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ORIGINAL ARTICLE

Serum ferritin, diabetes, diabetes control, and insulin resistance

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Abstract
Aims The present study aims to investigate the association between serum ferritin and diabetes, diabetes control, and insulin resistance (IR) and examine whether gender is a modifier for these associations in a community-based sample.
Methods A cross-sectional survey of 8,235 participants was conducted in 2009. Serum ferritin, glucose, hemoglobin A1c (HbA1c), insulin, inflammatory markers, and lipid markers were measured. IR was estimated with a Homeostasis Model Assessment (HOMA-IR) equation. Multiple logistic and linear regression models were applied to evaluate these associations.
Results The numbers of diabetic patients and non-diabetic participants in the present study were 644 (7.8 %) and 7,591 (92.2 %). After adjusting for multiple confounders, the odds ratios (ORs) and 95 % confidence intervals (CIs) for diabetes were 1.48 (1.31–1.69) in men and 1.43 (1.24–1.65) in women for one-unit increase in log-transformed serum ferritin levels. Likewise, ORs (95 % CIs) for poor diabetes control (HbA1c $\geq$7.5 %) were 1.58 (1.21–2.05) and 1.37 (1.07–1.77) in men and women, respectively. As for HOMA-IR, the respective betas (P value) for one-unit increase in log-transformed serum ferritin were 0.07 ($P < 0.0001$) and 0.06 ($P < 0.0001$) in men and women.
Conclusions In conclusion, elevated serum ferritin levels were associated with higher risks of diabetes, higher levels of HbA1c, and HOMA-IR independent of several confounders.

Keywords Ferritin · Diabetes · Insulin resistance · Hemoglobin A1c

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Introduction

Recent studies reported the prevalence of diabetes in China soared from 1.9 to 11.6 % between 1993 and 2010 [1–3]. As a country with the largest population in the world, China has to face the major public health problem with regard to the absolute number and economic burden of potential diabetic patients. Given the consequences of diabetes and its complications, clarifying its etiology, looking for modifiable risk factors, and exploring possible treatment strategies are of paramount importance for diabetes control and prevention.

During the last decades, accumulating evidences were suggestive of elevated serum ferritin concentrations associating with higher risks of diabetes [4–7], insulin resistance (IR) [8], metabolic syndrome [9, 10], and hypertension [11]. Likewise, heme iron intake was also reported to increase the risk of diabetes [12]. Anemia is another big public health problem in many developing countries with the prevalence ranging from 12.7 to 47.4 % [13]. A number of factors might contribute to anemia, but the most important one is iron

deficiency [14]. The prevalence of anemia and distribution of ferritin varied between men and women. Previous studies reported that the association between serum ferritin and IR was only found in men but not in women [8]. Thus, we hypothesized that gender might modify the association of ferritin with diabetes risk.

In the present study, we aimed to investigate the association between serum ferritin and diabetes, diabetes control, and IR and examined whether the associations differed by gender in a national representative sample from the China Health and Nutrition Survey (CHNS) 2009.

Methods

Participants

The CHNS [15] started in 1989 and aimed to understand the changes of health status with the follow-up intervals of 2 or 3 years. The CHNS selected individuals from 228 communities and was designed to represent 56 % of China's population from nine provinces including Liaoning, Shandong, Heilongjiang, Henan, Jiangsu, Hubei, Hunan, Guizhou, and Guangxi. A multistage, random cluster sampling design was used to draw study samples. This survey was approved by the institutional review committees of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety, the Chinese Center for Disease Control and Prevention, and the China–Japan Friendship Hospital, Ministry of Health. This study was performed in accordance with the ethical standards laid down in 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent. Details about the study design were reported elsewhere [15, 16].

In the 2009 wave of CHNS, blood samples were collected and assessed for the first time. In our study, we excluded those with missing information on serum ferritin, glucose, insulin, or other interested variables. Altogether, 8,235 adults aged 18 years and over were included in the analysis.

Data collection

All participants were interviewed by trained physicians and nutritionists using a validated questionnaire to collect demographic, anthropometric, and lifestyle data, which included date of birth, gender, education, height, weight, and smoking. Height and weight were measured by physicians following a standard protocol similar to that developed by the National Center for Health Statistics for the National Health and Nutrition Examination Survey in the USA. Height was measured without shoes and rounded to the nearest 0.1 cm. Weight was recorded in light clothing to the nearest 0.1 kg.

