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Both low and high body iron stores relate to metabolic syndrome in postmenopausal women: Findings from the VIKING Health Study-Shetland (VIKING I)

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Abstract

Background: There are conflicting results among studies on the association between serum ferritin (SF) and metabolic syndrome (MetS), and by groups of sex/menopausal status. To date, there are no studies on British populations. The SF-MetS association might be U/J-shaped. We evaluated whether SF was independently associated with MetS (harmonized definition) in people from Shetland, Scotland.

Methods: We analysed cross-sectional data from the Viking Health Study-Shetland (589 premenopausal women [PreMW], 625 postmenopausal women [PostW] and 832 men). Logistic regressions using two approaches, one with the lowest sex and menopausal status-specific ferritin quartile (Q) as the reference and other using the middle two quartiles combined (2–3) as the reference, were conducted to estimate the SF-MetS association. The shape of the association was verified via cubic spline analyses. The associations were adjusted for age, inflammatory and hepatic injury markers, alcohol intake, smoking and BMI.

Results: Prevalence of MetS was 18.3%. Among PostMW both low and high SF were associated with MetS (fully adjusted odds ratios [95% confidence interval] compared to the middle two quartiles combined were: 1.99 [1.17–3.38] $p = .011$ for Q1 and 2.10 [1.27–3.49] $p = .004$ for Q4) This *U*-shaped pattern was confirmed in the cubic spline analysis in PostMW with a ferritin range of 15–200 ug/L. In men,

a positive association between ferritin quartiles with Q1 as the reference, did not remain significant after adjustment for BMI.

Conclusion: Extreme quartiles of iron status were positively associated with MetS in PostMW, while no SF-MetS associations were found in men or PreMW. The ferritin-MetS association pattern differs between populations and U/J-shaped associations may exist.

KEYWORDS

ferritin, insulin resistance, iron, metabolic syndrome

1 | INTRODUCTION

Increased body iron stores, estimated by serum ferritin (SF) levels, are associated with higher risk of type 2 diabetes (T2D),[1,2] although their relationship with cardiovascular disease (CVD) is unclear.[3] Ferritin is an intracellular protein with a significant capacity to uptake and store iron ions, with each molecule capable of sequestering approximately 3000 iron atoms. Its synthesis is regulated by the intracellular iron concentration.[4] A portion of the synthesized ferritin is released into the bloodstream, serving as a biomarker for tissue iron storage.[5] Additionally, ferritin functions as an acute-phase reactant, with its synthesis upregulated in response to infection and/or inflammation.[5] This upregulation is presumed to be related to an evolutionary adaptation that involves additional iron-binding proteins, aimed at sequestering free iron to inhibit its utilization by pathogenic microorganisms.[4,5] Although inflammation is widely associated with an increased risk of cardiometabolic diseases,[6] the relationship between SF and T2D appears to be independent of an inflammatory context. This conclusion is supported by many meta-analysed studies which show that adjustments for inflammatory markers, such as C-reactive protein (CRP) and fibrinogen levels, do not substantially alter the effect estimates or the statistical significance of the association.[1,2]

In several studies, metabolic syndrome (MetS), a risk factor for T2D and CVD, has been associated with ferritin levels.[7–9] In a recent meta-analysis, we conducted on SF-MetS associations in adults, we found an overall positive significant association between iron stores and MetS. However, there are still conflicting results on the ferritin-MetS association, in sub-populations defined by sex/menopausal status. Additionally, robust adjustments for confounders of inflammation and hepatic injury were not made in all of the studies.[10] Moreover, in the meta-analysis, Asian populations were overrepresented since 14 out of 21 studies were conducted in individuals from that region, whereas no studies in populations at different cardiovascular risk such as British or Latin-American populations have been reported to date.[10]

The pro-oxidant properties of iron which lead to increased oxidative stress and alterations of insulin sensitivity and endothelial/vascular integrity mean that most studies have focused on iron excess as a cardiometabolic risk factor.[11] However, iron deficiency (ID) has been also related to higher cardiometabolic risk although biological mechanisms are still unclear. For instance, lower ferritin levels were associated with a higher risk of CVD in people with T2D.[12] Similarly, correction of anaemia and ID has been shown to improve cardiovascular health in patients with heart failure.[14] In general population, higher transferrin saturation (a marker of high iron status) was found to be a protective factor against coronary heart disease (CHD) and functional ID was associated with incident CHD.[13,14] The studies on SF and MetS only tested positive associations by using a comparison of extreme categories of ferritin level distribution. Therefore, U or J-shaped associations have not been explored despite the epidemiological evidence for a role of ID in cardio-metabolic risk.

In light of the above, we analysed the relationship between SF and MetS in a Scottish population from the Shetland Islands (Viking Health Study—Shetland, part of Viking Genes) investigating potential positive and U/J-shaped associations adjusting for inflammatory, hepatic injury and body mass markers among other covariates.

2 | METHODS

2.1 | Study population

The Viking Health Study—Shetland (part of Viking Genes and hereafter VIKING I) is a genetic epidemiology study on a relatively isolated population in the north of Scotland.[15] For this study, 2122 volunteers with at least two Shetlandic grandparents were examined over 2 years from March 2013 to March 2015. Each participant attended a measurement clinic and a venepuncture

clinic to give a fasting blood sample at a dedicated research centre in Lerwick, Shetland Islands. The population used in this study consisted of 2047 individuals after excluding 75 individuals with missing values for ferritin, MetS-related variables, or covariates. Ethical approval was issued by the NHS South East Scotland Research Ethics Committee and all participants gave written informed consent.

