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Sex-specific Differences in the Association between Insulin Resistance and Metabolic Syndrome and Ferritin in Korean Adults: A Nationwide Population-based Study

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ABSTRACT

OBJECTIVE This study assessed the association between metabolic syndrome (MetS) and homeostasis model assessment of insulin resistance (HOMA-IR) and ferritin based on gender in Korean adults.

METHODS This study was conducted using data from 5,730 adults (aged 20 or older) and the Korea National Health and Nutrition Examination Survey.

RESULTS This study included some key findings First, HOMA-IR levels showed a positive correlation with quartiles (Q) of ferritin both in postmenopausal women ($p = 0.001$) and in men ($p < 0.001$). However, there was no statistically significant difference between the HOMA-IR levels and the Q of ferritin in premenopausal women ($p = 0.149$). Second, using the Q1 of ferritin as the reference, the ORs of MetS were positively significant in men (Q3 [OR, 1.770; 95% CI, 1.308–2.397] and Q4 [OR, 2.385; 95% CI, 1.775–3.20]) and postmenopausal women (Q4 [OR, 1.873; 95% CI, 1.351–2.596]). However, there was no significant difference between MetS and the quartiles of ferritin in premenopausal women.

CONCLUSIONS An increase in ferritin is associated with both metabolic syndrome and insulin resistance in both Korean postmenopausal women and men. However, there is no significant difference between ferritin and metabolic syndrome in premenopausal women.

KEYWORDS ferritin, metabolic syndrome, insulin resistance, gender difference, Korean adults

INTRODUCTION

Metabolic syndrome (MetS) involves metabolic abnormalities indicated by central obesity, elevated blood pressure (BP), elevated triglycerides (TGs), reduced high-density lipoprotein cholesterol (HDL-C), and elevated fasting blood glucose (FBG) and is characterized by insulin resistance (1). MetS is a strong predictor of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) and is closely related to increased cardiovascular mortality and morbidity (2, 3).

Iron is a component of red blood cells in the human body and plays a crucial role in the proper functioning of the immune system, the synthesis of DNA and other amino acids, and various energy metabolism processes through its role in enzymes and proteins (4). Ferritin reflects the iron store because iron is combined with apo-ferritin and

stored as serum ferritin (5). Although increased ferritin levels are sometimes used as an indicator of reduced iron deficiency anemia (IDA), excessive ferritin levels are positively correlated with insulin resistance, CVD and inflammation (6-8).

Research on ferritin and MetS is being conducted worldwide. Most of the previous studies have reported that an increase in ferritin is associated with MetS (9-11). However, the relationship between MetS and ferritin can vary by sex because of the differences in sex hormones, eating habits, and menstruation. Blood loss due to menstruation and certain dietary patterns contribute to lower ferritin levels and iron deficiency in women (12). Sex hormones, testosterone in men and estrogen in women, play a key role in regulating iron metabolism and are also linked to MetS (13). Therefore, this study aimed to conduct an analysis of the relationship between MetS and ferritin in Korean men and pre- and post- menopausal Korean women using the Korea National Health and Nutrition Examination Survey data.

METHODS

Study subjects

In the data of KNHANES V-1, the number of adults aged 20 years or older was 6,665 out of 8,958. We excluded 935 subjects for whom analytic variable data were missing, such as ferritin and various blood chemistry tests. Finally, 5,730 subjects (men, 2,469; women, 3,261 [premenopausal women, 1,620; postmenopausal women, 1,641]) were included in the statistical analysis. This study was conducted according the principles expressed in the Declaration of Helsinki (Institutional Review Board No [IRB No], 2010-02CON-21-C).

General characteristics and blood chemistry

Research participants were classified by smoking status (non-smoker or current smoker), regular exercise (no or yes), and alcohol consumption (no or yes). Anthropometric measurements included waist circumference (WC), body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP). Clinical measurements included measurements of HDL-C, total cholesterol (TC), TGs, FBG, total iron binding capacity (TIBC), hematocrit (Hct), hemoglobin (Hb), serum iron (Fe), and ferritin levels.

Metabolic syndrome, metabolic syndrome score and HOMA-IR

MetS was defined using the diagnostic criteria of the National Cholesterol Education Program (NCEP) based on common clinical measures including WC, HDL-C, SBP, DBP, TGs, and FBG. Abdominal obesity was classified as WC ≥ 80 cm in women or WC ≥ 90 cm in men (14). Elevated BP was diagnosed by a physician as hypertension and classified as SBP ≥ 130 mmHg or DBP ≥ 85 mmHg. Elevated TGs was classified as TGs ≥ 150 mg/dL. Elevated FBG was classified as FBG ≥ 100 mg/dL. Reduced HDL-C was classified as HDL-C < 40 mg/dL in men and HDL-C < 50 mg/dL in women. If three or more of these five measures are present, it is classified as MetS (15). Participants without any of the components were classified as MSS 0, and those with 1, 2, 3, or 4 or more of the risk factors were classified as MSS 1, 2, 3, or ≥ 4, respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as [FBG (mg/dL) × fasting insulin (μU/mL)]/405 (16).

