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Associations between dietary iron intake from different sources and non-alcoholic fatty liver disease in adults

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ABSTRACT

Background and Objectives: Non-alcoholic fatty liver disease (NAFLD) has become a worldwide public health problem. Current evidence on the association between dietary iron intake and the risk of NAFLD is limited. The present study aimed to investigate the associations of animal-derived dietary iron (ADDI) intake, plant-derived dietary iron (PDDI) intake, and the ratio of PDDI:ADDI with NAFLD risk among U.S. adult population. **Methods and Study Design:** This was a repeated cross-sectional study. Data were collected from the National Health and Nutrition Examination Survey (NHANES) 2007-2018. NAFLD was defined as a United States Fatty Liver Index ≥ 30 , and dietary iron intake was assessed through two 24-h dietary recall interviews. Logistic regression and restricted cubic spline models were applied to examine the associations between dietary iron intake from different sources and NAFLD risk. **Results:** A total of 9478 participants aged ≥ 20 years were enrolled in the present study. After adjustment for multiple confounding factors, relative to the lowest quartile, the odds ratio (OR) and 95% confidence interval (CI) of NAFLD for the highest quartile was 1.01(95% CI, 0.82-1.24) for ADDI intake, 0.82 (95% CI, 0.64-0.99) for PDDI intake, and 1.00 (95% CI, 0.81-1.24) for the PDDI: ADDI intake ratio. In stratified analysis by sex and age, the significantly negative associations of PDDI intake with NAFLD was observed in women and participants older than 45 years. Dose-response analyses indicated that NAFLD was negatively associated with PDDI intake in a non-linear manner. **Conclusions:** PDDI intake was negatively associated with NAFLD in U.S. adults.

Key Words: animal-derived iron, plant-derived iron, non-alcoholic fatty liver disease (NAFLD), dietary intake, National Health and Nutrition Examination Survey (NHANES)

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become one of the most common liver diseases worldwide¹ with an estimated prevalence of approximately 25% among adults.² NAFLD is considered to be the hepatic manifestation of metabolic syndrome³ and comprises a spectrum of liver damage ranging from simple hepatic steatosis to non-alcoholic steatohepatitis, liver fibrosis, cirrhosis, and eventually liver failure and hepatocellular carcinoma.⁴ NAFLD is associated with obesity,⁵ diabetes mellitus,⁶ and dyslipidemia.⁷ Nowadays, there is no acceptable medical treatment for NAFLD,⁸ it is necessary to identify potential modifiable factors to control or prevent the development of NAFLD.

Several dietary contributors have been linked to the development of NAFLD, for example, intakes of processed meat, fried foods and fructose-rich foods have been reported to be related to the increased risk of NAFLD,⁹⁻¹¹ whereas negative associations were observed between NAFLD and some micronutrients intakes, such as vitamin C, zinc and selenium.¹²⁻¹⁴ Iron is an essential trace element in humans and plays an important role in mediating electron transfer, oxygen transport and cellular respiration. However, free iron can produce reactive oxygen species through Fenton reaction (an advanced oxidation process (AOPs) in which ferrous ions react with hydrogen peroxide to produce hydroxyl radicals), which leads to cell and tissue damage.¹⁵ It has been reported that high iron exposure may cause hepatic oxidative stress, inflammation, lipid accumulation,^{7,16} which in turn increases the risk of NAFLD.^{17,18} A healthy individual absorbs a certain amount of iron from the diet each day to compensate for the non-specific iron loss caused by cell desquamation in the skin and intestines¹⁵ and several studies have explored the association between dietary iron intake and NAFLD. Giovanni Musso et al.¹⁹ found that dietary iron intake in the NAFLD group was lower than that in the control group, and a study by H. Cortez-Pinto et al.²⁰ showed the similar results. On the contrary, a case-control study conducted in China revealed that dietary iron intake was higher in patients with NAFLD compared with the controls.²¹ In addition, in a matched case-control study, both lean and obese patients with NAFLD had significantly higher dietary iron intake than controls.²² However, another case-control study in U.S. found no significant difference in dietary iron intake between NAFLD group and non-NAFLD group.²³ Obviously, available information on the relationship between dietary iron intake and the risk of NAFLD was inconsistent. Given that the absorption and metabolism of dietary iron from plant foods and animal foods are different, the associations between dietary iron intake from different sources and NAFLD may also be different. To date, none study has investigated the relationship between dietary iron intake from different sources and NAFLD. Therefore, using the data from the National Health and Nutrition Examination Survey (NHANES) 2007–2018, we evaluated the associations between animal-derived dietary iron (ADDI) intake, plant-derived dietary iron (PDDI) intake, and the PDDI: ADDI intake ratio and NAFLD in U.S. adults.

MATERIALS AND METHODS

Study population

The National Health and Nutrition Examination Survey (NHANES) was a two-year-cycle cross-sectional survey conducted by the Centers for Disease Control and Prevention (CDC), United States, which adopted a stratified multistage probabilistic sampling method to select a

representative sample of the civilian non-institutionalized US population. The data for our combined analyses were merged from six cycles (2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018) of NHANES (<https://www.cdc.gov/nchs/nhanes/>). A total of 59,842 participants were included in the 2007–2018 NHANES. We excluded 25,072 participants under the age of 20 and those with missed information to calculate the United States fatty liver index (USFLI; $n = 20,522$). Furthermore, we also excluded individuals positive for hepatitis B surface antigen and hepatitis C virus antibodies ($n=583$), with elevated alcohol intake (≥ 10 g/day for females and ≥ 20 g/day for males; $n = 2,025$). Pregnant women ($n = 132$) and participants with unreliable or incomplete dietary recall ($n = 1,915$), with average energy intake $>$ mean + 3 SD (4,261 kcal) or $<$ mean – 3 SD (0 kcal) ($n = 115$) were also excluded. Finally, 9478 individuals (4,271 men and 5,017 women) were included in our analysis (Figure 1). The Re-view Board of the National Center for Health Statistics granted the approval for using the NHANES data, and all participants provided informed consent.