2.2 | Biochemical and clinical variables

Blood was collected via venepuncture after overnight fasting. Glucose, triglycerides, and HDL-C were measured by using enzymatic-colorimetric methods. Haemoglobin and transaminases levels (GGT, aspartate transaminase [AST] and alanine transaminase [ALT]), were measured by using standard Beckman-Coulter reagents in a Beckman-Coulter DxC600i combined chemistry and immunochemistry analyser. SF was measured via latex agglutination method using Beckman-Coulter reagents in the same autoanalyser brand.

Blood pressure was measured using digital sphygmomanometers and two readings after at least 10 min of supine rest were taken to calculate the average blood pressure. Body weight and height were measured using standard techniques and instruments.[16] Body mass index (BMI) was calculated as weight in kg/height in meters squared.[17] Waist circumference (WC) was measured from the midpoint between the lateral iliac crest and the lowest rib using a flexible steel tape measure.[18] The criterion of smoking included the following categories: never smoker, ex-regular or ex-occasional smoker and current smoker. Alcohol intake had three categories: nondrinker or rarely, trivial drinker (special occasions or one to three days per month) and drinker (one or more days per week). Anaemia was defined as haemoglobin levels <12 g/dL in women and <13 g/dL in men.[19] Overweight and obesity were defined as having a BMI ≥25 and BMI ≥30, respectively. Menopausal status was defined according to self-report.

2.3 | MetS and its components

Cut- points from the international consensus definition for MetS were used as follows[20]: high triglycerides (HTG) at ≥1.7 mmol/L, low HDL-C at <1.0 mmol/L in men and <1.3 in women, high fasting glucose (HFG) at ≥5.6 mmol/L, high blood pressure (HBP) as SBP ≥130 mm/Hg and/or DBP ≥85 mm/Hg (or antihypertensive drug treatment) and increased WC ≥94 cm in men and ≥80 cm in women. MetS was defined as the presence of three or more variables meeting the definitions above. In the case of high glucose and triglyceride levels, these MetS components did not include additional cases with specific pharmacological treatment since this information was not available in the dataset used for analysis.

2.4 | Data analysis

Medians and interquartile ranges or proportions were used to summarize continuous and categorical study variables, respectively, in the whole sample and by groups according to sex and menopausal status. Differences were estimated via the Mann–Whitney *U* test for continuous variables and by χ^2 test for categorical variables. For the association analyses, SF was the exposure variable and MetS and its components were the outcome variables. Since both ferritin levels and cardiometabolic risk factors vary with sex and menopausal status, all the analyses of the association between ferritin and MetS and its components were conducted by using logistic regression modelling in separate groups of men and pre-and post-menopausal women. Ferritin levels were used as a categorical variable of sex- and menopausal-specific quartiles and also as a continuous Z score of log-transformed ferritin. Associations between ferritin and MetS or its components were described before and after adjusting for potential confounders which were age, fibrinogen, transaminases levels (AST, ALT and GGT levels), smoking, alcohol consumption and BMI. The set of confounding factors was chosen based on the possible influence of acute phase or subclinical inflammation, adiposity and liver dysfunction on levels of ferritin and/or outcome variables.

We conducted two approaches for logistic regressions with ferritin quartiles: (1) using the lowest quartile as the reference to evaluate the progressive increase in the likelihood of the MetS and its components throughout upper quartiles, and (2) using the middle quartiles (2nd and 3rd) combined as the reference to evaluate J/U-shaped associations in terms of whether either the lowest and highest ferritin serum concentrations related to MetS and its components. The reason to additionally conduct the approach # 1 was for comparability purposes, by providing information on association patterns in a similar way as it was evaluated in all previous studies.

The shape of the SF-MetS association was also graphically examined via cubic spline analyses for each sex/menopausal status group. First, we log-transformed ferritin values and calculated sex/menopausal group-specific Z scores (standard deviation units) of the normalized variable to obtain a comparable distribution

across sex/menopausal groups, since ferritin distribution between these sub-groups is heterogeneous. For the cubic spline analyses, we placed three knots at the 25th, 50th, and 75th percentiles and used the median as the reference. We conducted the above analyses in the whole sample and also a sensitivity analysis after excluding individuals with ID (ferritin <15 μg/L)[21] and clinically relevant high SF (ferritin >200 μg/L in women and 300 μg/L in men).[22] No strategy for data imputation was carried out because the excluded individuals with missing values represented only the 3.5% of the original sample of the project.

All analyses were processed using STATA 8.0 software (Statistics/Data Analysis, Stata Corporation, 4905 Lakeway Drive, College Station, TX 77845, USA, 800-STATA-PC).

3 | RESULTS

Table 1 describes the study variables from the VIKING I study The prevalence of overweight and obesity was 70% and 24.%, respectively. The prevalence of MetS was 18.3% in the whole sample of individuals. In comparison with premenopausal women (PreMW) and postmenopausal women (PostMW), men had higher BMI, SF and transaminases levels, and higher prevalence of increased triglycerides and glucose levels, as well as higher prevalence of CVD. PostMW had higher fibrinogen levels and, a higher prevalence of increased WC than PreMW and men. Meanwhile, PreMW had a higher prevalence of low HDL cholesterol and a higher proportion of alcohol drinkers than PostMW and men. Along with men, PreMW had a higher proportion of current smokers than PostMW. Prevalence of MetS and diabetes was more common in PostMW and men than in PreMW.

