Iron Levels and Depression Symptoms in US Pregnant, Nonpregnant, and Postpartum Women: NHANES 2005-2010 & 2015-2018

Abstract

Background: Iron deficiency and depression disproportionately affect women. However, the relationship between iron status and depression across pregnancy and postpartum stages remains unclear, especially when considering socioeconomic factors.
Objective: Examine associations between iron deficiency, ferritin levels, and depressive symptoms in US women across pregnancy and the postpartum period, stratified by income.
Methods: Logistic and negative binomial regression analyses were conducted using NHANES 2005-2010 and 2015-2018 survey cycles for women aged 20-44 years, stratified by pregnancy status and income level. Iron deficiency was defined as ferritin < 15 µg/L, and ferritin levels were examined as a continuous variable. Depressive symptoms were assessed using the PHQ-9.
Results: Iron deficiency was not associated with depression in any subgroup. Higher ferritin levels were associated with lower depression scores in low-income pregnant women (IRR = 0.996, 95% CI: 0.993-0.999) but increased odds of depression (OR = 1.009, 95% CI: 1.002-1.017) and were associated with higher depression scores (IRR = 1.004, 95% CI: 1.001-1.006) among low-income postpartum women, but lower depression scores in low-income pregnant women (IRR = 0.996, 95% CI: 0.993-0.999).
Conclusion: The relationship between iron status and depression varies by pregnancy status and income level, with low-income pregnant women showing increased depression risk with lower ferritin levels and postpartum women showing increased depression risk with higher ferritin levels. Monitoring iron status and mental health during pregnancy and the postpartum period may be crucial for women, especially those with lower socioeconomic status.

Introduction

Iron deficiency (ID) is the most prevalent nutrient deficiency worldwide, disproportionately affecting women of reproductive age and children both in developing and developed nations[1]. In the United States, 10% of non-pregnant women of reproductive age struggle with ID[2]. The high prevalence of ID is concerning given its potential association with an increased risk of depressive symptoms[3]. A link between ID and depression is biologically plausible due to iron's critical role in neurotransmitter synthesis and function[4,5]. While observational studies have documented an association between ID and depression[3], evidence from randomized controlled trials remains limited.

Elucidating the relationship between ID and depression carries particular importance for women due to their increased susceptibility to both conditions. The prevalence of major depressive disorder in the US is higher among adult females (10.3%) compared to males (6.2%)[6]. Moreover, ID risk is heightened during pregnancy and the postpartum period due to increased iron demands[7]. However, data on the full spectrum of iron status in U.S. pregnant and postpartum

women has been lacking. Low income is an additional risk factor that may exacerbate vulnerability to both ID and depressive symptoms in women[3]. Evaluating income level as a potential effect modifier can help improve our understanding of this relationship.

Several studies have investigated the association between iron status and depression in women, with mixed results. In postpartum women, low iron status, particularly iron deficiency anemia, has been associated with increased risk of depression[8,9]. However, the direction of this association remains unclear and may be confounded by other factors[10]. In non-pregnant women of reproductive age, some observational studies have linked iron deficiency without anemia to decreased well-being[11] or increased depressive symptoms[12,13], while others have found no significant associations[14]. Despite these findings, significant gaps remain in understanding the association between iron status and depression across different populations. Most prior studies have used small, homogeneous samples, limiting generalizability[8,9]. Additionally, studies have inconsistently controlled for potential confounding factors such as inflammation, BMI, and socioeconomic status[8,9,15].

Limited data exists comparing associations of iron status with depressive symptoms across income levels, and previous studies have resulted in mixed findings. Ciulei et al.[3] used NHANES 2005-2010 data and found that nonpregnant US women with iron deficiency had a higher prevalence of somatic depressive symptoms than iron-sufficient women, especially among those with low income. In contrast, Bodnar et al.[16] used NHANES III data to investigate iron deficiency among low-income postpartum women in the US and found an increased risk compared to never-pregnant women with higher income, but did not examine depressive symptoms. Another study by Bodnar et al.[17] found a high prevalence of postpartum anemia among low-income and minority women in 12 US states using CDC Pregnancy Nutrition Surveillance System data, but also did not assess depression. Very limited data exists comparing associations between pregnant, postpartum, and non-pregnant women within the same population.

To address these gaps, the present study aims to investigate associations between iron levels and depressive symptoms in U.S. pregnant, non-pregnant, and postpartum women across income levels using nationally representative data from the National Health and Nutrition Examination Survey (NHANES) 2005-2010 and 2015-2018 cycles. We hypothesized that iron deficiency and lower ferritin levels would be associated with increased depression risk, with stronger associations among low-income pregnant and postpartum women. By leveraging this large, diverse sample and controlling for key confounding variables, we hope to clarify the relationship between iron status and depression in women across reproductive and socioeconomic groups. Such an investigation can provide valuable insights to guide prevention and treatment strategies for these intersecting public health issues that disproportionately impact women. Furthermore, examining the role of income may help identify subgroups most at risk and inform targeted interventions to reduce disparities in both iron deficiency and depression among women of reproductive age.

