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Association between dietary intake of iron and heart failure among American adults: data from NHANES 2009–2018

Yajie Wang[1], Jie Yang[2*], Lei Yang[1] and Liang Zheng[2]

Abstract

Patients with heart failure (HF) often experience iron deficiency. Intravenous iron supplementation has been widely used in clinical practice to facilitate the treatment of HF. However, the association between dietary iron intake and HF still needs to be elucidated. This study aimed to evaluate the impact of dietary iron intake on HF in American adults. The data were extracted from the National Health and Nutrition Examination Survey (NHANES) 2009–2018. Iron dietary intake data were obtained from two 24-h dietary recall interviews. We examined baseline data and HF prevalence in different quartile groups of dietary iron intake (Q1–Q4). Two logistic regression models were established to evaluate the impact of Q4 (highest iron consumption) on the risk of HF. The study included 20,853 American adults (age ≥ 20 years). The participants with the highest iron intake (Q4) had the lowest prevalence of HF (Q1: 3.25%, Q2: 2.18%, Q3: 1.92%, Q4: 1.72%; $P < 0.001$). After adjusting for possible confounding factors, the highest iron intake (Q4) was significantly associated with a reduced risk of HF compared with that of Q1 (odds ratio 0.58, 95% confidence interval 0.41–0.82; $P = 0.003$). This association remained stable in subgroups of women, current smokers, and Hispanics other than Mexican Americans. This study revealed that the dietary intake of iron was negatively associated with HF in adults without exceeding the tolerable maximum daily intake of 45 mg/day.

Keywords Heart failure, Iron, Dietary, Intake, NHANES

Introduction

Heart failure (HF) is a complex syndrome that often occurs in the terminal stage of various cardiovascular diseases [1]. It is characterized by high morbidity, high cost, high mortality, poor quality of life, and poor prognosis. It affects more than 64 million people globally and has become an increasingly serious global public health burden [2]. Therefore, curbing the occurrence and progression of HF has become crucial.

Dietary patterns and dietary supplements have been reported to be closely associated with the progression of HF [3]. Several studies have indicated that the Mediterranean diet can help prevent HF [4–6]. Reports have shown that increasing the intake of anthocyanins in the diet can reduce HF-related events [7]. Clinical trials have reported that the intake of some nutrients, such as hawthorn, coenzyme Q10, vitamin D, and omega-3 polyunsaturated fatty acids (PUFAs), is associated with improvements in functional parameters (ejection fraction, output per beat, and cardiac output) in patients with HF, with few side effects [8]. Iron is an essential nutrient in the human body. Its metabolism affects the normal

*Correspondence:
Jie Yang
sumuzheyangjie@163.com
[1]First College of Clinical Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250014, Shandong, China
[2]Department of Cardiology, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, 16369 Jingshi Road, Jinan City 250014, Shandong, China

function of cells, mediating respiratory oxidation, participating in productivity and metabolism, regulating body temperature, maintaining immune function, promoting physical development, and so on. Iron deficiency is believed to be associated with insufficient intracellular energy production in myocardial cells, leading to an inappropriate imbalance between the parameters required for sufficient cardiac perfusion and output, resulting in HF [9]. Patients with HF tend to be iron deficient because of traditional restrictive dietary guidelines and decreased appetite and dyspepsia caused by intestinal congestion [10]. Iron deficiency, with or without anemia, affects 37–61% of patients with chronic HF and results in exercise limitation, reduction in quality of life, increase in hospitalization rates, and a 40–60% increased risk of death [11]. Oral iron is often associated with a range of adverse effects, such as nausea, epigastric pain, diarrhea, and black stools [12]. The european society of cardiology (ESC) guidelines recommend that patients hospitalized for HF with iron deficiency should receive intravenous iron therapy to reduce the risk of readmission in the near future [13]. A meta-analysis reported that intravenous iron supplementation has a beneficial effect on cardiovascular mortality [14]. Intravenous iron has been widely used in the clinical treatment of HF. However, the relationship between dietary iron intake and heart failure has not been reported in detail. This study aimed to evaluate the association between dietary iron intake and HF in United States (US) adults. We tested our hypothesis by using the National Health and Nutrition Examination Survey (NHANES) 2009–2018 database.

