

Dietary factors associated with high serum ferritin levels in postmenopausal women with the Fifth Korea National Health and Nutrition Examination Survey (KNHANES V), 2010-2012

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BACKGROUND/OBJECTIVES: Serum ferritin levels are significantly increased after menopause and greatly affect women's health. The aim of this study was to investigate the dietary and non-dietary factors associated with high ferritin levels in postmenopausal women.

SUBJECTS/METHODS: Among adult women in 2010-2012, qualified postmenopausal women (n = 3880) were separated into quartiles of serum ferritin. The variable differences among the quartiles of ferritin were determined using either procsurvey chi-square test (χ^2 -test) among categorical variables, or GLM (Generalized Linear Model) among continuous variables. The odds ratio for high ferritin in relation to dietary factors was also determined using procsurvey logistic analysis.

RESULTS: Age, obesity, drinking habit, and blood glucose levels were found to be significant indicators of high serum ferritin level after adjusting for all confounding factors. Among the food groups, grain, milk, vegetable, and seaweed intakes were significantly associated with high ferritin levels, but after adjusting for all confounding factors, only grains and vegetables remained significant factors. Among the nutrient groups, calcium, vitamin A, and vitamin C intake were significant factors, but after adjustment, none of the nutrient groups analyzed were associated with a high risk of ferritin.

CONCLUSION: Age, obesity, drinking habit, and glucose levels, as well as inadequate intakes of grains and vegetables, were found to be significantly associated with high serum ferritin levels in postmenopausal Korean women.

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INTRODUCTION

Iron is stored in our body as a form of ferritin, and thus ferritin serves as a convenient and accurate indicator of iron status in humans [1]. It has been suggested that a high level of serum ferritin acts as a potent oxidant, increasing oxidative stress and leading to various diseases [2-4].

Studies have tried to identify factors, besides iron intake. That affect serum ferritin levels. The result of studies have shown that drinking, smoking, educational level, and regular exercise are possible factors associated with serum ferritin levels [5-7]. Dietary iron intake, such as the amount of iron intake and the type of iron consumed, is also one of the determinants of serum ferritin level [8].

There are two types of iron in food: heme and nonheme iron. Heme iron, mainly found in animal based foods, has high bioavailability in the body while non-heme iron is obtained from grains, legumes, vegetables, or fruits and is considered to have low bioavailability [9]. Interestingly, recent studies have shown

that a plant-based diet was beneficial in reducing serum ferritin level in either diabetes or anemia patients with high ferritin [10,11]. A study reported that vegetarian females had lower metabolic syndrome incidence, which was related with lower serum ferritin level compared to non-vegetarians [12].

High ferritin level in postmenopausal women has been implicated in the pathogenesis of many diseases, such as cardiovascular diseases, diabetes, and metabolic syndrome [13-16]. Furthermore, although increased iron resulting from menopause may be considered within normal physiologic range, it may also lead to potential health problems [17]. If the associations between high ferritin and diseases are truly causal, monitoring factors associated with the high risk of serum ferritin in this population will have substantial implications for public health.

While several studies have assessed the relation between serum ferritin and various chronic diseases [12-16] or dietary influences in subjects at risk of anemia [18-20], limited study has focused on the relationship between dietary factors and

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the high ferritin risk in postmenopausal women [21,22]. Therefore, the purpose of this study is to determine the association between serum ferritin levels and various factors including dietary intake in postmenopausal women by analyzing 3 years of KNHANES data (2010-2012).

SUBJECTS AND METHODS

Study population

The Korean National Health and Nutrition Examination Survey (KNHANES) is an ongoing series of cross-sectional surveys. It is conducted by the Korea Centers for Disease Control (KCDC) and is designed to assess health and nutritional information from a representative sample of Koreans. This study analyzed the fifth Korean National Health and Nutrition Examination Survey (KNHANES V, 2010-2012), which included a total number of 17,218 participants, 7,170 males and 10,048 females. Only postmenopausal women ($n = 4,667$) who answered "yes" to the question about menopausal status were included. The subjects for this study were selected based on the following criteria. First of all, individuals who did not respond to the food intake survey or lacked information on serum ferritin level were excluded. Those who had chronic liver or renal diseases, known diagnoses of malignancies, or probable hemochromatosis, based on abnormal values of serum ferritin (≥ 500 ng/mL), were also excluded. Thus, the postmenopausal women who met the above criteria ($n = 3880$) were selected, and the subjects were divided into quartiles, based on serum ferritin concentrations: Q1, ≤ 35.4 ng/mL (median; 24.5 ng/mL); Q2, 35.5-56.1 ng/mL (median; 45.3 ng/mL); Q3, 56.2-86.6 ng/mL (median; 69.1 ng/mL); and Q4, > 86.7 ng/mL (median; 114.9 ng/mL).