Methods

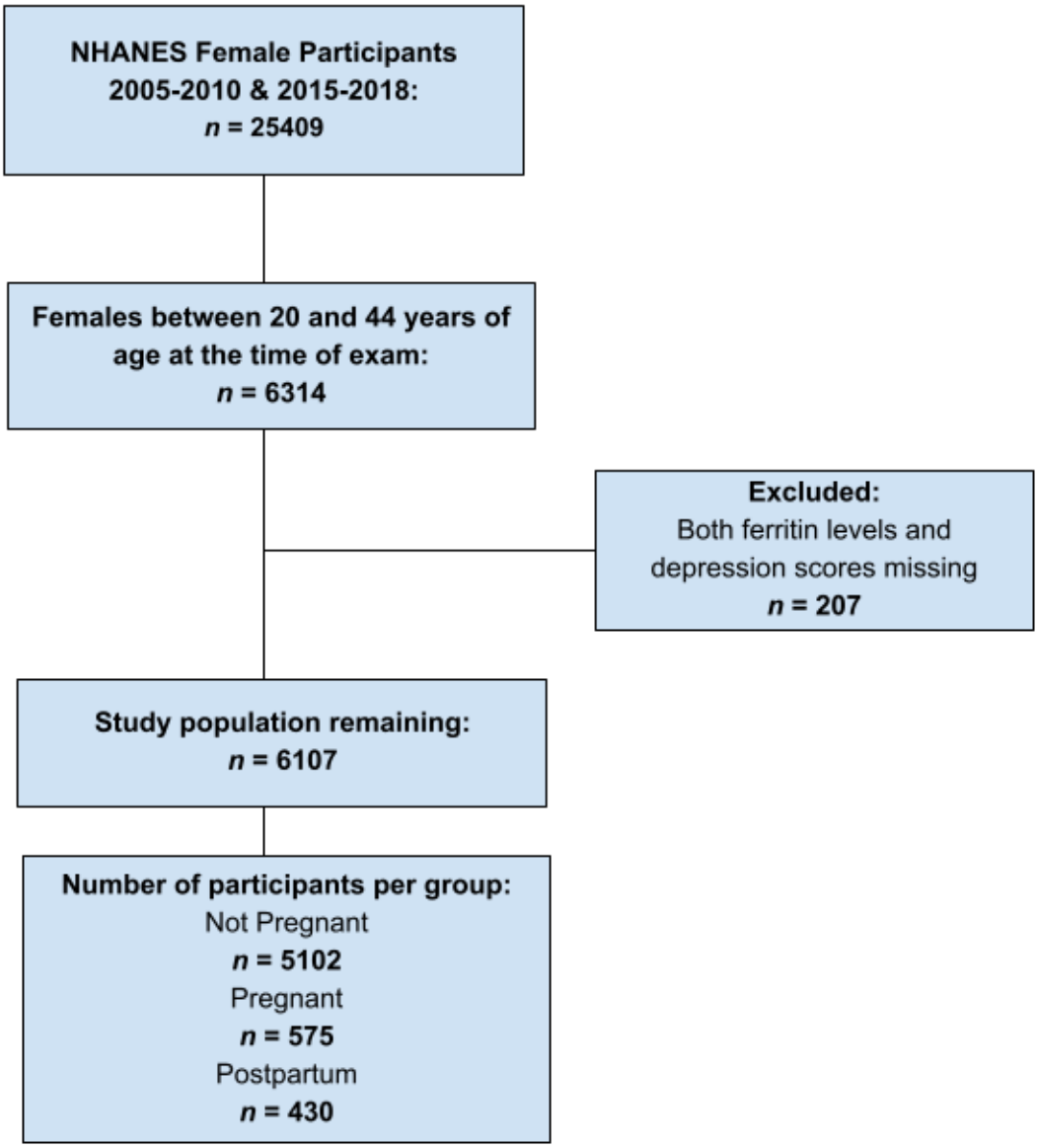
To investigate the associations between iron deficiency, ferritin levels, and depression scores across different stages of pregnancy and the postpartum period, while considering the role of income status, we conducted logistic regression and negative binomial regression analyses on a large, population-based dataset, stratifying by pregnancy status and income level and adjusting for relevant covariates.

Study population

The following analyses used data from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional dataset that gathers comprehensive information on the health and nutritional status of adults and children in the United States through interviews and physical examinations. The 2005-2010 and 2015-2018 NHANES cycles were used in this analysis. The years 2011-2014 were excluded due to the absence of measurements for ferritin (Ft). The data range was limited to 2018 as the NHANES program paused field operations in March 2020 in response to the COVID-19 pandemic, rendering data collection for the 2019-2020 cycle incomplete, and thus not nationally representative. The analyses were restricted to women between 20 and 44 years of age (N=6107) as the NHANES reproductive variables are confined to this age range.

Those with both Ft levels and depression scores missing were excluded (N=207). Pregnant women (N=575) were included based on the question from demographics (RIDEXPRG - Pregnancy Status at Exam), postpartum women (N=430) were defined as 12 months or less after giving birth, and non-pregnant women (N=5102) were also included in the analyses. The NHANES protocol was approved by the NCHS Ethics Review Board[18].

Population flow chart:



Assessment of iron biomarkers

The serum ferritin (Ft) measurement methodology used in NHANES from 2005 to 2010 involved immuno-turbidimetry using Roche assays on different clinical analyzers. Serum FT specimens were processed, stored, and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for analysis. The specific analyzer used changed from the Roche/Hitachi 912 in 2005-2008 to the Roche Elecsys 170 in 2009-2010. A crossover study was performed to compare the ferritin data

between these two analyzers, and a Deming regression equation was provided to trend the data: Log10 (E170) = 0.989*Log10(Hitachi 912) + 0.049. The equation was used in this analysis to standardize FT values across years[19,20,21,22,23]. Iron deficiency (ID) was classified as Ft < 15 µg/L.

