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ORIGINAL RESEARCH

Association of Serum Ferritin Levels With Obstructive Sleep Apnea in Overweight/Obese US Populations: A Population-Based Study From the NHANES

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Objective: To investigate the relationship between serum ferritin levels and OSA in overweight/obese individuals and assess the association between ferritin levels and all-cause mortality in overweight/obese female OSA patients.

Methods: Cross-sectional (n = 4,809) and prospective (n = 832) data from overweight/obese adults from the 2005–2008, and 2015-March 2020 NHANES cycles were analyzed. Participants were categorized into quartiles (Q1-Q4) based on their ln-transformed serum ferritin levels. Multivariable logistic regression and restricted cubic spline regression (RCS) investigate associations. Kaplan-Meier survival analyses and Cox proportional hazards regression examined the relationship between ferritin levels and all-cause mortality in OSA patients.

Results: After adjusting for potential confounding factors, we found that ln-transformed ferritin levels were associated with an increased risk of OSA (Q4 vs Q2: OR = 1.07, 95% CI: 1.01–1.13, P = 0.020, P for trend = 0.010). A non-linear U-shaped association was observed between ferritin levels and OSA risk (P-non-linear = 0.029), with an inflection point at ln-transformed ferritin of 4.58 (corresponding to a serum ferritin concentration of 97.51 ng/mL). In female OSA patients, elevated ferritin levels were associated with increased all-cause mortality risk (Q4 vs Q2: HR: 5.46, 95% CI: 1.18–25.16, P = 0.029, P for trend = 0.032).

Conclusion: Ferritin levels in overweight/obese individuals show a U-shaped relationship with OSA risk, and elevated levels correlate with increased all-cause mortality in female overweight/obese OSA patients. In the future, further research is needed to explore the potential associations between ferritin, inflammation, obesity, and OSA.

Keywords: ferritin, obstructive sleep apnea, overweight/obese, all-cause mortality, NHANES

Introduction

Obesity has become a growing global public health concern, with prevalence rates increasing dramatically since 1990. The rate of obesity among adults worldwide has more than doubled, while obesity among adolescents has tripled.[1] In the United States, the prevalence of obesity among adults has reached 42%.[2] Obesity is linked to the development of numerous diseases, including type 2 diabetes, hypertension, and atherosclerosis. Moreover, they have been identified as significant risk factors for OSA in adults and children. The severity of OSA correlates positively with the degree of obesity, with a 12% increase in OSA risk for every 1 kg/m² increase in body mass index (BMI) above the average level for age and sex.[3–6] Epidemiological data exemplify the substantial impact of BMI on OSA prevalence: among individuals

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aged 30–49 years, OSA affects just 7.0% of men and 1.4% of women with BMI < 25 kg/m², but these rates increase dramatically to 79.5% and 43.0%, respectively, in those with BMI > 40 kg/m^2.[7]

OSA is characterized by repeated partial or complete airway obstruction during sleep, leading to recurrent respiratory pauses and hypoventilation.[8] According to the American Academy of Sleep Medicine (AASM) guidelines, OSA can be diagnosed if a person reports symptoms such as snoring, excessive daytime sleepiness, morning headaches, or a sensation of choking or gasping upon waking, and has an Apnea-Hypopnea Index (AHI) of ≥ 5. Alternatively, an AHI of ≥ 15 may indicate OSA even without these symptoms.[9] Many studies have shown that OSA can increase the likelihood of developing various diseases, such as glaucoma,[10] hypertension,[11] arrhythmias,[12] stroke,[13] and diabetes.[14] Moreover, OSA can amplify mortality risks associated with these complications.[12,13,15]

Ferritin, an important marker of iron stores and inflammation, is associated with various chronic diseases. Ferritin was initially considered solely associated with iron levels in the body. However, subsequent research has revealed that ferritin levels are also linked to inflammation and various chronic diseases. In the presence of these abnormalities, ferritin levels can increase significantly.[16] This may be related to immune activation triggered by microorganisms or autoantigens, ultimately disrupting the body's iron metabolism.[17] Previous studies have revealed complex interactions among obesity, OSA, and iron metabolism. Obesity-induced chronic low-grade inflammation affects iron homeostasis through multiple mechanisms: adipose tissue secretes inflammatory mediators that interfere with iron absorption and transport while increasing hepcidin levels, further inhibiting iron absorption.[18,19] In OSA patients, this complexity is compounded by recurring cycles of intermittent hypoxia and reoxygenation, which trigger increased erythropoietin production and promote inflammatory responses through factors such as IL-6 and TNF-α.[20–22] The resulting oxidative stress can damage iron carrier proteins and disrupt the circadian regulation of iron metabolism genes, potentially affecting ferritin levels in overweight/obese OSA patients.

However, the relationship between OSA and ferritin remains controversial in large-scale population-based investigations. An epidemiological study of 796 individuals with sleep apnea in Iceland revealed significantly higher serum ferritin levels in men with OSA compared to the control group. However, this difference was not significant after adjusting for confounding factors.[23] Conversely, another study involving 90 patients suspected of OSA at a tertiary sleep center found a significant positive correlation between serum ferritin levels and AHI.[24] The sample sizes of these studies were generally too small, which may affect the generalizability of the conclusions.

To address these conflicting findings and overcome the limitations of previous research, this study aims to explore the relationship between ferritin levels and OSA in overweight/obese populations using the National Health and Nutrition Examination Survey (NHANES). NHANES offers extensive representation, large sample sizes, and detailed health information, providing robust evidence to verify or address controversies and gaps in previous research. The main objective of this study is to investigate the relationship between ferritin levels and OSA in obese/overweight populations and to provide insights for developing more accurate and effective diagnostic and prognostic strategies for OSA.

Materials and Methods

Study Design and Population

This investigation utilized data from the NHANES, a comprehensive cross-sectional study conducted by the Centers for Disease Control and Prevention (CDC). NHANES aims to assess the health and nutritional status of the non-institutionalized US population through a multifaceted approach, encompassing household interviews, physical examinations, laboratory tests, and health-related questionnaires. The survey employs a complex, multistage probability sampling design to ensure representativeness. All data utilized in this study are publicly accessible (https://www.cdc.gov/nchs/nhanes/index.htm).

For our analysis, we incorporated data from four NHANES cycles: 2005–2006, 2007–2008, 2015–2016, and 2017-March 2020. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort study reporting were adhered to throughout the investigation. The NHANES study protocol received approval from the National Center for Health Statistics Institutional Review Board, and all participants provided informed written consent upon enrollment.[25]

Cross-Sectional Analysis

The study initially encompassed 25,531 participants from the NHANES cycles conducted in 2015–2016 and 2017-March 2020. Following the application of stringent exclusion criteria, our final cross-sectional cohort consisted of 4,809 individuals. Exclusion criteria were as follows: age less than 20 years (n = 10,580), BMI < 25 kg/m² (n = 3,273), pregnancy (n = 121), absence of data on OSA (n = 944), lack of ferritin measurements (n = 3,461), and missing information on other essential covariates (n = 2,343) (Figure 1).