NAFLD measurement

We defined NAFLD on the basis of the USFLI. We calculated USFLI based on race, age, gamma glutamyl transferase level, waist circumference, fasting insulin level, and fasting blood glucose level, and defined a value of USFLI ≥ 30 as NAFLD. The USFLI has been validated and correlates well with the presence of NAFLD diagnosed through ultrasound in the multiethnic US general population.²⁴

Dietary iron intake

The dietary intake of iron was obtained from two 24-h dietary recall interviews, which were conducted by trained dietitians. The first dietary recall interview was conducted in person in the mobile examination centre, and the second interview was conducted via telephone 3–10 days later. If individuals completed both 24-h recalls, the average dietary iron intake for the two 24-h interviews was used.²⁵ Otherwise, we used single dietary recall data. Different sources of iron intake are identified by food codes. ADDI (meat, poultry, and fish; eggs; and dairy products) intake, PDDI (cereals; beans; vegetables; and fruits) intake and the PDDI:ADDI intake ratio were identified and considered as predominant exposures.²⁶

Covariates

To control potential confounders, factors that had been shown to be associated with dietary iron intake and NAFLD were included in our regression models. These factors included age

(20– 44 y, 45– 59 y, 60– 74 y, and ≥ 75 y), sex (men and women), body mass index (BMI), race (Mexican-Americans, other Hispanics, non-Hispanic Whites, non-Hispanic Blacks, and other races), education level (under high school, high school, and above high school), annual household income (<\$20,000, \$20,000–\$44,999, \$45,000–\$74,999, and \geq \$75,000), smoking status (smoking at least 100 cigarettes in life or not), vigorous recreational activity (that causes significant increase in breathing or heart rate, such as carrying or lifting heavy loads, heavy construction work for at least 10 minutes continuously, yes or no), average daily energy intake, diabetes (yes or no), hypertension (yes or no), polycystic ovarian syndrome (yes or no), levels of serum triglycerides (TG), total cholesterol (TC) and uric acid (UA). Diabetes was defined as a fasting blood glucose level ≥ 7.0 mmol/L, or 2-h plasma glucose level ≥ 11.1 mmol/L, or use of diabetes pills or insulin, or self-reported diabetes diagnosis.^{27,28} Hypertension was defined as mean systolic blood pressure ≥ 130 mmHg, or mean diastolic blood pressure ≥ 80 mmHg,²⁹ or use of prescription drugs for hypertension, or self-reported hypertension diagnosis.³⁰ Lifestyle and medical history were collected through face-to-face interviews by trained personnel. Blood indexes were analysed by certified laboratory professionals at a mobile screening center (<https://www.cdc.gov/nchs/nhanes/>).

Statistical analysis

Stata 15.0 was used to perform all statistical analyses. According to the NHANES analysis guidelines,³¹ new 12-year weights were calculated by dividing the 2-year weights by 6 (the number of 2-year cycles). The main characteristics of the participants were expressed as mean \pm standard deviation or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. Student's t-test or nonparametric test was used to compare the differences in continuous variables (normal or non-normally distributed data) between participants with and without NAFLD. Rao-Scott Chi-square test was used to compare the distribution of categorical variables between groups. The three dietary exposures (ADDI intake, PDDI intake, and the PDDI: ADDI intake ratio) were categorized according to quartiles (quartile 1: <25th percentile, quartile 2: ≥ 25 th–50th percentile, quartile 3: ≥ 50 th–75th percentile, and quartile 4: ≥ 75 th percentile), and quartile 1 was used as a reference category. Logistic regression models were used to examine the associations between the three dietary exposures and the risk of NAFLD. Model 1 was adjusted for age and sex. Model 2 was further adjusted for BMI, race, educational level, smoking status, recreational activities, annual household income, hypertension, diabetes, polycystic ovarian syndrome, average daily

energy intake, alcohol, iron supplements, TG, UA and TC levels. Then, stratified analyses by age (<45 y and \geq 45 y age groups)^{32,33} and sex were conducted separately to determine the associations between the three dietary exposures and the risk of NAFLD. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from logistic regression analyses. After 1% abnormal values before and after were rejected, dose–response relationships were evaluated by binary logistic regression models with the use of restricted cubic spline functions with three knots located at the 5th, 50th, and 95th percentiles of the exposure distribution in fully adjusted model 2. The *p*-value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. All *p*-values were two-sided and *p* < 0.05 was considered significant.

RESULTS

The comparisons of baseline characteristics between NAFLD and non-NAFLD groups are presented in Table 1. Among 9478 participants, the overall prevalence of NAFLD was approximately 35.34% (40.76% in men and 30.64% in women). Compared with non-NAFLD, participants with NAFLD were more likely to be older, Mexican-American, smokers and have hypertension, diabetes, and higher levels of BMI, serum UA, TC and ADDI intake. Levels of education, vigorous recreational physical activity, income, PDDI intake and PDDI: ADDI intake ratio were lower in the NAFLD group than non-NAFLD group (all *p* value < 0.05).

