Ferritin Concentrations, Metabolic Syndrome, and Type 2 Diabetes in Middle-Aged and Elderly Chinese

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Context: Elevated ferritin concentrations frequently cluster with well-established risk factors of diabetes including obesity, metabolic syndrome, chronic inflammation, and altered circulating adipokines. Few studies, however, have systematically evaluated the effect of these risk factors on ferritin-diabetes association, particularly in Chinese populations.

Objective: We aimed to investigate, in a middle-aged and elderly Chinese population, whether elevated ferritin concentrations are associated with higher risk of metabolic syndrome and type 2 diabetes and to what extent the associations were influenced by obesity, inflammation, and adipokines.

Design and Methods: We conducted a population-based, cross-sectional survey of 3289 participants aged 50–70 yr in Beijing and Shanghai in 2005. Fasting plasma ferritin, glucose, insulin, lipid profile, glycohemoglobin, inflammatory markers, adipokines, and dietary profile were measured.

Results: Median ferritin concentrations were 155.7 ng/ml for men and 111.9 ng/ml for women. After multiple adjustment, the odds ratios (ORs) were substantially higher for type 2 diabetes (OR 3.26, 95% confidence interval 2.36–4.51) and metabolic syndrome [OR 2.80 (95% confidence interval 2.24–3.49)] in the highest ferritin quartile compared with those in the lowest quartile. These associations remained significant after further adjustment for dietary factors, body mass index, inflammatory markers, and adipokines.

Conclusions: Elevated circulating ferritin concentrations were associated with higher risk of type 2 diabetes and metabolic syndrome in middle-aged and elderly Chinese independent of obesity, inflammation, adipokines, and other risk factors. Our data support the crucial role of iron overload for metabolic diseases, even in a country with relatively high prevalence of iron deficiency. **(*J Clin Endocrinol Metab* 93: 4690–4696, 2008)**

With rapid socioeconomic development and nutrition transition, the prevalence of type 2 diabetes in China increased from 1.9 to 5.6% during 1993–2003 (1). As one of the countries with the largest population suffering with diabetes mellitus in the world (2), the number of diabetic patients in China is estimated to increase from 20.8 million in 2000 to 42.3 million in 2030 (3). Meanwhile, iron deficiency is still highly prevalent and 15.2% of Chinese people have anemia (4).

Ferritin, one of the key proteins regulating iron homeostasis, is a widely available clinical biomarker to evaluate iron status and especially important for detecting iron deficiency. However, growing evidence has shown that even moderately increased iron stores, represented by high-normal ferritin concentrations, are associated with diabetes (5–8). More recently the results from prospective studies from Caucasian populations suggested that iron overload could predict the development of abnormal glucose metabolism (9).

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Abbreviations: BMI, Body mass index; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1c, glycohemoglobin; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein; OR, odds ratio; PAI, plasminogen activator inhibitor; RBP4, retinol-binding protein 4; TNF-R2, TNFα receptor 2.

Iron is a catalyst in the formation of hydroxyl radicals. In animal models, iron excess might result in β-cell oxidative stress and decreased insulin secretory capacity (10). Studies in patients with hemochromatosis indicated that iron accumulation in the hepatocytes might cause impaired hepatic insulin extraction and metabolism (11). The mechanism linking iron overload and diabetes is yet to be established. Accumulating evidence, mostly from studies conducted in Western populations, has demonstrated strong associations between ferritin concentrations and obesity, inflammation, and metabolic syndrome (12–14), factors that contribute to the development of type 2 diabetes (15–17).

However, no previous Chinese studies (18, 19) have evaluated the effects of inflammation on the ferritin-diabetes association, which may differ between Chinese and Caucasians owing to wide variations in levels of inflammatory marker such as C-reactive protein (CRP) among different ethnic populations. Indeed, we observed previously in this study population (20) that approximately 50% of our participants with metabolic syndrome had plasma CRP less than 1 mg/liter, which is considered low risk for subsequent cardiovascular diseases according to the criteria proposed by Centers for Disease Control and Prevention and the American Heart Association (21). Thus, it remains unknown to what extent ethnic differences in the profile of inflammatory markers in Chinese could influence the ferritin-diabetes association.

Given that metabolic syndrome is a major risk factor for type 2 diabetes, it is critical to clarify whether the association between ferritin and risk of type 2 diabetes is mediated through metabolic syndrome. However, most previous studies evaluated only individual components of metabolic syndrome rather than the clustered condition of metabolic syndrome *per se*.