Ferritin

Levels of ferritin were measured by immunofluorescence-mat ferritin (DiaSorin Inc., Stillwater, MN, USA) using a Wallac Wizard 1470 Automatic Gamma Counter (Perkin Elmer Life Sciences, Turku, Finland). Ferritin was classified in quartiles (Q) because the cut-offs for ferritin were not yet clear. The quartiles of ferritin by gender are classified as follows: men and women together quartile 1 (Q1), 29.5 μg/L or less; quartile 2 (Q2), 29.6-59.0 μg/L; quartile 3 (Q3), 59.1-103.8 μg/L; quartile 4 (Q4), 103.9 μg/L or more. In men, Q1, 63.5 μg/L or less; Q2, 63.6-98.0 μg/L; Q3, 98.1-150.9 μg/L; Q4, 151.0 μg/L or more. In women, Q1, 19.8 μg/L or less; Q2, 19.9-38.8 μg/L; Q3, 38.9-64.1 μg/L; Q4, 64.2 μg/L or more. In premenopausal women, Q1, 11.7 μg/L or less; Q2, 11.8-24.0 μg/L; Q3, 24.1-43.2 μg/L; Q4, 43.3 μg/L or more. In postmenopausal women, Q1, 35.3 μg/L or less; Q2, 35.4-55.0 μg/L; Q3, 55.1-85.2 μg/L; Q4, 85.3 μg/L or more.

Statistical analysis

Statistical analysis was performed using SPSS (version 18.0, IBM, Chicago, IL, USA). Differences in the means and distribution of characteristics by gender were analyzed using chi-square analysis

and analysis of variance tests (Table 1). The distribution in MetS components by the quartiles of ferritin were analyzed using chi-squared (Table 2). Analysis of the covariance of ferritin concentration was done according to MSS and MetS (Table 3). The ANCOVA test for HOMA-IR was conducted according to the quartiles of ferritin (Table 4). Logistic regression analysis of the odds ratio of MetS used the following four models: 1) non-adjusted; 2) adjusted for age; 3) further adjusted for regular exercise, alcohol drinking, and smoking status; 4) further adjusted for obesity and anemia (Table 5). The statistical significance of all analyses was based on $p < 0.05$.

RESULTS

Characteristics of research subjects

Characteristics of the research subjects are presented in Table 1. Serum ferritin, Fe, and TIBC in men (n = 2,469) were 114.88 ± 71.16, 126.00 ± 49.71, and 309.14 ± 40.06 μg/dL, respectively. Serum ferritin, Fe, and TIBC in premenopausal women (n = 1,620) were 31.13 ± 26.79, 98.70 ± 47.56, and 329.05 ± 50.06 μg/dL, respectively. Serum ferritin, Fe, and TIBC in postmenopausal women (n = 1,641) were 65.10 ± 43.58, 101.45 ± 34.09, and 313.72 ± 43.88 μg/dL, respectively. The prevalence of anemia in premenopausal women (15.9%) and postmenopausal women (11.1%) was higher than in men (3.6%). The prevalence of MetS in men (24.7%) and postmenopausal women (36.6%) was higher than in premenopausal women (8.6%).

MetS components of subjects according to the quartiles of ferritin

MetS components of subjects by ferritin quartiles (Q1-Q4) in postmenopausal women, men, and premenopausal women are presented in Table 2. In men, the reduced HDL-C ($p = 0.003$), abdominal obesity ($p < 0.001$), elevated FBG ($p < 0.001$), elevated

