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Threshold-effect of ferritin levels with pathoglycemia in Chinese adults: a cross-sectional study based on China health and nutrition survey data

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Abstract

Background The present study aimed to explore the threshold-effect association of serum ferritin levels with type 2 diabetes mellitus (T2DM) and prediabetes mellitus in Chinese adults.

Methods A total of 8365 people from CHNS a cross-sectional survey in 2009 were finally included. The biomarker data, including major cardiovascular biomarkers and important nutrition biomarkers were collected. The association of serum ferritin levels with T2DM and prediabetes mellitus were assessed by using restricted cubic spline function combined with multivariate logistic regression model.

Results The mean age of the study subjects was 50.3 years, and 46.5% were men. The risk of T2DM and prediabetes mellitus increased when the ferritin level was greater than 140 ng/ml. The OR(OR = 0.59, 95% *CI*, 0.35–0.98)was lowest between 40 to < 60 ng/ml in men with prediabetes mellitus. The OR(OR = 0.61, 95% *CI*, 0.41–0.90)was lowest between 20 to < 40 ng/ml in women with prediabetes mellitus. Serum ferritin levels and OR value of women younger than 50 years old are lower than those of other participants.

Conclusions There is a correlation between ferritin levels and pathoglycemia, with women under 50 years old having a lower risk for the same ferritin level, and maintaining low levels of ferritin can reduce the risk of developing diabetes mellitus.

Keywords Threshold-effect, Ferritin, Pathoglycemia, Type 2 diabetes mellitus

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Introduction

China is now the country with the fastest growing diabetes mellitus in the world, and about 11% of the population has diabetes mellitus [1, 2]. According to the results of the Global Burden of Disease (GBD) study, compared with 2007, the incidence and death rates of diabetes mellitus worldwide in 2017 increased by 27.3% and 25.6% respectively [3]. In addition, there are still many undiagnosed diabetics and prediabetics in China. Those already sick and potential diabetic patients will bring a heavy economic and social burden to China. Therefore, early detection and management of high-risk individuals is crucial to prevent numerous complications of diabetes, thereby potentially improving the social and economic effects of diabetes.

Serum ferritin is usually used as an important indicator of iron storage in the body [4]. Moreover, a number of studies have shown that serum ferritin is a strong marker of T2DM in recent decades. Cross-sectional surveys have shown that serum ferritin level was positively correlated with T2DM, independent of traditional diabetes mellitus risk factors, such as age, obesity or family history of diabetes mellitus [5, 6]. It has been suggested that high iron reserves contribute to the development of T2DM by increasing the level of oxidative stress and causing pancreatic β cell damage and insulin resistance [7, 8]. Iron can attack cell membrane, protein and DNA by catalyzing hydrogen peroxide into free radical ions [9], thus damaging tissues and possibly leading to diabetes mellitus [10, 11]. In addition, excessive iron reserves are thought to be related to the high risk of other metabolic disorders, including hypertension [12, 13]metabolic syndrome [14], and cardiovascular disease [15].

A number of prospective studies in western regions also showed that ferritin has a close relationship with T2DM [16–25]. Two of the studies based on the European Prospective Investigation into Cancer and Nutrition confirmed serum ferritin is an important and independent predictor of T2DM [16, 17]. The Asian cohort studies also showed that excessive iron reserves in the body was a risk factor for T2DM [18–25].

Although many studies all over the world have confirmed that ferritin may be used as a robust predictor of T2DM, there is still a lack of large-scale research in China and exploration on the threshold effect relationship between serum ferritin level and T2DM risk. In the present study, we aimed to explore the threshold-effect association of serum ferritin levels with diabetes mellitus and prediabetes mellitus in Chinese adults by China Health and Nutrition Survey (CHNS) 2009.

Subjects and methods

Study population

The China Health and Nutrition Survey (CHNS) began in 1989. Its goal is to establish a multi-level method of collecting data from individuals, families and their communities, so as to understand how the extensive social and economic changes in China affect a series of nutrition and health-related results. CHNS used a multistage random-cluster sampling process to select samples from 15 provinces in China. From 1989 to 2009, CHNS held nine rounds in nine provinces (autonomous regions). The 9th round was held in 12 provinces (autonomous regions) in 2011, with Beijing, Shanghai and Chongqing added; The 10th round was held in 15 provinces (autonomous regions) in 2015, with Shanxi, Yunnan and Zhejiang added. This survey was established by the National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention, the institutional review committees of the University of North Carolina at Chapel Hill, and the China–Japan Friendship Hospital, Ministry of Health. The survey design and methods have been described in detail elsewhere [26, 27].