Recent studies have shown that fasting glucose and type 2 diabetes were correlated with adipokines, including adiponectin, plasminogen activator inhibitor (PAI)-1 and retinol-binding protein 4 (RBP4) (22–24). However, the association between adipokines and ferritin and its role in the development of metabolic diseases has not been extensively studied, and one recent report showed that adjusting for adiponectin weakened the association between ferritin concentrations and the risk of type 2 diabetes (8). Therefore, our study aimed to investigate the associations of ferritin concentrations with the risk of type 2 diabetes and metabolic syndrome and evaluate to what extent the ferritin-diabetes association is explained by adiposity, metabolic syndrome, inflammation, and adipokines in a representative sample of middle-aged and elderly Chinese.

Subjects and Methods

Study population

The current study was based on the Nutrition and Health of Aging Population in China study, which recruited 3289 eligible participants (1458 men and 1831 women) aged 50–70 yr from urban and rural areas of north (Beijing) and south (Shanghai) China in 2005. The study was approved by the Institutional Review Board of the Institute for Nutritional Sciences, and written informed consent was obtained from all participants. Further detail can be found elsewhere (20).

Data collection

Information on demographic variables, health status, health behavior, and physical activity were obtained using a standardized questionnaire. Family history of chronic diseases was considered positive if the participants' parents or siblings had a history of having one of the following diseases: coronary heart disease, stroke, type 2 diabetes, or hypertension. All participants were required to fast overnight (≥7 h) before physical examination by trained staff and physicians using standard protocols. Measurements of body weight and height, waist circumference, and blood pressure have been described previously (20).

Dietary intake was assessed with a 74-item food frequency questionnaire modified from the food frequency questionnaire used in the national Survey on the Status of Nutrition and Health of the Chinese People in 2002 (25). The food-composition values were obtained from the Chinese Food Composition Table (26). All nutrient intakes were energy adjusted by the residual method (27). Heme iron content was calculated by applying a factor of 0.4 to the total iron content of all meat items. Pork, beef, lamb, bacon, and processed meats were categorized as red and processed meats.

Laboratory measurements

Hemoglobin was measured by HemoCueB-Hemoglobin analytical system (HemoCue B-Hemoglobin Microcuvettes and HemoCue B-Hemoglobin photometer; HemoCue AB, Ängelholm, Sweden) in the field. Peripheral venous blood samples were collected in tubes containing EDTA, centrifuged at 4 C and stored at −80 C until analysis. The measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, insulin, CRP, IL-6, adiponectin, PAI-1, and RBP4 were previously described (20, 28–30). TNFα receptor 2 (TNF-R2) was detected with a kit (Human Death Receptor 3-Plex) from Biosource International, Inc. (Camarillo, CA) in the Multiplex suspension array system (Bio-Plex System) with Bio-Plex Manager 4.0 (Bio-Rad Laboratories, Inc., Hercules, CA). Glycohemoglobin (HbA1c) was quantified from resolved erythrocyte with automated immunoassay (Tina-quant Hemoglobin A1c II; Roche Diagnostics, Indianapolis, IN).

Plasma ferritin was measured using a commercially available particle-enhanced immunoturbidimetric kit (Shanghai Gensource Co., Ltd., Shanghai, China). The ferritin calibrator was standardized against the International Federation of Clinical Chemistry and Laboratory Medicine reference material (certified reference material 470). The intraassay coefficients of variation were 0.8, 1.9, and 2.0% at 79.9, 123.2, and 199.0 ng/ml, respectively, whereas the interassay coefficients of variation were 6.1 and 5.2% at 68.0 and 83.0 ng/ml, respectively.

Definition of diseases

Metabolic syndrome was defined based on the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian-Americans (31) as presenting at least three of the following components: 1) waist circumferences 90 cm or greater in men or 80 cm or greater in women; 2) triglycerides 1.7 mmol/liter or greater; 3) HDL cholesterol less than 1.03 mmol/liter in men or less than 1.30 mmol/liter in women; 4) blood pressure 130/85 mm Hg or greater or current use of antihypertensive medications; and 5) fasting plasma glucose (FPG) 5.6 mmol/liter or greater or previously diagnosed type 2 diabetes or treatment with oral antidiabetic agents or insulin.

Type 2 diabetes was defined as presenting one or more of the following components: 1) FPG 7.0 mmol/liter or greater; 2) treatment with oral antidiabetic agents or insulin; and 3) previously diagnosis of type 2 diabetes. Impaired fasting glucose (IFG) was defined as 5.6 FPG less than 7.0 mmol/liter or less.