Table 1. Clinical characteristics of research subjects

Variables	Overall (n = 5,730)	Men (n = 2,469)	Women (n = 3,261)		p-value
			Premenopausal (n = 1,620)	Postmenopausal (n = 1,641)	
Age (years), M±SE	49.12±15.71	49.58±15.66	36.56±8.32	60.84±11.42	< 0.001
Current smoker, n (%)	1,156 (20.2)	966 (39.1)	122 (7.5)	68 (4.1)	< 0.001
Alcohol drinker, n (%)	3,061 (53.4)	1,830 (74.1)	802 (49.5)	429 (26.1)	< 0.001
Regular exerciser, n (%)	618 (10.8)	262 (10.6)	156 (9.6)	200 (12.2)	0.058
Menstruation, n (%)	–	–	248 (15.3)	–	
BMI (kg/m^2), M±SE	23.60±3.34	23.99±3.15	22.51±3.41	24.08±3.29	< 0.001
Obesity, n (%)	1,814 (31.7)	917 (37.1)	329 (20.3)	595 (36.3)	< 0.001
WC (cm), M±SE	81.03±13.71	84.76±16.88	74.68±9.01	81.67±9.29	< 0.001
SBP (mmHg), M±SE	120.91±17.61	123.72±16.02	109.91±13.38	127.56±18.55	< 0.001
DBP (mmHg), M±SE	77.32±10.61	80.39±10.43	72.44±9.22	77.52±10.37	< 0.001
TC (mg/dL), M±SE	188.73±36.35	187.81±36.34	178.43±31.95	200.28±37.17	< 0.001
TGs (mg/dL), M±SE	131.18±106.72	156.54±136.03	91.72±57.44	131.99±78.57	< 0.001
HDL-C (mg/dL), M±SE	52.78±12.77	49.34±12.05	57.11±12.26	53.68±12.88	< 0.001
FBG (mg/dL), M±SE	97.23±21.65	100.33±24.62	91.11±16.47	98.61±20.11	< 0.001
Hb (mg/dL), M±SE	13.92±1.58	15.16±1.18	12.84±1.21	13.13±1.04	< 0.001
Hct (mg/dL), M±SE	41.34±4.09	44.45±3.19	38.64±2.99	39.32±2.88	< 0.001
Anemia, n (%)	526 (9.2)	88 (3.6)	257 (15.9)	181 (11.1)	< 0.001
Ferritin (μg/L), M±SE	76.95±64.67	114.88±71.16	31.13±26.79	65.10±43.58	< 0.001
Fe (μg/dL), M±SE	111.25±46.93	126.00±49.71	98.70±47.56	101.45±34.09	< 0.001
TIBC (μg/dL), M±SE	316.08±44.95	309.14±40.06	329.05±50.06	313.72±43.88	< 0.001
MetS, n (%)	1,351 (23.6)	610 (24.7)	140 (8.6)	601 (36.6)	< 0.001
HOMA-IR, M±SE	2.57±1.74	2.67±2.04	2.32±1.19	2.66±1.68	< 0.001

M, mean; BMI, body mass index; obesity, BMI ≥ 25 kg/m^2; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total Cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; Hb, hemoglobin; Hct, hematocrit; Anemia, Hb < 13 g/dL in men or Hb < 12 g/dL in women, Fe, serum iron; TIBC, total iron binding capacity; MetS, metabolic syndrome; HOMA-IR, homeostasis model assessment of insulin resistance

Table 2. MetS components and anemia according to quartile of ferritin

Gender	Variables	Serum ferritin				
		Quartile 1 (≤ 63.5 μg/L) (n = 617)	Quartile 2 (63.6–98.0 μg/L) (n = 618)	Quartile 3 (98.1–150.9 μg/L) (n = 617)	Quartile 4 (≥ 151.0 μg/L) (n = 617)	*p*-value
Men (n = 2,469)						
	Abdominal obesity	123 (19.9)	139 (22.5)	170 (27.6)	196 (31.8)	< 0.001
	Elevated BP	283 (45.9)	261 (42.2)	274 (44.4)	286 (46.4)	0.464
	Elevated TGs	158 (25.6)	178 (28.8)	232 (37.6)	273 (44.2)	< 0.001
	Reduced HDL-C	113 (18.3)	111 (18.0)	133 (21.6)	157 (25.4)	0.003
	Elevated FBG	177 (28.7)	183 (29.6)	214 (34.7)	245 (39.7)	< 0.001
	MetS	113 (18.3)	127 (20.6)	164 (26.6)	206 (33.4)	< 0.001
		Quartile 1 (≤ 11.7 μg/L) (n = 405)	**Quartile 2 (11.8–24.0 μg/L) (n = 405)**	**Quartile 3 (24.1–43.2 μg/L) (n = 405)**	**Quartile 4 (≥ 43.3 μg/L) (n = 405)**	***p*-value**
Premenopausal women (n = 1,620)						
	Abdominal obesity	91 (22.5)	91 (22.5)	100 (24.7)	123 (30.4)	0.029
	Elevated BP	55 (13.6)	40 (9.9)	47 (11.6)	51 (12.6)	0.409
	Elevated TGs	27 (6.7)	37 (9.1)	45 (11.1)	29 (7.2)	0.092
	Reduced HDL-C	112 (27.7)	104 (25.7)	115 (28.4)	119 (29.4)	0.685
	Elevated FBG	44 (10.9)	40 (9.9)	42 (10.4)	58 (14.3)	0.179
	MetS	28 (6.9)	33 (8.1)	38 (9.4)	41 (10.1)	0.382
		Quartile 1 (≤ 35.3 μg/L) (n = 410)	**Quartile 2 (35.4–55.0 μg/L) (n = 411)**	**Quartile 3 (55.1–85.2 μg/L) (n = 410)**	**Quartile 4 (≥ 85.3 μg/L) (n = 410)**	***p*-value**
Postmenopausal women (n = 1,641)						
	Abdominal obesity	212 (51.7)	219 (53.3)	245 (59.8)	255 (62.2)	0.005
	Elevated BP	190 (46.3)	185 (45.0)	199 (48.5)	219 (53.4)	0.082
	Elevated TGs	94 (22.9)	100 (24.3)	107 (26.1)	142 (34.6)	0.001
	Reduced HDL-C	140 (34.1)	171 (41.6)	171 (41.7)	200 (48.8)	< 0.001
	Elevated FBG	101 (24.6)	125 (30.4)	135 (32.9)	150 (36.6)	0.002
	MetS	115 (28.0)	145 (35.3)	147 (35.9)	194 (47.3)	< 0.001

