron's role in promoting inflammation and tissue injury via oxidative stress pathways [16].

In our study, we observed significant inverse correlations between serum iron levels and both fasting glycaemia and HbA1c. These findings suggest that iron deficiency may influence the pathophysiology of T2D, potentially exacerbating insulin resistance and impairing glycaemic control. Consistent with our results, in patients with iron deficiency anaemia, HbA1c decreased significantly after iron treatment [17], as well as a previous cross-sectional study involving 143 adult patients with diabetes reported an association between iron deficiency anaemia and altered glycaemic control [18].

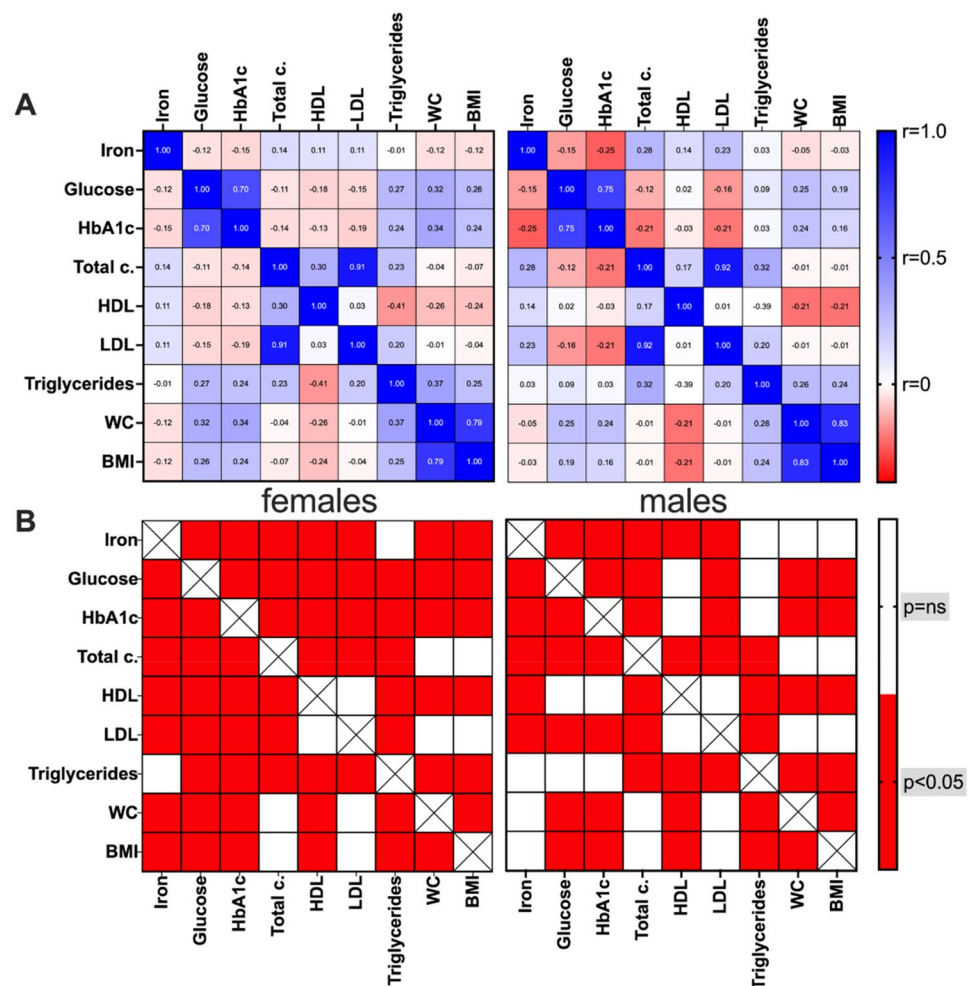
Similarly, an interventional clinical trial demonstrated that iron supplementation significantly reduced fasting blood glucose and HbA1c levels, thereby improving insulin resistance in women with T2D [19]. This sex-specific effect was further supported by a retrospective study showing that 39.3% of individuals with T2D had iron deficiency

anaemia, with higher prevalence among women and those with longer disease duration. Independent risk factors for anaemia included female sex, longer duration of diabetes, and elevated fasting plasma glucose levels [20].

Aligned with the sex-specific role of iron in diabetes, we found that obesity—assessed using both BMI and WC—was significantly and inversely correlated with serum iron levels in women, but not in men. Supporting our findings, a large multicentre population-based study conducted across four European countries reported a significantly higher prevalence of iron deficiency anaemia in women compared to men, primarily attributed to menstrual blood loss. Additional risk factors in both sexes included low dietary iron intake, gastrointestinal blood loss, and chronic disease [21].