Anemia was defined as hemoglobin concentration less than 130 g/liter for men and less than 120 g/liter for women (32). Iron deficiency anemia was defined as the presence of both anemia and a plasma ferritin concentration less than 15 ng/ml (18).

Iron overload was defined as ferritin greater than 300 ng/ml for men and greater than 200 ng/ml for women (32).

Statistical analyses

We excluded 37 (1.1%) individuals with total energy intake 5000 kcal/d or greater or 500 kcal/d or less. Therefore, the baseline analytical sample consisted of 3252 individuals (1424 men and 1,828 women). Log (common) transformations were performed for ferritin, triglycerides, insulin, inflammatory markers, adiponectin and PAI-1 to approximate normality. Analysis of covariance for continuous variables and logistic regression models for categorical variables were applied for the comparison across ferritin quartiles. Analysis of covariance was used to compare ferritin concentrations between sexes and geographic locations. Correlation coefficients between ferritin and various parameters were calculated by partial correlation analysis on ranks (Spearman correlation). Participants were classified into four groups according to their sex-specific plasma ferritin quartiles. Multivariate logistic regression models were used to estimate the odds ratio (ORs) for metabolic syndrome, type 2 diabetes, and IFG. Individuals with presumably acute inflammation (CRP >10 mg/liter) (n = 30, 0.9%), exceptionally high ferritin concentrations (ferritin >500 ng/ml) (n = 51, 1.6%), or both status (n = 6, 0.2%) were excluded from the analysis of metabolic syndrome and type 2 diabetes, leaving 3165 qualified subjects. In addition, we excluded 412 diabetic patients for the analysis of IFG, making the valid sample size of 2753 participants. Potential confounding variables included age (continuous), sex, geographic location, lifestyle factors, education level, and family histories of chronic diseases. In addition, we adjusted for dietary factors, including total energy intake, dietary iron, dietary magnesium, red and processed meats, fiber, fat intake, tea consumption, and use of iron supplements (n = 15, 0.5%). Body mass index (BMI), waist circumference, inflammatory markers, and adipokines were also adjusted for, to test the independent effect of ferritin. Data management and statistical analyses were performed using Stata 9.2 (Stata Corp., College Station, TX). Statistical tests were two sided and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The prevalence of iron overload in our study population was 10.6% in men and 14.7% in women. The prevalence of anemia was 4.4% in men and 12.6% in women. Only three women, but none of the male subjects, were diagnosed with iron deficiency anemia. The prevalence of metabolic syndrome, type 2 diabetes, and IFG were 42.3% (n = 1377), 13.5% (n = 440), and 27.1% (n = 882).

Overall, subjects with higher ferritin concentrations were older; more likely to live in North China (Beijing) and urban areas; to have family history of chronic diseases (all $P < 0.01$); and have a higher intake of fat, heme iron, and red and processed meats (all $P < 0.05$) (Table 1). With respect to metabolic parameters, subjects in the higher ferritin quartiles exhibited higher values of diastolic blood pressure ($P < 0.05$), BMI, waist circumference, and homeostatic model assessment of insulin resistance, and elevated concentrations of HbA1c, hemoglobin, glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, CRP, IL-6, PAI-1, and RBP4 (all $P < 0.001$), accompanied with lower concentrations of HDL cholesterol and adiponectin (all $P < 0.01$) (Table 1).

Distribution of ferritin concentrations

Median ferritin concentrations were higher in men than women (155.7 *vs.* 111.9 ng/ml, $P < 0.001$). Beijing and urban participants had higher ferritin concentrations than their Shanghai and rural counterparts ($P < 0.001$). The difference remained significant after further adjustment for age and BMI.

Association between ferritin concentrations and metabolic syndrome, type 2 diabetes, and impaired fasting glucose

Partial Spearman correlation analysis showed that ferritin was correlated significantly with metabolic parameters, inflammatory markers, and adipokines (all $P < 0.01$, Online appendix table A1, published as supplemental data on The Endocrine Society's Journals Online Web site at http://jcem.endojournals.org).

The ORs for metabolic syndrome increased progressively across the ferritin quartiles ($P < 0.001$ for trend) (Table 2). After adjusting for age, sex, geographic location, lifestyle factors, and family history of chronic diseases (model 2), the ORs for metabolic syndrome, hyperglycemia, and hypertriglyceridemia, comparing the highest with the lowest ferritin quartile, were 2.80 (2.24–3.49), 3.11 (2.48–3.91), and 2.86 (2.22–3.70). Further adjustment for dietary factors, BMI, and inflammatory makers (CRP, IL-6, and TNF-R2) (models 3, 4, and 5) only slightly reduced the magnitude of the ORs for metabolic syndrome, and its component, but did not affect their statistical significance.