Abdominal obesity is defined as WC ≥ 80 cm in women or WC ≥ 90 cm in men; Elevated BP is defined as SBP ≥ 130 mmHg or DBP ≥ 85 mmHg; elevated TGs is defined as TGs ≥ 150 mg/dL; reduced HDL-C is defined as HDL-C < 50 mg/dL in women or HDL-C < 40 mg/dL in men; elevated FBG is defined as FBG ≥ 100 mg/dL; MetS, metabolic syndrome

TGs ($p < 0.001$), and MetS ($p < 0.001$) showed statistically significant differences across ferritin quartiles, but elevated BP ($p = 0.464$) was not significantly different. In postmenopausal women, abdominal obesity ($p = 0.005$), reduced HDL-C ($p < 0.001$), elevated FBG ($p = 0.002$), elevated TGs ($p = 0.001$), and MetS ($p < 0.001$) showed statistically significant differences across ferritin quartiles, but elevated BP ($p = 0.082$) was not significantly different. In premenopausal women, abdominal obesity ($p = 0.029$) showed significant differences across ferritin quartiles, but the reduced HDL-C ($p = 0.685$), elevated FBG ($p = 0.179$), elevated BP ($p = 0.409$), elevated TGs ($p = 0.092$), and MetS ($p = 0.382$) were not statistically significantly different across ferritin quartiles.

Comparisons of ferritin levels according to MSS and MetS

Comparisons of ferritin concentration according to MSS and MetS in postmenopausal women, men, and premenopausal women are shown in Table 3. After adjusting for the related variables, the ferritin concentration in MetS in postmenopausal women ($p = 0.001$) and men ($p < 0.001$) were higher than in non-MetS but not in

Table 3. Comparisons of ferritin levels according to MetS and MSS in men, premenopausal women, and postmenopausal women (n = 5,730)

Gender	Category	Serum ferritin (μg/L) [M±SE (95% CI)]
Men (n = 2,469)	MSS 0	98.05±2.99 (92.19-103.91)
	MSS 1	109.66±2.71 (104.35-114.98)
	MSS 2	118.42±2.91 (112.72-124.12)
	MSS 3	131.38±3.59 (124.34-138.42)
	MSS ≥ 4	138.07±4.93 (128.40-147.73)
	p-value	< 0.001
	Non-MetS	109.12±1.64 (105.90 -122.35)
	MetS	131.53±2.99 (125.96-137.69)
	p-value	< 0.001
Premenopausal women (n = 1,620)	MSS 0	30.11±0.99 (28.16-32.05)
	MSS 1	30.10±1.17 (27.81-32.40)
	MSS 2	35.61±1.86 (31.95-39.26)
	MSS 3	35.48±2.75 (30.08-40.88)
	MSS ≥ 4	29.60±4.16 (21.45-37.76)
	p-value	0.101
	Non-MetS	30.92±0.60 (29.61-32.23)
	MetS	33.46±2.14 (28.91-38.01)
	p-value	0.299
Postmenopausal women (n = 1,641)	MSS 0	61.17±2.97 (55.36-66.99)
	MSS 1	60.74±2.29 (56.25-65.23)
	MSS 2	63.48±2.07 (59.42-67.54)
	MSS 3	68.80±2.40 (64.09-73.50)
	MSS ≥ 4	72.85±2.78 (67.40-78.30)
	p-value	0.008
	Non-MetS	62.10±1.38 (59.39-64.80)
	MetS	70.35±1.86 (66.70-74.01)
	p-value	0.001

M, mean; Adjusted for age, smoking, alcohol drinking, regular exercise, obesity, and anemia or menstruation (adjusted only premenopausal women)

premenopausal women (p = 0.299) (Table 3). In addition, ferritin levels increased with increasing MSS in postmenopausal women (p = 0.008) and men (p < 0.001) but not in premenopausal women (p = 0.101).