Methods

Study population

The NHANES is a nationally representative survey that assesses the health and nutritional status of non-institutionalized civilians in the U.S. It includes demographic data, dietary data, physical examinations, and health-related information. It combines interviews initially conducted at the participant's home, followed by health examinations conducted at the Mobile Examination Center. The sampling methods, weights, and details of data collection can be found on its official website [15]. To ensure the representativeness and validity of our research findings, we considered the sampling and weighting procedures in our study. All analyses used weighted samples ("wtdr2d"). Furthermore, stratification and primary sampling units (PSUs) were incorporated into our analysis to account for the complex survey design of the NHANES. Stratification ensures that subgroups within the population are adequately represented, whereas PSUs help maintain the integrity of the sampling frame and reduce sampling error. By combining these factors, we were able to generate estimates that are more accurately representative of the U.S. population. The present study was based on the analysis of NHANES data from 2009 to 2018. The NHANES research plan was approved by the Ethics Review Committee of the National Center for Health Statistics (NCHS). Prior to the interview and inspection steps, each participant signed an informed consent form.

Among the 49,693 participants in the NHANES database from 2009 to 2018, 28,835 were adults (age≥20), and 22,119 had complete dietary iron data and HF questionnaire data. Among these 22,119 subjects, 727 were excluded because their iron intake exceeded the tolerable upper intake level of >45 mg/day [16, 17]. In addition, we excluded pregnant and breastfeeding populations because pregnancy and breastfeeding might alter indicators such as dietary intake and body weight. An extremely small number of missing covariates, such as educational level and smoking were also excluded. Our study ultimately included 20,853 American adult participants. (Fig. 1)

Assessment of dietary iron intake

Dietary iron intake was assessed via two 24-h dietary recall interviews. The Mobile Examination Center was the site of the initial dietary interview, and the second interview was conducted telephonically after 3–10 days. Each participant's total daily energy and nutrient intake from food and beverages were calculated, along with data indicating whether their food intake was normal. These details were compiled into the total nutrient intake file for analysis. The 24-h dietary supplement use section was used to obtain information from NHANES participants on the type and amount of dietary supplements consumed 24 h before the interview and to estimate the amount of nutrients consumed from these dietary supplements to estimate nutrient intake. In accordance with the NHANES protocol, the mean total nutrient intake from two 24-h dietary recall interviews and the mean total dietary supplements from two 24-h dietary supplement uses were combined to assess nutrient intake as accurately as possible. Only participants who provided complete data for both 24-hour dietary recall interviews and two 24-hour dietary supplement uses were included in the study. For these participants, the average of the two assessments of total dietary iron intake was calculated and used in the analysis. In this study, dietary iron intake was further divided into quartiles.

Assessment of HF

In accordance with previous NHANES-based studies, participants who were asked in the health questionnaire "Has a doctor or other health professional ever told you that you had congestive HF?," and those who answered "yes" were considered to have HF [18].