Measurements of glucose, glycated hemoglobin, insulin, and serum ferritin

Blood samples were collected by venipuncture after an overnight fast. Plasma and serum samples were then frozen and stored at −86 °C for laboratory analysis. The samples were analyzed in a national central laboratory in Beijing (medical laboratory accreditation certificate ISO 15189:2007) with strict quality control. Fasting glucose was measured using by the GOD-PAP method (Randox Laboratories Ltd, UK), and glycated hemoglobin (HbA1C) was assessed with high-performance liquid chromatography method. The concentrations of fasting serum ferritin and insulin were determined by a commercial Radioimmunoassay Kit (Beijing North Institute of Biological Technology, China).

Diabetes, diabetes control, and insulin resistance

Diabetes was defined as fasting glucose $\geq$7.0 mmol/L or current usage of anti-diabetes medications, poor diabetes control was defined as HbA1C $\geq$7.5 % or 58 mmol/mol IFCC, and IR was estimated with a Homeostasis Model Assessment (HOMA-IR) equation.

Covariates

Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. Education level was classified into 0–9, 10–12, and $\geq$13 years. Smoking status was categorized as never smoker, former smoker, and current smoker. High-sensitivity C-reactive protein (hs-CRP) was analyzed by an automatic clinical chemistry analyzer (Hitachi 7600 D and P model, Japan). Hypertension was defined as systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or current antihypertensive drug use. Anemia was defined as hemoglobin <130 g/L in men and <120 g/L in women.

Statistical analysis

In the descriptive analysis, we presented the basic characteristics of the study participants as mean (standard deviation) for continuous variables and number (percentage) for category variables by quartiles of serum ferritin. Chi-square test was applied to compare the differences of category variables among the quartiles of serum ferritin, while ANOVA was used for continuous variables. Then we used multivariable logistic regression models to examine the association between serum ferritin and diabetes and poor diabetes control. In the exploratory analysis, we tested the interaction terms between ferritin and other covariates in all participants and found that the interaction terms

between gender and low serum ferritin was significant ($P < 0.0001$). Then we stratified the analysis by gender in the subsequent analysis. Three models were used in the present study. The first model included serum ferritin as an independent variable followed by the second model further adjusting age. The third model additionally included BMI, education, smoking, hsCRP, serum lipids, and hypertension. Additionally, since a linear relationship across the serum ferritin quartiles was observed, serum ferritin was treated as a continuous variable (log-transformed serum ferritin), and odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated with one-unit increase in log-transformed serum ferritin. We applied multivariable linear regression models to investigate the relationship between serum ferritin and HOMA-IR in the whole cohort and presented betas (P values). We also tested whether anemia was significantly associated with diabetes in the whole cohort using multivariable logistic regression models. P values were two-tailed, and $P < 0.05$ was considered as statistical significance. All analysis was conducted using R 3.0.

Results

Basic characteristics of participants

Tables 1, 2 summarize the basic characteristics by quartiles of serum ferritin in men and women, respectively. Because serum ferritin was not normally distributed, log-transformed serum ferritin was used in the following analysis. All basic demographic and metabolic parameters were significantly different among the four quartiles in both men and women except the prevalence of hypertension in men.

Association between serum ferritin and diabetes, diabetes control, and HOMA-IR

As shown in Table 3, higher serum ferritin levels were associated with a higher risk of diabetes in all models. Compared with participants in the first quartile of serum ferritin, the OR (95 % CI) for those in the fourth quartile was 2.32 (1.65–3.26) in men and 2.30 (1.39–3.80) in women after adjusting for multiple confounders in Model 3. When serum ferritin was treated as a continuous variable, each one-unit increase in log-transformed serum ferritin was associated with 48 % higher risk of diabetes in men (OR 1.48, 95 % CI 1.31–1.69) and 43 % higher risk of diabetes in women(OR 1.43, 95 % CI 1.24–1.65).