ID and anaemia, as expected, were more common in PreMW (22.6% and 3.1%) than in PostMW (5.9% and 1.8%) and men (1.6% and 3.4%). Ferritin levels were significantly higher in men than in PostMW and PreMW, and PostMW had higher SF than PreMW (Table 1). SF was higher in individuals with MetS than in those without MetS (median and interquartile range: 78 [39–124] vs. 53 [28–90] μg/L, $p < .001$). Ferritin levels (median and interquartile range) were also statistically significantly higher in subjects with MetS in each sex and menopausal status category (PreMW: MetS [prevalence 8.6%] 31 [16–64] μg/L vs. No MetS 25[15–40] μg/L, $p = .047$; PostMW: MetS [prevalence 22%] 68 [32–95] μg/L v. No MetS 57 [37–78] μg/L, $p = .016$; Men: MetS [prevalence 22.2%] 111 [63–163] μg/L v. No MetS 87 [57–129] μg/L, $p = .001$).

SF significantly increased throughout age groups [median and interquartile range: <40 years: 41 (22–74) μg/L; 40–59 years: 53 (27–98) μg/L; ≥60 years: 71 (44–114) μg/L. $p < .001$].

3.1 | Associations with MetS and its components (lowest quartile of ferritin as the reference)

In unadjusted and partially-adjusted analyses adjusting for age, alcohol consumption/smoking and inflammatory and liver injury markers, the highest ferritin levels were positively associated with MetS in men (Table 2). However, after further adjustment for BMI, this association did not remain statistically significant. Similar patterns were observed in associations with individual MetS components such as Low HDL-C, increased WC and high fasting glucose and triglycerides in men (Table S1). In the case of PreMW and PostMW, when levels of ferritin in the highest quartile were compared to levels in the lowest quartile there were no significant associations with MetS either unadjusted, partially, or fully adjusted. Nevertheless, in PostMW, there was a consistent significant persistent association of lower prevalence of MetS among people with ferritin in the second lowest quartile than those in the lowest quartile. A similar pattern was observed for low HDL-C and HBP in PostMW in unadjusted and fully-adjusted models (Table S1). Proportions with abdominal obesity progressively increased with increasing ferritin quartiles in PostMW women (Table S1).

3.2 | Associations with MetS and its components (middle quartiles 2 and 3 of ferritin as the reference)

Both extremes of ferritin levels remained statistically significantly associated with MetS in all models in PostMW when compared with the combined middle quartiles (Table 3). A nonstatistically significant similar pattern was also observed in PreMW after adjustment for BMI. The lowest quartile compared to. quartiles 2–3 was consistently and positively associated with MetS prevalence although without reaching statistical significance (Table 3). The association in PostMW was *U*-shaped between ferritin levels and low HDL-C, a partially significant U-shaped association was observed with HTG level (Q4 vs. Q2-Q3 of ferritin fully adjusted OR [95% CI] 1.91 [1.04–3.2] $p = .037$; Q1 vs. Q2-Q3 fully adjusted OR [95% CI] 1.18 [0.59–2.34] $p = .624$) and a trend for association between lowest SF (vs. middle levels) and HBP (OR [95% CI] 1.52 [0.92–2.51] $p = .095$) (Table S2).

TABLE 1 Study variables in the whole sample and by sex/menopausal status.

	All	Premenopausal women	Postmenopausal women	Men	*p* value		
					Men vs. PreM-W	Men vs. PostM-W	PreM-W vs. PostM-W
n	***n* = 2047**	***n* = 589**	***n* = 625**	***n* = 833**			
Age (years)	51 (38.9–63.2)	39.2 (31.2–46-2)	62.1 (55.8–68.2)	52.4 (40–64.8)	<.001	<.001	<.001
BMI (kg/m^2)	26.7 (24.1–29.9)	25.1 (22.6–28.2)	26.8 (24.1–30.2)	27.4 (25.1–30.2)	<.001	.002	<.001
Ferritin (μg/L)	56 (29–97)	25 (15.5–41)	55 (34–84)	90 (59–138)	<.001	<.001	<.001
Fibrinogen	3.3 (2.9–3.8)	3.2 (2.8–3.8)	3.6 (3.1–4.1)	3.2 (2.7–3.6)	.074	<.001	<.001
GGT	16 (12–24)	13 (10–17)	15 (12–23)	20 (15–29)	<.001	<.001	<.001
ALT	22 (17–29)	18 (15–23)	21 (17–26)	27 (21–36)	<.001	<.001	<.001
AST	22 (19–26)	20 (17–23)	22 (20–26)	24 (21–28)	<.001	<.001	<.001
HDL cholesterol (mmol/L)	1.4 (1.2–1.7)	1.54 (1.31–1.85)	1.62 (1.37–1.91)	1.29 (1.12–1.55)	<.001	<.001	.003
SBP (mmHg)	127.5 (116.5–142)	116 (109–124)	134 (121–149)	132 (122–145)	<.001	.230	<.001
DBP (mmHg)	75.5 (69–82.5)	70 (65–77)	76 (71–83)	78 (71–85)	<.001	.003	<.001
WC (cm)	91.2 (81.5–100.8)	82.5 (75.6–91.6)	89.1 (80.5–97.7)	97.4 (90–105.2)	<.001	<.001	<.001
Glucose (mmol/L)	4.8 (4.5–5.1)	4.6 (4.3–4.8)	4.8 (4.5–5.1)	4.9 (4.6–5.3)	<.001	<.001	<.001
Triglyceride (mmol/L)	0.9 (0.6–1.3)	0.7 (0.5–1.0)	0.9 (0.6–1.3)	.9 (0.7–1.4)	<.001	.100	<.001
Insulin mU/mL	37.1 (25.8–54)	34.6 (24.6–48.6)	37 (26–53)	39.3 (27–59.6)	<.001	.082	.011
HOMA-IR	7.8 (5.3–11.8)				<.001	.022	<.001
HbA1C (%)	5.3 (5.1–5.5)	5.2 (5–5.3)	5.5 (5.3–5.6)	5.3 (5.1–5.5)	<.001	<.001	<.001
High blood pressure	1032 (50.4)	107 (18.2)	404 (64.6)	521 (62.5)	<.001	.411	<.001
Low HDL-C	350 (17.1)	146 (24.8)	118 (18.9)	86 (10.3)	<.001	<.001	.013
High WC	1366 (66.7)	349 (59.3)	480 (76.8)	537 (64.5)	.046	<.001	.001
High glucose	147 (7.2)	12 (2)	45 (7.2)	90 (10.8)	<.001	.019	<.001
High triglycerides	244 (11.9)	31 (5.3)	72 (11.5)	141 (16.9)	<.001	.004	<.001
MetS *n* (%)	374 (18.3)	51 (8.7)	138 (22.1)	185 (22.2)	<.001	.953	<.001
Smoking *n* (%)							
Never smoker	1133 (55.3)	340 (57.7)	342 (54.7)	451 (54.1)			
Ex-regular or ex-occasional smoker	747 (36.5)	192 (32.6)	241 (38.6)	314 (37.7)			
Current smoker	167 (8.2)	57 (9.7)	42 (6.7)	68 (8.2)	.121	.583	.034
Alcohol consumption *n* (%)							
Non-drinker or rarely	84 (4.1)	10 (1.7)	47 (7.5)	27 (3.2)			