The weighted ORs (95% CIs) of NAFLD according to quartiles of the three dietary exposures for all participants are displayed in Table 2. In univariate logistic regression analysis, ORs (95% CIs) for NAFLD in the highest quartile compared with the lowest quartile indicated the PDDI: ADDI intake ratio was negatively correlated with NAFLD, while ADDI intake was positively correlated with NAFLD. After adjustment for age and sex (model 1), compared with the lowest quartile, the ORs (95% CIs) of NAFLD for the highest quartile were 0.77 (95% CI, 0.64-0.92), 0.75 (95% CI, 0.63-0.88) for PDDI intake and the PDDI: ADDI intake ratio, which indicated negatively related to NAFLD, whereas ADDI intake was positively associated with NAFLD. After further adjusting for BMI, race, education level, smoking status, vigorous recreational activities, average energy, hypertension, diabetes, income, alcohol, iron supplements, UA and TC level (model 2), PDDI intake remained significantly negatively associated with NAFLD, whereas the associations between ADDI intake and NAFLD was no longer statistically significant.

In the stratified analysis by sex, the associations between the three dietary exposures and NAFLD are shown in Table 3. Comparisons between the highest quartile and the lowest

quartile showed that no significant associations were found between the three dietary exposures and NAFLD risk in men. In women, PDDI intake and the ratio of PDDI: ADDI intake were inversely associated with the risk of NAFLD. After adjustment for age (model 1), compared with the lowest quartile, the OR (95% CIs) of NAFLD for the highest quartile were 0.62 (95% CI, 0.48-0.81) for PDDI intake, 0.62 (95% CI, 0.49-0.78) for the PDDI: ADDI intake ratio, and 1.40 (95% CI, 1.13-1.74) for ADDI intake. In model 2, compared with the lowest quartile, the OR (95% CIs) of NAFLD for the highest quartile of PDDI intake and the PDDI: ADDI intake ratio were 0.54 (95% CI, 0.39-0.74) and 0.67 (95% CI, 0.49-0.90); whereas there was no significant association between ADDI intake and the risk of NAFLD.

In the stratified analysis by age, the associations between the three dietary exposures and NAFLD are shown in Table 4. Multivariate analysis (model 2) indicated that for participants aged <45 years, relative to quartile 1, the ORs (95% CIs) of NAFLD for quartile 4 of ADDI intake, PDDI intake, and the PDDI: ADDI intake ratio were 1.02 (95% CI, 0.69-1.52), 0.83 (95% CI, 0.58-1.19), and 0.94 (95% CI, 0.64-1.37), respectively. For participants aged ≥45 years, compared with the lowest quartile, the ORs (95% CIs) of NAFLD for the highest quartile of PDDI intake, ADDI intake and the PDDI: ADDI intake ratio were 0.69 (95% CI, 0.54-0.86), 1.03 (95% CI, 0.80-1.34) and 0.80 (95% CI, 0.64-0.99), respectively, which indicated that PDDI intake was negatively related to the risk of NAFLD, whereas ADDI intake and the PDDI: ADDI intake ratio were not significantly associated with the risk of NAFLD.

The result of the dose-response relationship between PDDI intake and NAFLD is presented in Fig. 2. In women, PDDI intake showed a reverse correlation with NAFLD in a linear manner (p for nonlinearity = 0.136). When PDDI intake reached 3 mg/d (OR: 0.95; 95% CI: 0.92-0.99), it exhibited protective effects on NAFLD.

DISCUSSION

The current cross-sectional study comprehensively explored the relationship between dietary iron intake from different sources and the risk of NAFLD in the U.S. population. The prevalence of “USFLI defined NAFLD” among the study participants is 36.52 %, similar to the previous report.³⁴ After adjusting for various factors including age, sex, BMI, race, educational level, smoking status, recreational activities, annual household income, hypertension, diabetes, polycystic ovarian syndrome, average energy intake, alcohol, iron supplements, serum TG, UA and TC levels, PDDI intake and the PDDI: ADDI intake ratio

were inversely associated with the risk of NAFLD. When stratified by sex and age, the negative relationships were observed in women and participants older than 45 years old.

Several studies have examined the association between dietary iron intake and NAFLD with controversial results. A case-control study in Italy showed that iron intake was higher in the control group than in the NAFLD group.¹⁹ Another case-control study in Portugal found a negative association between iron intake and the risk of NAFLD.²⁰ However, Peng et al.²¹ found that dietary iron intake was positively associated with NAFLD in China. Furthermore, similar result was found in a matched case-control study.²² Nevertheless, another case-control study in the United States found no significant difference in dietary iron intake between NAFLD and non-NAFLD groups.²³ To our knowledge, our study is the first to examine the association between dietary iron intake from different sources and the risk of NAFLD in the U.S. adult population.

Currently, available studies on the relationships between dietary iron from different sources and NAFLD are very limited. Our results showed no significant relationship between ADDI and the risk of NAFLD in either men or women. However, in a case-control study in China, animal-derived iron was positively associated with NAFLD in men; interestingly, plant-derived iron was inversely associated with NAFLD in women.²¹ Differences in demographics and definitions of NAFLD may partly explain the inconsistent results. People in U.S. tend to consume more animal-based products, while those of Eastern countries, like China, tend to consume more plant-based foods.³⁵ Moreover, the aforementioned study used “abdominal ultrasound” to diagnose NAFLD while our study employed “USFLI defined NAFLD”.