The ORs for type 2 diabetes substantially increased with increasing concentrations of ferritin ($P < 0.001$ for trend) (Table 2). Compared with individuals in the lowest ferritin quartile, those in the highest quartile had an OR of 3.26 (2.36–4.51) in the multivariate model (model 2). A similar positive association was observed between elevated ferritin concentrations and presence of IFG ($P < 0.001$ for trend). The ORs were slightly attenuated but remained statistically significant after further adjustment for dietary factors, BMI, and inflammatory markers (models 3, 4, and 5). Little change in the magnitude and direction of associations was observed when BMI and waist circumference were adjusted separately or combined in the models.

Further controlling for adiponectin, PAI-1, and RBP4 did not attenuate the associations between ferritin and metabolic syndrome, type 2 diabetes, or IFG (Table 2, model 6).

The risks of metabolic syndrome, type 2 diabetes, and IFG were most pronounced among subjects with higher concentrations of both ferritin and CRP (Fig. 1). Those participants in the highest quartiles of both CRP and ferritin had an OR of 6.80 (4.00–11.56) for metabolic syndrome, 5.60 (2.94–10.66) for type 2 diabetes, and 3.46 (2.11–5.67) for IFG compared with their reference groups. No significant interactions were observed between ferritin and CRP (P for interaction = 0.54, 0.54, and 0.36 for metabolic syndrome, type 2 diabetes, and IFG, respectively). In addition, ferritin concentrations were associated with diabetes, regardless of metabolic syndrome status (Fig. 2). Among the participants without metabolic syndrome, those in the fourth ferritin quartile had an OR of 3.30 (1.87–5.81) for type 2 diabetes compared with those in the first quartile (reference group). The OR increased remarkably with the combination of metabolic syndrome and high ferritin concentrations [OR 13.83 (8.13–23.54)]. No significant interaction was observed between ferritin and metabolic syndrome (P for interaction = 0.40).

TABLE 1. Characteristics of participants according to quartile of ferritin (n = 3252)