Associations between serum ferritin and poor diabetes control in diabetic patients are presented in Table 4. Similar to the results in Table 3, one-unit increase in the log-transformed serum ferritin was associated with 58 % higher risk of poor diabetes control in men and 37 % higher risk of poor diabetes control in women after adjusting for multiple confounders. Likewise, regarding the relationship between serum ferritin and log-transformed HOMA-IR, each one-unit increase in the log-transformed serum ferritin was associated with 0.07 ($P < 0.0001$) higher of log-transformed HOMA-IR in men. The result was similar in women with effect size being 0.06 ($P < 0.0001$). The respective prevalence of anemia was 8.5 and 10.5 % ($P = 0.2308$) in men with and without diabetes, while that of anemia was 18.4 and 19.7 % ($P = 0.6151$) in women with and without diabetes, respectively. The respective ORs (95 % CI) of diabetes were 1.16 (0.79–1.70) and 1.18 (0.86–1.63) in men and women with anemia after adjusting for multiple confounders. No significant difference between men and women was observed.

Discussion

In the present study with a large sample size, we observed a significant association between serum ferritin levels and the prevalence of diabetes, poor diabetes control, and HOMA-IR in both men and women. Higher serum ferritin levels were associated with a higher risk of diabetes, higher levels of HbA1c and HOMA-IR. These associations were independent of several established confounders and risk factors of diabetes and were slightly different in men than women. The prevalence of anemia was not associated with having diabetes. These findings provided us with new evidence of serum ferritin being regarded as biomarker for diabetes and HOMA-IR.

The overall prevalence of diabetes in this national sample was lower than that previously reported in other surveys [2, 3]. The discrepancy might be largely attributed to the methodology and definition of diabetes as well as age distributions of study populations. Previous surveys used oral glucose tolerance test which is one of the gold standards for diabetes diagnosis, and the participants were mainly the middle and elderly people. In the present study, the study population was younger than those in other studies. In addition to that, diabetes was mainly defined by fasting glucose, which could underestimate the true prevalence of diabetes.

Although several studies were conducted to examine the association between serum ferritin and diabetes, most of them were based on Caucasian samples [17–22]. To the best of our knowledge, only a few studies [7, 9, 23–25] were published to investigate the association in the Chinese population and few of them extensively studied serum ferritin and its association with diabetes, diabetes control, and IR simultaneously. Recent cohort studies

Table 1 Basic characteristics of study participants in men

Variables	Q1 (n = 960, 1.67–73.87 ng/ml)	Q2 (n = 958, 73.88–122.49 ng/ml)	Q3 (n = 959, 122.50–212.29 ng/ml)	Q4 (n = 959, 212.30–1,279.00 ng/ml)	P value
Age(years)	52.8 ± 15.0	50.9 ± 15.0	50.5 ± 14.7	49.5 ± 13.7	<0.0001
BMI(kg/m2)	22.5 ± 3.4	22.9 ± 3.3	23.5 ± 3.4	24.4 ± 3.6	<0.0001
Ferritin(ng/ml)	48.8 ± 22.3	97.2 ± 32.0	158.0 ± 48.0	500.8 ± 270.3	<0.0001
Hemoglobin(g/L)	147.2 ± 22.6	152.0 ± 18.7	153.1 ± 19.5	155.1 ± 20.7	<0.0001
TC(mmol/L)	4.61 ± 0.91	4.71 ± 0.94	4.86 ± 0.98	5.08 ± 1.09	<0.0001
TG(mmol/L)	1.33 ± 0.95	1.53 ± 1.14	1.82 ± 1.39	2.52 ± 2.02	<0.0001
LDL-C(mmol/L)	2.84 ± 0.83	2.91 ± 0.92	2.95 ± 0.98	2.98 ± 1.13	<0.0001
HDL-C(mmol/L)	1.45 ± 0.44	1.40 ± 0.38	1.39 ± 0.47	1.31 ± 0.61	<0.0001
Glucose(mmol/L)	5.15 ± 0.92	5.32 ± 1.1	5.49 ± 1.40	5.96 ± 2.06	<0.0001
Insulin(μU/ml)	14.36 ± 25.95	14.32 ± 20.12	13.83 ± 17.96	16.06 ± 24.73	<0.0001
HbA1c(%)	5.53 ± 0.60	5.59 ± 0.95	5.62 ± 0.83	5.85 ± 1.15	<0.0001
HOMA-IR(mmol/L*μU/ml)	3.59 ± 7.26	3.56 ± 5.10	3.72 ± 6.63	4.72 ± 9.02	<0.0001
Education					0.0100
0∼9 years	736 (76.7)	681 (71.1)	678 (70.7)	671 (70.0)	
10–12 years	173 (18.0)	203 (21.2)	221 (23.0)	227 (23.7)	
13 years	51 (5.3)	74 (7.7)	60 (6.3)	61 (6.4)	
Smoking status					0.0051
Never	385 (40.1)	377 (39.4)	348 (36.3)	355 (37.0)	
Former	83 (8.6)	59 (6.2)	67 (7.0)	46 (4.8)	
Current	492 (51.2)	522 (54.5)	544 (56.7)	558 (58.2)	
hsCRP					<0.0001
Level-1 (<3 mg/l)	762 (79.4)	747 (78)	742 (77.4)	671 (70.0)	
Level-2 (3–10 mg/l)	151 (15.7)	175 (18.3)	175 (18.2)	236 (24.6)	
Level-3 (>10 mg/l)	47 (4.9)	36 (3.8)	42 (4.4)	52 (5.4)	
Hypertension					0.5893
No	688 (71.7)	685 (71.5)	691 (72.1)	666 (69.4)	
Yes	272 (28.3)	273 (28.5)	268 (27.9)	293 (30.6)	
Diabetes					<0.0001
No	903 (94.1)	898 (93.7)	871 (90.8)	814 (84.9)	
Yes	57 (5.9)	60 (6.3)	88 (9.2)	145 (15.1)	