General characteristics

The subjects in this study were grouped according to the general characteristics of the subjects: survey year (2011, 2012, 2013), age (less than 50, 50-59, 60-69 and over 70 years), current smoking status (yes or no to 'current smoking'), regular exercise ('yes' and 'no', based on self-reported regular physical exercise), education (less than middle school graduate, high school graduate, and college graduate or higher), drinking habit (none-drinker, drinking frequency ≤ 1 -2 times/year; occasional drinker, drinking frequency ≤ 2 -4 times/month; heavy drinker, drinking frequency alcohol ≥ 2 times/week), living area (large city, mid-sized or small city, rural area), and monthly income (divided into 4 groups - Low, Mid-low, Mid-high, and High groups by mean values based on the income of the participant's age group).

Physical and hematological measurements

Body mass index (BMI) was calculated by dividing the weight (kilograms) by the height squared (square meters). Since subjects who were underweight (BMI < less than 18.5) comprised only 2.1%, BMI was separated into 3 categories: less than 22.9 as normal, $23 < \text{BMI} < 24.9$ as overweight, and more than 25.0 kg/m^2 as obese. Blood pressure was measured in the sitting position with a mercury sphygmomanometer on the right arm and averaged for a final blood pressure reading.

Blood samples were obtained in the morning following an overnight fast. The serum concentrations of glucose, cholesterol,

high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) were measured using a Hitachi automatic analyzer 7600 (Tokyo, Japan). Serum ferritin and iron were measured by immunoradiometric assays using a 1470 Wizard gamma-counter (Perkin-Elmer, Turku, Finland). Total blood heavy metals were measured by a cold-vapor atomic absorption spectrometric method using a dedicated mercury analyzer (M-6000A, CETAC Technologies). All clinical analyses were performed by the Neodin Medical Institute, a laboratory certified by the Korea Ministry of Health and Welfare.

Food groups and nutrient intakes

The consumptions of major food groups and nutrient intakes were estimated based on 24-hour dietary recalls interviews. Nutrient intakes and the ratios of energy intake from each macronutrient to total energy (percentage (%) of energy intake from carbohydrate, fat, and protein) were determined. To estimate the intake of food groups by the participants, the secondary food code for 24 hour recall data was used. The KNHANES applied 18 food group classifications based on the Rural Development Administration (RDA) food ingredient tables: 16 general food groups, one cooking processed food group, and one other group [23]. Briefly, 5000 different food codes were used to code the intake of adult respondents and these individual KNHANES food codes were collapsed into 144 food items. In addition to the 144 food item codes, the foods were further collapsed into 18 food groups.

Statistical analysis

To make valid inferences accounting for the KNHANES 2010-2012 complex multistage sampling design, sampling weights were incorporated to produce population estimates using SAS software (version 9.2; SAS Institute, Cary, NC, USA). The survey sample weights were calculated taking into consideration the sampling rate, response rate, and proportion of the reference population. The data results were reported as weighted %, mean values, and standard errors.

Chi-square test (χ^2 -test) was performed to identify significant differences among categorical variables, and significant differences among continuous variables were verified by GLM (Generalized Linear Model) through the proc surveyreg procedure. To analyze nutrient and food intake, descriptive statistics were generated for mean values and standard errors of nutrient intake, using ferritin quartiles as the independent variable and the nutrient and food group intake as the dependent variable. Significance testing was conducted for P for trends using the proc surveyreg procedure.