	Ferritin quartile				
	Q1 (n = 815)	Q2 (n = 814)	Q3 (n = 810)	Q4 (n = 813)	*P* value
Ferritin (ng/ml)[a]					
Men	70.6 (68.1–73.2)	129.2 (127.7–130.8)	184.9 (182.8–187.1)	327.8 (316.1–339.8)	<0.001
Women	52.1 (50.5–53.7)	93.7 (92.7–94.6)	134.2 (132.9–135.5)	231.6 (224.4–239.1)	<0.001
Age (yr)[b]	57.5 (6.2)	58.3 (6.0)	58.9 (5.9)	59.8 (5.8)	<0.001
North residents (n, %)[b]	362 (44.4)	420 (51.6)	412 (50.9)	418 (51.4)	0.004
Rural residents (n, %)[b]	450 (55.2)	400 (49.1)	411 (50.7)	362 (44.5)	<0.001
Low physical activity (n, %)	62 (7.6)	52 (6.4)	71 (8.8)	58 (7.1)	0.382
Current smoker (yes, n, %)	220 (27.0)	217 (26.7)	236 (29.1)	223 (27.4)	0.539
Alcohol drinker (yes, n, %)	210 (25.8)	226 (27.8)	244 (30.1)	236 (29.0)	0.328
Family history of chronic diseases (n, %)	418 (51.3)	467 (57.4)	473 (58.4)	461 (56.7)	0.007
BMI (kg/m^2)	23.8 (3.4)	24.3 (3.6)	24.7 (3.6)	25.1 (3.6)	<0.001
Waist circumference (cm)	80.9 (10.2)	83.1 (10.5)	84.6 (10.7)	86.2 (10.2)	<0.001
SBP (mm Hg)	138.0 (22.0)	139.5 (22.7)	141.0 (22.6)	141.9 (22.3)	0.492
DBP (mm Hg)	79.3 (10.8)	79.9 (10.6)	80.4 (11.3)	80.9 (10.4)	0.011
Total cholesterol (mmol/liter)	4.46 (0.94)	4.68 (0.98)	4.73 (0.91)	4.92 (1.03)	<0.001
LDL cholesterol (mmol/liter)	3.06 (0.95)	3.28 (0.98)	3.29 (0.90)	3.43 (1.03)	<0.001
HDL cholesterol (mmol/liter)	1.30 (0.33)	1.29 (0.33)	1.27 (0.33)	1.24 (0.34)	0.002
Triglycerides (mmol/liter)[a]	0.95 (0.92–0.99)	1.08 (1.03–1.12)	1.20 (1.15–1.25)	1.39 (1.33–1.46)	<0.001
Glucose (mmol/liter)	5.45 (1.17)	5.57 (1.12)	5.86 (1.61)	6.48 (2.48)	<0.001
Insulin (μU/ml)[a]	12.6 (12.1–13.1)	12.8 (12.4–13.3)	13.6 (13.1–14.1)	14.9 (14.4–15.5)	<0.001
HOMA-IR[a]	3.00 (2.89–3.12)	3.13 (3.01–3.26)	3.45 (3.32–3.60)	4.10 (3.93–4.28)	<0.001
HbA1c (%)	5.79 (0.76)	5.84 (0.81)	5.99 (1.09)	6.34 (1.51)	<0.001
Hemoglobin (g/liter)	137.8 (16.6)	141.5 (15.3)	141.4 (15.7)	144.1 (16.2)	<0.001
CRP (mg/liter)[a]	0.52 (0.48–0.55)	0.63 (0.58–0.68)	0.75 (0.69–0.81)	1.04 (0.95–1.13)	<0.001
IL-6 (pg/ml)[a]	0.95 (0.91–1.00)	0.97 (0.92–1.03)	1.09 (1.03–1.15)	1.25 (1.19–1.33)	<0.001
TNF-R2 (pg/ml)[a]	1558.9 (1512.4–1606.8)	1553.0 (1509.2–1598.0)	1543.3 (1502.2–1585.5)	1533.4 (1483.9–1584.6)	0.338
Adiponectin (μg/ml)[a]	14.4 (13.7–15.2)	13.2 (12.5–13.9)	12.8 (12.2–13.5)	11.1 (10.5–11.8)	<0.001
PAI-1 (pg/ml)[a]	1988.6 (1569.5–2519.8)	3509.1 (2847.3–4324.5)	3799.9 (3081.8–4685.3)	5698.3 (4701.7–6906.1)	<0.001
RBP4 (μg/ml)	37.5 (11.1)	40.0 (11.0)	41.5 (12.1)	41.3 (12.3)	<0.001
Dietary factors					
Total energy (kcal/d)	2344.3 (735.6)	2306.1 (715.9)	2297.7 (727.3)	2224.0 (673.5)	0.057
Fat (g/d)	68.7 (21.4)	72.8 (21.7)	72.4 (22.9)	72.3 (20.8)	0.032
Iron (mg/d)	24.7 (6.2)	24.8 (5.9)	24.9 (6.3)	25.2 (6.9)	0.341
Heme iron (mg/d)	0.26 (0.21)	0.29 (0.23)	0.29 (0.24)	0.30 (0.21)	0.027
Magnesium (mg/d)	362.2 (77.2)	365.1 (78.8)	360.4 (74.3)	367.7 (84.0)	0.122
Fiber (g/d)	13.3 (5.6)	13.5 (5.4)	13.4 (5.3)	13.7 (5.5)	0.190
Red and processed meats (g/d)	41.1 (41.3)	49.5 (50.8)	49.0 (50.1)	50.8 (44.2)	0.011

P value was calculated after adjustment for age, sex, region (Beijing/Shanghai), and residence (urban/rural). Data are arithmetic mean (SD). Percentages may not sum to 100 because of rounding. SBP, Systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostatic model assessment of insulin resistance.

[a] Data are geometric mean (95% confidence interval).

[b] Data not adjusted for itself.

Discussion

We found a strong positive association between elevated iron stores, measured by plasma ferritin concentrations, and the risks of type 2 diabetes, IFG, and metabolic syndrome in middle-aged and elderly Chinese men and women. This association was independent of not only lifestyle factors, education level, family history of chronic diseases, and dietary factors but also adiposity, inflammatory markers, and adipokines. We also discovered a significant positive correlation between ferritin and HbA1c in diabetic participants for both sexes, which might suggest a role of ferritin in chronic glycemic control. Our data suggested the crucial role of iron overload as an important independent risk factor for metabolic diseases in the subgroups of developing countries like China.