Furthermore, our findings corroborate evidence from a cross-sectional study showing a significantly higher risk of iron deficiency in women with the highest body fat percentage (BF%) compared to those with the lowest BF% [22]. Similarly, lower serum iron levels have been reported in women with obesity compared to those with normal body weight [23].

**Fig. 6** Correlations among bio-humoral and clinical parameters in females and males. Heatmap representation of R values (**A**) and the respective p-values (**B**) of Pearson's correlations among bio-humoral and clinical parameters in females and males. Lateral bars show colours in the legend. The brightness of the colours indicates how strong the correlation is (**A**).  $p < 0.05$  were considered significant and are indicated as red squares (**B**)



If previous evidence suggests a relationship between low serum iron levels and obesity, the biological underpinnings of such sex-specific findings warrant further investigation. Adipose tissue is not merely a fat storage depot, but an active endocrine organ that plays a critical role in systemic energy homeostasis. Men and women exhibit distinct patterns of adipose tissue distribution and function, with women generally having greater subcutaneous fat and men presenting with increased visceral adiposity [24]. These differences are largely regulated by sex hormones, which also influence iron metabolism.

Indeed, fluctuations in oestrogen and testosterone levels modulate not only iron absorption, storage, and mobilization, but also adipocyte differentiation, lipid storage, and the inflammatory milieu within adipose tissue. These hormone-driven processes impact systemic metabolic pathways, including insulin sensitivity and lipid metabolism.

Importantly, iron availability within adipocytes influences mitochondrial activity and adipogenesis—processes essential for the healthy expansion and metabolic function of adipose tissue [25]. Dysregulation of iron metabolism can

lead to oxidative stress and chronic inflammation, contributing to adipose tissue dysfunction [26]. Of note, individuals with obesity frequently display altered iron homeostasis, characterized by reduced serum iron levels despite normal or elevated total body iron stores. This paradox is partially explained by inflammation-induced upregulation of hepcidin, which restricts iron mobilization from stores [27]. In this context, the typically lower serum iron levels observed in women—including in our cohort—may differentially affect adipose tissue metabolism, potentially influencing adipose tissue expansion, insulin sensitivity, and inflammatory responses. Conversely, men's relatively higher serum iron levels may predispose to increased oxidative stress, particularly in visceral fat, thereby contributing to a greater cardiometabolic risk.

Moreover, the chronic low-grade inflammation associated with increased visceral adiposity in men may alter the relationship between anthropometric measurements and serum iron levels. This sex-specific inflammatory environment could account for the absence of significant correlations between serum iron and anthropometric markers in men. It



may also help explain why, in our stratified analysis, serum iron levels were significantly associated with BMI, but not with WC in the general population.

Furthermore, oestrogens are known to influence iron homeostasis by regulating the expression of hepcidin, the key hormone controlling systemic iron absorption and distribution [28]. Hepcidin acts by inhibiting intestinal iron absorption and the release of iron from macrophages, thereby contributing to functional iron deficiency [29, 30]. Within macrophages, iron is stored as ferritin and released as needed via the iron exporter ferroportin.

During inflammatory states, hepatic production of hepcidin is upregulated, leading to downregulation of ferroportin. This process impairs the transfer of dietary iron from enterocytes in the small intestine into the bloodstream and restricts the release of recycled iron from macrophages located in the spleen and liver, potentially resulting in iron deficiency [31]. Conversely, ferritin—an acute-phase reactant—increases during both acute and chronic inflammation, as well as oxidative stress. As also calculated in our population, elevated ferritin levels have been reported in T2D, CVD [32], MetS, and its clinical components [33] with higher concentrations being associated with increased odds of these conditions [34]; notably, the rise in ferritin levels and its associated disease risk appears more pronounced in females [35].

Nevertheless, to clarify this relationship, further molecular, genomic, and histopathological studies are required also in view of some contrasting evidence. For instance, a large cross-sectional study in a Chinese population [36] found that higher levels of serum iron were positively associated with the prevalence of MetS. However, some factors could explain this discrepancy. First, our population was composed of patients who already presented with a high prevalence of cardiometabolic risk factors. Second, ethnic variations in genetics, diet, and iron metabolism could play a substantial role. Finally, also the iron content of adipocytes should be investigated. Indeed, Zhang et al. [37] showed that lowering iron in adipocytes protects mice from high-fat-diet-induced metabolic dysfunction, suggesting that iron content can be used as a sensor to activate an adipose–gut cross talk to regulate lipid absorption.