Odds ratios (ORs) were used as a measure of association. For OR calculation, the subjects were categorized into two classes based on the value of ferritin: a high-risk group (4Q, serum ferritin level > 86.7 ng/mL) and a control group (1Q-3Q, serum ferritin level ≤ 86.7 ng/mL). In comparing the effect of the selected variable, the remaining covariates were adjusted. For example, to determine the effect of age on high ferritin risk, variables other than age were adjusted: drinking habit, educational level, BMI, Blood glucose, SBP, HDL, TG, serum iron, and energy intake. Significance level was set at the 95% Confidence Interval (CI).

RESULTS

Descriptive characteristics of subjects by ferritin quartiles

The baseline characteristics of the subjects by ferritin quartiles are presented in Table 1. Age, education levels, and drinking habits were significantly associated with ferritin levels. Subjects aged 70 or higher constituted the highest weighted percentage (32.2%) in the 4th quartile of ferritin levels, whereas those aged 50-59 years had higher proportions in the 2nd and 3rd quartiles. In terms of education, the proportion of individuals with low education level (middle school or less) significantly increased as the quartile of serum ferritin increased. The percentage of subjects who drank more than 2-4 times/week significantly increased as the quartile of serum ferritin increased (1st quartile 5.4%, 2nd quartile 6.1%, 3rd quartile 9.3%, 4th quartile 10.7%. *P*

= 0.0003). Other variables such as survey year, smoking status, exercise habit, living area, or monthly income, were not associated with ferritin level in postmenopausal women.

Physical and hematological parameters of subjects by ferritin quartiles

Subjects with higher ferritin levels tended to have higher mean BMI (Table 2). Systolic blood pressure (SBP) and blood glucose levels also showed a positive association with serum ferritin levels. The high density lipoprotein (HDL) cholesterol had a negative correlation with serum ferritin levels, while TG showed a positive association. Serum Fe level was positively correlated with serum ferritin level, whereas heavy metals such as Pb and Cd were not significantly associated with ferritin level.

Table 1. Descriptive characteristics of subjects in postmenopausal women

	Q1 (N = 970)		Q2 (N = 970)		Q3 (N = 971)		Q4 (N = 969) ¹⁾		<i>P</i> -value ³⁾
	N	% ²⁾	N	%	N	%	N	%	
Survey year									
2010	294	31.5	333	33.5	295	29.2	312	31.2	0.571
2011	326	34.6	339	35.5	328	33.4	361	36.3	
2012	350	33.9	298	30.9	348	37.3	296	32.4	
Age									
less than 50	135	20.1	68	10.5	60	9.6	50	8.9	0.017
50-59	260	29.8	330	38.8	318	38.7	272	32.2	
60-69	290	25.2	320	27.9	317	26.9	296	26.7	
70 or higher	285	24.9	252	22.7	276	24.8	351	32.2	
Current smoking status									
No	931	95.9	937	95.3	945	96.5	929	94.3	0.304
Yes	38	4.1	33	4.7	26	3.5	40	5.7	
Regular exercise									
No	565	68.7	557	66.0	529	62.6	562	66.5	0.296
Yes	265	31.3	279	34.0	317	37.4	283	33.5	
Education level									
Middle school or less	581	67.2	641	75.6	624	75.7	643	72.7	< 0.001
High school	150	18.7	149	18.5	155	17.4	134	18.3	
≥ College	101	14.0	47	6.0	66	6.8	67	9.0	
Drinking									
no drinking	202	35.6	177	29.8	148	24.6	157	26.3	< 0.001
1-4/month	327	58.7	349	61.4	371	66.1	360	63.4	
≥ 2-4/weeks	33	5.6	38	8.8	47	9.4	47	10.3	
Living area									
Large city	372	40.3	404	43.0	405	41.8	384	40.1	0.437
Middle & Small city	320	31.0	326	31.7	308	31.7	276	29.6	
Rural area	278	28.7	240	25.4	258	26.5	309	30.3	
Income									
Low	302	33.7	292	30.5	287	31.0	299	33.2	0.063
Middle-low	214	27.4	228	28.4	219	25.4	219	26.2	
Middle-high	152	20.3	169	22.0	164	22.3	165	22.3	
High	153	18.6	141	19.1	172	21.3	157	18.4	

¹⁾ Quartiles based on serum ferritin concentrations: Q1, ≤ 35.4 ng/mL (median; 24, 5 ng/mL); Q2, 35.5-56.1 ng/mL (median; 45.3 ng/mL); Q3, 56.2-86.6 ng/mL (median; 69.1 ng/mL); and Q4, > 86.7 ng/mL (median; 114.9 ng/mL).