Comparisons of HOMA-IR by quartiles of ferritin

Comparisons of HOMA-IR by Q of ferritin in postmenopausal women, men, and premenopausal women are presented in Table 4. After adjusting for related variables, HOMA-IR levels were positively statistically significantly associated with the Q of ferritin in postmenopausal women (p = 0.001) and men (p < 0.001). However, there was no statistically significant difference between the HOMA-IR levels and the Q of ferritin in premenopausal women (p = 0.149).

Comparisons of MetS according to ferritin quartiles

Comparisons of MetS by the Q of ferritin in postmenopausal women, men, and premenopausal women are presented in Table 5. In men, after adjusting for the related variables and using the Q1 of ferritin as the reference, the ORs of MetS were positively significantly statistically correlated with Q3 (OR, 1.770; 95%CI: 1.308-2.397) and Q4 (OR, 2.385; 95%CI: 1.775-3.201) of ferritin. In postmenopausal women, using the Q1 of ferritin as the reference, the OR of MetS was significantly statistically correlated with Q4 (OR, 1.873; 95%CI: 1.351-2.596) of ferritin. However, the relationship between MetS and the ferritin quartiles in premenopausal women was not significant.

DISCUSSION

This study investigated sex-specific differences in the relationship between ferritin and MetS and MSS in Korean adults. The key finding was that serum ferritin levels showed a positive correlation with MetS and HOMA-IR in postmenopausal women and men, but not in premenopausal women.

Ferritin is found as a Fe (II)-apoferritin complex in most human organs, including the heart, liver, spleen, and kidneys, and serum ferritin levels are generally higher in men than women (17). Serum ferritin, which is an acute-phase reactant, is a marker of acute and chronic inflammation. Serum ferritin levels increase nonspecifically in chronic diseases, such as diabetes mellitus, chronic kidney disease, and coronary artery disease (18-20), and are associated with cardiovascular and all-cause mortality (21). Research on the relationship between ferritin and both MetS and HOMA-IR are being conducted all over the world. In a cohort study of Finnish adults, Hämäläinen et al. revealed that the serum ferritin level showed a positive correlation with the development of MetS (22). Chen et al. supported that serum ferritin levels were independently associated with MetS and insulin resistance in Chinese adults (23). In the present study, MetS and HOMA-IR showed a positive correlation with ferritin in the overall

Table 4. Comparisons of ferritin levels according to MetS and MSS in men, premenopausal women, and postmenopausal women (n = 5,730)

Gender	Serum ferritin	MetS, [M±SE (95% CI)]		
		Model 1	Model 2	Model 3
Men (n = 2,469)	Quartile 1	2.44±0.08 (2.38-2.60)	2.43±0.08 (2.27-2.59)	2.47±0.08 (2.31-2.63)
	Quartile 2	2.46±0.08 (2.30-2.62)	2.46±0.08 (2.30-2.62)	2.48±0.08 (2.33-2.64)
	Quartile 3	2.71±0.08 (2.55-2.87)	2.72±0.08 (2.56-2.88)	2.70±0.08 (2.55-2.86)
	Quartile 4	3.09±0.08 (2.93-3.25)	3.10±0.08 (2.94-3.26)	3.05±0.08 (2.89-3.20)
	p-value	< 0.001	< 0.001	< 0.001
Premenopausal women (n = 1,620)	Quartile 1	2.35±0.06 (2.24-2.47)	2.35±0.06 (2.23-2.47)	2.42±0.06 (2.29-2.54)
	Quartile 2	2.24±0.06 (2.12-2.35)	2.25±0.06 (2.13-2.36)	2.23±0.06 (2.12-2.34)
	Quartile 3	2.28±0.06 (2.17-2.40)	2.28±0.06 (2.17-2.40)	2.29±0.06 (2.17-2.40)
	Quartile 4	2.39±0.06 (2.28-2.51)	2.39±0.06 (2.17-2.50)	2.35±0.06 (2.23-2.46)
	p-value	0.253	0.328	0.149
Postmenopausal women (n = 1,641)	Quartile 1	2.52±0.08 (2.36-2.68)	2.45±0.08 (2.29-2.60)	2.49±0.08 (2.33-2.64)
	Quartile 2	2.53±0.08 (2.37-2.69)	2.54±0.08 (2.39-2.70)	2.51±0.08 (2.36-2.66)
	Quartile 3	2.63±0.08 (2.47-2.79)	2.60±0.08 (2.45-2.76)	2.64±0.08 (2.49-2.79)
	Quartile 4	2.96±0.08 (2.80-3.12)	2.97±0.08 (2.82-3.13)	2.93±0.08 (2.78-3.08)
	p-value	< 0.001	< 0.001	< 0.001