During the CHNS wave in the 2009, blood samples were collected and evaluated for the first time. We excluded those with missing information on serum ferritin, glucose, or other interested variables. A total of 8365 adults aged 18 years and over were included in the final analyses(Figure S1). This study is reported as per the STROBE guideline (Table S1 STROBE Statement—Checklist).

Diabetes mellitus and prediabetes mellitus

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 were determined by a commercial Radioimmunoassay Kit (Beijing North Institute of Biological Technology, China). Diabetes mellitus was defined as fasting glucose≥126 mg/dl or current usage of anti-diabetes medications. Participants with fasting blood glucose>100 mg/dl and HbA1C>5.7% without type 2 diabetes mellitus were defined as prediabetes mellitus.

Covariates

Covariates including age, highest level of education, Body mass index (BMI) and hypertension were obtained by general information questionnaires. BMI was calculated as weight in kilograms divided by the square of height in meters. In the CHNS, education level is defined as the highest level of education that participants attained. Hypertension is defined as systolic blood pressure≥140 mm Hg, diastolic blood pressure≥90 mm Hg,

or current antihypertensive medications use. Cigarette smoking is defined by individuals who have ever smoked cigarettes. Ferritin levels were categorized as <20 ng/ml, 20 to <40 ng/ml, 40 to <60 ng/ml, 60 to <80 ng/ml, 80 to <100 ng/ml, 100 to <120 ng/ml, 120 to <140 ng/ml, 140 to <160 ng/ml, 160 to <180 ng/ml, 180 to <200 ng/ml, and ≥200 ng/ml.

Statistical analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables were presented as n(%). The Kolmogorov-Smirnov test is employed to assess the adherence of variables to a normal distribution. Differences among serum ferritin levels were examined using the Wilcoxon rank-sum and Kruskal–Wallis H test for continuous variables and Chi-square test for categorical variables. The odds ratios (OR) and 95% confidence intervals (CI) were used to assess the risk of prediabetes mellitus with different serum ferritin levels, after adjusting for potential confounding factors. The threshold effect between serum ferritin levels and patients with prediabetes mellitus was explored using restricted cubic splines. All analyses were performed using STATA version 15.0. The significance level was $P<0.05$.

Results

Baseline characteristics

The baseline characteristics of participants across levels of serum ferritin are summarized in Table 1. The mean age of the study subjects was 50.3 years, and 46.5% were men. Of all participants, the prevalence, basic demographics (age, gender, education level, BMI and smoking status) and metabolic parameters (insulin, LDL-C, HDL-C, TC and TG) of serum ferritin levels were significantly different ($P<0.01$). There are more women than men with diabetes mellitus or prediabetes mellitus between 0-100ng/ml serum ferritin, and there are more men with diabetes mellitus or prediabetes mellitus above 100ng/ml serum ferritin. The median ferritin of the total population was 79.72ng/ml, the median ferritin of the men population was 122.72ng/ml, and the median ferritin of the women population was 51.08ng/ml, and the difference was statistically significant (Table S2).

Associations of ferritin levels with prediabetes mellitus and diabetes mellitus

The overload threshold of women and men ferritin level was used as the reference value. The Fig. 1 shows adjusted ORs (95%*CI*) for prediabetes mellitus and diabetes mellitus across the levels of ferritin. In all participants, the risk of developing diabetes increased as ferritin levels increased. This was statistically significant in women with prediabetes mellitus.

Table 2 shows the ORs of prediabetes mellitus according to levels of ferritin in Chinese adults. In all participants, when the serum ferritin level is higher than 140 ng/ml, the risk of diabetes mellitus and prediabetes mellitus will increase. After adjusting for potential confounders in each model, in the prediabetes mellitus participants, the OR (OR=1.85, 95% *CI*, 1.31–2.62)was highest when ferritin levels were >200ng/ml and the OR(OR=0.59, 95% *CI*, 0.35–0.98)was lowest between 40 to <60 ng/ml in men($P<0.01$). In women with prediabetes mellitus, the OR (OR=2.66, 95% *CI*, 1.39–5.09) were highest when ferritin levels were 180 to <200 ng/ml and the OR(OR=0.61, 95% *CI*, 0.41–0.90)was lowest between 20 to <40 ng/m($P<0.01$). In the diabetes mellitus participants, the OR(OR=2.06, 95% *CI*, 0.87–4.84) was highest that ferritin levels were 160 to <180 ng/ml in men. The OR(OR=1.35, 95% *CI*, 0.56–3.24)was highest that ferritin levels were 120 to <140 ng/ml in women diabetes mellitus (Table S3).