While the WHO recommends a ferritin cutoff of <15 ng/mL to define iron deficiency, recent evidence suggests this may fail to identify early stages of iron deficiency. Physiologically-based thresholds derived from biomarkers of iron-deficient red blood cell production indicate the onset of iron deficiency at higher ferritin levels, around 20-25 µg/L in children and young women[24] and potentially up to 50 ng/mL in adults[25]. To capture potential effects of these early stages of iron deficiency and to examine the nuanced relationships between iron stores and depression across the entire spectrum of iron status, we used ferritin as a continuous predictor in addition to the binary WHO cut off. This approach allows for a more comprehensive assessment of the association between iron status and depression, rather than just comparing iron-deficient and non-deficient individuals based on a single cutoff value.

Depressive symptoms

Depression was measured using the Patient Health Questionnaire (PHQ-9)[26], a publicly available nine-item depression screening instrument (variable name prefix DPQ) that asks questions about the frequency of symptoms of depression over the past 2 weeks. The PHQ-9 scale was administered through Computer Assisted Personal Interviews in mobile examination units. Response categories "not at all," "several days," "more than half the days," and "nearly every day" were given a score ranging from 0 to 3, resulting in a total score between 0 and 27. A final follow-up question assesses the overall impairment of the depressive symptoms. A score of 10 or higher has been well validated and is commonly used in clinical studies to define depression, demonstrating 88% sensitivity and specificity in an adult primary care sample. Other methods for defining depression based on this instrument are also used. NHANES data [27–31] has shown that the PHQ-9 scale measures depressive symptoms across the entire spectrum, with symptoms grouped under two constructs: cognitive/affective and somatic. The cognitive/affective construct includes items 1 (anhedonia), 2 (depressed mood), 6 (low self-esteem), 7 (concentration difficulties), 8 (psychomotor disturbances), and 9 (suicidal ideation), with a possible score ranging from 0 to 18. The somatic construct comprises items 3 (sleep disturbance), 4 (fatigue), and 5 (appetite changes), with a possible score ranging from 0 to 9.

Assessment of confounders

High Sensitivity C-reactive protein (hsCRP) levels were controlled for in the adjusted models because Ferritin is known to be an acute-phase reactant, meaning that its levels can increase in response to inflammation or infection, independent of iron status[32]. In some cases, elevated ferritin levels may not accurately reflect iron stores but rather indicate an underlying inflammatory process. Controlling for hsCRP, as a marker of inflammation, was used to help determine if the association between iron levels and depression scores in women is primarily driven by inflammation. Due to a change in lab methodology between 2017-2018 and 2015-2016 data

cycles, a regression equation derived from the bridging study was recommended when examining values collected on the DxC 660i (2015-2016 instrument) that were less than ≤ 23 mg/L33. The following equation was applied: **Y** *(Cobas 6000)* **= 0.8695** (95%CI: 0.8419 to 0.8971) *** X** *(DxC 660i)* **+ 0.2954** (95%CI: 0.2786 to 0.3121)

Body mass index (BMI) was included as a covariate in the analyses to control for potential confounding effects on the relationship between iron status and depression. Obesity, typically defined as a BMI ≥ 30 kg/m², has been associated with both iron deficiency34 and an increased risk of depression34–36. By controlling for BMI in the analyses, we aimed to isolate the independent effect of iron status on depression, minimizing the potential confounding influence of obesity on this relationship.

Several socio-demographic variables were also controlled for including age at screening, race and ethnicity, and income level.

Statistical analysis

For NHANES datasets, the use of sampling weights and sample design variables is necessary to obtain unbiased estimates and accurate standard errors and confidence intervals[37]. When combining 5 survey cycles (10 years)[38] of continuous NHANES data, constructing weights is essential. In this paper, the combined MEC exam weight was used for the analyses.

All data preparation was performed in Python[39] (version 3.11.4) and all statistical analyses were performed in R[40] (version 4.3.2), using the Survey[41] package for analysis of complex survey samples.

To investigate the potential impact of missing data on the analyses, a Chi-square test for independence was conducted to determine if there was a statistically significant difference in the proportion of missing ferritin values among different race-ethnicity groups. The Chi-square test resulted in a statistic of approximately 41.00 with a p-value of 2.69e-08. As the p-value was significantly less than 0.05, the null hypothesis was rejected, indicating a statistically significant difference in the proportion of missing ferritin values among the race-ethnicity groups. This finding suggests that the missingness may not be completely random and should be considered in further analyses and handling of missing ferritin values.

Given the association between the likelihood of missing ferritin values and race-ethnicity, the k-Nearest Neighbors (k-NN) method was used for data imputation to minimize bias and retain as much information as possible. The k-NN method imputes missing ferritin values based on the most similar respondents, considering variables such as race-ethnicity, household income, and income-to-poverty ratio. Before imputation, all predictor variables were appropriately scaled to ensure equal contribution to the distance calculation. Finally, the k-NN imputation was performed using the available variables as predictors to impute missing transformed ferritin values.

The association between iron status and presence of depression (based on the recommended cutoff score ≥10) was evaluated using logistic regression models. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated.