Our findings indicated that PDDI intake and the PDDI: ADDI intake ratio were inversely associated with the “USFLI defined NAFLD” and the underlying mechanism of this association remained undetermined. The differences in diet composition may partly explain the inconsistent results. In this study, PDDI consumption was mainly from grains, vegetables and fruits, which are rich in vitamin C, dietary fiber, carotenoids, α -tocopherol and magnesium.^{36,37} Carotenoids and α -tocopherols contain antioxidant capacity,³⁸ which can effectively reduce lipid peroxidation and prevent the occurrence of NAFLD. In addition, related studies have also proved that carotenoids can reduce insulin resistance,^{39,40} which is thought to be an important factor in the development of NAFLD.⁴¹ Moreover, studies have shown a negative association between dietary fiber intake and the risk of NAFLD.⁴²

There are several strengths in this study. First, we explored the associations between different sources of dietary iron intake and “USFLI defined NAFLD”. Second, the large,

nationally representative sample increased the statistical power and reliability of the results. In addition, we investigated the associations stratified by sex and age.

Nevertheless, our study also has some limitations. First, the cross-sectional design makes it difficult to determine the causal association between dietary iron intake and the risk of NAFLD. Second, dietary data were calculated from the average of two 24-hour dietary recalls, which may have recall bias. Third, USFLI, which is used to define NAFLD, cannot stage NAFLD, and the association between PDDI intake and NAFLD severity is unclear. In addition, it should be emphasized that NAFLD in this study is not diagnosed by liver biopsy (gold standard for diagnosis of NAFLD), but only estimated according to the USFLI index. The last, our study is limited to the American population, and extrapolation of the conclusions may be limited due to the differences in races, dietary habits and eating patterns.

Conclusion

In conclusion, PDDI intake and the PDDI: ADDI intake ratio were negatively associated with the risk of NAFLD in U.S. adults. The results of this study provide potential guiding significance for dietary iron intake of NAFLD adults in American.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

There are no conflicts to declare.

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Table 1. Baseline characteristics of the participants by NAFLD, U.S. adult[†]

Characteristic	NAFLD (total)			NAFLD (men, n=4380)		
	No	Yes	<i>p</i> -value	No	Yes	<i>p</i> -value
Number of participants (%)	6027(64.54%)	3451(35.46%)		2581(58.93%)	1799(41.07%)	
Age group (n, %)			<0.001			<0.001
20–44 years	2733(73.61%)	986(26.39%)		1172(69.19%)	531(30.81%)	
45–59 years	1384(60.61%)	937(39.39%)		587(53.76%)	455(46.24%)	
60–74 years	1247(53.69%)	1081(46.31%)		529(46.77%)	560(53.23%)	
≥75 years	663(59.83%)	447(40.17%)		293(52.62%)	253(47.38%)	
Race (n, %)			<0.001			<0.001
Mexican American	693 (48.10%)	846 (51.90%)		290(44.37%)	406(55.63%)	
Other Hispanic	662 (64.03%)	444 (35.97%)		270(62.02%)	210(37.98%)	
Non-Hispanic White	2412 (63.04%)	1548 (36.96%)		1031(56.59%)	882(43.41%)	
Non-Hispanic Black	1383 (79.41%)	392 (20.59%)		590(79.80%)	171(20.20%)	
Other Race	480 (75.71%)	151 (24.29%)		219(69.77%)	91(30.23%)	
Educational Level (n, %)			<0.001			0.006
<High school	1269 (55.46%)	1099 (44.54%)		584(54.56%)	527(45.44%)	
High school	1351 (63.31%)	780 (36.69%)		597(59.79%)	412(40.21%)	
>High school	3402 (67.50%)	1568 (32.50%)		1398(59.89%)	858(40.11%)	
<hr/>						
Characteristic	NAFLD (women, n=5098)					
	No	Yes	<i>p</i> -value	No	Yes	<i>p</i> -value
Number of participants (%)	3446(67.60%)	1652(32.40%)				
Age group (n, %)			<0.001			
20–44 years	1561(77.80%)	455(22.20%)				
45–59 years	797(66.36%)	482(33.64%)				
60–74 years	718(59.52%)	521(40.48%)				
≥75 years	370(65.01%)	194(34.99%)				
Race (n, %)			<0.001			
Mexican American	403(51.63%)	440(48.37%)				
Other Hispanic	392(65.84%)	234(34.16%)				
Non-Hispanic White	1381(68.84%)	666(31.16%)				
Non-Hispanic Black	793(79.16%)	221(21.84%)				
Other Race	261(81.17%)	60(18.83%)				
Educational Level (n, %)			<0.001			
<High school	685(56.26%)	572(43.74%)				
High school	754(66.34%)	368(33.66%)				
>High school	2004(74.16%)	710(25.84%)				

BMI, body mass index; TC, total cholesterol; UA, uric acid

[†]Data are presented as participants (percentage) for categorical variables or 50th (25th, 75th) for continuous variable.

Table 1. Baseline characteristics of the participants by NAFLD, U.S. adult[†] (cont.)