Prospective Analysis

To clarify the association between ferritin levels and clinical outcomes in patients with OSA, we also conducted a prospective study that expanded the observational data set to include the 2005–2006 and 2007–2008 NHANES cycles. Due to ferritin measurements being limited to females aged 12–49 years in the 2005–2008 and 2015–2016 cycles, insufficient male samples were available for inclusion in our prospective analysis. Therefore, our prospective study was conducted only in females with OSA between 20 and 49. After consolidating data from four NHANES cycles and incorporating mortality data, our initial cohort comprised 46,028 participants. We then applied the following exclusion criteria: age below 20 years (n = 20,163), Males (n = 6,821), BMI < 25 kg/m² (n = 4,496), pregnancy (n = 390), absence of data on OSA (n = 40), and lack of ferritin measurements (n = 3,122). Further exclusions were made for missing data on key covariates (n =1,477) and the absence of mortality data (n = 2,016). Consequently, 832 overweight/obese female OSA patients were included in the final prospective analysis (Supplementary Figure 1).

Survival outcomes were ascertained through a linkage process between personal identifiers from NHANES and death records from the National Death Index, with follow-up until December 31, 2019. Detailed information regarding this linkage methodology is available at https://www.cdc.gov/nchs/data-linkage/mortality.htm.

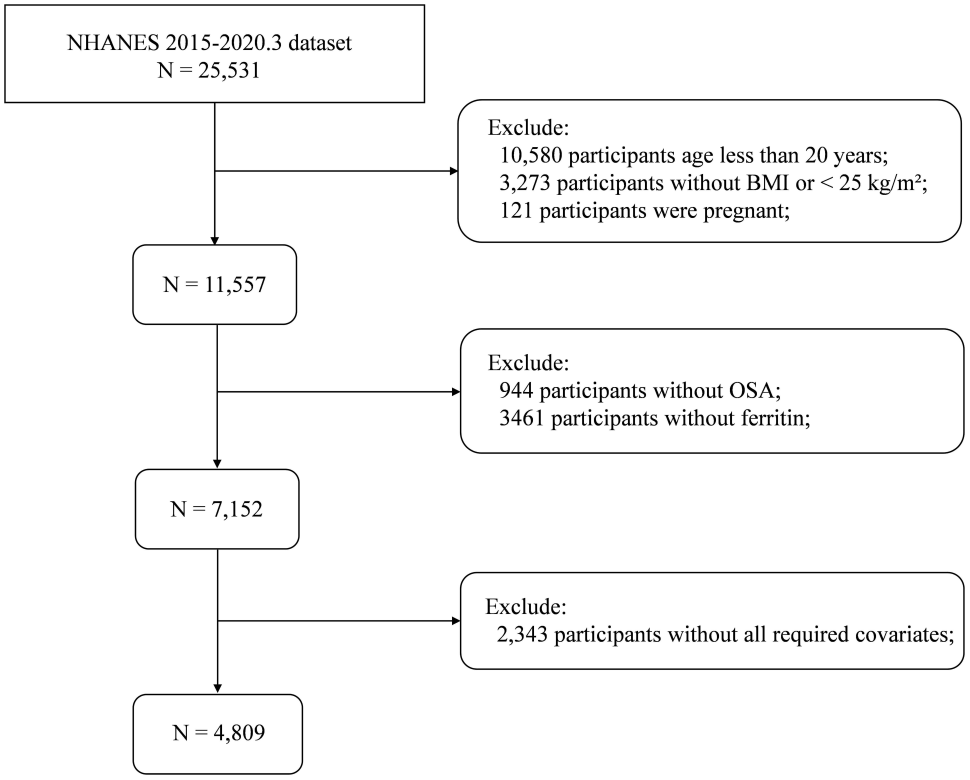

Figure 1 Flow chart of participants' enrollment process in cross-sectional analysis.

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Diagnosis of OSA

OSA is ascertained through the responses to three dichotomous questions. These questions are: (1) "Do you snore for 3 or more nights per week?" (2) "Do you experience snorting, gasping, or stopping breathing for 3 or more nights per week?" (3) "Do you feel excessively sleepy during the day, ranging from 16 to 30 times per month, despite getting around 7 or more hours of sleep per night on weekdays or work nights?".

If individuals respond positively to any of these three questions, they are considered to exhibit symptoms indicative of OSA. Our definition was first proposed by Scinicariello et al and has been adopted by the previous literature.[26–29]

Measurement of Ferritin

Ferritin measurement methodologies have evolved across NHANES cycles. As documented in the NHANES Laboratory/Medical Technologist Procedures Manual, during the 2005–2008 cycle, ferritin quantification was primarily conducted using the Hitachi 912 clinical analyzer. Following the manufacturer's discontinuation of the Hitachi 912 in 2009, subsequent NHANES cycles, including the March 2020 cycle, employed the Roche Elecsys 170 clinical analyzer for serum ferritin concentration measurements. NHANES conducted a comprehensive regression analysis (n = 773) as reported on their official website to ensure data comparability between these two methodologies. The regression equation demonstrated a high correlation between the two measurement methods (r=0.986). This strong correlation substantiates the validity of combining ferritin data obtained from both analytical platforms for integrated analysis.[30]

Dietary and Supplemental Intakes

In each cycle, dietary intake of iron was assessed using two 24-hour recall interviews. The first 24-hour recall interview was conducted face-to-face during the Medical Examination Center (MEC) interview, and the second was undertaken through telephone interviews several days later. For the analysis, dietary intake of iron was calculated by averaging data from the two dietary recalls when both were available; otherwise, the single dietary recall data was used.

In addition, iron supplements intake during the past 30 days were also collected from the survey and averaged to represent the daily iron supplementary intake amount. The total daily iron intake was calculated by summing the daily dietary and supplemental iron intake.[31,32]

Covariates

Our study meticulously accounted for an extensive array of potential confounding factors. Demographic variables were comprehensively considered, including age, gender, race, and BMI. For cross-sectional analyses, age was stratified into three categories (20–40, 40–60, and 60+ years), while prospective studies employed narrower brackets (20–30, 30–40, 40–50 years) due to data limitations beyond age 50. Sex was dichotomized as male or female, and race was classified into five distinct groups: Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other/Multi-racial. BMI was categorized according to established clinical guidelines: Overweight (25–30 kg/m²), Class I Obesity (30–35 kg/m²), Class II Obesity (35–40 kg/m²), and Class III Obesity (≥ 40 kg/m²).[33]

Lifestyle factors were also carefully considered, encompassing smoking status (categorized as former, never, or current smoker) and alcohol consumption patterns. Socioeconomic status was assessed using the Poverty Income Ratio (PIR), which was stratified into high (PIR ≥ 3.5), medium (1.3 ≤ PIR < 3.5), and low (PIR < 1.3) categories. Physical activity levels were evaluated through the measurement of daily sedentary time, categorized as < 3 hours/day, 3–6 hours/day, or ≥ 6 hours/day. Additionally, we included population health status factors such as CVD, diabetes, and hypertension.[34]