Additionally, negative binomial regression models were employed to estimate the prevalence ratio and corresponding 95% CI, using the count data of the number of depressive symptoms as the outcome variable. The negative binomial model was chosen because the depressive symptoms data exhibited overdispersion, and it had the lowest Bayesian Information Criterion (BIC) value among the tested models, indicating the best fit. For the negative binomial models, incidence rate ratios (IRRs) and 95% CIs were reported.

Results

In the total sample of US women from NHANES combined cycles 2005-2010 and 2015-2018 the average age was 32.1y. The weighted proportions of US women who were Hispanic, non-Hispanic white, non-Hispanic black, and Other were 17.93%, 59.06%, 13.62%, and 9.39%, respectively. The proportion of women who were considered low income (poverty-to-income ratio less than or equal to 1.85) was 37.97%. The proportion of women who were not pregnant, pregnant, and postpartum (less than or equal to 12 months after giving birth at the time of survey) were 87.90%, 5.54%, and 6.56% respectively. Prevalence of absence and presence of depressive symptoms by each group are shown in Table 1, with women in the low-income group having the highest prevalence of depression (DPQ score > 10) at 15.95%.

The prevalence of iron deficiency by pregnancy grouping, and by absences or presence of depressive symptoms, is shown in Table 2, as well as the median ferritin values by group. Women who were pregnant had the highest prevalence of iron deficiency, at 22.69%, when measured as ferritin less than or equal to 15 ng/mL.

Table 1: Descriptive Statistics

Variables	Total sample		Depressive Symptoms	
	N (unweighted)	% (SE)	Absence N = 5440 %(SE)	Presence N = 667 %(SE)
Age (y, mean SE)	6107	32.1 (0.14)	32.07 (0.14)	32.33 (0.39)
Race/Ethnicity				
Hispanic	1880	17.93% (0.01)	89.76% (0.01)	10.24% (0.01)

NH White	2254	59.06% (0.02)	89.52% (0.01)	10.48% (0.01)
NH Black	1300	13.62% (0.01)	88.77% (0.01)	11.23% (0.01)
Other	673	9.39% (0.01)	91.38% (0.01)	8.62% (0.01)
Low Income (PIR ≤ 1.85)	2977	37.97% (0.20)	6.97% (0.01)	15.95% (0.01)
Pregnancy Status				
Not pregnant	5102	87.90% (0.005)	89.19% (0.01)	10.81% (0.01)
Pregnant	575	5.54% (0.003)	93.09% (0.01)	6.91% (0.01)
Postpartum	430	6.56% (0.004)	92.64% (0.02)	7.36% (0.02)

N are unweighted; means (SE) or % are weighted.

Table 2: Concentration and prevalence of iron deficiency

	Total Sample		Depressive Symptoms	
Variables	N (*unweighted*)	%(SE)	Absence N = %(SE)	Presence N = %(SE)
Not-Pregnant				
FT (median and SE)	5212	46.62 (0.65)	46.62 (0.65)	49.21 (3.22)
FT ≤ 15	743	12.54 % (0.004)	12.50% (0.004)	12.93% (0.01)
Pregnant				

FT (median and SE)	575	30.44 (1.75)	30.44 (1.83)	35.12 (8.11)
FT ≤ 15	150	22.69% (0.03)	22.4% (0.03)	25.57% (0.08)
Postpartum				
FT (median and SE)	320	37.43 (1.88)	37.43 (2.05)	31.52 (6.26)
FT ≤ 15	70	16.23% (0.03)	16.45% (0.03)	13.45% (0.07)

N are unweighted; means (SE) or % are weighted.

Logistic Regression

Logistic regression models were used to examine the associations between iron deficiency (defined as ferritin < 15 mg/L) and depression, as well as ferritin levels as continuous meaure and depression, among all women, non-pregnant women, pregnant women, and postpartum women, stratified by low-income status (Table 3a). For each subgroup, two models were fitted: Model 1 included the main effects, while Model 2 additionally adjusted for BMI, race/ethnicity, age, and high-sensitivity C-reactive protein (hsCRP) levels as a biomarker for inflammation.

Table 3a: OR of presence of depressive symptoms by iron levels as a binary value and pregnancy status

	Crude Model				**Adjusted Model (BMI, race, age, & hscrp)**			
Iron Deficiency (Ferritin < 15 mg/L)	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**
Not low Income								
Iron deficiency	1.07 (0.67,1.70)	1.13 (0.7, 1.8)	0.77 (0.16, 3.95)	0.31 (0.03, 2.91)	1.10 (0.68,| 1.76)	1.16 (0.73, 1.88)	0.78 (0.16, 3.72)	0.30| (0.03, 3.34)
BMI					**1.04 (1.02, 1.06) ****	**1.03 (1.01, 1.06)****	**1.14 (1.06,1.21)****	1.08 (0.98,1.18)