Characteristic	NAFLD (total)			NAFLD (men, n=4380)		
	No	Yes	<i>p</i> -value	No	Yes	<i>p</i> -value
Smoking status (n, %)			<0.001			<0.001
Yes	2274 (59.88%)	1586 (40.12%)		1229(54.29%)	987(44.71%)	
No	3753 (67.79%)	1865 (32.31%)		1352(62.42%)	812(37.58%)	
Vigorous recreational activity (n, %)			<0.001			<0.001
Yes	1530 (80.83%)	407 (19.17%)		839(76.53%)	281(23.47%)	
No	4497 (59.45%)	3044 (40.55%)		1742(51.58%)	1518(48.42%)	
Hypertension (n, %)			<0.001			<0.001
Yes	2491 (50.99%)	2212 (49.01%)		1141(47.14%)	1161(52.86%)	
No	3476 (75.29%)	1216 (24.71%)		1413(69.25%)	629(30.75%)	
Diabetes (n, %)			<0.001			<0.001
Yes	754 (31.75%)	1385 (68.25%)		348(28.90%)	702(71.10%)	
No	5273 (71.63%)	2066 (28.37%)		2233(65.87%)	1097(34.13%)	
Characteristic	NAFLD (women, n=5098)					
	No	Yes	<i>p</i> -value			
Smoking status (n, %)			<0.001			
Yes	1045(65.39%)	599(34.61%)				
No	2401(71.53%)	1053(28.47%)				
Vigorous recreational activity (n, %)			<0.001			
Yes	691(86.83%)	126(13.17%)				
No	2755(65.39%)	1526(34.61%)				
Hypertension (n, %)			<0.001			
Yes	1350(54.71%)	1051(45.29%)				
No	2063(80.18%)	587(19.82%)				
Diabetes (n, %)			<0.001			
Yes	406(34.47%)	683(65.53%)				
No	3040(76.58%)	969(23.42%)				

BMI, body mass index; TC, total cholesterol; UA, uric acid

[†]Data are presented as participants (percentage) for categorical variables or 50th (25th, 75th) for continuous variable

Table 1. Baseline characteristics of the participants by NAFLD, U.S. adult[†] (cont.)

Characteristic	NAFLD (total)			NAFLD (men, n=4380)		
	No	Yes	<i>p</i> -value	No	Yes	<i>p</i> -value
Annual household income (n, %)			<0.001			<0.001
<\$20,000	1081 (61%)	784 (39.00%)		390(58.49%)	331(41.51%)	
\$20,000–\$44,999	1846 (60.43%)	1211 (39.57%)		767(53.48%)	628(46.52%)	
\$20,000–\$44,999	1126 (62.84%)	625 (37.16%)		491(57.45%)	341(42.55%)	
≥\$75,000	1593 (70.10%)	621 (29.90%)		743(60.07%)	397(36.93%)	
BMI (kg/m ²)	26.1 (23.15,29.29)	33.5 (29.81,38.3)	<0.001	26.19(23.50, 28.70)	32.40(29.20, 36.39)	<0.001
TC (mg/dL)	188 (164,215)	191 (164,220)	0.0037	182(160,208)	188(160,217)	0.0014
UA (mg/dL)	5(4.2,5.9)	6(5.20,6.90)	<0.001	5.7(5.6,4)	6.4(5.6,7.2)	<0.001
Average energy intake (kcal/day)	1871(1462,2368)	1935(1479,2471)	0.19	2198(1754,2720)	2199(1719,2739)	0.19
Animal derived iron intake (mg/day)	2.62(1.50,4.21)	2.91(1.64,4.74)	<0.001	3.06(1.77,4.86)	3.31(1.86,5.21)	0.11
Plant-derived iron intake (mg/day)	9.81 (6.49,14.47)	9.25 (6.41,13.64)	0.0062	10.42(7.03,16.12)	10.23(6.91,15.08)	0.28
Plant-derived iron: animal-derived iron intake ratio	3.80 (1.95,7.43)	3.29 (1.71,6.54)	<0.001	3.52(1.80,7.11)	3.23(1.76,6.35)	0.069
Characteristic	NAFLD (women, n=5098)					
	No	Yes	<i>p</i> -value			
Annual household income (n, %)			<0.001			
<\$20,000	691(62.40%)	453(37.60%)				
\$20,000–\$44,999	1079(65.92%)	583(34.08%)				
\$20,000–\$44,999	635(67.67%)	284(32.33%)				
≥\$75,000	850(77.70%)	224(22.30%)				
BMI (kg/m ²)	26.02(22.71, 30.00)	35.30(30.90, 40.50)	<0.001			
TC (mg/dL)	193(168,220)	194(169,222)	0.039			
UA (mg/dL)	4.5(3.8,5.2)	5.5(4.7,6.3)	<0.001			
Average energy intake (kcal/day)	1647(1332,2038)	1680(1233,2104)	0.23			
Animal derived iron intake (mg/day)	2.34(1.34,3.73)	2.58(1.44,4.28)	0.04			
Plant-derived iron intake (mg/day)	9.41(6.15,13.41)	8.48(5.73,11.85)	<0.001			
Plant-derived iron: animal-derived iron intake ratio	4.06(2.06,7.75)	3.34(1.66,6.70)	<0.001			

BMI, body mass index; TC, total cholesterol; UA, uric acid

[†]Data are presented as participants (percentage) for categorical variables or 50th (25th, 75th) for continuous variable