Ferritin levels are associated with prediabetes mellitus in women

The median ferritin level over age 50 is 82.88 ng/ml and the median ferritin level under age 50 is 28.14 ng/ml in women (Table S2), median ferritin levels were lower in participants younger than 50 years of age. The Fig. 2 shows adjusted ORs (95%*CI*) for prediabetes mellitus across the levels of ferritin in adult women younger than 50. A comparison of Fig. 2 and Figure S2 shows that when stratified by age, participants younger than 50 years of age had a lower risk of developing the disease at the same ferritin level compared to the entire prediabetes mellitus women participants.

Discussion

In this study, we found that the serum ferritin level of men is generally higher than that of women, and maintaining low levels of ferritin can reduce the risk of developing diabetes mellitus. Median ferritin levels were lowest in women younger than 50 with prediabetes mellitus. The previous study had been showed that a significant association of ferritin concentration and the risk of diabetes according to gender [28]. Ford also found that elevated stored iron was associated with an increased risk of developing T2DM in women [29]. Kato found that the average serum ferritin concentration in postmenopausal women was more than twice that of premenopausal women [30].

Estrogen can affect iron storage by regulating iron responsive elements in the body. That is, a decrease in estrogen levels leads to a decrease in iron-responsive elements, which leads to an increase in iron stores in the body and an increase in serum ferritin levels [30]. Before menopause, women lose some iron each month

Table 1 Basic characteristics of the study population

Variables	Total	< 20 ng/ml	20-<40 ng/ml	40-<60 ng/ml	60-<80 ng/ml	80-<100 ng/ml	100-<120 ng/ml	120-<140 ng/ml	140-<160 ng/ml	160-<180 ng/ml	180-<200 ng/ml	> 200 ng/ml	*P*-value
Percent of all adults (%)	100	12.2	12.8	13	12.1	9.4	7.9	5.8	4.6	3.4	2.5	16.2	< 0.001
Gender(%)													< 0.001
Men	46.5	9.6	16.3	34.3	45	51.9	60.3	66.7	67.1	69	75.4	76.9	
Women	53.5	90.4	83.7	65.7	55	48.1	39.7	33.3	32.9	31	24.6	23.1	
Age(years)	50.27 ± 15.04	41.64 ± 12.66	45.82 ± 14.84	50.09 ± 14.87	53.19 ± 15.14	52.84 ± 14.74	53.75 ± 14.50	53.18 ± 14.79	53.88 ± 15.47	54.69 ± 13.21	50.66 ± 14.96	51.97 ± 14.32	< 0.001
BMI(kg/m2)	23.38 ± 3.48	22.79 ± 3.46	22.75 ± 3.28	23.14 ± 3.42	23.31 ± 3.54	23.17 ± 3.37	23.49 ± 3.50	23.37 ± 3.32	23.38 ± 3.43	23.90 ± 3.62	24.37 ± 3.57	24.37 ± 3.48	< 0.001
Glucose(mmol/L)	4.87 ± 1.38	4.87 ± 0.84	4.87 ± 0.98	4.84 ± 1.06	4.87 ± 1.18	4.81 ± 1.23	4.89 ± 1.17	4.83 ± 1.46	4.90 ± 1.46	4.87 ± 1.75	4.92 ± 1.59	4.93 ± 2.16	< 0.001
Insulin(μIU/ml)	14.39 ± 22.32	12.81 ± 20.21	13.00 ± 15.58	12.94 ± 12.40	15.26 ± 32.60	15.00 ± 29.69	13.96 ± 14.33	15.35 ± 34.25	12.59 ± 8.83	16.05 ± 20.04	15.49 ± 19.39	16.69 ± 21.18	< 0.001
LDL-C(mmol/L)	2.98 ± 0.98	2.76 ± 0.83	2.85 ± 0.83	2.96 ± 0.91	3.06 ± 1.03	3.01 ± 0.92	3.06 ± 1.05	3.05 ± 0.96	3.09 ± 1.01	3.07 ± 0.96	3.01 ± 0.99	3.06 ± 1.15	< 0.001
HDL-C(mmol/L)	1.44 ± 0.48	1.50 ± 0.39	1.48 ± 0.36	1.48 ± 0.45	1.46 ± 0.42	1.45 ± 0.49	1.42 ± 0.62	1.39 ± 0.38	1.40 ± 0.40	1.46 ± 0.76	1.33 ± 0.39	1.34 ± 0.58	< 0.001
TC(mmol/L)	4.86 ± 1.01	4.56 ± 0.94	4.64 ± 0.91	4.78 ± 0.96	4.89 ± 0.98	4.87 ± 0.98	4.91 ± 1.00	4.96 ± 0.98	5.02 ± 1.09	5.07 ± 1.02	5.00 ± 0.98	5.14 ± 1.08	< 0.001
TG(mmol/L)	1.67 ± 1.47	1.28 ± 0.95	1.33 ± 1.12	1.41 ± 1.11	1.52 ± 1.05	1.58 ± 1.29	1.63 ± 1.06	1.81 ± 1.51	1.82 ± 1.61	1.99 ± 1.64	2.03 ± 1.61	2.43 ± 2.22	< 0.001
Education(%)													< 0.001
0–9 years	76.3	76.7	76.9	76.4	78.8	76.5	75.4	78.5	75.7	77.4	72.9	73.4	
10–12 years	18.8	19	19	18.2	15.5	17.8	20	19.2	17.8	17.8	20.8	21.4	
13 years	4.9	4.3	4.1	5.4	5.7	5.7	4.7	2.3	6.6	4.9	6.3	5.2	
Smoking status(%)													< 0.001
Never	69.1	92.3	88.4	75.4	71.5	67.2	58.9	55.6	57.7	55.4	49.3	50.3	
Former	3.2	1.1	1.8	2.8	3.6	3.3	4.5	4.5	5	4.9	4.3	4	
Current	27.6	6.7	9.8	21.9	24.9	29.5	36.6	39.9	37.3	39.7	46.4	45.7	
Hypertension(%)													< 0.001
No	86.7	94.1	89.5	88.5	83.5	83.3	84.1	85.3	85.1	81.9	87	85.2	
Yes	13.2	5.6	10.5	11.4	16.4	16.5	15.7	14.7	14.9	18.1	13	14.7	