Race/Ethnicity					0.97 (0.87, 1.07)	0.97 (0.87, 1.08)	0.92 (0.467, 1.81)	0.86 (0.56, 1.30)
Age					0.99 (0.97, 1.02)	0.99 (0.97, 1.02)	0.92 (0.85, 1.00)	1.00 (0.87,1.15)
C-reactive protein (crp)					1.00 (0.99, 1.03)	1.00 (0.97,1. 03)	1.02 (0.98, 1.06)	1.02 (0.94,1.12)
Low income (PIR ≤ 1.85)								
Iron deficiency	0.87 (0.62, 1.21)	0.91 (0.63, 1.31)	1.03 (0.43, 2.49(	0.81 (0.25, 2.65)	0.89 (0.64, 1.24)	0.93 (0.64, 1.34)	1.12 (0.49, 2.58)	0.82 (0.24,2.84)
BMI					1.02 (1.00, 1.03)	**1.02 (1.00,1. 03) .**	1.01 (0.93, 1.09)	0.98 (0.91,1.07)
Race/Ethnicity					1.08 (0.99, 1.18)	1.08 (0.99,1. 19)	1.01 (0.78, 1.31)	1.07 (0.74, 1.56)
Age					**1.02 (1.01, 1.04) ****	**1.02 (1.01,1. 04) ***	1.03 (0.96, 1.11)	**0.90 (0.81, 0.99)***
C-reactive protein (crp)					1.01 (0.99 1.03)	1.02 (1.00,1. 03)	1.00 (0.96, 1.05)	1.01 (0.92, 1.10)

Note: 95% confidence intervals are reported in parentheses. Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 3b: OR of presence of depressive symptoms by iron levels as a continuous value and pregnancy status

	Crude Model				Adjusted Model (BMI, race, age, & hscrp)			
Ferritin Levels (continuous)	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**
Not low Income								
Ferritin levels	1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99,1.02)	0.98 (0.97,1.00)	1.00 (0.99, 1.004)	1.00 (0.99, 1.00)	1.01 (0.99, 1.01)	0.98 (0.96, 1.01)
BMI					**1.04 (1.02, 1.06)****	**1.04 (1.01, 1.06)****	**1.13 (1.06, 1.22)****	1.06 (0.95, 1.16)
Race/Ethnicity					0.97 (0.87, 1.07)	0.97 (0.87, 1.08)	0.92 (0.47, 1.82)	0.88, (0.56, 1.37)
Age					0.99 (0.97, 1.02)	0.99 (0.97, 1.02)	0.92 (0.84, 1.01)	1.00 (0.88, 1.13)
C-reactive protein (hsCRP)					1.00 (0.98, 1.02)	1.00 (0.97,1.03)	1.03 (0.99, 1.06)	1.04 (0.95, 1.13)
Low income (PIR ≤ 1.85)								
Ferritin	1.00 (1.00, 1.003)	1.00 (0.99, 1.00)	0.99 (0.98, 1.00)	**1.01 (1.001, 1.01)***	1.00 (0.99, 1.002)	1.00 (0.99,1.00)	0.99 (0.98, 1.00)	**1.01 (1.002, 1.02)***
BMI					1.02 (1.00, 1.03)	**1.02 (1.00,1.03).**	1.01 (0.93, 1.09)	0.99 (0.91,| 1.06)

Race/Ethnicity					1.08 (0.99, 1.17)	1.08 (0.99, 1.19)	1.03 (0.79, 1.34)	1.07 (0.76,1.50)
Age					**1.02 (1.01, 1.04)***	**1.02 (1.004, 1.04)***	1.04 (0.96, 1.12)	**0.87 (0.79, 0.97)***
C-reactive protein (hsCRP)					1.01 (0.99, 1.03)	**1.02 (1.00,1.03).**	1.00 (0.96, 1.05)	1.01 (0.92, 1.10)

Note: 95% confidence intervals are reported in parentheses. Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Binary Models (Iron Deficiency)

In the binary models, iron deficiency was not significantly associated with depression in any of the subgroups, regardless of income status. Among all women, the odds ratios for iron deficiency were 1.065 (95% CI: 0.667-1.698, p = 0.794) in the not low-income group and 0.867 (95% CI: 0.624-1.205, p = 0.399) in the low-income group (Model 1). After adjusting for covariates (Model 2), the odds ratios were 1.095 (95% CI: 0.680-1.764, p = 0.710) and 0.887 (95% CI: 0.636-1.236, p = 0.480) for the not low-income and low-income groups, respectively.

Similarly, among non-pregnant, pregnant, and postpartum women, iron deficiency was not significantly associated with depression in either income group, with or without adjustment for covariates (see Table 3a for detailed results).

Continuous Models (Ferritin Levels)

In the continuous models, ferritin levels were not significantly associated with depression in the combined all women group, non-pregnant women, or pregnant women, regardless of income status. However, among postpartum women, higher ferritin levels were significantly associated with increased odds of depression in the low-income group after adjusting for covariates (Model 2: OR = 1.009, 95% CI: 1.002-1.017, p = 0.023). This association was not observed in the not low-income group of postpartum women or in any other subgroup (Table3b).

Covariates

Among the covariates, higher BMI was significantly associated with increased odds of depression in all women (OR = 1.040, 95% CI: 1.017-1.063, p = 0.001) and non-pregnant women (OR = 1.038, 95% CI: 1.014-1.062, p = 0.003) in the not low-income group, as well as in pregnant women (OR = 1.135, 95% CI: 1.061-1.214, p = 0.001) in the not low-income group. Older age was significantly associated with increased odds of depression in all women (OR = 1.024, 95% CI: 1.007-1.042, p = 0.008), non-pregnant women (OR = 1.024, 95% CI: 1.005-1.043, p = 0.015), and

postpartum women (OR = 0.896, 95% CI: 0.813-0.987, p = 0.032) in the low-income group. Race/ethnicity and hsCRP levels were not significantly associated with depression in any of the subgroups.