BMI body mass index, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *HbA1c* hemoglobin A1C, *HOMA-IR* homeostatic model assessment-insulin resistance, *hsCRP* high-sensitivity C-reactive protein

reported higher serum ferritin was associated with diabetes incidence in an elderly Chinese population [7] and Korean men [6]. Previous studies also found serum ferritin level is higher in the poorly controlled patients with Type 2 diabetes [26]. Our results were consistent with the aforementioned studies and those conclusions from studies which collected data from Caucasian descent [17–22].

Serum ferritin differed between men and women to a large extent, but the prevalence of diabetes in men and women was comparable. Thus, we hypothesized that gender might have an effect on the association between serum ferritin and diabetes, poor diabetes control, or HOMA-IR. Our results were not contradictory to the hypothesis and were parallel to several studies. In a Japanese study, gender was found to modify the association between serum ferritin and IR [8]. Likewise, a Korean study also found gender might modify the effects of serum ferritin on diabetes and IR [27]. Sex difference of these associations was also reported in the SUNSET Study, which included South Asian Surinamese, African Surinamese, and ethnic Dutch participants [5]. Similar result was also reported in another study, which found elevated serum ferritin concentration was associated with IR only in women with diabetes but not in men [28]. However, although the interaction term between gender and serum ferritin was statistically significant, the differences of the absolute effect sizes in men and women were not too large. Thus, the hypothesis that gender modifies the association of ferritin with diabetes should be