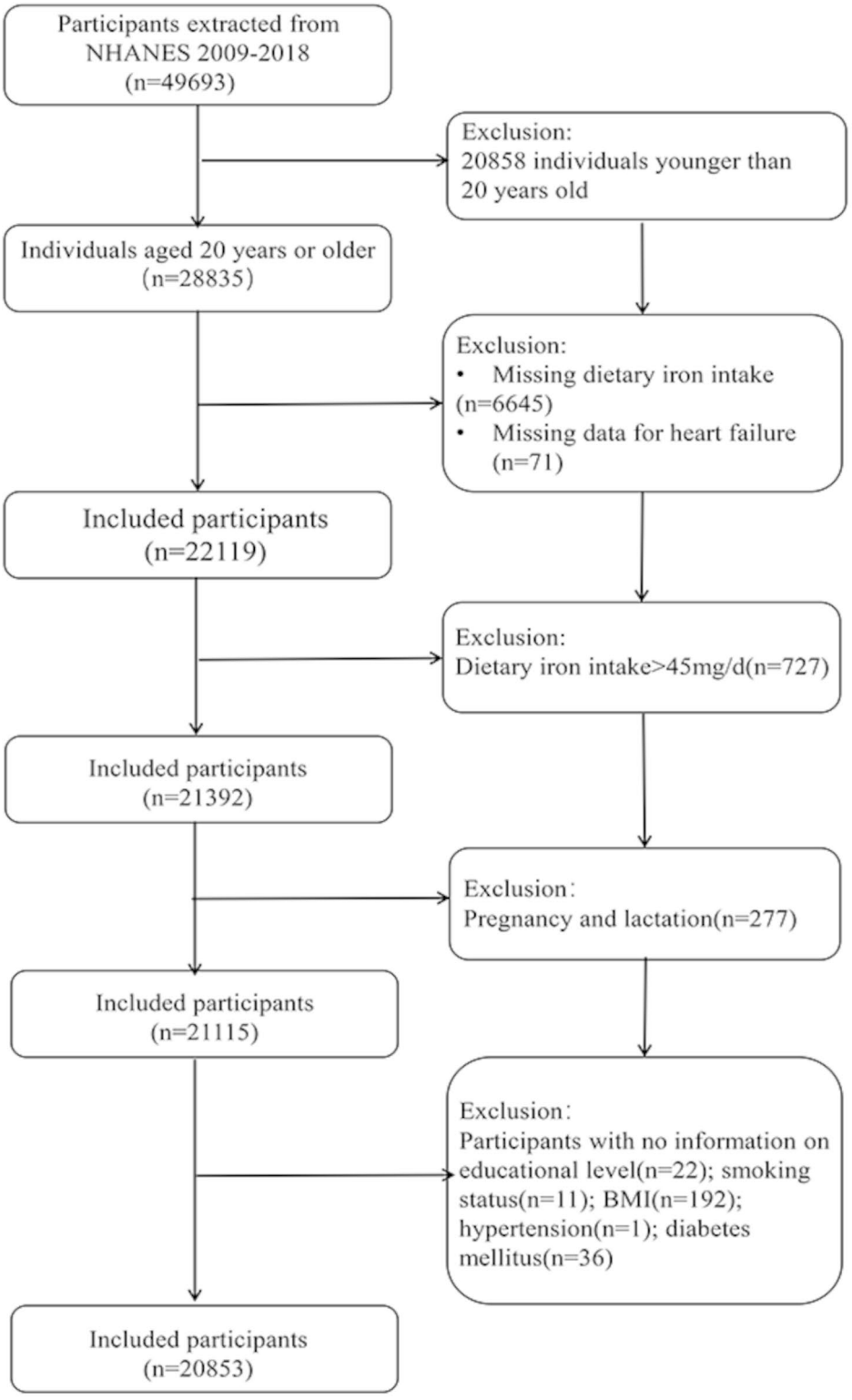

Fig. 1 Flow chart of participant selection. Abbreviations: NHANES, National Health and Nutrition Examination Survey

Covariates

We screened nine possible confounding factors related to HF and dietary iron: age, gender, race/ethnicity, educational level, smoking, alcohol consumption, body mass index (BMI), hypertension, and diabetes mellitus (DM). Ethnicity was divided into five categories: non-Hispanic white, non-Hispanic black, Mexican American, other Hispanics, and others. Educational level was divided into three categories: college or above, high school or equivalent, and less than high school. The degree of smoking was classified according to the following indicators: [1] never: smoked fewer than 100 cigarettes in life; [2] former: smoked more than 100 cigarettes in life but did not smoke at all; [3] now: has smoked more than 100 cigarettes in life and smokes some days or every day. The daily alcohol consumption data are the average of the alcohol consumption data from the two 24-hour dietary recall interviews. BMI was calculated by dividing weight in kilograms by the square of height in meters and then rounding it to one decimal place. Hypertension was defined when an individual met at least one of the following three criteria: [1] used antihypertensive drugs [2], was diagnosed with high blood pressure by a doctor, and [3] had a mean blood pressure higher than 130/80 mmHg. The average blood pressure was obtained as described in the NHANES. It was calculated via the following protocol: the diastolic reading with zero was not used to calculate the diastolic average. If all diastolic readings were zero, the average was zero. If only one blood pressure reading was obtained, it was considered the average. In the case of more than one blood pressure reading, the first reading was always excluded from the average. There were four types of diabetes: none, impaired glucose tolerance, impaired fasting glucose, and DM. DM was defined in this article as meeting at least one of the following criteria: having been diagnosed with diabetes by the doctor, glycosylated hemoglobin type A1C (HbA1c) (%) ≥6.5, fasting glucose (mmol/L) ≥7.0, random blood glucose (mmol/L) ≥11.1, 2-h oral glucose tolerance test blood glucose (mmol/L) ≥11.1, or the use of diabetes-related medication or insulin. BMI was measured by experts using routine physical examination techniques.