In summary, when stratifying by income status, neither iron deficiency nor ferritin levels were significantly associated with depression in all women, non-pregnant women, or pregnant women. However, higher ferritin levels were associated with increased odds of depression among low-income postpartum women after adjusting for covariates. The effect sizes were generally small, and the clinical significance of these findings remains uncertain. Further research is needed to clarify the complex relationships between iron status, income, and depression across different stages of pregnancy and the postpartum period, as well as the role of potential confounding factors such as BMI and age.

Negative Binomial Regression Results

Negative binomial regression models were used to examine the associations between iron deficiency and depression scores (Table 4a)., as well as ferritin levels and depression scores (Table 4b), among all women, not-pregnant women, pregnant women, and postpartum women, stratified by low income status. For each subgroup, two models were fitted: Model 1 included the main effects, while Model 2 additionally adjusted for BMI, race/ethnicity, age, and high-sensitivity C-reactive protein (hsCRP) levels as a biomarker for inflammation.

Table 4a: Binary Predictor Variable: Incidence rate ratios (IRRs) of depression scores

	Crude Model				**Adjusted Model (BMI, race, age, & hscrp)**			
Iron Deficiency (ferritin < 15 mg/L)	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**
Not low Income								
Iron deficiency	0.98 (0.84, 1.13)	0.99 (0.85, 1.14)	0.89 (0.55, 1.44)	0.94 (0.52, 1.69)	0.99 (0.85, 1.15)	1.00 (0.86, 1.18)	0.87 (0.55, 1.36)	0.88 (0.48, 1.58)
BMI					**1.02 (1.01, 1.02)*** **	**1.02 (1.01, 1.03)*** **	**1.03 (1.01, 1.05)***	**1.05 (1.02, 1.07)*** *

race.ethnicity					0.99 (0.95, 1.03)	1.00 (0.96, 1.04)	0.98 (0.85, 1.20)	0.91 (0.80, 1.03)
age					1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	0.99 (0.96, 1.02)	0.99 (0.96, 1.03)
hscrp					1.00 (0.99, 1.00)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	0.99 (0.96, 1.02)
Low income (PIR ≤ 1.85)								
Iron deficiency	0.97 (0.85, 1.11)	0.98 (0.84, 1.15)	1.22 (0.92, 1.62)	0.81 (0.55, 1.21)	0.99 (0.86, 1.13)	1.00 (0.85, 1.17)	1.28 (0.98, 1.67)	0.84 (0.56, 1.25)
BMI					**1.01 (1.01, 1.02)*** **	**1.01 (1.01, 1.02)*** **	1.01 (0.99, 1.03)	1.00 (0.97, 1.03)
race.ethnicity					**1.05 (1.00, 1.08)***	**1.05 (1.01, 1.09)***	0.94 (0.86, 1.02)	0.99 (0.87, 1.13)
age					**1.01 (1.01, 1.02)** **	**1.02 (1.01, 1.02)** **	1.01 (0.98, 1.03)	**0.95 (0.93, 0.97)** **
hscrp					1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.99 (0.97, 1.01)	1.01 (0.97, 1.05)

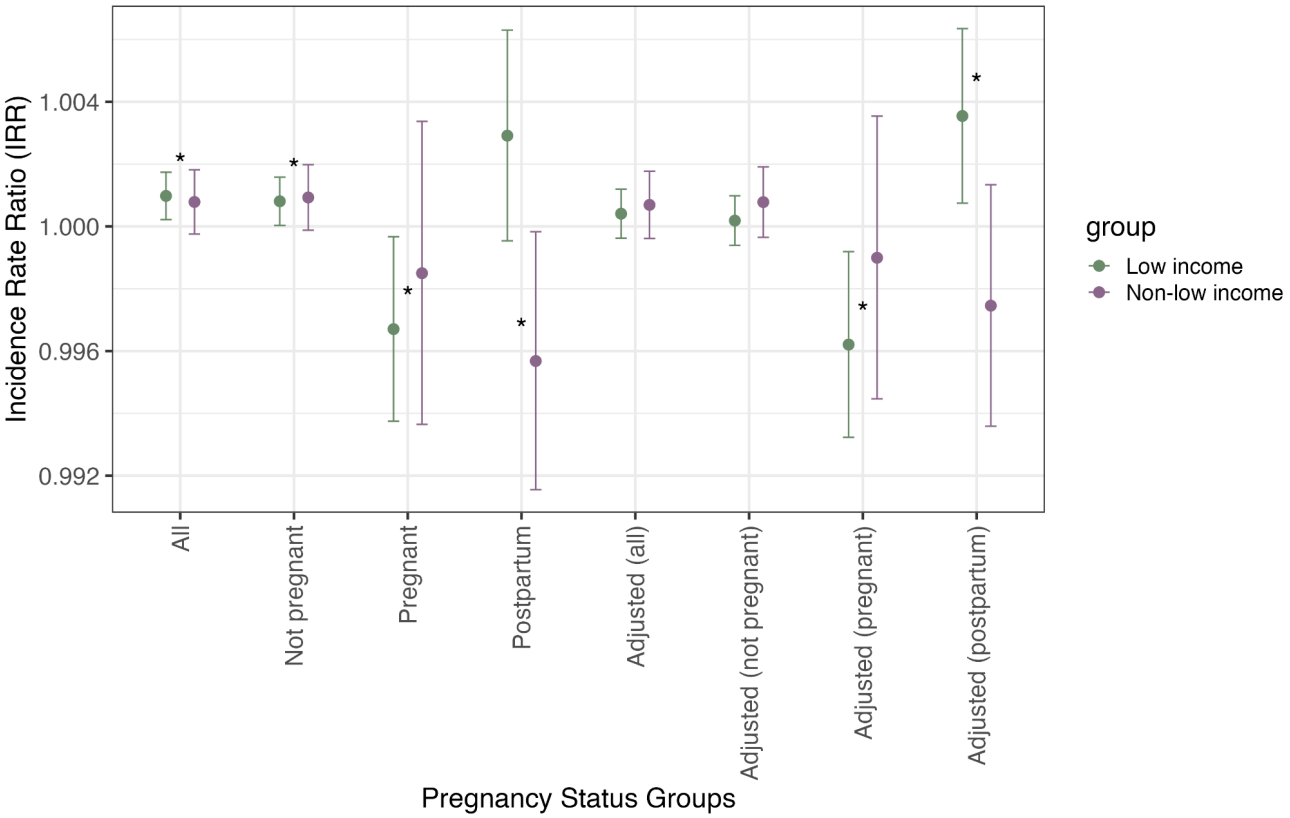
Note: 95% confidence intervals are reported in parentheses. Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Table 4b: Continuous Predictor Variable: Incidence rate ratios (IRRs) of depression scores associated with a one-unit change in ferritin levels