²⁾ Weighted %

³⁾ *P*-value by chi-square (χ^2) test by proc survey frequency procedure

Table 2. Physical and hematological parameters in postmenopausal women

	Q1 (N = 970)		Q2 (N = 970)		Q3 (N = 970)		Q4 (N = 969) ¹⁾		P for trend ²⁾
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Height (cm)	153.9	0.2	153.7	0.3	153.8	0.3	153.3	0.3	0.086
Weight (kg)	57.3	0.4	57.5	0.4	57.7	0.4	58.3	0.4	0.001
BMI (kg/m ²) ³⁾	24.2	0.1	24.3	0.1	24.4	0.2	24.8	0.2	< 0.0001
Sbp (mmHg)	125.0	0.9	125.6	0.7	127.5	0.8	127.5	0.8	0.006
Dbp (mmHg)	75.4	0.5	75.8	0.4	77.4	0.4	76.5	0.5	0.071
Glucose (mg/dL)	97.4	0.8	98.5	0.7	98.9	0.7	102.7	0.9	< 0.0001
Cholesterol (mg/dL)	201.6	1.6	201.9	1.5	204.5	1.6	202.5	1.5	0.88
HDL (mg/dL)	53.7	0.6	51.9	0.6	51.9	0.6	49.5	0.6	< 0.0001
TG (mg/dL)	138.8	2.9	137.7	2.9	141.3	2.9	149.7	3.1	0.009
Ferritin(ng/mL)	22.2	0.4	45.4	0.3	69.7	0.4	136.0	2.5	< 0.0001
Fe (umol/L)	94.0	1.5	102.5	1.4	102.4	1.4	106.8	1.4	< 0.0001
Pb (ug/dL)	2.1	0.1	2.4	0.1	2.4	0.1	2.3	0.1	0.113
Cd (ug/dL)	1.3	0.1	1.5	0.1	1.5	0.1	1.4	0.1	0.133

¹⁾ Quartiles based on serum ferritin concentrations: Q1, ≤ 35.4 ng/mL (median; 24, 5 ng/mL); Q2, 35.5-56.1 ng/mL (median; 45.3 ng/mL); Q3, 56.2-86.6 ng/mL (median; 69.1 ng/mL); and Q4, > 86.7 ng/mL (median; 114.9 ng/mL).

²⁾ P for trend (crude P) obtained by proc survey regression procedure.

³⁾ BMI: Body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, Sbp: Systolic blood pressure, Dbp: Diastolic blood pressure, Pb: plumbum (lead), Cd: cadmium

Table 3 Daily consumption of food groups in postmenopausal women

	Q1 (N = 970)		Q2 (N = 970)		Q3 (N = 970)		Q4 (N = 969) ¹⁾		P for trend ²⁾
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Grain (g)	282.7	5.0	291.7	5.8	284.1	5.0	271.1	4.9	0.032*
Potato (g)	38.0	4.4	37.2	4.6	39.6	4.7	35.5	5.0	0.999
Legume (g)	26.3	1.8	27.4	2.1	27.6	2.0	27.7	2.1	0.059
Sugar (g)	5.8	0.5	5.8	0.4	6.1	0.6	5.4	0.4	0.451
Meat (g)	49.8	3.8	47.0	3.1	40.2	3.2	44.4	3.0	0.173
Egg (g)	11.8	1.0	12.0	1.1	10.6	1.0	12.8	1.4	0.128
Milk (g)	73.8	5.7	67.5	6.4	66.5	5.8	56.0	4.7	0.015*
Fruit (g)	144.2	8.4	151.3	7.7	136.9	7.6	146.3	8.1	0.537
Vegetable (g)	257.7	6.6	268.5	6.4	264.8	6.4	243.7	7.2	0.030*
Mushroom (g)	3.4	0.5	2.3	0.4	3.1	0.5	3.2	0.5	0.891
Seafood (g)	26.3	1.4	30.1	2.0	30.7	1.7	26.5	1.5	0.082
Seaweed (g)	5.24	1.98	5.00	0.52	5.79	0.68	4.25	0.57	0.043*
Nuts (g)	3.1	0.3	3.8	0.4	2.8	0.7	3.4	0.5	0.641
Oil (g)	4.8	0.3	4.5	0.2	4.4	0.3	4.5	0.3	0.322
Drink (g)	62.4	6.8	66.2	5.3	63.1	6.2	72.2	7.8	0.076