Statistical analyses

We used the R programming language (version 4.3.2) for all the statistical analyses. The statistical significance was determined as two-tailed, with $P<0.05$. The analysis method was similar to that used in a previous study [19] as follows: Participants were divided into four groups according to the quartile of iron intake (Q1–Q4). The continuous variables associated with the covariates are expressed as the means (standard errors), and the categorical variables are expressed as quantities (percentages). The baseline differences between the continuous and categorical variables were assessed using ANOVA and $\chi 2$ tests, respectively. We adjusted the weights in the analysis to prevent oversampling and reduce nonresponse. Univariate and multivariate logistic regression models were used to analyze the relationships between HF and iron intake in all participants and different subgroups, taking covariates into account, and were divided into three models: the model with unadjusted covariates; Model 1 adjusted for gender, age, race and education level; and Model 2 was fully adjusted for covariates. To assess the dose–response relationship between dietary iron intake and heart failure, restricted cubic spline (RCS) was used. In addition, a stratified analysis was performed, taking into account age, gender, ethnicity, smoking, alcohol consumption, hypertension and DM.

Results

Baseline characteristics of the study population

The study recruited 20,853 participants (Fig. 1), including 655 (2.23%) patients with HF. The average age of all participants was 47.86 (0.30) years; men accounted for 48.99%, and women accounted for 51.01% of the study population. The baseline characteristics were based on the quartiles of dietary iron intake (Q1: 0.13–9.735 mg; Q2: 9.735–13.54 mg; Q3: 13.54–19.07 mg; and Q4: 19.07–44.96 mg) (Table 1). Compared with those in the other quartiles, individuals in the Q4 quartile were more likely to be older, male, non-Hispanic white, and college educated. In terms of traditional risk factors for cardiovascular diseases, the Q4 group presented lower BMIs ($P=0.002$) and smoking ($P<0.001$). The prevalence of HF was lower in the Q4 subgroup (Q1: 3.25%, Q2: 2.18%, Q3: 1.92%, and Q4: 1.72%; $P<0.001$) (Fig. 2). However, no significant difference was found in the prevalence of hypertension or diabetes (Table 1).

Association between dietary iron intake and HF

The results of the univariate logistic regression analysis for HF are presented in Supplementary Table S1. Dietary iron intake was negatively correlated with HF; alcohol consumption was positively correlated with HF; and age, smoking, BMI, hypertension, diabetes, and other cardiovascular disease risk factors were positively correlated with HF. Table 2 presents the results of a multivariate logistic regression analysis of the relationship between dietary iron intake and HF. Compared with those in the Q1 group, participants with the highest dietary iron intake (Q4) had a lower prevalence of HF in the unadjusted model (OR 0.52, 95% CI 0.37–0.74; $P<0.001$). The highest dietary iron intake (Q4) was independently associated with a lower prevalence of HF, adjusting for age, gender, race, educational level, smoking, alcohol consumption, BMI, hypertension, and diabetes [odds ratio (OR) 0.58, 95% CI 0.41–0.82; $P=0.003$]. In addition, we