	Crude Model				Adjusted Model (BMI, race, age, & hscrp)			
Ferritin Levels (continuous)	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**	**All**	**Not Pregnant**	**Pregnant**	**Postpartum**
Not low Income								
ferritin	1.00 (1.00,1.002)	1.00 (1.00, 1.002)	1.00 (0.99, 1.00)	**0.99 (0.99, 1.00)***	1.00 (1.00,1.002)	1.00 (1.00, 1.002)	1.00 (1.00, 1.003)	1.00 (0.99, 1.00)
BMI					**1.02 (1.01, 1.03)*****	**1.02 (1.01, 1.03)*****	**1.03 (1.01, 1.05)***	**1.04 (1.02, 1.06)****
race.ethnicity					0.99 (0.95, 1.03)	1.00 (1.00, 1.04)	0.97 (0.85, 1.11)	0.92 (0.81, 1.05)
age					1.00 (0.99, 1.00)	1.00 (0.99, 1.00)	0.99 (0.96, 1.02)	1.00 (0.96, 1.03)
hscrp					1.00 (0.99,| 1.00)	1.00 (0.99, 1.01)	0.99 (0.99, 1.00)	0.99 (0.96, 1.02)
Low income (PIR ≤ 1.85)								
ferritin	**1.001 (1.001, 1.002)***	**1.001 (1.001, 1.002)***	**0.997 (0.99, 1.00)***	1.00 (1.00, 1.01)	1.00 (1.00, 1.001)	1.00 (1.00, 1.001)	**0.996 (0.99, 1.00)***	**1.004 (1.001 1.01)***
BMI					**1.01 (1.01,**	**1.01 (1.01,**	1.01 (0.99,	1.00 (0.97,

					1.02)* **	**1.02)*** **	1.03)	1.02)
race.ethnicity					**1.04 (1.00, 1.09)***	**1.05 (1.01, 1.09)***	0.95 (0.88, 1.03)	0.97 (0.86, 1.09)
age					**1.01 (1.01, 1.02)****	**1.01 (1.01, 1.02)****	1.01 (0.98, 1.04)	**0.95 (0.92, 0.98)****
hscrp					1.00 (0.99, 1.01)	1.00 (1.00, 1.01)	0.99 (0.97,| 1.01)	1.02 (0.98, 1.05)

Figure 1. Incidence Rate Ratios of Depressive Symptoms Scores



Binary Models (Iron Deficiency)

In the binary models, iron deficiency was not significantly associated with depression scores in any of the subgroups, regardless of income status. Among the all women group, the incidence rate ratios (IRRs) for iron deficiency were 0.976 (95% CI: 0.842-1.131, p = 0.748) in the not low-income group and 0.972 (95% CI: 0.847-1.115, p = 0.683) in the low-income group (Model 1). After adjusting for covariates (Model 2), the IRRs were 0.990 (95% CI: 0.848-1.154, p = 0.894) and 0.990 (95% CI: 0.861-1.139, p = 0.894) for the not low-income and low-income groups, respectively.

Similarly, among non-pregnant, pregnant, and postpartum women, iron deficiency was not significantly associated with depression scores in either income group, with or without adjustment for covariates (see Table 4a for detailed results).

Continuous Models (Ferritin Levels)

In the continuous models, ferritin levels were not significantly associated with depression scores in the all women group or non-pregnant women, regardless of income status. However, among pregnant women, higher ferritin levels were significantly associated with lower depression scores in the low-income group (Model 1: IRR = 0.997, 95% CI: 0.994-1.000, p = 0.03; Model 2: IRR = 0.996, 95% CI: 0.993-0.999, p = 0.015), but not in the not low-income group (see Table 4b for detailed results). This indicates that for each unit increase in ferritin levels, depression scores decreased by 0.4% for pregnant women in the low-income group. However, these effect sizes are small and so the results should be interpreted with caution.

Among postpartum women, higher ferritin levels were significantly associated with lower depression scores in the not low-income group before adjustment (Model 1: IRR = 0.996, 95% CI: 0.992-1.000, p = 0.042), but this association did not remain significant after adjustment. In the low-income postpartum group, higher ferritin levels were significantly associated with higher depression scores after adjustment (Model 2: IRR = 1.004, 95% CI: 1.001-1.006, p = 0.014). This result means that for each unit increase in ferritin levels, the depression scores increased by 0.4%. This finding is opposite to what we see in the low-income pregnant group. The effect size is small and the results should be interpreted with caution, however it could warrant further investigation into the potential influence of the postpartum period on the relationship between ferritin levels and depression scores.