¹⁾ Quartiles based on serum ferritin concentrations: Q1, ≤ 35.4 ng/mL (median; 24, 5 ng/mL); Q2, 35.5-56.1 ng/mL (median; 45.3 ng/mL); Q3, 56.2-86.6 ng/mL (median; 69.1 ng/mL); and Q4, > 86.7 ng/mL (median; 114.9 ng/mL).

²⁾ P for trend (crude P) obtained by proc survey regression

Major food intakes by serum ferritin quartile

Grain consumption was found to negatively relate with serum ferritin levels in postmenopausal women (Table 3). Furthermore, milk intake was also found to have a negative association among the groups. Vegetable intake also showed a negative correlation with serum ferritin levels. There were no significant associations between the intakes of potatoes, legume, sugar, meat, egg, fruit, mushroom, seafood, nuts, oil, or eggs and ferritin quartiles.

Major nutrient intakes by serum ferritin quartile

The daily intakes of energy, carbohydrate, protein, and fat showed a significantly negative association with increasing ferritin

quartiles (Table 4). However, when calculating the percent ratio of these energy nutrients to the total daily intake, no significant relationship between ferritin levels and the energy nutrients was found. Serum ferritin levels were also found to have a significantly negative association with calcium, vitamin A, and vitamin C intakes.

Odds Ratios of potential factors associated with serum ferritin level

In comparing the effect of the selected variable, the remaining covariates were adjusted (Table 5). ORs greater than 1 indicated an increased likelihood of having high ferritin among postmenopausal women after adjustment of covariates. Postmenopausal women aged 50-59 were significantly less likely

Table 4. Daily dietary energy and nutrient intakes in postmenopausal women

	Q1 (N = 970)		Q2 (N = 970)		Q3 (N = 970)		Q4 (N = 969) ¹⁾		P for trend ²⁾
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Energy (Kcal) ³⁾	1,540.0	25.4	1,570.9	23.0	1,512.3	21.3	1,477.4	21.9	0.0002
Carbohydrate (g)	281.4	4.1	288.9	4.4	280.9	3.9	272.1	3.9	0.014
Protein (g)	50.6	1.1	51.0	1.0	49.6	0.9	48.2	0.9	0.043
Fat (g)	24.9	0.9	23.7	0.7	22.3	0.7	22.3	0.8	0.007
Fiber (g)	6.3	0.2	6.3	0.2	6.4	0.2	6.3	0.2	0.704
Calcium (mg)	405.9	10.2	402.2	11.3	403.7	10.4	385.7	11.9	0.050
Phosphorus (mg)	909.2	15.6	923.2	15.3	902.2	14.0	877.7	15.6	0.119
Iron (mg)	12.0	0.3	12.3	0.4	12.2	0.4	12.2	0.5	0.231
Sodium (mg)	3,654.2	104.6	3,657.0	104.4	3,705.9	110.2	3,715.2	85.8	0.071
Vitamin A (ug RE)	598.6	20.7	655.3	31.0	630.2	27.5	583.1	27.9	0.050
Carotene (ug)	3,215.8	123.4	3,490.9	175.6	3,391.1	156.4	3,044.3	155.3	0.536
Retinol (ug)	56.4	3.3	60.8	5.3	56.3	6.1	55.9	4.6	0.202
vitamin B1 (mg)	1.0	0.0	1.0	0.0	0.9	0.0	0.9	0.0	0.061
Vitamin B2 (mg)	0.9	0.0	0.9	0.0	0.9	0.0	0.8	0.0	0.071
Niacin (mg)	11.9	0.2	12.4	0.2	11.8	0.2	11.6	0.2	0.226
Vitamin C (mg)	93.1	4.9	88.6	3.1	87.8	2.9	81.4	3.1	0.02
Protein (% ⁴⁾	13.0	0.1	12.9	0.1	13.0	0.1	13.0	0.2	0.685
Fat (% ⁴⁾	13.7	0.4	13.1	0.3	12.8	0.3	13.0	0.3	0.193
CHO (% ⁴⁾	73.3	0.4	74.0	0.4	74.1	0.4	74.0	0.4	0.251

¹⁾ Quartiles based on serum ferritin concentrations: Q1, ≤ 35.4 ng/mL (median; 24.5 ng/mL); Q2, 35.5-56.1 ng/mL (median; 45.3 ng/mL); Q3, 56.2-86.6 ng/mL (median; 69.1 ng/mL); and Q4, > 86.7 ng/mL (median; 114.9 ng/mL).