Table 2. Weighted ORs and 95% CIs for NAFLD according to the quartiles of dietary iron intake (mg/day)^{†‡}

	Crude OR (95% CI)	Model 1 [§] OR (95% CI)	Model 2 [¶] OR (95% CI)
Animal-derived iron (mg/day)			
Q1 (<1.55)	1.00 (ref)	1.00 (ref)	1.00(ref)
Q2 (1.55-<2.71)	0.96 (0.81-1.14)	0.94 (0.79-1.11)	0.79(0.62-1.00)
Q3 (2.71-<4.38)	1.12 (0.97-1.30)	1.07 (0.92-1.24)	0.95(0.78-1.16)
Q4 (≥4.38)	1.40 (1.19-1.65) **	1.32 (1.12-1.55) **	1.01(0.82-1.24)
Plant-derived iron (mg/day)			
Q1 (<6.46)	1.00 (ref)	1.00 (ref)	1.00(ref)
Q2 (6.46-<9.64)	1.08 (0.91-1.28)	1.02 (0.87-1.21)	0.99(0.75-1.31)
Q3 (9.64-<14.16)	0.96 (0.82-1.12)	0.92 (0.79-1.07)	0.93(0.75-1.15)
Q4 (≥14.16)	0.84 (0.70-1.01)	0.77 (0.64-0.92) **	0.82(0.64-0.99) *
Plant-derived iron: animal-derived iron intake ratio			
Q1 (<1.83)	1.00 (ref)	1.00 (ref)	1.00(ref)
Q2 (1.83-<3.59)	0.95 (0.82-1.11)	0.93 (0.80-1.08)	1.08(0.87-1.35)
Q3 (3.59-<7.14)	0.83 (0.68-1.00)	0.83 (0.68-1.00)	0.92(0.74-1.15)
Q4 (≥7.14)	0.74 (0.63-0.88) **	0.75 (0.63-0.88) **	1.00(0.81-1.24)

OR, odds ratio; CI, confidence interval.

[†]The lowest quartile of animal-derived iron intake, plant-derived iron intake and the plant-derived iron: animal-derived iron intake ratio separately was used as the reference group.

[‡]Results are survey-weighted.

[§]Model 1 adjusted for age and sex.

[¶]Model 2 adjusted for age, sex, BMI, race, education level, smoking status, vigorous recreational activities, average energy, hypertension, diabetes, income, alcohol, iron supplements, TG, UA and TC level.

* $p < 0.05$; ** $p < 0.01$.

Table 3. Weighted ORs and 95% CIs for NAFLD according to the quartiles of dietary iron intake (mg/day), stratified by sex^{†‡}

	Crude OR (95% CI)	Model 1 [§] OR (95% CI)	Model 2 [¶] OR (95% CI)
Men (n=4380)			
Animal-derived iron (mg/day)			
Q1 (<2.16)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (2.16-<3.59)	0.99(0.76-1.28)	0.98(0.76-1.27)	0.80(0.58-1.10)
Q3 (3.59-<5.45)	1.11(0.87-1.40)	1.13(0.88-1.44)	0.89(0.68-1.16)
Q4 (≥5.45)	1.21(0.93-1.57)	1.24(0.96-1.60)	0.95(0.71-1.28)
Plant-derived iron (mg/day)			
Q1 (<7.84)	0.00(ref)	1.00(ref)	1.00(ref)
Q2 (7.84-<11.50)	0.99(0.78-1.24)	0.97(0.77-1.22)	1.05(0.77-1.43)
Q3 (11.50-<17.31)	1.05(0.85-1.29)	1.06(0.86-1.30)	1.05(0.81-1.33)
Q4 (≥17.31)	0.84(0.65-1.09)	0.83(0.64-1.07)	0.85(0.62-1.15)
Plant-derived iron: animal-derived iron intake ratio			
Q1 (<1.80)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (1.80-<3.37)	1.09(0.90-1.31)	1.09(0.90-1.32)	1.19(0.91-1.55)
Q3 (3.37-<6.51)	0.98(0.74-1.30)	1.00(0.74-1.33)	1.03(0.74-1.41)
Q4 (≥6.51)	0.87(0.69-1.09)	0.87(0.69-1.10)	1.04(0.81-1.35)
Women (n=5398)			
Animal-derived iron (mg/day)			
Q1 (<1.39)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (1.39-<2.37)	0.97(0.76-1.22)	0.96(0.76-1.21)	0.84(0.63-1.11)
Q3 (2.37-<3.73)	1.05(0.84-1.31)	1.04(0.83-1.29)	0.92(0.71-1.18)
Q4 (≥3.73)	1.36(1.10-1.69) **	1.40(1.13-1.74) **	1.20(0.94-1.19)
Plant-derived iron (mg/day)			
Q1 (<6.23)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (6.23-<9.18)	1.06(0.82-1.38)	1.04(0.80-1.34)	0.93(0.68-1.28)
Q3 (9.18-<13.04)	0.86(0.67-1.12)	0.85(0.66-1.09)	0.75(0.54-1.03)
Q4 (≥13.04)	0.61(0.47-0.80) **	0.62(0.48-0.81) **	0.54(0.39-0.74) **
Plant-derived iron: animal-derived iron intake ratio			
Q1 (<2.08)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (2.08-<3.90)	0.78(0.62-0.99) *	0.76(0.60-0.95) *	0.72(0.55-0.94) *
Q3 (3.90-<7.30)	0.64(0.52-0.80) **	0.62(0.51-0.76) **	0.62(0.47-0.82) **
Q4 (≥7.30)	0.63(0.50-0.80) **	0.62(0.49-0.78) **	0.67(0.49-0.90) **

OR, odds ratio; CI, confidence interval.