Table 2 Basic characteristics of study participants in women

Variables	Q1 (n = 1,103, 0.05–24.01 ng/ml)	Q2 (n = 1,097, 24.02–51.21 ng/ml)	Q3 (n = 1,099, 51.22–93.48 ng/ml)	Q4 (n = 1,100, 93.49–1,276.00 ng/ml)	P value
Age(years)	41.0 ± 15.0	46.7 ± 15.0	54.8 ± 14.7	61.0 ± 13.7	<0.0001
BMI(kg/m2)	22.9 ± 3.4	23.1 ± 3.3	23.6 ± 3.4	24.2 ± 3.5	<0.0001
Ferritin(ng/ml)	12.9 ± 22.3	36.8 ± 32.0	69.8 ± 48.0	203.8 ± 270.4	<0.0001
Hemoglobin(g/L)	126.5 ± 22.6	134.0 ± 18.7	134.1 ± 19.5	133.4 ± 20.7	<0.0001
TC(mmol/L)	4.56 ± 0.91	4.74 ± 0.94	5.07 ± 0.98	5.27 ± 1.09	<0.0001
TG(mmol/L)	1.27 ± 0.95	1.40 ± 1.14	1.59 ± 1.39	2.01 ± 2.02	<0.0001
LDL-C(mmol/L)	2.76 ± 0.83	2.92 ± 0.92	3.17 ± 0.98	3.27 ± 1.13	<0.0001
HDL-C(mmol/L)	1.51 ± 0.44	1.48 ± 0.38	1.49 ± 0.47	1.44 ± 0.61	<0.0001
Glucose(mmol/L)	5.01 ± 0.92	5.16 ± 1.10	5.34 ± 1.40	5.81 ± 2.06	<0.0001
Insulin(μU/ml)	12.99 ± 25.95	13.04 ± 20.12	13.79 ± 17.96	16.91 ± 24.73	<0.0001
HbA1c(%)	5.42 ± 0.60	5.52 ± 0.95	5.64 ± 0.83	5.86 ± 1.15	<0.0001
HOMA-IR(mmol/L*μU/ml)	3.02 ± 7.26	3.17 ± 5.10	3.55 ± 6.63	4.83 ± 9.02	<0.0001
Education					<0.0001
0∼9 years	856 (77.6)	834 (76)	887 (80.7)	961 (87.4)	
10–12 years	205 (18.6)	207 (18.9)	168 (15.3)	125 (11.4)	
13 years	42 (3.8)	56 (5.1)	44 (4.0)	14 (1.3)	
Smoking status					0.0005
Never	1,079 (97.8)	1,058 (96.4)	1,049 (95.5)	1,035 (94.1)	
Former	2 (0.2)	2 (0.2)	3 (0.3)	8 (0.7)	
Current	22 (2.0)	37 (3.4)	47 (4.3)	57 (5.2)	
hsCRP					<0.0001
Level-1 (<3 mg/l)	956 (86.7)	905 (82.5)	797 (72.5)	672 (61.1)	
Level-2 (3–10 mg/l)	134 (12.1)	162 (14.8)	255 (23.2)	358 (32.5)	
Level-3 (>10 mg/l)	13 (1.2)	30 (2.7)	47 (4.3)	70 (6.4)	
Hypertension					<0.0001
No	957 (86.8)	892 (81.3)	752 (68.4)	662 (60.2)	
Yes	146 (13.2)	205 (18.7)	347 (31.6)	438 (39.8)	
Diabetes					<0.0001
No	1,081 (98.0)	1,048 (95.5)	1,021 (92.9)	955 (86.8)	
Yes	22 (2.0)	49 (4.5)	78 (7.1)	145 (13.2)	

BMI body mass index, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *HbA1c* hemoglobin A1C, *HOMA-IR* homeostatic model assessment-insulin resistance, *hsCRP* high-sensitivity C-reactive protein

interpreted with caution from our results. This might be merely statistical interaction, which does not mean biological interaction between gender and ferritin.

The exact mechanism of the association between serum ferritin and diabetic disorder remains to be clarified. Till now, several possible biological pathways might be proposed to explain the observed findings. Firstly, serum ferritin is regarded as a biomarker of body iron store, whose catalytic effects could induce lipid peroxidation [29]. A recent study suggested lipid peroxidation might be involved in the development of IR [30]. Secondly, iron is able to form highly reactive free radicals [31], which can lead to disturbed glucose metabolism and subsequent hyperglycemia [32]. Additionally, iron deposition and accumulation in hepatocytes may directly involve in insulin signaling [33]. Finally, iron was closely related to inflammation, which imposed a higher risk on diabetes and IR. However, in our study after adjusting for hsCRP, the associations between serum ferritin and diabetes were still significant, which might be suggestive of other pathways of the effects of serum ferritin on diabetes and IR.