Abbreviation: BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride

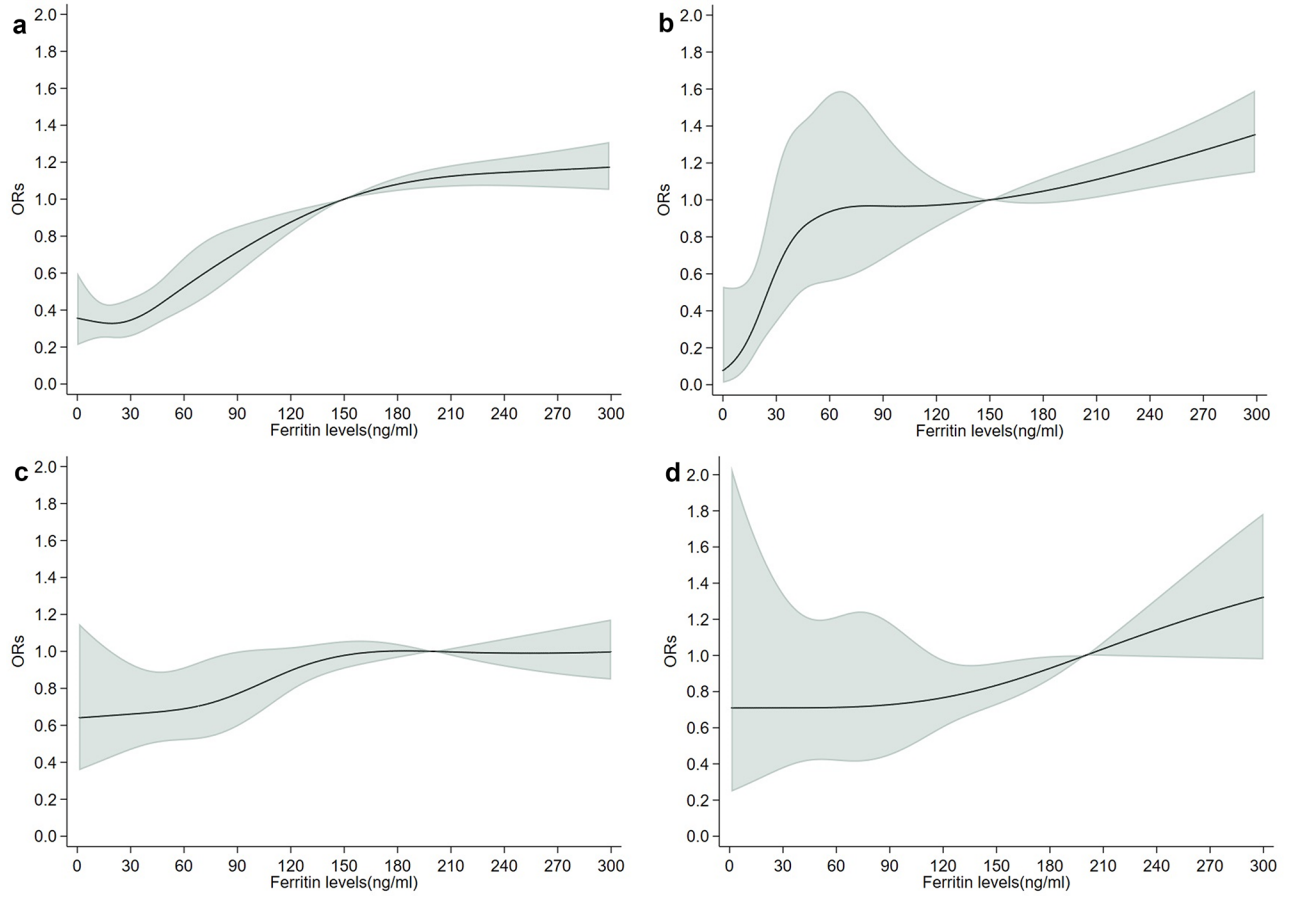

Fig. 1 Adjusted ORs (95%CI) for prediabetes in adult women (**a**) and men (**c**) and diabetes in adult women (**b**) and men (**d**) across the levels of ferritin

Table 2 Adjusted ORs (95%CI) for prediabetes across the levels of ferritin in adults

Levels of ferritin(ng/ml)	Men			Women		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
< 20	0.75(0.35,1.59)	0.85(0.40,1.83)	0.88(0.41,1.88)	0.89(0.61,1.30)	1.01(0.68,1.49)	1.01(0.68,1.49)
20-<40	0.76(0.42,1.37)	0.83(0.46,1.50)	0.81(0.45,1.47)	**0.61(0.41,0.90)***	0.70(0.48,1.04)*	0.69(0.46,1.03)
40-<60	0.55(0.33,0.91)*	0.60(0.36,0.99)*	**0.59(0.35,0.98)***	1.08(0.76,1.54)	1.10(0.77,1.58)	1.11(0.77,1.59)
60-<80	Reference	Reference	Reference	Reference	Reference	Reference