Furthermore, our analysis incorporated adjustments for crucial laboratory and biochemical parameters. Considering the potential link between inflammation, ferritin levels, and OSA development, we included white blood cell count (WBC) as a marker of inflammatory status to control for potential confounding effects. We additionally incorporated C-reactive protein (CRP), a sensitive acute-phase inflammatory biomarker reflecting systemic inflammatory processes.[35] Erythrocyte-related indicators, including hemoglobin (HGB), hematocrit (HCT), and red blood cell distribution width (RDW), were also considered. These parameters provide direct insight into iron metabolism and red cell function, with

hemoglobin and hematocrit offering a comprehensive view of blood oxygen-carrying capacity—a factor potentially affecting OSA symptoms.[36–38] RDW serves as an indicator of iron deficiency and may be associated with both ferritin levels and OSA. Additionally, lipid metabolism indicators such as high-density lipoprotein cholesterol (HDL) and total cholesterol (TC) were included, which reflect participants' cardiovascular health status and may influence both OSA severity and ferritin levels.[27,39–42]

Statistical Analysis

Given the complex multistage sampling design of the NHANES, we applied appropriate survey weights (MEC weights) from different survey cycles according to the NHANES analytical guidelines. Normally distributed continuous variables were presented as mean ± standard error (SE) and analyzed using weighted *t*-tests. Non-normally distributed continuous variables were expressed as median (interquartile range) and analyzed using weighted Kruskal–Wallis *H*-tests. Categorical variables were presented as absolute numbers (n) or percentages (%) and analyzed using weighted chi-square tests.

Due to the skewed distribution of ferritin levels, we applied natural logarithmic (ln)- transformation to normalize the distribution and categorized ln-transformation ferritin into quartiles (Q1-Q4). Multivariable logistic regression models were employed to investigate the association between ln-transformation ferritin levels and OSA prevalence, adjusting for potential confounders. RCS was utilized to explore potential non-linear relationships between ln-transformation ferritin levels and OSA risk. Subgroup analyses were conducted to examine the consistency of the association between ln-transformation ferritin levels and OSA risk across different subpopulations. To correct for multiple analyses, we applied Bonferroni correction, set at a Bonferroni-corrected $P < 0.005$ (0.05/11). Receiver Operating Characteristic (ROC) curve analyses were conducted to confirm the diagnostic and prognostic performance of the various biomarkers.

To explore the relationship between ferritin levels and survival in OSA patients, subjects were followed up, and Kaplan-Meier survival analyses and Cox proportional hazards regression were conducted to assess the correlation between ln-transformation ferritin levels and mortality, estimating hazard ratios (HRs) and 95% confidence intervals (95% CI). The RCS curve was also used to explore the association between ln-transformation ferritin and all-cause death in OSA patients.

All statistical analyses were performed using R software version 4.4.0 (https://www.r-project.org/). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Participants

Cross-Sectional Study

In this cross-sectional study, 4,809 overweight/obese participants were recruited from the NHANES database between 2015 and March 2020. The sample comprised 2,202 non-OSA and 2,607 OSA patients, with an OSA prevalence of 54%. As shown in Supplementary Table 1, OSA patients exhibited higher ln-transformation ferritin levels compared to non-OSA individuals. In OSA patients, the ln-transformation ferritin level was 4.75 (IQR: 4.02–5.35), which was higher than that in non-OSA patients (4.52, IQR: 3.85–5.17, $P < 0.001$). Additionally, OSA patients demonstrated significantly higher CRP (2.8 mg/L, IQR: 1.1–5.5) and total iron (12 mg/d, IQR: 9–17) levels compared to non-OSA participants (CRP: 2.2 mg/L, IQR: 1.0–4.6; total iron: 12 mg/d, IQR: 8–17) ($P < 0.05$).

Among non-OSA participants, the 20–40 age group was predominant (39%, n = 792), while in the OSA group, the 40–60 age range was most common (41%, n = 1,034). OSA prevalence was significantly higher in males (51%) than females (49%) ($P < 0.001$). OSA patients demonstrated higher rates of current smoking (18%), diabetes (15%), and hypertension (40%) compared to non-OSA subjects. Additionally, OSA patients exhibited elevated levels of WBC, HGB, HCT, HDL, and ln-transformation ferritin (all $P < 0.05$) (Supplementary Table 1).

Table 1 categorizes overweight/obese participants into quartiles based on ln-transformation ferritin concentrations: Q1 (ln-ferritin: 0.04–3.84, ferritin: 1.04–47.7, n = 1,203), Q2 (3.87–4.65, ferritin: 47.7–105.0, n = 1,214), Q3 (4.65–5.28, ferritin: 105.0–197.0, n = 1,197), and Q4 (5.28–7.80, ferritin: 197.0–2430.0, n = 1,195). As illustrated in Table 1,

Table 1 Characteristics of Overweight/Obese People Grouped According to Ln-Transformation Ferritin Quartiles in Cross-Sectional Analysis