(Continues)

TABLE 1 (Continued)

	All	Premenopausal women	Postmenopausal women	Men	*p* value		
					Men vs. PreM-W	Men vs. PostM-W	PreM-W vs. PostM-W
n	***n* = 2047**	***n* = 589**	***n* = 625**	***n* = 833**			
Trivial drinker	152 (7.4)	29 (4.9)	59 (9.4)	64 (7.7)			
Drinker	1811 (88.5)	550 (93.4)	519 (83)	742 (89.1)	.019	<.001	<.001
CVD *n* (%)	64 (3.1)	2 (0.3)	18 (2.9)	44 (5.3)	<.001	.024	<.001
Diabetes *n* (%)	46 (2.2)	1 (0.2)	19 (3.1)	24 (2.9)	<.001	.725	<.001

Abbreviations: ALT, alanine-aminotransferase levels; AST, aspartate-aminotransferase levels; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase levels; MetS, metabolic syndrome; PostM-W, postmenopausal women; PreM-W, premenopausal women; SBP, systolic blod pressure.

We conducted additional adjustments for prevalent CVD and diabetes but this did not substantially modify the effect estimates for the associations.

3.3 | The shape of ferritin-MetS association

The cubic spline analyses confirmed the patterns previously described by comparing SF quartiles. In the whole sample of PostMW, a *U*-shaped pattern was observed (Figure 1C) and this was accentuated when cases with ID and clinically increased SF were removed (Figure 1D). The association of lower ferritin with MetS seems to begin from −0.5 SD units of log-ferritin (36 ug/L) and the association between higher SF and MetS become evident from approximately +0.8 SD units of log-ferritin (89 ug/L) (Figure 1D). A similar pattern occurred in PreMW, in which a trend of association between lower ferritin and MetS was identified in the sample with SF within the normal range (Figure 1A,B). The enhanced associations in PreMW and PostMW women after excluding women with ID and clinically increased SF may be due to the small number of cases with extremely low or high SF distorted the SF-MetS association. In men, no association between SF as a continuous variable and MetS was observed in either the whole sample or after the sensitivity analysis excluding individuals with extremely low and increased SF (Figure 1E,F).

4 | DISCUSSION

In this study, we found that the association between ferritin and MetS differed by sex/menopausal status. In PostMW, SF had a *U*-shaped association pattern with MetS and several of its components, while in men there were positive associations markedly influenced by BMI. These findings suggest that the ferritin-cardiometabolic risk relationship differ within as well as between (as described in the introduction) populations and that nonlinear associations should be explored for sex and menopausal status sub-groups. Further research reporting the association in populations not examined so far is warranted.

In the PostMW in our study, either high or low SF levels were associated with higher odds of MetS. In terms of high ferritin levels and MetS, our findings replicate previous similar association patterns reported in several studies.[10] However, whereas those studies compared extremely high and low ferritin levels, in our study higher ferritin levels only reached a significant association with MetS when these were compared with middle concentrations of ferritin. On the other hand, it was not feasible to directly

TABLE 2 Odds ratios (95% confidence interval) for metabolic syndrome by sex- and menopausal-specific quartiles (Q) of serum ferritin.