Table 1 Baseline characteristics according to the dietary iron intake quartiles

Variable	Total	Q1 [0.13,9.74]	Q2 (9.74,13.54]	Q3 (13.54,19.07]	Q4 (19.07,44.96]	*p* value
Age	47.86(0.30)	47.78(0.44)	47.45(0.40)	47.93(0.39)	48.24(0.43)	0.43
Gender						< 0.001
Female	10752(51.01)	3488(67.38)	2887(55.37)	2273(43.62)	2104(40.24)	
Male	10101(48.99)	1728(32.62)	2327(44.63)	2938(56.38)	3108(59.76)	
Race/ethnicity						< 0.001
Non-Hispanic White	8641(65.76)	1913(61.99)	2073(63.59)	2161(66.37)	2494(70.35)	
Non-Hispanic Black	4563(11.33)	1478(15.88)	1132(11.87)	1046(9.90)	907(8.35)	
Mexican American	2907(8.59)	651(7.79)	719(8.64)	790(9.09)	747(8.76)	
Other Hispanic	2124(5.87)	595(6.70)	562(6.08)	525(5.80)	442(5.05)	
Other Race	2618(8.45)	579(7.64)	728(9.82)	689(8.84)	622(7.49)	
Educational level						< 0.001
College or above	11683(63.62)	2591(56.58)	2978(64.78)	3046(65.85)	3068(66.37)	
High school or equivalent	4697(22.53)	1245(25.84)	1143(21.79)	1141(21.66)	1168(21.24)	
Less than high school	4473(13.85)	1380(17.58)	1093(13.43)	1024(12.49)	976(12.39)	
Body mass index, kg/m2	29.26(0.11)	29.55(0.15)	29.23(0.16)	29.49(0.16)	28.80(0.18)	0.002
HeartFailure						< 0.001
No	20198(97.77)	4994(96.75)	5047(97.82)	5074(98.08)	5083(98.28)	
Yes	655(2.23)	222(3.25)	167(2.18)	137(1.92)	129(1.72)	
Alcohol consumption, g/day	9.55(0.30)	8.02(0.52)	10.26(0.62)	10.42(0.62)	9.34(0.49)	0.01
Smoking						< 0.001
Never	11738(56.55)	2899(54.16)	3020(57.84)	2964(57.60)	2855(56.38)	
Former	5050(24.91)	1111(21.86)	1193(24.65)	1350(25.72)	1396(26.95)	
Now	4065(18.54)	1206(23.98)	1001(17.50)	897(16.68)	961(16.68)	
Hypertension						0.5
No	9389(50.08)	2243(49.95)	2380(51.44)	2392(49.50)	2374(49.51)	
Yes	11464(49.92)	2973(50.05)	2834(48.56)	2819(50.50)	2838(50.49)	
DM						0.05
No	15236(78.71)	3709(78.46)	3779(77.66)	3835(78.70)	3913(79.89)	
IGT	687(2.89)	157(2.40)	186(3.07)	180(3.45)	164(2.61)	
IFG	957(4.39)	230(3.61)	260(4.98)	233(4.90)	234(4.04)	
DM	3973(14.01)	1120(15.53)	989(14.30)	963(12.94)	901(13.47)	

Abbreviations: DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NHANES, National Health and Nutrition Examination Survey

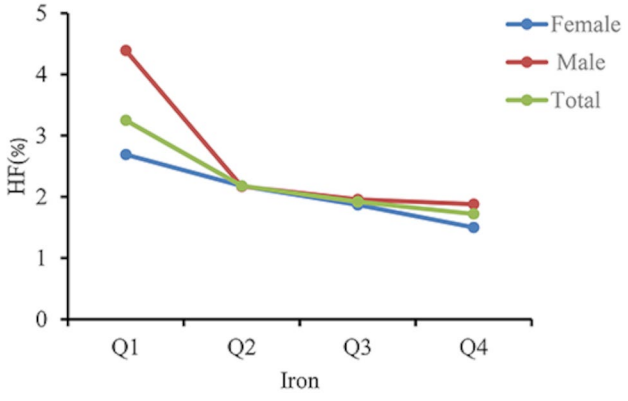

Fig. 2 Proportion of HF in the quartile of iron in American adults from NHANES 2009–2018. Abbreviations: HF, heart failure; NHANES, National Health and Nutrition Examination Survey

converted dietary iron intake into a categorical variable (Q1–Q4), indicating a significant trend *P* in both the unadjusted (*P* for trend < 0.001) and adjusted (*P* for trend < 0.001) models.

The dose–response relationship between dietary iron intake and HF was analyzed (Fig. 3). A linear relationship existed between dietary iron intake and HF when the tolerable daily intake of dietary iron did not exceed the maximum dosage (45 mg/day). The prevalence of HF decreased significantly with increasing dietary iron intake.

Subgroup analyses

We further investigated the associations between dietary iron intake and HF in different populations through subgroup analysis (Fig. 4). The entire population was stratified by age, gender, ethnicity, smoking, alcohol consumption, and disease state. The association remained stable for women (OR 0.95, 95% CI 0.90–1.00), other

Table 2 Odds ratio (95%CI) for heart failure in American adults from the 2009–2018 NHANES according to quartile of iron analyzed by weighted logistic regression