Characteristic	Q1, N = 1203 (23%)	Q2, N = 1214 (27%)	Q3, N = 1197 (26%)	Q4, N = 1195 (24%)	P-value
Age (years)					<0.001
20–40 years	535 (47%)	366 (33%)	304 (32%)	251 (25%)	
40–60 years	388 (32%)	404 (35%)	401 (35%)	482 (45%)	
60+ years	280 (21%)	444 (32%)	492 (32%)	462 (29%)	
Gender, n (%)					<0.001
Female	1,045 (85%)	787 (68%)	513 (40%)	281 (21%)	
Male	158 (15%)	427 (32%)	684 (60%)	914 (79%)	
Race, n (%)					<0.001
Mexican American	226 (13%)	157 (8.1%)	161 (8.5%)	154 (8.8%)	
Other Hispanic	118 (7.2%)	121 (6.4%)	140 (7.6%)	131 (7.2%)	
Non-Hispanic White	419 (60%)	507 (69%)	483 (68%)	429 (65%)	
Non-Hispanic Black	330 (13%)	290 (9.4%)	297 (9.7%)	313 (9.9%)	
Other/multiracial	110 (6.3%)	139 (7.5%)	116 (5.9%)	168 (9.3%)	
BMI, n (%)					0.110
Overweight (25–30 kg/m^2)	354 (28%)	331 (28%)	348 (31%)	373 (34%)	
Class I Obesity (30–35 kg/m^2)	199 (17%)	206 (16%)	188 (14%)	197 (15%)	
Class II Obesity (35–40 kg/m^2)	193 (14%)	190 (16%)	150 (11%)	129 (10.0%)	
Class III Obesity (≥ 40 kg/m^2)	354 (28%)	331 (28%)	348 (31%)	373 (34%)	
PIR, n (%)					0.006
Low (<1.3)	391 (25%)	328 (18%)	307 (16%)	294 (15%)	
Medium (1.3–3.5)	470 (36%)	490 (37%)	494 (34%)	471 (35%)	
High (≥3.5)	342 (39%)	396 (46%)	396 (50%)	430 (50%)	
Alcohol, n (%)	389 (35%)	501 (47%)	560 (53%)	673 (64%)	<0.001
Smoking, n (%)					0.005
Former	244 (23%)	318 (28%)	355 (31%)	380 (35%)	
Never	771 (61%)	675 (54%)	633 (53%)	612 (53%)	
Now	188 (16%)	221 (19%)	209 (16%)	203 (13%)	
Sedentary time, n (%)					0.030
< 3h/d	189 (14%)	164 (9.6%)	184 (11%)	182 (12%)	
3–6 h/d	599 (54%)	604 (56%)	533 (47%)	570 (54%)	
≥ 6 h/d	415 (32%)	446 (34%)	480 (41%)	443 (34%)	
CVD, n (%)	72 (4.8%)	107 (7.2%)	109 (8.3%)	119 (7.4%)	0.092
Diabetes, n (%)	159 (9.6%)	190 (13%)	197 (13%)	245 (16%)	0.035
Hypertension, n (%)	362 (27%)	506 (38%)	521 (38%)	558 (39%)	<0.001
WBC (1000 cells/uL)	7.30 (6.00, 8.80)	7.40 (5.90, 8.90)	7.40 (6.10, 8.70)	7.00 (5.90, 8.50)	0.036
HGB (g/dL)	13.30 (12.40, 13.90)	14.10 (13.30, 14.90)	14.60 (13.80, 15.50)	15.10 (14.30, 15.80)	<0.001
HCT (%)	39.7 (37.5, 41.7)	41.9 (39.6, 43.8)	43.1 (40.7, 45.4)	44.2 (42.0, 46.3)	<0.001
RDW (%)	14.00 (13.20, 15.20)	13.50 (13.00, 14.00)	13.40 (13.00, 13.80)	13.30 (12.90, 13.80)	<0.001
HDL (mg/dL)	51 (43, 62)	50 (42, 62)	48 (41, 57)	46 (39, 55)	<0.001
TC (mg/dL)	179 (155, 206)	187 (162, 213)	191 (161, 214)	187 (165, 223)	<0.001
CRP (mg/L)	2.5 (1.1, 5.4)	2.7 (1.1, 5.6)	2.5 (1.1, 5.2)	2.2 (1.1, 4.4)	0.150
Total iron (mg/d)	11 (8, 16)	12 (8, 16)	12 (9, 17)	13 (9, 18)	<0.001

Abbreviations: PIR, Family poverty income ratio; BMI, Body mass index; CVD, Cardiovascular disease; CRP, C-reactive protein; WBC, White blood cell; HGB, Hemoglobin; HCT, Hematocrit; RDW, Red cell distribution width; HDL, High-Density Lipoprotein; TC, Total Cholesterol.

significant differences were observed in age, sex, race, PIR, alcohol consumption, and smoking status among the quartiles ($P < 0.05$), while BMI classifications showed no significant differences ($P = 0.110$).

The highest ferritin quartile (Q4) was characterized by a larger proportion of individuals aged 40–60 (45%), males (79%), those with PIR ≥ 3.5 (50%), alcohol consumers (64%), and lower current smoking rates (13%). This group also demonstrated longer sedentary time (34% reporting ≥6 h/d) and a higher prevalence of diabetes (16%) and hypertension

(39%) (all P < 0.05). Q4 exhibited significantly elevated levels of HGB (15.10 g/dL) and HCT (44.2%) (both P < 0.001), while Q2 showed the highest HDL (50 mg/dL). Interestingly, WBC counts in Q4 were lower (7.00 × 1000 cells/uL) compared to other quartiles (P = 0.036).

Notably, the CRP levels showed no significant differences across quartiles (P = 0.150). Conversely, total iron intake demonstrated a progressive increase across quartiles, with Q4 showing the highest mean intake of 13 mg/d, which was statistically significant (P < 0.001), indicating a potential relationship between ferritin levels and dietary iron consumption.

Prospective Study

As shown in Supplementary Figure 1, our prospective study initially included 1,801 participants, comprising 832 OSA female patients and 969 non-OSA female participants. The mean follow-up duration was 140 months (IQR: 54 −158 months).

Based on the baseline characteristics of 832 overweight/obese female OSA patients, the cohort primarily consisted of middle-aged women. The majority of participants (50%) were aged 40–50 years, with 31% in the 30–40 years age group. Regarding racial composition, Non-Hispanic White participants predominated (64%), followed by Non-Hispanic Black (16%) and Mexican American (10%) participants.

In terms of obesity status, 29% were overweight, 27% had Class I obesity, 25% had Class II obesity, and 19% had Class III obesity. The PIR distribution showed 38% in the medium category, 36% in the high category, and 25% in the low category. Lifestyle factors revealed that 49% consumed alcohol, and smoking status varied, with 52% never smoking, 29% currently smoking, and 20% being former smokers.

Comorbidities were relatively low, with cardiovascular disease at 1.7%, diabetes at 7.5%, and hypertension at 28%. Biochemical analyses showed median values for HGB at 13.50 g/dL, HDL at 49 mg/dL, TC at 190 mg/dL, and CRP at 2.8 mg/L (Table 2).

Table 2 Characteristics of Overweight/Obese Female OSA Patients in Prospective Study

Characteristic	N = 832 (100%)
Age (years)	
20–30 years	165 (19%)
30–40 years	271 (31%)
40–50 years	396 (50%)
Race, n (%)	
Mexican American	175 (10%)
Other Hispanic	84 (6.0%)
Non-Hispanic White	312 (64%)
Non-Hispanic Black	225 (16%)
Other/multiracial	36 (4.2%)
BMI, n (%)	
Overweight (25–30 kg/m^2)	240 (29%)
Class I Obesity (30–35 kg/m^2)	223 (27%)
Class II Obesity (35–40 kg/m^2)	196 (25%)
Class III Obesity (≥ 40 kg/m^2)	173 (19%)
PIR, n (%)	
Low (<1.3)	285 (25%)
Medium (1.3–3.5)	321 (38%)
High (≥3.5)	226 (36%)
Alcohol, n (%)	382 (49%)
Smoking, n (%)	
Former	133 (20%)
Never	472 (52%)
Now	227 (29%)

(*Continued*)

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Table 2 (Continued).

Characteristic	N = 832 (100%)
CVD, n (%)	18 (1.7%)
Diabetes, n (%)	74 (7.5%)
Hypertension, n (%)	247 (28%)
WBC (1000 cells/uL)	7.80 (6.50, 9.50)
HGB (g/dL)	13.50 (12.90, 14.10)
HCT (%)	39.8 (38.0, 41.6)
RDW (%)	13.00 (12.40, 13.80)
HDL (mg/dL)	49 (42, 58)
TC (mg/dL)	190 (165, 220)
CRP (mg/L)	2.8 (1.0, 5.6)
Total iron (mg/d)	11 (8, 16)

Abbreviations: PIR, Family poverty income ratio; BMI, Body mass index; CVD, Cardiovascular disease; CRP, C-reactive protein; WBC, White blood cell; HGB, Hemoglobin; HCT, Hematocrit; RDW, Red cell distribution width; HDL, High-Density Lipoprotein; TC, Total Cholesterol.