	Unadjusted		Adjusted for model 1		Adjusted for model 2		Adjusted for model 3	
	OR (IC 95%)	***p* value**	**OR (IC 95%)**	***p* value**	**OR (IC 95%)**	***p* value**	**OR (IC 95%)**	***p* value**
Premenopausal women								
Q1 2–15 μg/L	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Q2 16–25 μg/L	.99 (.43–2.28)	.986	.97 (.41–2.30)	.957	.86 (.34–2.22)	.744	1.00 (.39–2.54)	.999
Q3 26–41 μg/L	.39 (.13–1.14)	.087	.39 (1.33–1.18)	.097	.28 (0.08–0.91)	.035	.27 (0.08–0.92)	.038
Q4 42–160 μg/L	1.99 (0.94–4.20)	.069	2.02 (0.94–4.35)	.070	1.31 (0.57–3.01)	.516	1.03 (0.43–2.47)	.945
Postmenopausal women								
Q1 5–34 μg/L	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Q2 35–54 μg/L	**.37 (.20–.71)**	**.003**	**0.37 (.19–.71)**	**.003**	**.41 (.21–.79)**	**.009**	**.43 (.22–.87)**	**.019**
Q3 55–84 μg/L	.88 (.52–1.50)	.657	0.80 (0.46–1.37)	.421	0.68 (0.38–1.19)	.184	**.54 (.30–.99)**	**.049**
Q4 85–450 μg/L	1.46 (.89–2.39)	.133	1.26 (.75–2.11)	.368	1.07 (.62–1.84)	.783	1.06 (0.60–1.85)	.833
Men								
Q1 4–58 μg/L	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Q2 59–89 μg/L	.96 (.58–1.58)	.874	1.00 (.59–1.69)	.971	1.00 (.59–1.71)	.983	1.13 (.63–2.01)	.662
Q3 90–138 μg/L	1.24 (.76–2.03)	.373	1.27 (.77–2.11)	.342	1.05 (.62–1.77)	.854	1.15 (.65–2-03)	.615
Q4 139–772 μg/L	**2.15 (1.36–3.41)**	**.001**	**2.20 (1.36–3.55)**	**.001**	**1.66 (1.00–2.74)**	**.046**	1.40 (0.81–2.42)	0.218

Note: Model 1: Adjusted for age, smoking, and alcohol consumption. Model 2: Adjusted for model 1 plus gamma-glutamyl transferase levels, alanine-aminotransferase levels, aspartate-aminotransferase levels, fibrinogen levels. Model 3: Adjusted for model 2 plus BMI. Q, quartile. Ref, reference. Significant associations are shown in bold ($p < .05$). Ferritin range by quartiles are shown in Table 2.

TABLE 3 Odds ratios (OR) and 95% confidence interval (CI 95%) for metabolic syndrome by sex- and menopausal-specific quartiles (Q) of serum ferritin.

	Unadjusted		Adjusted for model 1		Adjusted for model 2		Adjusted for model 3	
	OR (IC 95%)	*p* value	OR (IC 95%)	*p* value	OR (IC 95%)	*p* value	OR (IC 95%)	*p* value
Premenopausal women								
Q1 2–15 µg/L	1.45 (.67–3.14)	.335	1.46 (.66–3.21)	.344	1.78 (.77–4.10)	.171	1.65 (.69–3.91)	.252
Q2-Q3 16–41 µg/L	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Q4 42–160 µg/L	**2.91 (1.49–5.67)**	**.002**	**2.96 (1.48–5.90)**	**.002**	**2.39 (1.15–4.96)**	**.018**	1.75 (.80–3.80)	.156
Postmenopausal women								
Q1 5–34 µg/L	**1.61 (1.00–2.59)**	**.048**	**1.71 (1.05–2.78)**	**.030**	**1.80 (1.08–2.98)**	**.022**	**1.99 (1.17–3.38)**	**.011**
Q2-Q3 35–84 µg/L	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Q4 85–450 µg/L	**2.35 (1.50–3.70)**	**<.001**	**2.15 (1.35–3.4)**	**.001**	**1.92 (1.18–3.12)**	**.008**	**2.10 (1.27–3.49)**	**.004**
Men								
Q1 4–58 µg/L	.91 (0.59–1.40)	.671	.87 (.56–1.37)	.565	.97 (.61–1.54)	.905	.87 (.52–1.43)	.591
Q2-Q3 59–138 µg/L	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Q4 139–772 µg/L	**1.96 (1.34–2.86)**	**<.001**	**1.93 (1.31–2.85)**	**.001**	**1.61 (1.07–2.43)**	**.621**	1.22 (0.78–1.91)	.368

Note: Model 1: Adjusted for age, smoking, and alcohol consumption. Model 2: Adjusted for model 1 plus gamma-glutamyl transferase levels, alanine-aminotransferase levels, aspartate-aminotransferase levels, fibrinogen levels. Model 3: Adjusted for model 2 plus BMI. Q, quartile. Ref, reference. Significant associations are shown in bold ($p < .05$). Ferritin range by quartiles are shown in Table 4.

contrast our finding of additional low ferritin-MetS association in PostM-W because J or *U*-shaped associations were not tested in previous studies. Nevertheless, higher odds of MetS and/or specific MetS components in the lowest quantile of ferritin (vs. intermediate quantiles) have been identified in some studies particularly among PreMW or PostMW. Cho et al. and Lee et al. reported trends of lower odds for MetS in quartile 2 vs. 1 of ferritin concentration in pre and PostMW, respectively (OR: 0.65 confidence interval [CI] 0.39–1.09).[7,9] In addition, Yoon et al. described a higher incidence of MetS in the lowest tertile of ferritin levels (16.2%) vs. tertile 2 (12.2%) in PostMW.[23] Similarly, in U.S. PreMW and Korean women, the likelihood of increased triglycerides and increased blood pressure was lower in ferritin quartile 2 vs. quartile 1.[8,9] In other studies there was no evidence for an inverse association between ferritin and cardiometabolic risk variables.[24,25]

The graphical analyses to evaluate the shape of the SF-MetS association supported the results found via comparisons of extreme vs. middle categories of SF concentration in PostMW. This was also partially supported by the pattern in PreMW, which showed a trend for a relationship between lower SF and MetS. The above patterns were particularly evident after the exclusion of the small number of cases with extremely low (ID) and high (clinically increased) SF that presumably distorted the association observed within the intermediate range. This observation suggests that low and high levels of SF within the normal range are linked to cardiometabolic risk. However, ID might be potentially present in individuals with SF above 15 ug/L (WHO cut-off for ID),[21] since a higher cut point of <30 ug/L has been proposed for moderate ID.[26] PostMW with lower iron status regardless of ID thresholds might be more likely to have higher cardiometabolic risk.