Mets, metabolic syndrome; M, mean
Model 1 [M ± SE (95%CI)], adjusted for age; Model 2 [M ± SE (95%CI)], Model 2 further adjusted for smoking, alcohol drinking, and regular exercise; Model 3 [M ± SE (95%CI)], Model 2 further adjusted for obesity and anemia or menstruation (adjusted only premenopausal women)

Table 5. Comparisons of Mets according to quartile of ferritin in men, premenopausal women, and postmenopausal women

Gender	Serum ferritin	MetS, [OR (95%CI)]			
		Model 1	Model 2	Model 3	Model 4
Men (n = 2,469)	Quartile 1	1	1	1	1
	Quartile 2	1.145 (0.861-1.521)	1.239 (0.928-1.653)	1.239 (0.927-1.655)	1.204 (0.883-1.641)
	Quartile 3	1.626 (1.237-2.136)**	1.875 (1.418-2.480)**	1.869 (1.411-2.476)**	1.770 (1.308-2.397)**
	Quartile 4	2.273 (1.743-2.964)***	2.646 (2.014-3.476)***	2.607 (1.981-3.432)***	2.385 (1.775-3.201)***
Premenopausal women (n = 1,620)	Quartile 1	1	1	1	1
	Quartile 2	1.194 (0.708-2.016)	1.346 (0.790-2.291)	1.325 (0.777-2.259)	1.070 (0.557-2.057)
	Quartile 3	1.406 (0.845-2.339)	1.537 (0.916-2.577)	1.536 (0.913-2.582)	1.530 (0.803-2.914)
	Quartile 4	1.517 (0.918-2.505)	1.810 (1.085-3.019)*	1.798 (1.075-3.009)*	1.521 (0.803-2.879)
Postmenopausal women (n = 1,641)	Quartile 1	1	1	1	1
	Quartile 2	1.416 (1.050-1.910)*	1.354 (0.992-1.849)	1.347 (0.986-1.840)	1.355 (0.972-1.890)
	Quartile 3	1.427 (1.058-1.925)*	1.271 (0.931-1.736)	1.273 (0.930-1.742)	1.136 (0.814-1.585)
	Quartile 4	2.363 (1.763-3.167)***	2.052 (1.512-2.784)**	2.064 (1.519-2.085)**	1.873 (1.351-2.596)**

Mets, metabolic syndrome; *$p < 0.05$, **$p < 0.01$, *** $p < 0.001$. Model 1 [OR (95%CI)], Non-adjusted; Model 2 [OR (95%CI)], adjusted for age; Model 3 [OR (95%CI)], Model 2 further adjusted for smoking, alcohol drinking, and regular exercise; Model 4 [OR (95%CI)], Model 3 further adjusted for obesity and anemia or menstruation (adjusted only for premenopausal women)

Korean population (Supplementary Tables 1, 2 and 3). The mechanism for the relationship between MetS and ferritin may contribute to impaired insulin extraction and insulin secretion. MetS is characterized by insulin resistance (1), and iron overload can contribute to insulin resistance. Hepatic iron overload can be caused by impaired insulin extraction (24), and iron overload in pancreatic beta cells can result from impaired insulin secretion (25). Another mechanism in the relationship involves hepcidin, which is produced by the liver and serves as a key regulator of iron homeostasis. In insulin resistant diseases such as T2DM and MetS, an increase in hepcidin increases the ferritin levels (26).

In the present study, we analyzed men, premenopausal women, and postmenopausal women separately. Our results found that MetS and