Association Between Ferritin and OSA

Association between ferritin and OSA multivariable logistic regression analysis was performed to examine the relationship between ln-transformation ferritin levels and OSA risk. Compared to the second quartile (Q2, reference group), subjects in Q4 showed consistently higher OSA risk across all models. In the crude model, Q4 vs Q2: OR = 1.11, 95% CI: 1.05–1.18, P < 0.001, P for trend < 0.001. This association remained significant after adjusting for demographic and clinical factors in Model 1 (Q4 vs Q2: OR = 1.07, 95% CI: 1.02–1.13, P = 0.010, P for trend = 0.001) and Model 2 (Q4 vs Q2: OR = 1.07, 95% CI: 1.01–1.13, P = 0.020, P for trend = 0.010) (Table 3).

Furthermore, we conducted a sensitivity analysis investigating the association between ferritin levels and OSA using three different symptomatic definitions (Question 1: focusing on snoring frequency, Question 2: emphasizing gasping, snorting, or breathing cessation, Question 3: addressing daytime sleepiness). Among OSA patients primarily characterized by snorting, gasping, or breathing interruptions, ferritin showed a significantly strong association (Q3 vs Q2: OR = 1.35, 95% CI: 1.06–1.72, P = 0.017; Q4 vs Q2: OR = 1.63, 95% CI: 1.06–2.49, P = 0.028, P for trend = 0.001). However, in OSA patients with predominant daytime sleepiness, the association with ferritin was not statistically significant (all P > 0.05) (Supplementary Table 2).

Nonlinear Relationship Between Ferritin Levels and OSA in Overweight/Obese Individuals

We investigated the potential non-linear relationship between ferritin levels and OSA in overweight/obese individuals. Supplementary Figure 2 illustrates a significant non-linear association between ln-transformed ferritin and OSA risk in the crude model and Model 1 (P = 0.042 and P = 0.090, respectively). Interestingly, the RCS curve in the crude model,

Table 3 Multivariate Logistic Regression Analysis of Ferritin for Risk of OSA

Variables	Crude Model		Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Q1 group	0.99 (0.95, 1.04)	0.800	1.03 (0.97, 1.08)	0.300	1.05 (0.99, 1.10)	0.095
Q2 group	Reference		Reference		Reference	
Q3 group	1.06 (1.00, 1.13)	0.055	1.04 (0.99, 1.11)	0.130	1.05 (0.99, 1.11)	0.110
Q4 group	1.11 (1.05, 1.18)	<0.001	1.07 (1.02, 1.13)	0.010	1.07 (1.01, 1.13)	0.020
P for trend	< 0.001		0.001		0.010	

Notes: Crude model: No covariates. Model 1: Adjusted for Age, Gender, Race, BMI, PIR. Model 2: Adjusted for Model 1 + Alcohol, Smoking, Sedentary time, CVD, Diabetes, Hypertension, WBC, CRP, HGB, HCT, RDW, HDL, TC, Total Iron intake.
Abbreviations: OR, odd ratio; CI, confidence interval.

without adjustment for any confounding factors, exhibited a monotonic increasing trend. In contrast, Model 1, which adjusted for demographic-related confounding factors and BMI, revealed a U-shaped non-linear association. In Model 2, which adjusted for all potential confounders, the RCS curve demonstrated a significant U-shaped nonlinear association (P-non-linear = 0.029) (Figure 2).

Moreover, we stratified the analysis by BMI categories corresponding to different obesity levels. This revealed varying associations across BMI subgroups. Specifically, a non-linear U-shaped association was observed in the overweight group (P-non-linear = 0.050). However, this non-linear relationship was not evident in the Class I Obesity (P-non-linear = 0.050), Class II Obesity (P-non-linear = 0.509), or Class III Obesity (P-non-linear = 0.110) groups (Figure 3).

Subgroup Analysis

We further performed subgroup analyses with ln-transformed ferritin level as a continuous variable to explore the association between serum ferritin level and OSA (Figure 4). The interaction was not significant after stratification by age, gender, race, BMI, PIR, alcohol consumption, smoking status, diabetes, hypertension, CVD, and sedentary time. These results confirm the strong association between ln-transformed ferritin levels and OSA risk across different subgroups (P > 0.005 for interaction).

Diagnostic Performance of Ferritin for OSA

We evaluated the predictive capability of various biomarkers for the diagnosis of OSA. As shown in Supplementary Figure 3, ferritin demonstrated an AUC of 0.54 (95% CI: 0.52–0.55), slightly outperforming HGB (AUC: 0.53, 95% CI: 0.51–0.54) and WBC (AUC: 0.52, 95% CI: 0.51–0.54). Among the biomarkers tested, CRP exhibited the highest diagnostic performance, with an AUC of 0.55 (95% CI: 0.53–0.56).

While ferritin showed a marginal advantage over hemoglobin and white blood cell count, the diagnostic performance of ferritin alone, as well as the other individual biomarkers, remains modest.

Associations of Ferritin With All-cause Mortality in OSA

As we stated above, since ferritin measurements were performed only in female patients during the three earlier cycles, we only targeted female obese/overweight patients. In this prospective study, we included 832 obese/overweight female OSA patients (Supplementary Figure 1). The relationship between ln-transformed serum ferritin levels and all-cause mortality was comprehensively examined.

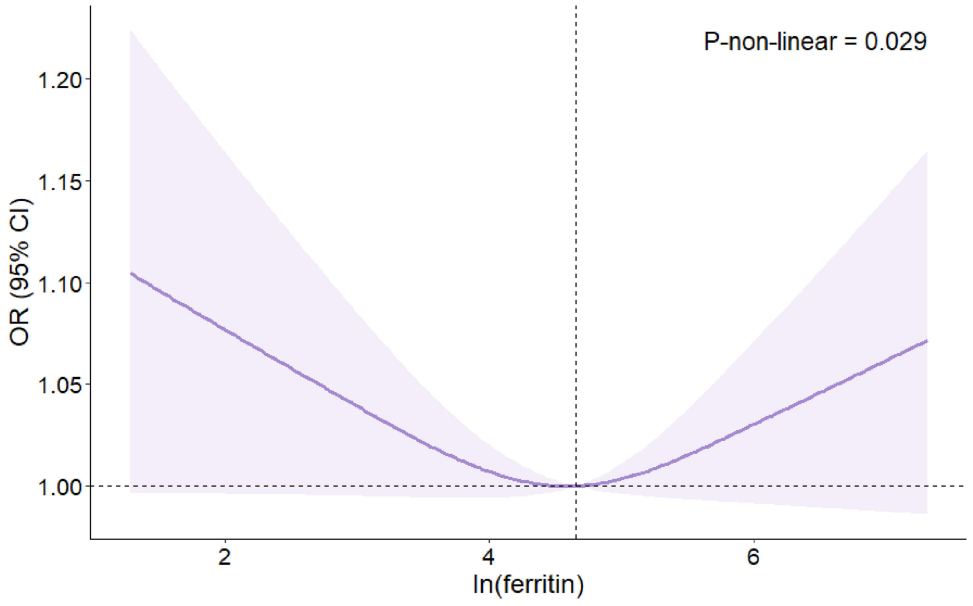

Figure 2 Odds ratio of OSA according to ln-transformation ferritin levels in overweight /obese people.