The pattern of low and high ferritin concentration related to MetS identified in PostMW could be explained in terms of SF ranges. PostMW have intermediate iron status, not as low as in PreMW and not as high as in men. In this way, disturbances in both directions to the SF distribution would be more likely to show associations with health outcomes. This could be additionally related to the metabolic transition that includes marked iron status changes. While some PostMW still carry effects of previous low iron or iron-deficient status, other women with previous adequate iron stores might experience iron excess and its prooxidant collateral effects in the postmenopausal stage. However, this hypothesis should be properly tested in large and representative samples of women with trajectories of changes in iron status throughout premenopausal, perimenopausal and postmenopausal stages.

Increased iron status in PostMW is mainly inferred from the cessation of iron loss due to menstrual bleeding, which occurs during the female reproductive stage. It is

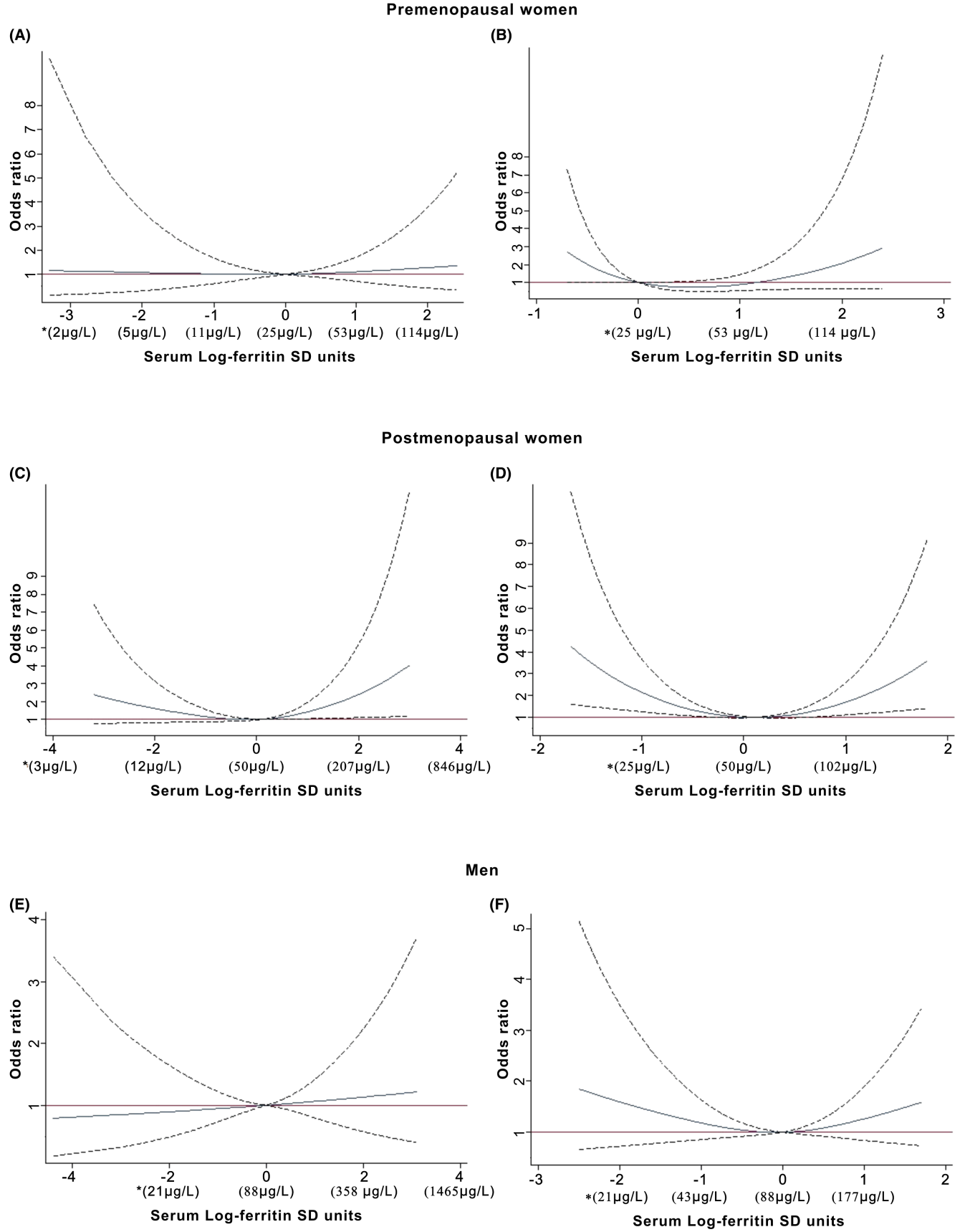

FIGURE 1 Legend on next page

FIGURE 1 Cubic spline analysis for the shape of the association between serum ferritin (standard deviation (SD) units of log-transformed values) and metabolic syndrome by groups of sex and menopausal status. A, C, and E are analyses in the whole groups of sex and menopausal status. B, D, and E are analyses excluding individuals with either iron deficiency (Ferritin <15 ug/L) and excess (Ferritin >200 ug/L in women, >300 ug/L in men). *Values in parenthesis are the equivalent ferritin concentrations of the SD units. Blue line is the value of the odds ratio, red line is the null value[1] of the association, and dot lines are the upper lower limits of the confidence interval for the odds ratios.