80-<100	1.12(0.73,1.73)	1.15(0.75,1.79)	1.16(0.75,1.80)	1.36(0.93,1.98)	1.42(0.97,2.08)	1.42(0.97,2.09)
100-<120	1.15(0.75,1.76)	1.14(0.74,1.76)	1.11(0.72,1.71)	1.24(0.81,1.89)	1.20(0.78,1.85)	1.19(0.77,1.84)
120-<140	1.01(0.63,1.61)	0.98(0.61,1.57)	0.95(0.59.1.54)	1.14(0.69,1.90)	1.23(0.74,2.05)	1.22(0.73,2.04)
140-<160	1.43(0.90,2.27)	1.44(0.90,2.31)	1.44(0.90,2.31)	1.79(1.09,2.93)*	1.84(1.11,3.04)*	**1.83(1.10,3.03)***
160-<180	1.37(0.83,2.26)	1.30(0.79,2.16)	1.28(0.78,2.14)	2.26(1.31,3.88)*	2.08(1.19,3.63)*	2.02(1.16,3.54)*
180-<200	1.17(0.65,2.11)	1.03(0.56,1.88)	1.00(0.55,1.83)	3.34(1.76,6.31)*	2.71(1.42,5.17)*	2.66(1.39,5.09)*
> 200	2.20(1.56,3.08)*	1.91(1.35,2.69)*	**1.85(1.31,2.62)***	2.26(1.58,3.25)*	2.11(1.46,3.06)*	2.13(1.47,3.08)*
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