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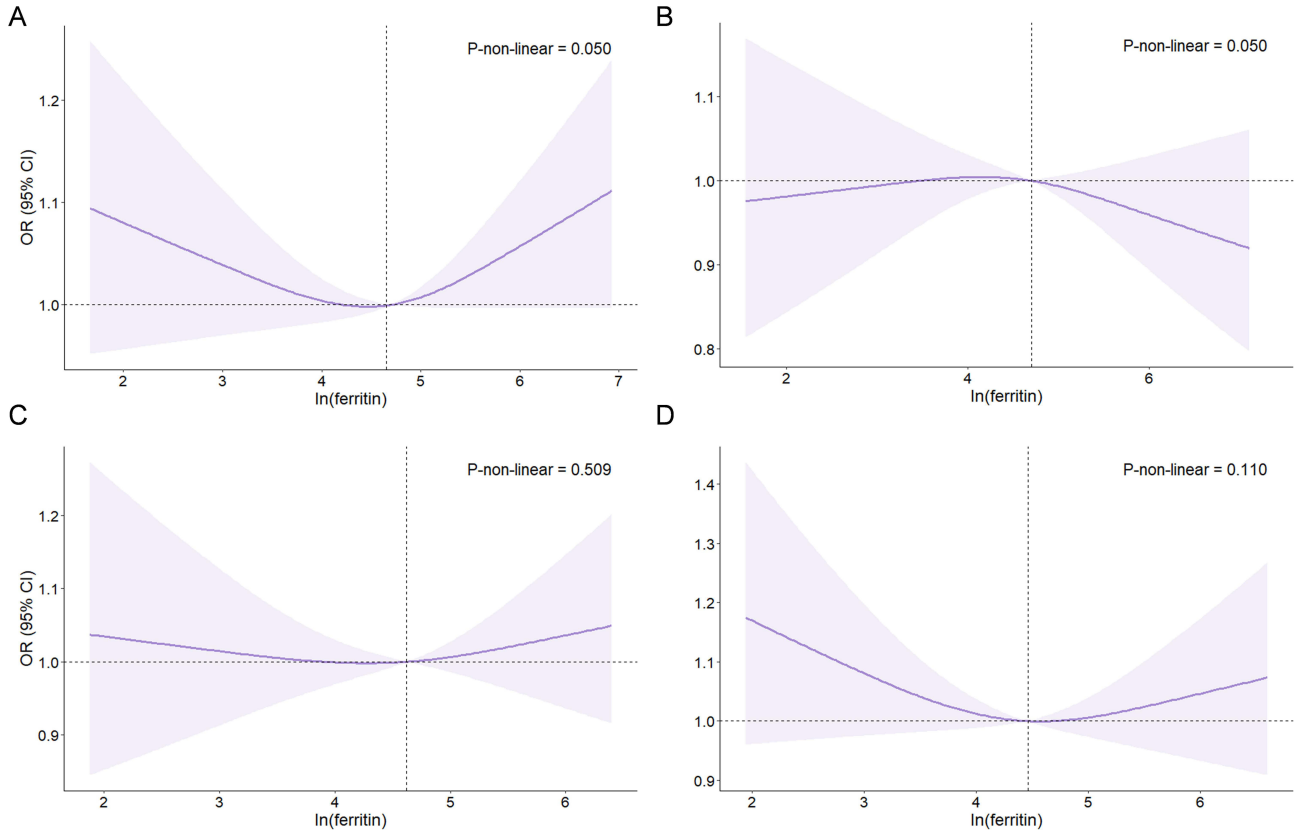

Figure 3 RCS curves of OSA derived from ln-transformed ferritin levels stratified by BMI in overweight/obese individuals. (**A**) Overweight, (**B**) Class I Obesity, (**C**) Class II Obesity, (**D**) Class III Obesity.All covariates in Model 2 except BMI were adjusted.

Supplementary Figure 4 presents the Kaplan-Meier all-cause mortality curves for different ln-transformation ferritin levels groups. After rigorous statistical analysis, we observed differential mortality risks across ferritin level quartiles. In the fully adjusted Model II, which controlled for potential confounding factors including alcohol consumption, smoking status, cardiovascular disease, diabetes, hypertension, and multiple hematological parameters, the highest quartile (Q4) demonstrated a significantly increased mortality risk (HR: 5.46, 95% CI: 1.18–25.16, P = 0.029) compared to Q2. Trend analysis revealed a statistically significant association across ferritin quartiles (P for trend = 0.032), suggesting a potential dose-response relationship. Although the Q1 and Q3 groups showed elevated mortality risks, these did not reach statistical significance (Q1: HR 3.29, 95% CI: 0.58–18.67, P = 0.178; Q3: HR 3.30, 95% CI: 0.70–15.47, P = 0.130) (Table 4).

Notably, RCS analysis indicated a monotonically increasing relationship between ln-transformed ferritin levels and all-cause mortality, with a non-linear component test yielding P non-linear = 0.797 (Figure 5).

Discussion

In this comprehensive investigation, we utilized the NHANES database to conduct both cross-sectional and prospective analyses, aiming to elucidate the complex relationship between serum ferritin levels and the risk and prognosis of OSA in overweight/obese individuals. Our findings revealed a nonlinear U-shaped association between ferritin levels and OSA risk in overweight/obese adults, with an inflection point at 97.51 ng/mL (ln-transformed ferritin = 4.58). Furthermore, we demonstrated that elevated ferritin levels were significantly associated with an increased risk of all-cause mortality in female OSA patients.

The association between serum ferritin levels and OSA risk has been extensively studied across diverse populations, yielding inconsistent results. Our findings align with those of Seifen et al, who conducted a retrospective analysis of polysomnographic records and serum ferritin levels in 90 carefully selected patients with suspected OSA at a tertiary sleep medicine center. Their study revealed a significant positive correlation between serum ferritin levels and the AHI,