not clear whether changes in oestrogen levels during the transition from premenopausal to postmenopausal stages affect iron status. For instance, an in vitro study showed inhibition of hepcidin synthesis when human liver cells were exposed to 17β-estradiol, and hepcidin is a peptide hormone that downregulates intestinal iron absorption.[27] This effect might be a compensatory mechanism in the premenopausal stage to increase intestinal iron uptake and counterbalance iron losses during the menstrual cycle.[27] In contrast, a study reported lower iron status in post-reproductive age women undergoing hormone replacement therapy (HRT) compared to those without this therapy.[28] This finding could imply a differential pattern in the oestrogen-iron status link according to reproductive and post-reproductive age. Our study lacked information on HRT, and future studies should evaluate this covariate in the relationship between SF and other iron biomarkers with cardiometabolic risk in PostMW.

Both ID and excess have been linked to glucose and fat metabolic disturbances in animal and in vitro models. Molecular mechanisms of iron excess appear to be clearer than those of iron-deficiency. In vitro and animal models, iron excess seems to increase oxidative damage in insulin signalling, and interferes with GLUT transporters translocation in the cell membrane, predisposing to insulin resistance and hyperglycemia.[11] These molecular alterations are consistent with the broad body of literature linking increased SF and higher risk of diabetes in many populations and cohorts.[1,2]

Although experimental in vitro evidence points out the negative effects of iron overload on vascular function and the development of atherosclerotic plaque via oxidative stress,[29,30] previously reviewed prospective evidence does not support a specific independent epidemiological association between iron excess and the onset of CVD in the general population.[13] Moreover, individuals with hereditary hemochromatosis, a disease characterized by extreme iron overload, do not show any increased incidence of atherosclerosis.[31] Similarly, to date, there is no clear equivalence between SF and the amount of free circulating iron in blood in relation to atherogenesis. In the absence of infection and/or inflammation, SF reflects tissue iron stores and much higher stores might indicate a higher cellular synthesis of ferritin in response to constant exposure to free iron.[4,5] This intracellular free iron is primarily in the pro-oxidant ferrous form and ferritin has an enzymatic domain that catalyses the conversion of ferrous iron into the ferric ion to store it in this nondamaging form.[4] Therefore, if a direct link between high SF and disrupted vascular function exists, it might be supported more by insulin resistance-derived effects than by direct atherogenic effects of iron. In this way, the role of iron in atherogenesis could be more contributory than etiological, but this understanding remains debatable until deeper studies can probe which iron sources (systemic, tissue or macrophage iron) worsen atherosclerotic plaque.[31]

On the other hand, hyperinsulinemic, hyperglycemic and dyslipidemic effects of an iron-deficient diet have been reported in rats.[32] These effects were linked to a concurrent increase in lipogenic gene expression and a decrease in gene expression related to β-oxidation in both the liver and skeletal muscle. In a recent study conducted on mice, dietary ID was associated with decreased SF levels, increased weight gain and insulin resistance (159%, $p < .01$), partly attributed to reduced activation of AMP-activated protein kinase.[33]

In 170 adults, significant disparities ($p < .001$) were observed between control subjects and those with ID in their average insulin levels (68.7 ± 0.5 vs. 100.0 ± 2.0 pmol/dL) and insulin-to-glucagon ratio (IGR, 4.0 ± 0.1 vs. 19.5 ± 2.1).[34] Similarly, a very recent mendelian randomisation analysis of the UK Biobank showed that higher levels of iron biomarkers had moderate protective effect for coronary artery disease.[35] These same biomarkers levels showed an adverse effect for T2D, implying a dual behaviour of iron metabolism with regard cardiometabolic risk.

ID has been also related to hemodynamic alterations related to raised blood pressure. Intracellular ID in pulmonary arterial smooth muscle cells from genetically modified rats triggered overexpression of vasoconstrictor-endothelin and consequently pulmonary arterial hypertension.[36] In addition, maternal ID has been shown to program hypertension in rats' offspring via reduction effects in renal cortex angiotensin II receptor type 2 and an increase in renal cortex angiotensin II receptor type 1 and angiotensin-converting enzyme abundance.[37] Ferritin is also involved in the suppression of a strong inhibitor of angiogenesis, HKa and thus low ferritin concentrations might be harmful to the integrity of vascular tissue concentration. Similarly, low-birth infants supplemented with

iron during the first six life months exhibited significantly lower blood pressure values at the age of 7 in comparison with nonsupplemented low-birth infants.[38]

Applying a conventional approach of progressive comparison throughout SF quartiles, did not identify a significant association between higher ferritin levels and MetS in any of the sex/menopausal status subgroups. Although in general, we identified a pooled positive significant association between ferritin and MetS in a previous meta-analysis,[10] our negative finding in the Viking I study is similar to those of several studies. Zelberg et al. did not find a significant association in the Israeli population,[39] and Kilani et al., in men or women.[40] Other studies have failed to find significant associations in men particularly, those who have much higher iron stores than women.[8,9,41,42] Similarly, some studies have reported associations in women but not in men and others have reported the opposite pattern.[10]

A nonsignificant progressive increased likelihood of MetS across categories of ferritin concentration in this Scottish study could be explained if there is a threshold effect in the association between ferritin and MetS. A study in Spanish men found that the relationship between ferritin and MetS and its components was nonlinear.[43] The lower ferritin levels in Scottish than Spanish populations may mean that it is not possible to identify a threshold effect since the studies that found associations between ferritin and most or all of the MetS components often reported much higher ferritin levels. For example, the 60th and 80th percentile of ferritin in the Spanish study (181 and 261 μg/L, respectively)[43] were higher than those for men in the present study (108 and 151 μg/L). Higher median (interquartile range) of 318 (221–459) and 152 (107–212) μg/L were reported in Chinese and Korean men, respectively,[44,45] compared to that in men from the VIKING I study (90 [58–138] μg/L). Removing cases with anaemia or ID in our study population did not explain these differences in ferritin concentrations. In addition, the observed nonassociations in our study were not affected by adjusting for anaemia (data not shown). SF levels might have been too low to trigger a significant independent association with MetS or several of its components.