²⁾ P for trend (crude P) obtained by proc survey regression.

³⁾ Excluded groups with < 500 kcal or $> 5,000$ kcal of total daily caloric intake.

⁴⁾ (%) Percent of usual energy intake from energy nutrient = $100 \times \{ \text{usual intake of energy nutrient (kcal)} \} / \{ \text{usual intake of energy (kcal)} \}$

to have high ferritin levels than women of age 70 or more. Drinking habit (no drinking vs. 2-4 times /week) was significantly associated with high ferritin levels even after adjustment of covariates. Subjects with normal weight (BMI less than 23) were significantly less likely than obese subjects to have high ferritin levels, both with crude or adjusted covariates. The significant associations between high ferritin levels and SBP, HDL, or TG levels disappeared after the adjustment of covariates. Subjects with high fasting blood glucose levels were significantly more likely to have high ferritin levels, even after adjustment of covariates. The OR for high ferritin in relation to serum iron levels was statistically significant in postmenopausal women after adjustments.

Odds Ratios (ORs) for potential food groups and nutrients associated with high serum ferritin levels

The ORs and confidence interval (CI) for the risk of high ferritin levels in relation to the intakes of foods and nutrients are presented in Table 6. Subjects with low grain intake were significantly more likely than those with high grain intake to have high ferritin levels, for either crude or adjusted confounding cofactors. The significant negative association between milk intake and ferritin levels disappeared after adjustment. The significant negative association between vegetable intake and ferritin levels remained after the adjustment of confounding cofactors. The significant negative association between seaweed intake and ferritin levels also disappeared after adjustment. The significant association between ferritin risk and vitamin A or vitamin C and iron intakes was attenuated after adjustment.

DISCUSSION

In light of the dearth of reports on health problems caused by high ferritin in women in recent years, it is important to assess which factors, besides hormonal changes, are related to high ferritin levels. Thus, we selected postmenopausal women to minimize the effects of hormonal changes, and to evaluate the dietary and lifestyle factors related to high ferritin levels. We applied logistic regression models to determine the independent effect of those factors on the risk of serum ferritin. A previous study reported that moderately elevated iron levels (median level of 75-85 ng/mL in postmenopausal women) were associated with an increased prevalence of metabolic syndrome and diabetes [24]. Based on the above study, we compared the high-risk group (4Q, serum median ferritin level > 86.7 ng/mL) to the control group (1Q-3Q, serum median ferritin level ≤ 86.7 ng/mL). Odds ratios (ORs) and 95% confidence intervals (95% CIs) for high ferritin risk were calculated using multivariate logistic regression analyses after adjusting for confounding variables.

In this study, upon fully adjusting for covariates, age, BMI, and blood glucose still remained as significant factors for high risk of ferritin in postmenopausal women. Age seems to be an important factor for high ferritin risk in postmenopausal women. Our study showed that women over 70 comprised the highest percentage of the high-risk ferritin group (Q4). This result is consistent with a previous study that reported that plasma ferritin concentrations increased with age in postmenopausal women [8]. We believe that older women, especially

Table 5. Odds Ratios (ORs) and 95% Confidence Intervals (CI) for factors associated with high serum ferritin levels in postmenopausal women