Consistent with previous studies (33, 34), we observed substantial differences of ferritin concentrations by age, sex, and geographic location. In particular, Beijing and urban participants had significantly higher ferritin concentrations than their Shanghai and rural counterparts. Indeed, geographic or urban-rural differences have also been observed in this population for the prevalence of obesity, metabolic syndrome, and diabetes as well as the concentrations of CRP, adiponectin, and RBP4 (20, 28, 29). In addition, a significantly lower prevalence of anemia was also documented in Beijing and urban areas than in Shanghai and rural areas (4, 35, 36). The difference in iron status may be attributed to different dietary patterns (34).

Our study reported a strong positive association between elevated plasma ferritin concentrations, and the risks of type 2

TABLE 2. Odds ratios and 95% confidence interval for metabolic syndrome, type 2 diabetes, and IPG according to quartile of ferritin

	Quartile of ferritin				
	Q1	Q2	Q3	Q4	*P* for trend
Metabolic syndrome (n = 3165)					
Model 1	1	1.43 (1.15–1.77)	1.79 (1.45–2.22)	2.83 (2.28–3.50)	<0.001
Model 2	1	1.40 (1.12–1.74)	1.79 (1.44–2.24)	2.80 (2.24–3.49)	<0.001
Model 3	1	1.41 (1.13–1.76)	1.82 (1.46–2.27)	2.83 (2.27–3.54)	<0.001
Model 4	1	1.40 (1.08–1.82)	1.71 (1.32–2.22)	2.59 (1.99–3.36)	<0.001
Model 5	1	1.31 (1.00–1.72)	1.66 (1.27–2.17)	2.35 (1.79–3.07)	<0.001
Model 6	1	1.18 (0.90–1.56)	1.49 (1.13–1.96)	1.95 (1.48–2.57)	<0.001
Type 2 diabetes (n = 3165)					
Model 1	1	1.23 (0.86–1.75)	1.56 (1.11–2.20)	3.18 (2.32–4.36)	<0.001
Model 2	1	1.23 (0.86–1.77)	1.63 (1.15–2.31)	3.26 (2.36–4.51)	<0.001
Model 3	1	1.21 (0.84–1.74)	1.62 (1.14–2.31)	3.27 (2.35–4.55)	<0.001
Model 4	1	1.17 (0.81–1.69)	1.56 (1.09–2.22)	3.06 (2.20–4.27)	<0.001
Model 5	1	1.19 (0.82–1.72)	1.60 (1.11–2.29)	2.99 (2.13–4.19)	<0.001
Model 6	1	1.13 (0.78–1.65)	1.51 (1.05–2.18)	2.76 (1.96–3.90)	<0.001
IFG (n = 2753)					
Model 1	1	1.45 (1.12–1.87)	1.88 (1.46–2.41)	2.62 (2.04–3.36)	<0.001
Model 2	1	1.49 (1.15–1.94)	1.98 (1.53–2.56)	2.75 (2.13–3.56)	<0.001
Model 3	1	1.48 (1.14–1.93)	1.98 (1.53–2.57)	2.77 (2.14–3.59)	<0.001
Model 4	1	1.43 (1.09–1.86)	1.85 (1.42–2.41)	2.50 (1.92–3.25)	<0.001
Model 5	1	1.37 (1.04–1.79)	1.84 (1.41–2.41)	2.38 (1.82–3.11)	<0.001
Model 6	1	1.33 (1.01–1.75)	1.79 (1.37–2.35)	2.27 (1.73–2.97)	<0.001

Model 1, adjusted for age, sex, region, and residence; model 2, further adjusted for smoking, alcohol drinking, physical activity, education, and family histories of chronic diseases (for metabolic syndrome) or family histories of diabetes (for type 2 diabetes and IFG); model 3, further adjusted for dietary factors (total energy intake, dietary iron, dietary magnesium, red and processed meats, fiber, fat intake, and tea consumption; all nutrient intakes were energy adjusted), and use of iron supplements; model 4, further adjusted for BMI; model 5, further adjusted for inflammatory factors (CRP, IL-6, and TNF-R2); model 6, further adjusted for adipokines (adiponectin, PAI-1, and RBP4).

diabetes, IFG, and metabolic syndrome in both Chinese men and women. In contrast, the findings from two previous studies, regionally restricted in either south (Jiangsu) or north (Liaoning) China, were conflicting and inconclusive among Chinese men (18, 19). It should be noted that the prevalence of diabetes was much higher in our study (n = 440, 13.5%) than that in previous studies (18, 19). Moreover, our participants were recruited from the north (Beijing) and the south (Shanghai) and urban and multiple rural areas, representing a wider variety of Chinese.