Another reason for the general lack of independent associations between higher SF and MetS in this Scottish population could be, at least partially, related to the high prevalence of confounding factors. BMI values affected the associations found in men and PostMW. BMI is widely associated with T2D and CVD,[46] and also positively influences ferritin levels[47] through mechanisms of excess adiposity-related inflammation[48] or insulin resistance.[49] Similarly, although to a lower extent, obesity also can lead to ID and anaemia due to chronic inflammation, even in this condition ferritin levels might be increased because active sequestering of iron in tissues.[48] More than half of the individuals in the VIKING study were overweight (70%) or obese (24%). Moreover, Scotland has the second highest prevalence of obesity among the members of the Organization for Economic Co-operation and Development after the United States of America, reaching figures of 22% and 24% of Scottish men and women, respectively, in 2003.[50] Levels of transaminases were an additional attenuating factor of the associations. This might be expected since liver injury has been associated with cardiovascular risk[51] and also triggers releasing of intra-hepatic ferritin into the bloodstream, increasing circulating ferritin levels.[52] The link between transaminase levels and SF appears to have a specific pattern when body mass index and sex/menopausal status is considered. In premenopausal women affected by obesity who undertook a hypocaloric diet to lose weight, transaminase levels were positively related to SF both before the intervention and after weight changes. This relationship remained unaffected after adjusting for the respective weight changes.[53] Meanwhile, in men in the same study, weight loss led to concomitant reductions in SF and transaminase levels.[53] However, further mechanistic studies are needed to elucidate additional pathways explaining the relationship between liver function and iron metabolism markers.

The association between ferritin levels and cardiometabolic risk markers could differ between populations of different countries owing to genetic and/or ethnic differences influencing the amount of body iron and interaction with other dietary and nondietary factors and differences in the distribution of confounding factors.

4.1 | Strengths and limitations

Some limitations of this study have to be mentioned. Cause-effect relationships cannot be inferred due to the cross-sectional design of the study. MetS components of high glucose and triglyceride levels did not include additional cases who might have met the criteria if they had not been prescribed pharmacological treatment. In addition, only SF was available as iron biomarker in the VIKING study, and other measurements such as serum transferrin or soluble transferrin receptor levels might have enriched our analysis and conclusions. Chance findings due to the multi-test nature of the analysis cannot be discarded. However, the association patterns found were coherent and consistent. We avoided to generate artificial *p* values via Bonferroni correction, and instead discussed the plausibility of the findings. Similarly, the findings of this study might not be generalisable for other

populations until further validation in studies with similar analysis approach. Particularly, our study population showed an unexpectedly significantly higher prevalence of cardiovascular disease in men than in postmenopausal women (PostMW). However, markers of cardiometabolic risk had more consistent patterns. For instance, the prevalence of metabolic syndrome (MetS) was comparable between men and PostMW, and the insulin resistance index (HOMA-IR) was significantly higher in PostMW than in men. According to a preliminary brief report of the Scottish Burden of Disease in 2019 for the Shetland region, the Shetland Islands population appears to exhibit a marked difference of -30.6% in the grouped rate of ischemic heart disease and early death from this cause compared to the general rate in Scotland.[54] The lower cases in Shetlanders might influence differences by sex and menopausal status.

To the best of our knowledge, this study appears to be the first to describe the association between ferritin and MetS in a British population, and examining the shape of this association in each subgroup of sex/menopausal status. This study would also be the first to report a U-shaped association in post-MW.

In conclusion, both low or increased ferritin levels were independently associated with MetS in post-MW. Increased ferritin, when compared to the lowest levels, was not associated with MetS after adjustment for a variety of factors in this Scottish population. BMI markedly influenced the ferritin-MetS association. Lower ferritin levels in comparison with other populations, may contribute to the lack of independent association between increased ferritin and MetS or its components in most of the population if threshold effects of ferritin concentration existed in the association. The kind of association between SF and MetS could differ between populations of different countries owing to genetic and/or ethnic differences influencing the amount of body iron and interaction with other dietary and nondietary factors, and differences in the distribution of confounding variables.

The assessment of cardiometabolic risk might be relevant in individuals with both low and elevated iron status, but further research is needed to improve our understanding of this association. Interventions and treatments should aim to achieve and maintain a normal, middle-range iron status to avoid marginal iron excess or deficiency. However, this approach might require individualized strategies due to the wide clinical range of normal ferritin values. Evaluating historical records of SF and other iron markers might help achieve this goal.

AUTHOR CONTRIBUTIONS

M.F.S.O conceived the study design, analysed data, and drafted the manuscript. S.M and J.F.W reviewed and edited the manuscript. J.M.F.R and S.H.W reviewed and edited the manuscript, and contributed to the discussion.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. There are no conflicts of interest related to the study design or its results.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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