Figure 1 presents the incidence rate ratios (IRRs) for ferritin levels across the different models and subgroups. The figure illustrates the varying associations between ferritin levels and depression scores by income status and pregnancy status, with significant associations observed in low-income pregnant women (lower depression scores) and low-income postpartum women (higher depression scores) after adjusting for covariates.

Covariates

Among the covariates, higher BMI was significantly associated with higher depression scores in all women (IRR = 1.021, 95% CI: 1.013-1.029, $p < 0.001$), non-pregnant women (IRR = 1.020, 95% CI: 1.011-1.028, $p < 0.001$), and pregnant women (IRR = 1.031, 95% CI: 1.007-1.056, $p = 0.014$) in the not low-income group, as well as in all women (IRR = 1.012, 95% CI: 1.006-1.018, $p < 0.001$) and non-pregnant women (IRR = 1.013, 95% CI: 1.007-1.020, $p < 0.001$) in the low-income group. Older age was significantly associated with higher depression scores in all women (IRR = 1.012, 95% CI: 1.005-1.019, $p = 0.001$) and non-pregnant women (IRR = 1.014, 95% CI: 1.006-1.022, $p = 0.001$) in the low-income group, while it was associated with lower depression scores in postpartum women (IRR = 0.952, 95% CI: 0.927-0.978, $p = 0.001$) in the low-income group. Race/ethnicity was significantly associated with higher depression scores in all women (IRR = 1.045, 95% CI: 1.004-1.088, $p = 0.033$) and non-pregnant women (IRR = 1.054, 95% CI: 1.011-1.099, $p = 0.017$) in the low-income group. HsCRP levels were not significantly associated with depression scores in any of the subgroups.

Discussion

This study investigated the associations between iron deficiency, ferritin levels, and depressive symptoms among US women across different stages of pregnancy and the postpartum period, stratified by income status. The results suggest that the relationship between iron status and depression varies depending on pregnancy status and income level.

In the logistic regression models, iron deficiency was not significantly associated with depression in any subgroup, regardless of income status. However, when examining ferritin levels as a continuous variable, higher ferritin levels were significantly associated with increased odds of depression among low-income postpartum women after adjusting for covariates.

The negative binomial regression models revealed that iron deficiency was not significantly associated with depression scores in any subgroup, regardless of income status. When considering ferritin levels, higher levels were associated with lower depression scores in low-income pregnant women and higher depression scores in low-income postpartum women after adjusting for covariates.

These findings suggest that the relationship between iron status and depression is complex and may be influenced by both pregnancy status and socioeconomic factors. The observed associations between higher ferritin levels and increased odds of depression and higher depression scores among low-income postpartum women are particularly noteworthy. This may indicate that the postpartum period is a critical time for monitoring iron status and mental health, especially among women with lower socioeconomic status.

Several limitations of this study should be acknowledged. The cross-sectional design of NHANES data prevents the establishment of causal relationships between iron status and depression. It is

possible that depression may influence iron status through changes in diet or other behavioral factors, rather than iron status directly affecting depression risk. Additionally, while the study adjusted for several potential confounding factors, such as BMI, race/ethnicity, age, and inflammation, there may be other unmeasured confounders that could have influenced the results. For example, the study did not account for dietary factors, such as overall nutrient intake or the consumption of iron-rich foods, which could impact both iron status and mental health.

Additionally, the study's subgroup analyses, particularly among pregnant and postpartum women, may have been limited by smaller sample sizes, reducing statistical power to detect significant associations. Specifically, the low number of low-income iron-deficient women in the postpartum subgroup may have affected the reliability of the findings for this group.

Finally, using ferritin as a continuous measure is not a common approach to assess iron deficiency. While this method allows for a more nuanced examination of the relationship between iron status and depression, it may limit comparability with other studies that primarily rely on established cutoff values for iron deficiency.

The findings of this study highlight the need for further research to clarify the relationship between iron status and depression across different stages of pregnancy and the postpartum period, as well as the role of socioeconomic factors in modifying these associations. Future studies should employ longitudinal designs to better establish the temporal relationship between changes in iron status and the development or progression of depressive symptoms. This could involve following women from preconception through pregnancy and the postpartum period, with regular assessments of iron status and mental health.

Future research should aim to include more comprehensive assessments of both iron status and depression. This could involve using multiple biomarkers of iron status, such as hepcidin or soluble transferrin receptor, in addition to ferritin. Depression should be assessed using structured clinical interviews to establish formal diagnoses, as well as self-reported symptom measures. To further explore the relationship between continuous ferritin levels and depression, future research could employ advanced statistical techniques such as restricted cubic spline analysis. This approach would allow for the examination of potential non-linear associations between ferritin levels and depression, helping to identify critical thresholds or ranges of ferritin concentrations that may be particularly relevant for mental health outcomes.

In conclusion, this study provides new insights into the complex relationship between iron status and depression among US women across different stages of pregnancy and the postpartum period, highlighting the potential role of socioeconomic factors in modifying these associations. Further research is needed to clarify these relationships and inform the development of targeted interventions to improve both iron status and mental health among pregnant and postpartum women.

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