Because elevated ferritin concentrations frequently cluster with well-established risk factors of type 2 diabetes such as obesity, metabolic syndrome, and inflammation, we extensively evaluated the effect of these risk factors in the present analyses. In accordance with prospective studies in Caucasian populations (7, 8), we also found that controlling for BMI or waist circumference had no appreciable effect on the associations between ferritin and the risks of metabolic syndrome, IFG, and type 2 diabetes, suggesting the elevated risks for metabolic abnormalities could not be explained merely by excess adipose tissue. Because adipose-derived cytokines are believed to link obesity mechanistically to type 2 diabetes (16), we further examined the effect of three adipokines, namely adiponectin, PAI-1, and RBP4, and found that the associations between ferritin and type 2 diabetes and IFG remained significant, even after adjusting simultaneously for these adipokines. Few studies have investigated how adipokines interact with ferritin in the pathogenesis of diabetes, and one report from the European Prospective Investigation into Cancer and Nutrition-Norfolk prospective study suggested that the magnitude of ferritin associated risk of diabetes was slightly reduced by adjustment for adiponectin (8). Our study suggests that neither adiposity nor adipokines can explain the ferritin-diabetes association.

Inflammation was suggested to regulate not only ferritin mRNA and protein levels but also its secretion (37). As a result, elevated ferritin concentrations might reflect systemic inflammation in addition to elevated body iron stores (13). Meanwhile, inflammation was postulated to be involved in the physiopathological mechanisms behind metabolic syndrome and diabetes (17, 38). In our study, the concentration of ferritin was positively correlated with the concentrations of CRP ($r = 0.18$, $P < 0.001$) and IL-6 ($r = 0.12$, $P < 0.001$) and negatively correlated with the concentration of TNF-R2 weakly ($r = -0.05$, $P < 0.01$). After adjusting for CRP, IL-6, and TNF-R2 in the multivariate models, no substantial change was observed in the associations of ferritin and type 2 diabetes, IFG, or metabolic syndrome. Indeed, our observations were consistent with the previous findings from a prospective study (9) in which ferritin was showed to predict the onset of hyperglycemia independent of CRP concentrations. In addition, our data also indicate that the associations of diabetes with ferritin and CRP tended to be independent of each other, in agreement with the data from the Nurses' Health study (7). Therefore, it is possible that ferritin may increase the risk of type 2 diabetes, IFG, or metabolic syndrome through a pathway not greatly overlapping with CRP and other inflammatory factors.

Metabolic syndrome is a powerful risk factor for type 2 diabetes mellitus (15). However, metabolic syndrome status has rarely been evaluated in the ferritin-diabetes association in previous studies. Interestingly, we observed a strong positive asso-