The strength of the present study was its large sample size that enabled us to stratify the analysis by gender. Our

Table 3 Results of logistic regression analyses of the association between having diabetes (dependent variable, yes $n = 644$ vs. no $n = 7{,}591$) and serum ferritin in the whole cohort ($n = 8{,}235$) OR(95 % CI)

	Model 1	Model 2	Model 3
Men			
Q1 (1.67–73.87 ng/ml)	1	1	1
Q2 (73.88–122.49 ng/ml)	1.06 (0.73–1.54)	1.13 (0.77–1.65)	1.01 (0.69–1.48)
Q3 (122.50–212.29 ng/ml)	1.60 (1.13–2.26)	1.75 (1.23–2.48)	1.50 (1.05–2.14)
Q4 (212.30–1279.00 ng/ml)	2.82 (2.05–3.89)	3.27 (2.36–4.54)	2.32 (1.65–3.26)
1 unit of log-transformed ferritin increase	1.62 (1.43–1.82)	1.73 (1.53–1.96)	1.48 (1.31–1.69)
Women			
Q1 (0.05–24.01 ng/ml)	1	1	1
Q2 (24.02–51.21 ng/ml)	2.30 (1.38–3.83)	1.74 (1.04–2.92)	1.57 (0.93–2.66)
Q3 (51.22–93.48 ng/ml)	3.75 (2.32–6.07)	2.07 (1.25–3.42)	1.58 (0.94–2.64)
Q4 (93.49–1276.00 ng/ml)	7.46 (4.72–11.78)	3.38 (2.07–5.51)	2.30 (1.39–3.80)
1 unit of log-transformed ferritin increase	2.06 (1.8–2.33)	1.63 (1.42–1.87)	1.43 (1.24–1.65)

Model 1 adjusted for: serum ferritin

Model 2 adjusted for: serum ferritin and age

Model 3 adjusted for: serum ferritin, age, BMI, education, smoking, hsCRP, serum lipids, and hypertension

Table 4 Results of logistic regression analyses of the association between glycemic control [dependent variable HbA1c $\geq$7.5 % ($n = 233$) vs. HbA1c <7.5 % ($n = 411$)] and serum ferritin in the diabetic cohort ($n = 644$) OR(95 % CI)

	Model 1	Model 2	Model 3
Men			
Q1 (1.67–73.87 ng/ml)	1	1	1
Q2 (73.88–122.49 ng/ml)	1.14 (0.58–2.24)	1.18 (0.60–2.33)	1.17 (0.59–2.32)
Q3 (122.50–212.29 ng/ml)	2.67 (1.41–5.07)	2.98 (1.55–5.73)	2.89 (1.48–5.65)
Q4 (212.30–1279.00 ng/ml)	2.28 (1.20–4.33)	2.84 (1.43–5.63)	2.68 (1.33–5.39)
1 unit of log-transformed ferritin increase	1.49 (1.18–1.88)	1.63 (1.26–2.10)	1.58 (1.21–2.05)
Women			
Q1 (0.05–24.01 ng/ml)	1	1	1
Q2 (24.02–51.21 ng/ml)	1.02 (0.50–2.05)	1.08 (0.53–2.21)	1.11 (0.54–2.29)
Q3 (51.22–93.48 ng/ml)	1.02 (0.51- 2.05)	1.07 (0.53–2.18)	1.06 (0.52–2.18)
Q4 (93.49–1276.00 ng/ml)	2.47 (1.26–4.83)	2.63 (1.31–5.25)	2.59 (1.29–5.22)
1 unit of log-transformed ferritin increase	1.35 (1.06–1.72)	1.39 (1.08–1.78)	1.37 (1.07–1.77)

Model 1 adjusted for: serum ferritin

Model 2 adjusted for: serum ferritin and age

Model 3 adjusted for: serum ferritin, age, BMI, education, smoking, hsCRP, serum lipids, and hypertension

findings provide new evidence to support the relationship between serum ferritin and diabetes. Admittedly, the current study had some limitations that deserved to be considered when interpreting the results. The cross-sectional study design prevents us from drawing causal inference and highlights the necessity of prospective study with repeated measurements of serum ferritin, glucose, HbA1C, and insulin. In addition to that, the residual confounding is still possible to exist although several confounders were considered in the analysis. Future studies are warranted to clarify the underlying biological mechanisms and causal pathways between serum ferritin and diabetes.

In conclusion, our study suggested that higher serum ferritin was associated with higher prevalence of diabetes, higher levels of HbA1c, and HOMA-IR. The observed results were independent of several confounders including age, gender, education, smoking, BMI, serum lipids, and hypertension.

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Conflict of interest Yiqiang Zhan, Zheng Tang, and Jinming Yu declare that they have no conflict of interest.

Ethical standard All the authors declare that there is no ethical problem associated with this manuscript.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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