This study has several notable strengths. The use of real-world clinical data enhances the external validity and applicability of our findings. Additionally, the large sample size provides sufficient statistical power, increasing the reliability and robustness of the results. The comprehensive profiling of participants—including anthropometric, biochemical, and imaging parameters—represents a reproducible assessment of the associations between serum iron levels and cardiometabolic risk factors. Importantly, stratified analyses revealed significant sex-specific differences, particularly regarding the correlation between circulating iron and obesity-related measures in women. These findings further support the

emerging concept linking iron metabolism and ferroptosis-mediated inflammation as pivotal contributors to metabolic dysfunction and its clinical manifestations.

However, several limitations should be acknowledged. The degree of systemic inflammation may have influenced iron status; unfortunately, key inflammatory biomarkers involved in the iron homeostasis-inflammation axis—such as interleukin-6, hepcidin, and soluble transferrin receptor—were not available for analysis. Moreover, ethnic differences may limit the worldwide generalizability of our results, especially considering the influence of environmental factors such as dietary habits and pollution, which are known to contribute to both metabolic and cardiovascular diseases. Finally, the lack of information about menstrual status does not allow to precisely depict the iron status of women in our cohort.

## Conclusions

Our study underscores the potential utility of serum iron as a biomarker for the evaluation of patients with MetS and its related clinical conditions. Within our cohort, reduced serum iron levels were consistently associated with T2D and arterial hypertension, two central components of MetS. Notably, these associations extended to glucose, HbA1c, and lipid panel, suggesting that alterations in iron status may reflect the convergence of multiple metabolic pathways. Surprisingly, while no significant correlations were detected between iron and WC and BMI in the overall cohort, such correlations were found to be significant only in women, supporting the hypothesis that iron metabolism and related pathophysiological mechanisms differ between men and women. These insights may have important implications for risk stratification and personalized management strategies, particularly in women presenting with early metabolic disturbances.

Clinically, our findings advocate for a more nuanced interpretation of serum iron levels in patients exhibiting features of MetS. Assessing iron status could be particularly valuable for risk stratification in high-risk individuals, such as women with obesity. Moreover, although it may be premature to recommend iron supplementation based only on our findings, our finding encourages further research into iron-related pathways as putative novel diagnostic and therapeutic hits in metabolic diseases.

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**Data availability** Data presented in this study are available on request from the corresponding author.

## Declarations

**Human and animal rights statement and Informed consent** The study was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Policlinico di Bari (Bari, Italy) in accordance with the requirements of the Declaration of Helsinki. Reference number: n.311, MSC/PBMC/2015. Written informed consent for the use of clinical data was obtained from all participants in the study. In accordance with the approved Ethics Committee, only patients who were already 18 years old or more were included.

**Conflict of interest** The authors declare no conflict of interest.

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## Authors and Affiliations

Antonio Francesco Maria Giuliano<sup>1,2</sup> · Carlo De Matteis<sup>1</sup> · Salvatore Cantatore<sup>1</sup> · Ersilia Di Buduo<sup>1</sup> · Fabio Novielli<sup>1</sup> · Elsa Berardi<sup>1</sup> · Gianfranco Antonica<sup>1</sup> · Antonio Moschetta<sup>1,3</sup>  · Lucilla Crudele<sup>1,3</sup>

✉ Antonio Moschetta  
antonio.moschetta@uniba.it

✉ Lucilla Crudele  
lucilla.crudele@uniba.it

Antonio Francesco Maria Giuliano  
drgiuliano.a@gmail.com

Carlo De Matteis  
carlo.dematteis@uniba.it

Salvatore Cantatore  
salvatore.cantatore@gmail.com

Ersilia Di Buduo  
ersiliadibuduo9704@gmail.com

Fabio Novielli  
fabio.novielli@uniba.it

Elsa Berardi  
elsabera@libero.it

Gianfranco Antonica  
g.antonica@gmail.com

<sup>1</sup> Department of Interdisciplinary Medicine, University of Bari “Aldo Moro”, 70124 Bari, Italy

<sup>2</sup> Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), Clinica Medica “A. Murri”, University of Bari “Aldo Moro” Medical School, Bari, Italy

<sup>3</sup> INBB National Institute for Biostructure and Biosystems, Viale Delle Medaglie d’Oro 305, 00136 Rome, Italy