Character	Unadjusted model		Model 1		Model 2	
	95%CI	*P*	95%CI	*P*	95%CI	*P*
Quartile 1	ref		ref		ref	
Quartile 2	0.66(0.50,0.89)	0.01	0.72(0.53,0.98)	0.04	0.79(0.58,1.08)	0.13
Quartile 3	0.58(0.44,0.78)	< 0.001	0.62(0.47,0.82)	0.001	0.64(0.48,0.85)	0.003
Quartile 4	0.52(0.37,0.74)	< 0.001	0.53(0.37,0.75)	< 0.001	0.58(0.41,0.82)	0.003
p for trend		< 0.001		< 0.001		< 0.001

Unadjusted model: univariate logistic regression analyses. Model 1 was adjusted for age, gender, race/ethnicity, and educational level. Model 2 was adjusted for variables included in Model 1 and smoking, alcohol, BMI, hypertension and DM. Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio

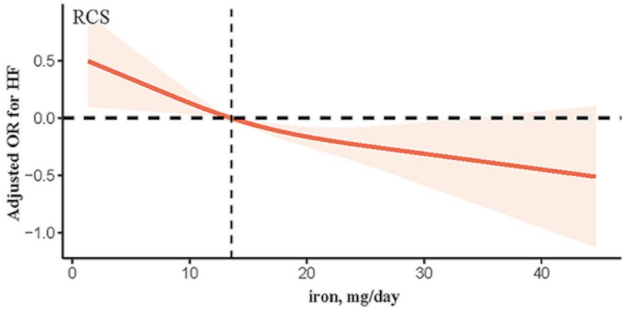

Fig. 3 The restricted cubic spline model revealed a dose–response relationship between iron intake and HF among American adults from NHANES 2009–2018. The restricted cubic spline model was adjusted for age, gender, race, educational level, smoking status, alcohol consumption, BMI, hypertension, and diabetes. The dotted line represents the corresponding 95% confidence interval. Abbreviations: BMI, body mass index; HF, heart failure; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; RCS, restricted cubic spline

Hispanics (OR 0.85, 95% CI 0.78–0.92), and current smokers (OR 0.89, 95% CI 0.83–0.96).

Discussion

This novel study demonstrated a relationship between dietary iron intake and HF. In NHANES 2009–2018, dietary iron intake was inversely associated with HF at concentrations not exceeding 45 mg/day. After adjusting for possible confounding factors, dietary iron intake was negatively associated with HF risk. This negative association remained stable in the subgroups of women, current smokers, and other Hispanics. In addition, Q4 iron intake was different between patients with and without HF; it was greater in patients without HF (Supplementary Table S2).

Cardiovascular diseases, including HF, impose a significant social burden. Additionally, the role of dietary habits in preventing and treating cardiovascular diseases has gradually received increasing attention from the public. A study in the U.S. revealed that increased iron intake reduced the risk of all-cause mortality [20]. Our study was novel in revealing the association between dietary iron intake and the presence of HF in the general population.

Although our clinical study revealed an association between dietary iron intake and HF, the underlying mechanism remains to be elucidated. Iron facilitates redox reactions, which is crucial for oxygen metabolism and oxidative phosphorylation in the heart [21, 22]. Studies have suggested that chronic HF is a chronic inflammatory disease. Iron homeostasis is abnormal in patients with HF, and high concentrations of inflammatory cytokines increase the concentration of hepcidin, leading to iron chelation (functional iron deficiency) in reticuloendothelial system cells [23]. Excess iron might trigger cellular senescence, causing organ dysfunction by generating reactive oxygen species, which could further lead to heart disease [24]. Ischemic myocardial cells undergo a nonapoptotic and iron-dependent form of regulated cell death, named ferroptosis, in HF caused by myocardial infarction [25]. Free iron reacts with oxygen to generate reactive oxygen species, which can damage lipids and lead to lipid peroxidation, ultimately resulting in ferroptosis and even cell death [26, 27]. Importantly, studies have confirmed that among elderly men aged 75 and above, a higher intake of heme iron is associated with an increased risk of congestive cardiac failure [28]. The clinical symptoms of iron deficiency, including fatigue, are often confused with those of the primary disease because they are not specific. Evaluating iron parameters in patients with chronic inflammatory diseases is still insufficient and deserves further exploration. Excess iron can increase the risk of cancer, iron overload cardiomyopathy, and other diseases [29]. Therefore, iron intake should not exceed the maximum tolerable daily amount of 45 mg/day, and only accurate control of iron reserves can scientifically prevent diseases.