*$P<0.05$. Model 1 adjusted multivariable logistic regression models for age. Model 2 adjusted for age and bmi. Model 3 adjusted for age, bmi, current smoking, hypertension and educational level

from menstruation, while iron accumulates in the body after menopause due to lack of menstruation. This accumulation increases serum ferritin levels by 2–3 times in postmenopausal women [31, 32]. The average age of menopause for Chinese women is around 50 years old [33]and women younger than 50 had a lower risk than women as a whole, possibly because the majority of women before age 50 were premenopausal. Therefore, attention to ferritin levels in health check-up programs may be beneficial to better prevent the occurrence of diabetes in postmenopausal women.

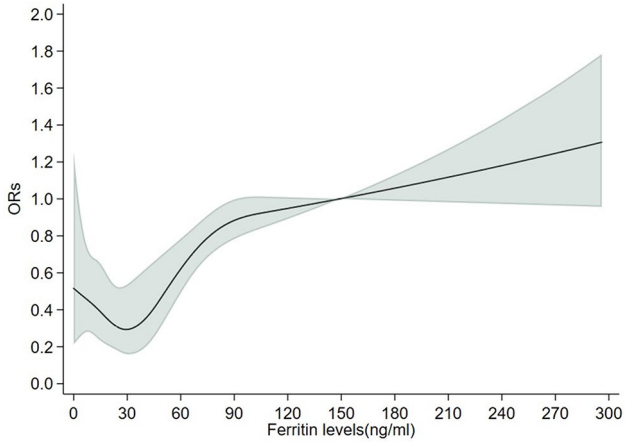

Fig. 2 Adjusted ORs (95%*CI*) for prediabetes across the levels of ferritin in adult women younger than 50

However, the amount of blood lost during menstruation varies from person to person, and many women with small cell anemia have low levels of ferritin. Because the CHNS database lacks this part of the information on whether women have small cell anemia, it is not possible to exclude the effect of this population, which may affect the generality of the results. In addition, the number of diabetes mellitus and prediabetes mellitus in the sample population is much lower than other reports, which may be mainly due to the different definitions of diabetes mellitus and the different age structure of the study population. Unlike previous studies that used oral glucose tolerance tests to diagnose diabetes, CHNS defined diabetes by fasting blood glucose or current use of antidiabetic drugs, which would significantly underestimate the true number of people with diabetes. Due to the limited number of people with T2DM, the tables was mainly focused on participants with prediabetes mellitus. Especially for the women participants stratified by age, the restricted cubic spline graph was used for comparison and analysis.

Our research is a cross-sectional study, so we can't infer causality. Nevertheless, the advantage of our study is that the sample size is large, and the threshold effect relationship is discussed, which has not been addressed in previous studies. It should be noted that elevated serum ferritin levels can be attributed to various causes, including excessive iron intake or pathological alterations within the body. Therefore, the treatment of high serum ferritin levels should be individualized based on the specific etiological factors. In summary, serum ferritin serves as a robust marker for predicting the risk of type T2DM, yet its underlying biological mechanism demands further investigation and exploration. Our study suggests an optimal range for maintaining serum ferritin levels in prediabetic patients, and individuals with iron overload should be vigilant in preventing the development of T2DM.

Conclusions

In conclusion, we found that for the whole population, the risk of pathoglycemia increased when ferritin levels were greater than 140 ng/ml. In thewoman population, maintaining the serum ferritin level between 20 and 40 ng/ml is beneficial for reducing the risk of developing diabetes. In the man population, maintaining the ferritin level between 40 and 60 ng/ml is conducive to reducing the risk of diabetes.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
YCY was responsible for drafting the article and for overall content. LJT assisted with the drafting and revision of the article. YJY, GYP, LGH, LXT provided input to the study concept and design, critically reviewed the results of analyses, and reviewed and contributed significantly to article revision. Statistical analyses were performed by LC and YCY, and LXQ provided full access to the study data as well as study oversight and article revision. All authors have read and agreed to the published version of the manuscript.

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Data availability
The CHNS data that support the findings of this study are available upon application from https://www.cpc.unc.edu/projects/china.

Declarations

Ethics approval and consent to participate
The analysis was based on the publicly available database CHNS. The CHNS was approved by the Institutional Review Committees of the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. All participants provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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