[†]The lowest quartile of animal-derived iron intake, plant-derived iron intake and the plant-derived iron: animal-derived iron intake ratio separately was used as the reference group.

[‡]Results are survey-weighted.

[§]Model 1 adjusted for age.

[¶]Model 2 adjusted for age, BMI, race, education level, smoking status, vigorous recreational activities, average energy, polycystic ovarian syndrome, hypertension, diabetes, income, alcohol, iron supplements, TG, UA and TC level.

* $p < 0.05$; ** $p < 0.01$.

Table 4. Weighted ORs and 95% CIs for NAFLD according to the quartiles of dietary iron intake (mg/day), stratified by age^{†‡}

	Crude OR (95% CI)	Model 1 [§] OR (95% CI)	Model 2 [¶] OR (95% CI)
<45 years (n=3719)			
Animal-derived iron (mg/day)			
Q1 (<1.68)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (1.68-<3.00)	1.11(0.82-1.52)	1.11(0.82-1.51)	0.94(0.66-1.36)
Q3 (3.00-<4.76)	1.13(0.83-1.54)	1.07(0.78-1.47)	0.86(0.55-1.33)
Q4 (≥4.76)	1.48(1.10-1.98) **	1.37(1.01-1.85) *	1.02(0.69-1.52)
Plant-derived iron (mg/day)			
Q1 (<6.91)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (6.91-<10.27)	1.09(0.84-1.40)	1.06(0.82-1.35)	1.12(0.82-1.53)
Q3 (10.27-<15.02)	0.95(0.75-1.21)	0.91(0.72-1.16)	1.11(0.80-1.55)
Q4 (≥15.02)	0.96(0.71-1.29)	0.89(0.65-1.20)	0.83(0.58-1.19)
Plant-derived iron: animal-derived iron intake ratio			
Q1 (<1.83)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (1.83-<3.58)	0.82(0.63-1.08)	0.82(0.63-1.07)	0.93(0.65-1.34)
Q3 (3.58-<6.85)	0.68(0.50-0.92) *	0.69(0.51-0.93) *	0.81(0.57-1.34)
Q4 (≥6.85)	0.75(0.56-0.99) *	0.76(0.57-1.01)	0.94(0.64-1.37)
≥45 years (n=5759)			
Animal-derived iron (mg/day)			
Q1 (<1.64)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (1.64-<2.74)	0.85(0.68-1.06)	0.84(0.67-1.04)	0.71(0.56-0.91) *
Q3 (2.74-<4.28)	1.14(0.95-1.38)	1.09(0.90-1.31)	0.99(0.79-1.25)
Q4 (≥4.28)	1.38(1.12-1.69) **	1.26(1.02-1.55) *	1.03(0.80-1.34)
Plant-derived iron (mg/day)			
Q1 (<6.89)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (6.89-<10.00)	1.08(0.88-1.32)	1.05(0.85-1.29)	0.98(0.75-1.28)
Q3 (10.00-<14.61)	0.95(0.78-1.15)	0.91(0.75-1.11)	0.80(0.63-0.99) *
Q4 (≥14.61)	0.80(0.65-0.98) *	0.72(0.59-0.87) **	0.69(0.54-0.86) **
Plant-derived iron: animal-derived iron intake ratio			
Q1 (<2.03)	1.00(ref)	1.00(ref)	1.00(ref)
Q2 (2.03-<3.68)	0.95(0.78-1.16)	0.94(0.76-1.15)	0.94(0.74-1.19) *
Q3 (3.68-<7.11)	0.82(0.66-1.03)	0.83(0.66-1.05)	0.83(0.63-0.90) *
Q4 (≥7.11)	0.69(0.57-0.83) **	0.70(0.58-0.84) **	0.80(0.64-0.99) *

OR, odds ratio; CI, confidence interval.

[†]The lowest quartile of animal-derived iron intake, plant-derived iron intake and the plant-derived iron: animal-derived iron intake ratio separately was used as the reference group.

[‡]Results are survey-weighted.

[§] Model 1 adjusted for age and sex.

[¶] Model 2 adjusted for age, sex, BMI, race, education level, smoking status, vigorous recreational activities, average energy, hypertension, diabetes, income, alcohol, iron supplements, TG, UA and TC level.

* $p < 0.05$; ** $p < 0.01$.