This study had several limitations. First, while our current study provides valuable insights, it falls short of definitively establishing a cause–and–effect relationship between dietary iron and heart failure due to its cross-sectional nature. To truly understand the directionality of this association, larger-scale longitudinal studies, particularly cohort studies, are necessary. Second, the NHANES database did not provide data on brain natriuretic peptide levels or echocardiography data. Therefore, this

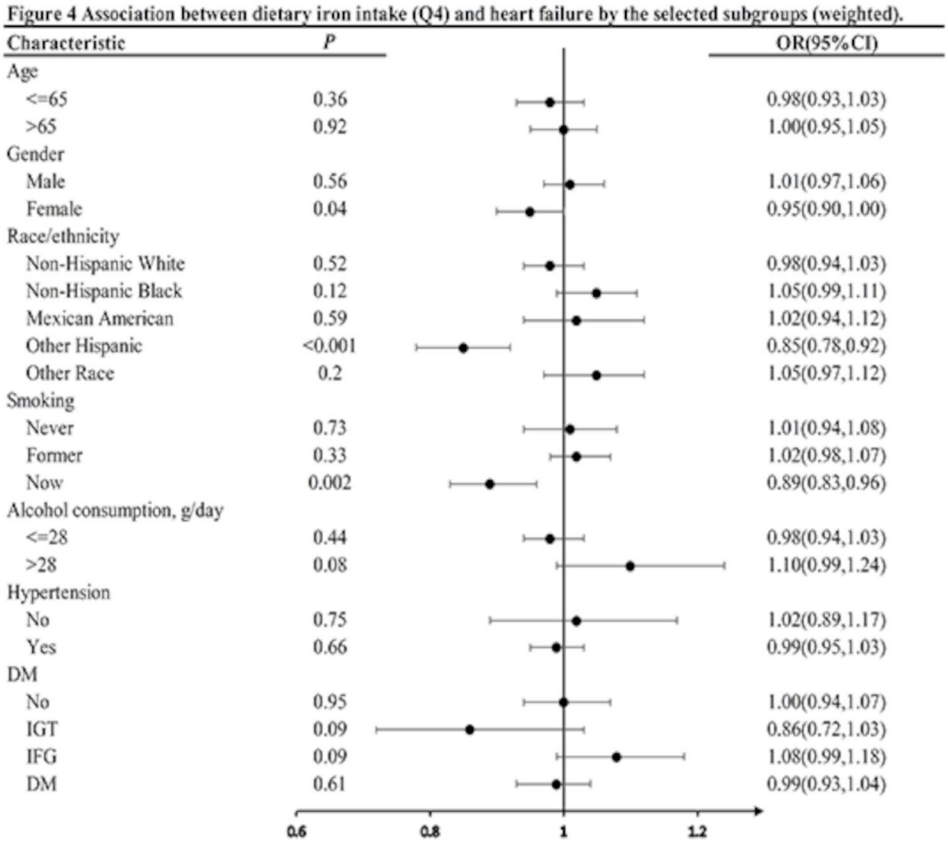

Fig. 4 Association between iron (Quartile 4) and heart failure in various stratifications. Abbreviations: CI, confidence interval; DM, diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OR, odds ratio

study could not further evaluate the relationship between dietary iron intake and HF severity. Third, the study focused on American adults and did not include teenagers or children. Consequently, the findings may not be applicable to the whole population.

Conclusions

The dietary intake of iron was inversely associated with HF when the maximum recommended daily intake of iron was not exceeded. On the basis of the current evidence, there is insufficient support for the use of oral iron supplementation in patients with HF owing to a lack of demonstrated benefits. More experimental and clinical studies are needed to determine the exact relationship between dietary iron intake and HF.

Abbreviations

BMI	Body mass index
CI	Confidence interval
DM	Diabetes mellitus
HF	Heart failure
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio

Supplementary Information

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Supplementary Material 1

Author contributions

All authors contributed to the study conception and design. J.Y. and Y.W. designed the study. Y.W., L.Y. and L.Z. collected the data and drafted the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

Notably, the data collected adhered to the ethical guidelines set forth by the relevant institutional and/or national research committee, as well as the 1964 Helsinki declaration and its subsequent amendments or equivalent ethical

standards. This study protocol was reviewed and approved by the Ethics Review Committee of the National Center for Health Statistics (NCHS).

Informed consent
All research data are publicly available, and no research permission is needed.

Consent for publication
Not Applicable.

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