HOMA-IR showed a statistically positive correlation with the quartiles of ferritin in both men and postmenopausal women, but in premenopausal women (Tables 4 and 5). The relationship between MetS and ferritin can differ by country, race, gender, and subjects with or without an underlying disease. Ghamarchehreh et al. showed that in Iranian patients with non-alcoholic fatty liver disease, the serum ferritin and MetS levels were not statistically significantly different in men (p = 0.952), but serum ferritin levels in MetS were lower than those in non-MetS in women (p = 0.004) (27). In a study based on the Third National Health and Nutrition Examination Survey (NHANES III) data in the US, Jehn et al. reported that serum ferritin levels were independently associated with MetS in non-diabetic premenopausal (p trend = 0.03) and postmenopausal women (p trend < 0.001), but not in men (p trend = 0.11) (28). In our results in men and postmenopausal women, four components of MetS, but not elevated BP, were positively associated with ferritin (Table 2). However, only abdominal obesity among the MetS components showed a positive correlation with ferritin in premenopausal women. This suggests that a positive correlation with ferritin exists between MetS and MSS in postmenopausal women and men, but not in premenopausal women. In addition, HOMA-IR showed a positive correlation with ferritin in postmenopausal women and men, but not in premenopausal women (Table 4). The findings of these studies are similar to our results. Han et al. investigated gender differences in the relationship between MetS and ferritin in the population-based China Health and Nutrition Survey (29). In men, four components of MetS (with the exception of high BP) were positively associated with ferritin, and MetS showed a positive correlation with the quartiles of ferritin (p < 0.001). In women, only high TG among the MetS components showed a positive correlation with ferritin, and the incidence of MetS was not statistically significant (p = 0.192). In another study, Ma et al. revealed that HOMA-IR showed a positive correlation with the tertiles of ferritin in men (p trend < 0.001) and postmenopausal women (p trend < 0.001), but not in premenopausal women (p trend = 0.929) after adjusting for related variables (30).

Although we cannot definitively specify the mechanisms for the sex-specific difference in the relationship between ferritin and MetS found in our study, we think that menopause and sex hormones may be a contributing factor. Menopause causes many physiological changes because of the decrease in estrogens. Premenopausal women have a lower risk of developing MetS than men, but the incidence of MetS can increase in postmenopausal women because the protective function of female hormones is greatly reduced due to a rapid decline in estrogen levels (31). In our results, the incidence of MetS in premenopausal women was lower than in men, but the incidence of MetS in postmenopausal women higher than in men. In terms of iron homeostasis, elevated levels of stored iron result in upregulation of hepcidin production to prevent iron overload, inhibiting further uptake of exogenous iron (32). Estrogens markedly decrease circulating hepcidin levels in humans (33). When estrogen decreases in premenopausal women, iron and stored iron levels in the body decrease due to upregulation of hepcidin levels, but this may be different in postmenopausal women. Sze et al. reported that an aberrant ferritin upregulation in the ovaries of aging female rats resulted in iron accumulation and inflamm-aging via NF-κB-induced nitric oxide synthase (34). They argued that acute ferritin upregulation exerts beneficial effects, but chronic upregulation may cause toxicity to cells due to iron accumulation and accelerate the decrease in endogenous estradiol biosynthesis. In addition, Matta et al. revealed that ferritin in postmenopausal women showed a positive correlation with hepcidin regardless of the level of estradiol, and that estradiol, hepcidin, and ferritin were higher in the metabolic syndrome than in the non-metabolic syndrome (35).

Estrogens prevent pancreatic β cell apoptosis and help protect functions, adapt to insulin resistance and maintain insulin content (36). Among the estrogens, 17β-estradiol improves insulin sensitivity and suppresses hepatic gluconeogenesis through inhibition of Foxo-1 via activation of estrogen receptor α-PI3K-Akt signaling (37). Male Zucker diabetic fat rats treated with 17β-estradiol had reduced levels of TGs and free fatty acids in the pancreatic islets, indicating reduced lipotoxicity and beta cell dysfunction (38). In our results,

MetS and HOMA-IR showed a positive correlation with the quartiles of ferritin in postmenopausal women and men, but were not significant in premenopausal women. These results suggest that insulin resistance could be expected to increase as ferritin increases, but it is thought that insulin resistance and glucose homeostasis in premenopausal women are maintained due to female hormones. Gender differences (the presence or absence of menopause in women) are evidenced in lifestyles (eating habits, physical activity, drinking, and smoking) and acute and chronic diseases (39, 40). For this reason, several researchers have argued that the model of medical hypotheses should consider these effects in women and men (especially, menopause in women) (41, 42).

Our research has several limitations. First, although we analyzed data of a representative sample of Korean adults from the KNHANES V-1, our findings have limitations in terms of generalizing to all ethnicities and the global population due to the study population and sample size. Second, C-reactive protein, estrogens, and hepcidin are important determinants of ferritin levels in men and women. However, these variables were not included in the KNHANES V-1 study, and so they should be included as variables for MetS and ferritin in future studies. Third, Although the sample is representative of the Korean population, the findings may not apply to other ethnicities or global populations due to genetic, dietary, and lifestyle differences. Fourth, this study was cross-sectional, which may limit its ability to establish a causal gender-specific relationship between ferritin and MetS. Therefore, to obtain more accurate and generalizable results, studies on hormonal regulation and gene-environment interaction or cohort studies on these relationships are needed.