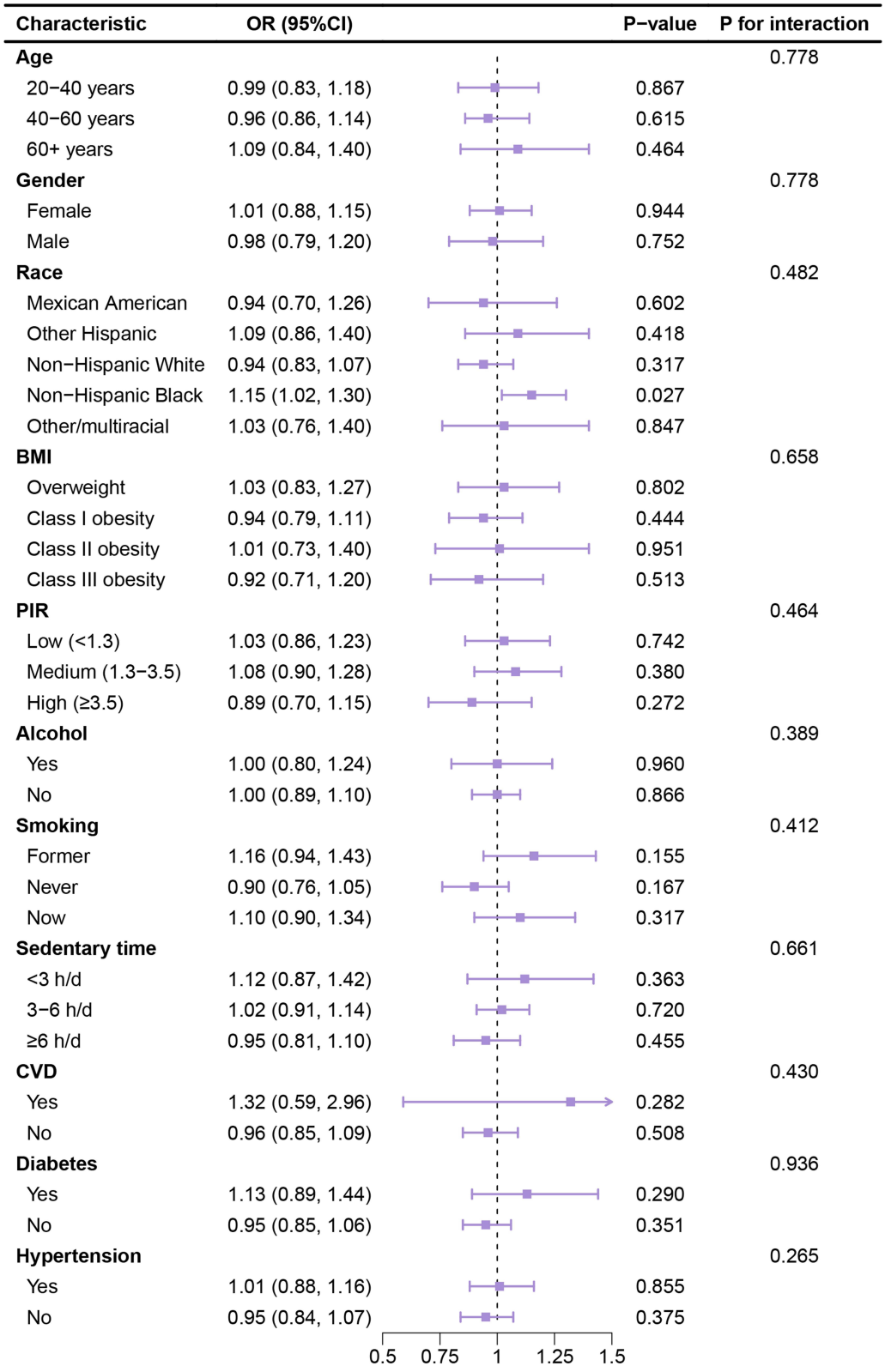

Figure 4 Subgroup analyses between ferritin levels and OSA in overweight/obese individuals. Bonferroni correction was used to adjust for multiple comparisons, with significance set at $P < 0.005$.

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Table 4 The Association Between Ln-Transformation Ferritin and All-Cause Mortality

Variables	Crude Model		Model I		Model II	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Q1 group	2.00 (0.50, 8.02)	0.325	1.65 (0.41, 6.63)	0.481	3.29 (0.58, 18.67)	0.178
Q2 group	Reference		Reference		Reference	
Q3 group	1.85 (0.46, 7.42)	0.382	1.88 (0.46, 7.63)	0.225	3.30 (0.70, 15.47)	0.130
Q4 group	2.88 (0.78, 10.63)	0.113	2.17 (0.57, 8.31)	0.256	5.46 (1.18, 25.16)	0.029
P for trend	0.129		0.258		0.032	

Notes: Crude model: No covariates. Model I: Adjusted for Age, Race, BMI, PIR.Model II: Adjusted for Model I + Alcohol, Smoking, CVD, Diabetes, Hypertension, WBC, CRP, HGB, HCT, RDW, HDL, TC, Total Iron intake.
Abbreviations: HR, hazard ratio; CI, confidence interval.

which persisted after age adjustment. However, their analysis did not account for BMI, leaving the potential influence of obesity on ferritin levels unaddressed.[24]

Contrasting our results, a study on an Icelandic OSA cohort by Thorarinsdottir et al found no OSA-induced differences in serum ferritin levels after adjusting for age, BMI, smoking history, hypertension, CVD, and type 2 diabetes. In subgroup analyses of patients with BMI 30–35 kg/m^2 (corresponding to Class I Obesity in our study) and BMI ≥ 35 kg/m^2 (Class II and III Obesity in our research), they observed no association between ferritin and OSA after controlling for confounding factors. However, their adjustment model did not consider the potential impact of erythrocyte-related indicators and lipid metabolism biomarkers on this association.[23]

Based on our findings and existing literature, we propose several hypotheses to explain the observed U-shaped association. Regarding the association between low ferritin levels and increased OSA risk, one potential mechanism involves iron deficiency anemia. Ferritin is a crucial indicator of iron status, and low levels may lead to reduced oxygen-carrying capacity of red blood cells. Consequently, this could lower $SpaO_2$ levels during wakefulness and sleep, thereby increasing OSA risk. While studies directly linking iron deficiency anemia to OSA are limited, research on children with sickle cell anemia has shown a marked increase in OSA risk.[43] Moreover, the neurological impact of iron deficiency may play a role. Iron is an essential cofactor in the nervous system, and its deficiency may impair dopaminergic function, affecting sleep-wake cycles. This mechanism helps explain the frequent occurrence of periodic limb movements (PLM) and excessive daytime sleepiness in OSA patients. Notably, PLM and restless legs syndrome (RLS) frequently co-occur

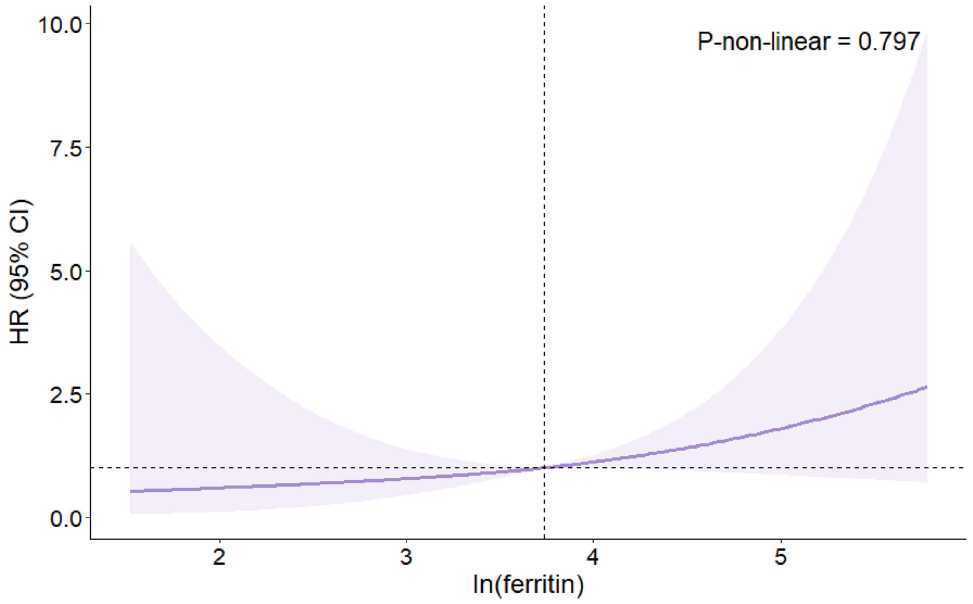

Figure 5 Association of ln-transformation ferritin levels with all-cause mortality.