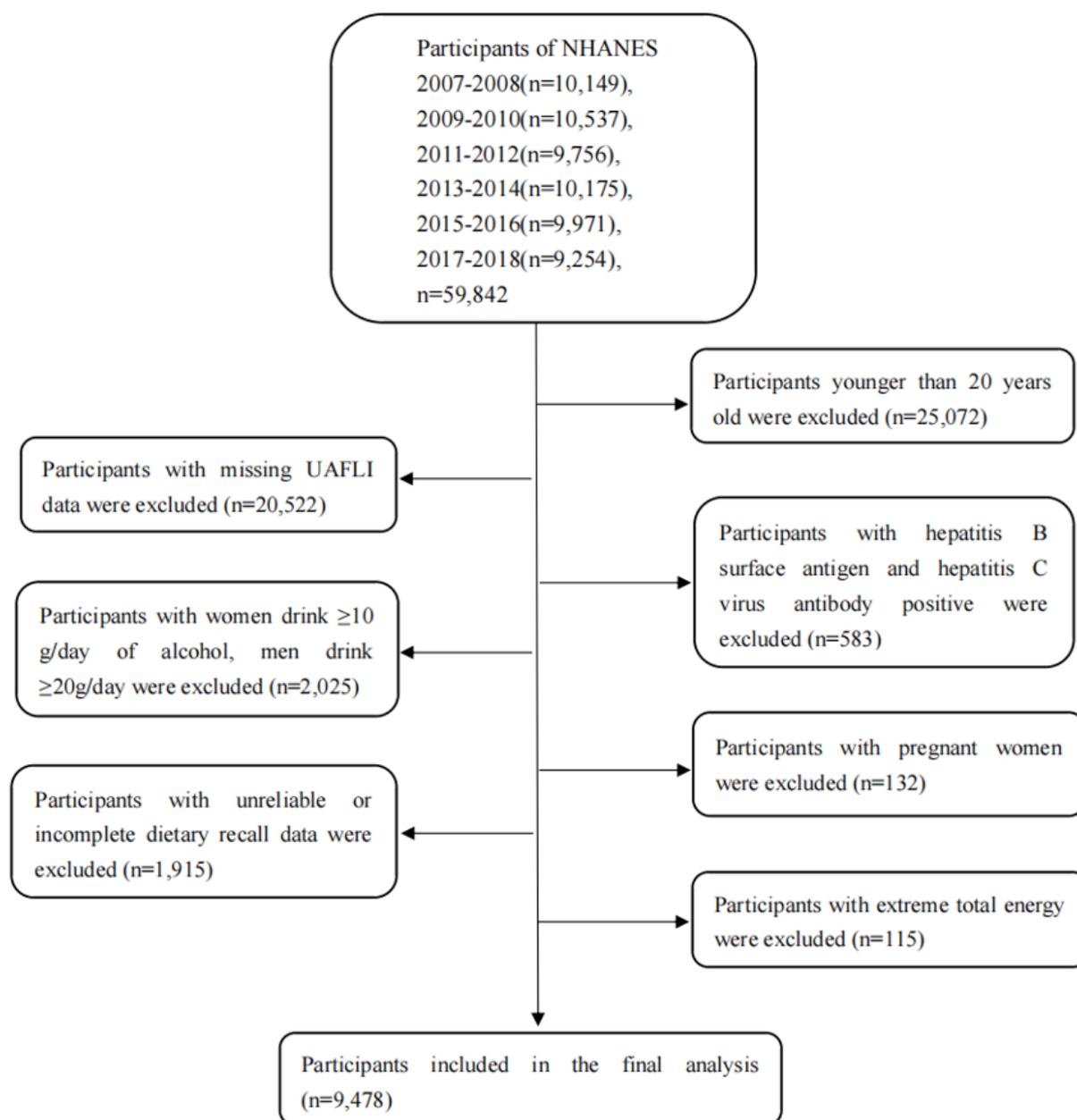


Figure 1. Flow chart of the selection process

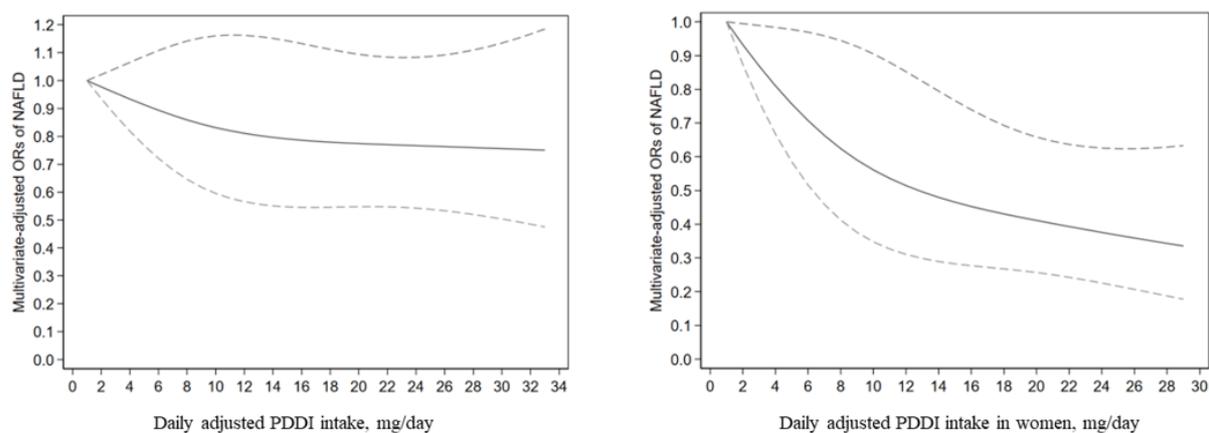


Figure 2. The dose–response relationship between PDDI intake and NAFLD. The model adjusted for age, sex, BMI, race, educational level, smoking status, recreational activities, annual household income, hypertension, diabetes, polycystic ovarian syndrome, average daily energy intake, alcohol, iron supplements, TG, UA and TC levels. The solid line and dashed line represent the estimated ORs and the corresponding 95% CIs, respectively. OR, odds ratio; CI, confidence interval