	High Ferritin ¹⁾	
	Crude OR (95% CI)	Adjusted OR (95% CI) ²⁾
Age (yrs)		
less than 50	0.723 (0.457, 1.078)	0.673 (0.417, 1.087)
50-59	0.661 (0.539, 0.810)***	0.641 (0.485, 0.846)**
60-69	0.681 (0.551, 0.842)**	0.654 (0.494, 0.867)**
≥ 70	1	1
Drinking		
no drinking	0.649 (0.431, 0.963)*	0.631 (0.417, 0.956)*
1-4/month	0.721 (0.491, 1.059)	0.847 (0.501, 1.112)
≥ 2-4/ weeks	1	1
Education		
Middle school or less	1.071 (0.753,1.524)	0.652 (0.413, 1.028)
High school	1.090 (0.731, 1.625)	0.675 (0.408, 1.116)
≥ College	1	1
BMI (Obesity)		
Normal	0.673 (0.588, 0.884)**	0.539 (0.42, 0.724)**
Overweight	0.843 (0.654, 1.086)	0.800 (0.589,1.087)
Obese	1	1
SBP ³⁾		
< 130 mmHg	0.955 (0.770, 1.186)	0.997 (0.740, 1.344)
≥ 130 mmHg	1	1
Fasting blood glucose ³⁾		
< 100 mg/dL	0.597 (0.467, 0.764)***	0.676 (0.492, 0.930)**
≥ 100 mg/dL	1	1
Blood HDL ³⁾		
≥ 50 mg/dL	0.752 (0.500, 0.959)*	0.776 (0.576, 1.044)
< 50 mg/dL	1	1
Blood TG ³⁾		
< 150 mg/dL	0.703 (0.580, 0.853)***	0.803 (0.625, 1.032)
≥ 150 mg/dL	1	1
Serum iron ⁴⁾		
< 100 ug/dL	0.616 (1.011, 1.568)***	0.662 (0.516, 0.752)**
≥ 100 ug/dL	1	1
Total energy intake ⁴⁾		
< 1,500 kcal	1.321 (1.089, 1.604)**	1.310 (1.020, 1.684)*
≥ 1,500 kcal	1	1

* $P < 0,05$, ** $P < 0,01$, *** $P < 0,001$ ¹⁾ The high ferritin levels (Q4, > 86,7 ng/mL, median; 114,9 ng/mL).²⁾ In comparing the effect of the selected variable, the remaining variables listed above were adjusted. For example, to determine the effect of age on high ferritin risk, variables other than age were adjusted: drinking habit, educational level, BMI, SBP, Blood glucose, HDL, TG, glucose, serum iron, and energy intake.³⁾ Subjects were separated into two groups in accordance with the 2005 revised National Cholesterol Education Program Adult Treatment Panel III criteria.⁴⁾ Subjects were separated into two groups based on their mean intake.

those older than 70, face greater health risk from various external factors as well as hormonal decline, which may have triggered an increase in ferritin levels [17].

Besides age, other important cofactors of ferritin risk in postmenopausal women were BMI and blood glucose level. This result is consistent with studies showing that BMI and glucose were positively associated with serum ferritin [24-26]. These two factors are also indicators of metabolic syndromes, which arise

Table 6. Odds Ratios (ORs) and 95% Confidence Intervals (CI) for food intakes associated with high serum ferritin levels (Q4, > 86.5 ng/mL) in postmenopausal women

	High Ferritin levels ¹⁾	
	Crude OR (95% CI)	Adjusted OR (95% CI) ³⁾
Grain ⁴⁾		
< 200 g/day	1.423 (1.136, 1.782)**	1.416 (1.041, 1.926)* ⁵⁾
≥ 200 g/day	1	1
Milk		
< 25 g	1.272 (1.007, 1.606)*	1.181 (0.885, 1.575)
≥ 25 g	1	1
Vegetables		
< 200 g	1.336 (1.034, 1.527)*	1.396 (1.056,1.705)*
≥ 200 g	1	1
Seaweeds		
< 0.4 g	1.322 (1.074, 1.627)*	1.263 (0.976, 1.636)
≥ 0.4 g	1	1
Vitamin A		
< 700 mg	1.350 (1.074, 1.627)*	1.276 (0.745, 1.296)
≥ 700 mg	1	1
Vitamin C		
< 100 mg	1.288 (1.049, 1.582)*	1.282 (0.984, 1.670)
≥ 100 mg	1	1
Iron		
< 8 mg	1.127 (0.915, 1.387)	0.854 (0.639, 1.143)
≥ 8 mg	1	1