with OSA, and their pathogenesis is closely linked to iron metabolism. Low iron states are likely associated with genetic polymorphisms and altered catabolic enzyme activity in PLM and RLS.[44–46] Conversely, the link between high ferritin levels and increased OSA risk likely involves different mechanisms. Elevated ferritin levels often indicate systemic inflammation, with acute inflammation prompting rapid ferritin synthesis in the liver. High ferritin levels often reflect underlying metabolic disorders, including insulin resistance and hyperlipidemia, which recent animal studies have shown to be closely associated with OSA development.[39,47] This correlation demonstrates the complex interplay between iron metabolism, metabolic dysfunction, inflammation, and OSA.

Our prospective study demonstrated an association between ferritin levels and increased all-cause mortality in overweight/obese female OSA patients. However, the interpretation of these findings must be considered within the context of current literature on gender-specific OSA outcomes, which remains inconclusive. A recent study found that female OSA patients with acute coronary syndrome exhibited higher rates of major adverse cardiovascular and cerebrovascular events (MACCE) compared to their male counterparts.[48] An earlier prospective cohort study reported contrasting results, showing that OSA was associated with increased all-cause mortality only in males aged ≥ 70, with no significant association observed in females.[49] Given these disparate findings, we emphasize that our results should be interpreted with careful consideration of gender differences. The applicability of our findings is specifically limited to overweight/obese female OSA patients aged 20–49 years, and further prospective studies are needed to validate these relationships in male patients.

Currently, the latest American Academy of Sleep Medicine clinical guidelines recommend iron supplementation for ferritin levels below 50 ng/mL and have shown that iron supplementation can alleviate RLS symptoms in patients with ferritin levels below 45 ng/mL.[50] Additionally, while a study has demonstrated improvements in AHI following intravenous carboxymaltose iron administration in anemic chronic heart failure patients,[51] there remains insufficient clinical trial evidence to establish the relationship between iron supplementation or iron overload reduction and OSA outcomes in the general population. While ferritin's AUC value for OSA classification is suboptimal, making it unlikely to serve as an ideal OSA screening indicator, its significance in OSA management cannot be overlooked. Based on our findings, we particularly recommend prioritizing OSA screening in patients with anemia and obesity.[52] Furthermore, we recommend that clinicians exercise particular caution when using iron supplementation to correct anemia or RLS symptoms in female OSA patients, as excessive supplementation leading to iron overload may increase the risk of all-cause mortality.[53]

Our study possesses several notable strengths. Firstly, to our knowledge, this research represents the most extensive cross-sectional and prospective investigation examining the relationship between ferritin levels, OSA risk, and all-cause mortality in overweight/obese individuals. Notably, we are the first to explore the association between ferritin levels and OSA-related all-cause mortality in this population cohort, addressing a critical gap in the current literature. Moreover, given that overweight/obesity is a well-established risk factor for OSA, focusing on this population is of paramount importance for monitoring and prevention strategies. However, research data on ferritin levels within this range of overweight/obese individuals remains insufficient. Our study not only enriches the findings of studies targeting this specific population but also stratifies the overweight/obese group according to BMI, further investigating the relationship between ferritin and OSA across different obesity grades.

Despite these strengths, our study has several significant limitations that warrant consideration. Firstly, our operational definition of OSA relied solely on three primary symptoms: snoring, observed respiratory pauses, and daytime sleepiness. While this definition captures a substantial proportion of OSA patients, it represents a simplified screening approach for the general population.[54] Notably, it does not incorporate other crucial patient characteristics such as high blood pressure, BMI, age, neck circumference, and gender, which could enhance diagnostic accuracy. Therefore, the interpretation of our findings should be approached with caution. Secondly, due to the lack of necessary data, we could not employ more accurate diagnostic methods for OSA, such as laboratory PSG, which is widely recognized as the gold standard for OSA diagnosis. The absence of critical data, including AHI or detailed descriptions of OSA symptoms, restricted our ability to conduct stratified analyses or subgroup clustering of high-risk OSA populations. Third, owing to the nature of the observational study design, our findings cannot be used to infer causality. Additionally, while we controlled for numerous confounding factors, we acknowledge that not all potential confounders could be accounted for in our analysis. Fourth, the prospective part of our study observed relatively few death cases (only 24 all-cause deaths), potentially introducing bias. The small number of events indeed limits the statistical power of our analysis and may affect the robustness of our findings, potentially increasing the risk of type II errors.

More extended observation periods and larger cohorts are needed better to elucidate the prognostic role of ferritin levels in OSA. Fifth, our prospective study was limited to overweight/obese female OSA patients, which prevents us from concluding ferritin associations in male OSA patients. This gender-specific limitation is particularly noteworthy considering the potential differences in OSA prognosis between males and females. Sixth, our broad exclusion criteria may have introduced potential selection bias. Lastly, as the NHANES study was conducted on a US population, extrapolating these findings to other populations requires further verification.

Conclusion

This comprehensive study utilizing the NHANES database investigated the relationship between serum ferritin levels and OSA in overweight/obese individuals. We found that ferritin levels in overweight/obese individuals show a U-shaped relationship with OSA risk. Additionally, elevated ferritin levels correlate with increased all-cause mortality in female overweight/obese OSA patients. In the future, further research is needed to explore the potential associations between ferritin, inflammation, obesity, and OSA.

Data Sharing Statement

The datasets generated and analyzed during the current study are available on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

Ethics Approval

The Ethics Committee of the First Affiliated Hospital of Nanchang University strictly adheres to the Declaration of Helsinki and the International Ethical Guidelines for Health-related Research Involving Humans, performing independent ethical review responsibilities. Since this study used publicly available database data obtained legally, it met the exemption from review conditions stipulated by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

Author Contributions

YZ: Conceptualization, Methodology, Formal Analysis, Writing - Original Draft. PLZ: Methodology, Data Curation, Writing - Original Draft, Writing - Review & Editing. CX: Investigation, Software, Visualization, Writing - Original Draft. HS: Data Curation, Statistical Analysis. RDL: Statistical Analysis, Validation. LHS: Supervision, Project Administration, Funding Acquisition, Writing - Review & Editing. YHY: Supervision, Project Administration, Resources, Funding Acquisition, Writing - Review & Editing. All authors contributed significantly to the work, drafted or revised the article, approved the final version for publication, and agreed on the journal and to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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