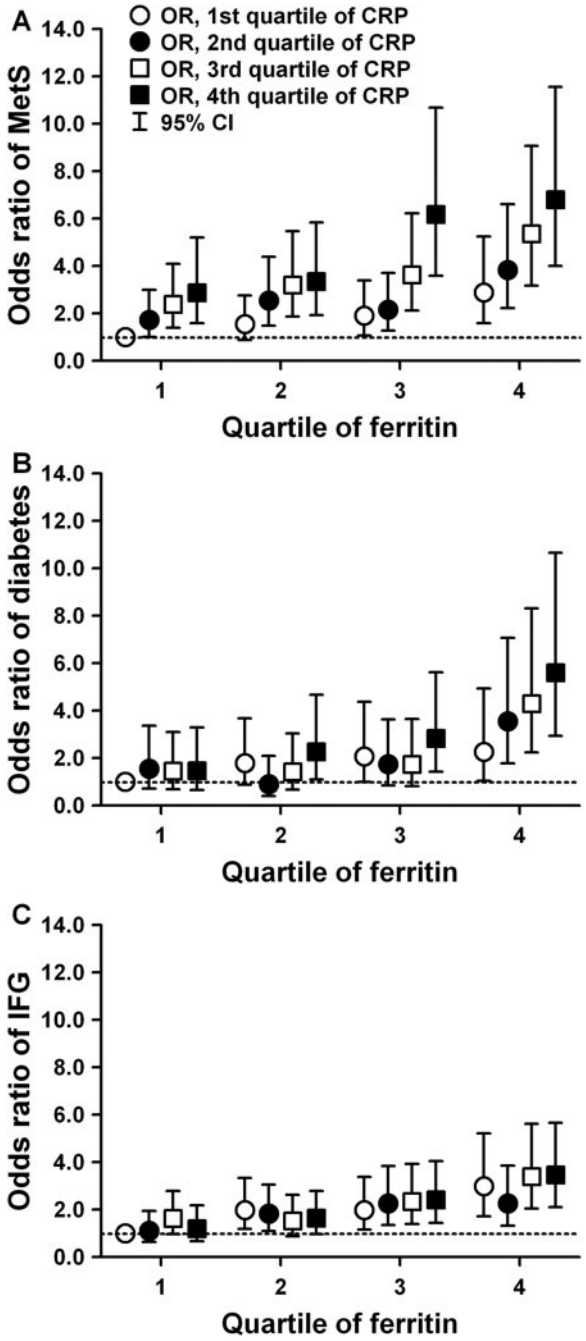

FIG. 1. OR and 95% confidence interval (CI) for metabolic syndrome (A), type 2 diabetes (B), and IFG (C) according to joint classification of ferritin and CRP concentrations. Adjusted for age, sex, region, residence, BMI, smoking, drinking, physical activity, education levels, dietary factors, and family histories of chronic diseases (A) or family histories of diabetes (B and C). *P* for interaction = 0.54, 0.54, and 0.36 for metabolic syndrome (MetS), type 2 diabetes, and IFG, respectively. *White circles*, OR for first quartile of CRP; *black circles*, OR for second quartile of CRP; *white squares*, OR for third quartile of CRP; *black squares*, OR for fourth quartile of CRP; *black bars*, 95% CI; *broken line*, odds ratio = 1.

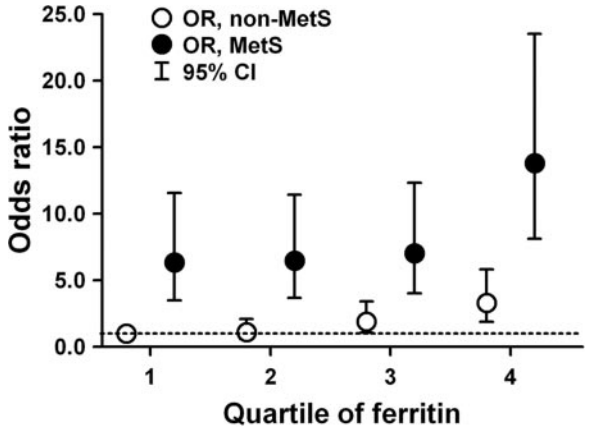

FIG. 2. OR and 95% confidence interval (CI) for type 2 diabetes according to joint classification of metabolic syndrome (MetS) and ferritin concentrations. The ORs were adjusted for age, sex, region, residence, BMI, smoking, drinking, physical activity, education levels, dietary factors, and family histories of diabetes. *P* for interaction = 0.40. *White circles*, OR for subjects without MetS; *black circles*, OR for subjects with MetS; *black bars*, 95% CI; *broken line*, odds ratio = 1.

ciation between elevated ferritin concentrations and the risks of type 2 diabetes among the participants with and without metabolic syndrome. Hence, our data suggested that an elevated ferritin concentration may increase the risk of developing type 2 diabetes via mechanism(s) other than metabolic syndrome. A possible route might be the formation of hydroxyl radicals catalyzed by iron (39) and destruction of hepatic function (40) related to high ferritin concentrations.

To our knowledge, this is the first study to investigate not only the associations of ferritin concentrations with the risk of type 2 diabetes and metabolic syndrome simultaneously but also simultaneously evaluate the effects of adiposity, metabolic syndrome, inflammation, and adipokines on the ferritin-diabetes association in a large population-based sample from the north and south of China. Our findings provide novel insights into the potential role of iron overload in the development of type 2 diabetes. Our data also draw special attention to subgroups in developing countries to whom iron supplementation is commonly recommended to treat iron deficiency. Admittedly, the cross-sectional nature of our study prevents us from establishing the causal relation between elevated ferritin and type 2 diabetes but highlights the necessity of longitudinal studies evaluating these associations among Chinese populations. Another limitation is that we measured only hemoglobin and plasma ferritin as the markers of iron status but did not evaluate other markers such as transferrin receptor due to very limited blood sample. A previous study suggested that lower ratio of transferrin receptor to ferritin was associated with higher risk of type 2 diabetes in a healthy Western population (7). Obviously, future studies are needed to verify this association in non-Caucasian populations.

In conclusion, our study indicates that elevated ferritin concentration is strongly associated with type 2 diabetes among middle-aged and elderly Chinese men and women, independent of lifestyle factors, obesity, inflammation, adipokines, and metabolic syndrome.

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