* $P < 0,05$, ** $P < 0,01$, *** $P < 0,001$ ¹⁾ The high ferritin levels (Q4, > 86,7 ng/mL, median; 114,9 ng/mL).²⁾ Adjusted for age, drinking habit, education levels, BMI, TG, Blood glucose, energy intake³⁾ Food group intakes such as grain, legume, milk, seaweed were divided into two groups based on mean intake values of the subjects. For nutrient intakes such as vitamin A, vitamin C, and iron intake, the groups were separated in accordance with KDRI recommendation.

as a combination of medical disorders closely linked to insulin resistance and increased risk of cardiovascular diseases [3,4]. Several studies have revealed that increased iron stores in postmenopausal women are associated with such diseases. Recent meta-analysis also indicated that elevated levels of ferritin (individuals in the top fifth of ferritin levels) have about a 70% higher risk of T2DM events compared with those in the bottom fifth [25]. Possible mechanisms underlying how high ferritin levels affect metabolic syndromes or diabetes have been suggested: high levels of serum ferritin acts as a potent oxidant, which may cause cell damage in the body and lead to the development of various diseases [2]. Based on these studies, it may be that high glucose, high BMI, and high serum ferritin act synergistically, contributing to these diseases. However, this is only a cross sectional study, and thus the results of this study do not explain the causal effect relationship; longitudinal studies are needed to clarify this relationship.

Several studies have reported that socio- economical and lifestyle factors such as smoking, drinking, exercise, monthly income and educational level were associated with high ferritin [5,8,17]. However, in this study only drinking habit was associated with high ferritin levels. This discrepancy may have resulted from the selection of the study subjects and their

gender. Previous studies have reported smoking as an especially important factor associated with ferritin risk, but the subjects of this study had less than a 5% smoking population (possibly due to cultural and gender norms), which may have affected the results of our study.

This study found that the intake of grains and vegetables are important dietary factors negatively associated with serum ferritin level. It was reported that the subjects who consumed whole grains had a 77% lower risk of high iron stores than did the subjects who did not consume grains [8]. Another study also reported negative associations with serum ferritin and bread intake, independent of other potential confounders [21]. The intake of vegetables has been linked to anti-inflammatory effects, which may have caused the negative association with high serum ferritin level in women [12]. The negative influence of grain and vegetable consumption on serum ferritin may be related to various components in these plant based foods, most importantly fiber, phytate, and phytochemicals including polyphenols [11,12,26,27].

Interestingly, the total iron intake was not significantly associated with serum ferritin levels, in contrast to some previous studies [8,20]. Yet, this result is consistent with previous studies showing no significant correlation between serum ferritin and total iron intake in both young and adult women [28-30]. However, Fleming DJ *et al.* [31] reported that exclusion of supplemental iron from total iron intake may be the reason for the lack of association between total iron intake and serum ferritin. Since the information on vitamin or mineral supplements that contain iron is not available in KNHANES data at present, we did not include iron supplements in the total amount of iron intake. Therefore, further study of iron intake from supplements or health functional foods which may affect ferritin levels in postmenopausal women is needed.

There are also other limitations in this study. First, this is a cross sectional study and thus only shows statistical associations, rather than any cause-and-effect relationships. Second, because of the nature of the survey questionnaires, we could not exclude the effects of information bias. Third, the estimated amounts of food consumption were based on one 24 hour dietary recall, which is known to have high within-person variability. Despite these limitations, the present study has several strengths. First, we used data from a reliable nationally representative database, collected for 3 years from 2010-2012. Second, strict quality controls were applied to the study procedures within KNHANES. In dietary intake data using 24 hour recall, despite within-person variability, the average intake level of the population drawn from a large, representative sample is believed to be unaffected by day-to-day variation [32]. Thus the result of this diet study is unlikely to be distorted due to a single day of 24 hour recall [33]. Overall, this study is meaningful because we think this is the first study showing that intakes of grains and vegetables are associated with high ferritin risk in postmenopausal women. Prospective studies are needed to further identify the causal relationship between dietary intake and reduction of blood ferritin concentration in postmenopausal women.

In conclusion, we have demonstrated that age, obesity, drinking habit, and blood glucose were the most influential factors for elevated serum ferritin levels in postmenopausal

women. To reduce the risk of high ferritin in postmenopausal women, proper intake of plant based foods, especially whole grains and vegetables may be helpful.

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