CONCLUSIONS

This study investigated the sex-specific differences in the association between ferritin and MetS in Korean adults. Ferritin showed a statistically significant positive correlation with MetS in Korean postmenopausal women and men, but not in premenopausal women.

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CONFLICTS OF INTEREST

We declare no conflicts of interests.

AUTHOR CONTRIBUTIONS

M.Y.G.: performed formal analysis and wrote the manuscript, integrated the data, contributed to the study design and revised the manuscript; H.Y.: performed formal analysis and wrote the manuscript, integrated the data, contributed to the study design and revised the manuscript; J.A.C.: integrated the data.

All authors read and approved the final version of this manuscript for publication.

DATA AVAILABILITY STATEMENT

Approval of the KNHANES data is available through https://knhanes.kdca.go.kr/knhanes/. Korea Disease Control and Prevention Agency (KDCA) permits access to all of these data via download for any researcher who promises to follow the research ethics.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study has been conducted according the principles expressed in the Declaration of Helsinki (Institutional Review Board No, 2010-02CON-21-C).

INFORMED CONSENT STATEMENT

All participants in the survey signed an informed written consent.

SUPPLEMENTARY MATERIALS

The following supporting information can be downloaded at: Supplementary file

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Supplementary table 1. Comparisons of Mets according to quartile of ferritin in overall population

(*n* = 5,730)

Gender	Serum ferritin (μg/L)	MetS			
		Model 1	Model 2	Model 3	Model 4
Overall population (*n* = 5,730)	Quartile 1 (*n* = 1,434)	1	1	1	1
	Quartile 2 (*n* = 1,431)	1.768 (1.451–2.153)**	1.414 (1.150–1.737)**	1.415 (1.151–1.739)**	1.306 (1.041–1.638)*
	Quartile 3 (*n* = 1,433)	2.166 (1.786–2.627)***	1.708 (1.386–2.406)**	1.713 (1.390–2.113)**	1.456 (1.157–1.832)**
	Quartile 4 (*n* = 1,432)	3.143 (2.606–3.791)***	3.044 (2.448–3.787)***	3.055 (2.455–3.802)***	2.504 (1.972–3.180)***

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$. Model 1 [OR (95% CI)], Non-adjusted; Model 2 [OR (95% CI)], adjusted for age and gender; Model 3 [OR (95% CI)], Model 2 further adjusted for smoking, alcohol drinking, and regular exercise; Model 4 [OR (95% CI)], Model 3 further adjusted for obesity and anemia

Supplementary table 2. Comparisons of HOMA-IR according to quartile of ferritin in overall population

(*n* = 5,730)

Gender	Serum ferritin (μg/L)	HOMA-IR		
		Model 1	Model 2	Model 3
Overall population (*n* = 5,730)	Quartile 1 (*n* = 1,434)	2.38 ± 0.05 (2.29–2.48)	2.37 ± 0.05 (2.28–2.47)	2.44 ± 0.05 (2.35–2.54)
	Quartile 2 (*n* = 1,431)	2.47 ± 0.05 (2.38–2.56)	2.45 ± 0.05 (2.36–2.54)	2.48 ± 0.05 (2.39–2.57)
	Quartile 3 (*n* = 1,433)	2.50 ± 0.05 (2.42–2.59)	2.51 ± 0.05 (2.42–2.60)	2.49 ± 0.05 (2.40–2.58)
	Quartile 4 (*n* = 1,432)	2.92 ± 0.05 (2.82–3.10)	2.92 ± 0.05 (2.83–3.02)	2.84 ± 0.05 (2.75–2.93)
	p-value	< 0.001	< 0.001	< 0.001

Model 1 [M ± SE (95% CI)], adjusted for age and gender; Model 2 [M ± SE (95% CI)], Model 2 further adjusted for smoking, alcohol drinking, and regular exercise; Model 3 [M ± SE (95% CI)], Model 2 further adjusted for obesity and anemia.

Supplementary table 3. Comparisons of ferritin levels according to MetS and MSS in overall population (*n* = 5,730)

Gender	Category	Serum ferritin (μg/L) [M ± SE (95% CI)]
Overall population	MSS 0	65.62 ± 1.56 (62.56–68.68)
(*n* = 5,730)	MSS 1	71.98 ± 1.47 (69.10–74.86)
	MSS 2	81.32 ± 1.66 (78.06–84.57)
	MSS 3	91.08 ± 2.07 (87.02–95.15)
	MSS ≥ 4	96.13 ± 2.66 (90.92–101.35)
	p-value	< 0.001
	Non-MetS	72.85 ± 0.89 (71.12–74.59)
	MetS	90.76 ± 1.70 (87.43–94.08)
	p-value	< 0.001

Adjusted for age, gender, smoking, alcohol drinking, regular exercise, obesity, and anemia.