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Iron Deficiency is Related to Depressive Symptoms in United States Nonpregnant Women of Reproductive Age: A Cross-Sectional Analysis of NHANES 2005-2010

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A B S T R A C T

Background: Findings of the association between iron status and depressive symptoms in nonpregnant women of reproductive age (WRA) are equivocal, limited by a small sample size, or did not consistently control for confounders.
Objective: We tested the association between iron status and depressive symptoms in WRA with the NHANES data (2005-2010).
Methods: Nonpregnant WRA (20-44 y) with complete data on iron (ferritin and transferrin receptor (TfR)) and anemia (hemoglobin) biomarkers, depressive symptoms (Patient Health Questionnaire-9), and sociodemographic variables were included. Logistic and negative binomial regressions were used to estimate presence (odds ratios) and magnitude (prevalence ratios), respectively, for depressive symptoms by iron deficiency (ID)/anemia/ID anemia in the total sample and stratified by poverty:income ratio ($\leq$ 1.85 or >1.85).
Results: Among 2516 females, the prevalence of ID was 8 to 16% (depending on the iron biomarker used), of anemia 8%, of which 52 to 65% were also ID. The prevalence of depressive symptoms was 10%. Crude logistic models showed that females with ID (TfR $\geq$ 8.3 mg/L or body iron <0 mg/kg) from the total sample had 1.82 (95% confidence interval [CI]: 1.24, 2.68) and 1.62 (95% CI: 1.05, 2.48), respectively, higher odds of depressive symptoms than females with iron sufficiency; these associations were attenuated after adjustments for confounders. Adjusted negative binomial models showed that females with ID (TfR $\geq$ 8.3 mg/L) from the total and low-income samples showed 1.19 (95% CI: 1:00, 1.40) and 1.27 (95% CI: 1.03, 1.58), respectively, higher prevalence ratios of depressive symptoms scores than females with iron sufficiency.
Conclusions: These nationally representative data indicate that nonpregnant WRA with ID (based on high TfR) in the United States have higher prevalence of somatic depressive symptoms scores than those with iron sufficiency, especially if they are of low income.

Keywords: iron deficiency, depressive symptoms, US, nonpregnant females of reproductive age, NHANES

Introduction

The latest report from the World Health Organization indicates that iron deficiency (ID) is still the most common single-nutrient deficiency worldwide and disproportionately affects women of reproductive age (WRA) between the ages of 18 to 45 y and children from both developing and developed countries [1]. The US National Health and Nutrition Examination Survey (NHANES) data indicate that 10% of nonpregnant WRA struggle with ID [2]. Additionally, females between the ages of 25 and 44 y have a 10 to 25% lifetime risk of major depressive disorder [3], and nutrient deficiencies such as ID may contribute to this risk [4].

ID may be associated with negative psychosocial health consequences such as depression due to iron's role in neurotransmitter biochemistry [5]. Based on two reviews [5,6], an association between ID and depressive symptoms in human

Abbreviations: BodyFe, Body iron; CRP, C-reactive protein; Ft, Ferritin; Hb, Hemoglobin; ID, Iron deficiency; IDA, Iron deficiency anemia; NHANES, National Health and Nutrition Examination Survey; PIR, Poverty:income ratio; RCT, Randomized controlled trial; IS, Iron sufficient/sufficiency; TfR, Transferrin receptor; WRA, Women of reproductive age.

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observational studies has been documented, but results from randomized controlled trials (RCTs) are limited and inconclusive. Further, the cumulative evidence is also limited by small sample size, inconsistent control for environmental and biological factors, and lack of specificity (such as a relation with a specific construct [e.g., cognitive]) of depressive symptoms [5,6]. Although depressive symptoms have been measured in NHANES since 2005, the instrument's (Patient Health Questionnaire, PHQ-9) psychometric performance has only recently been assessed and proven robust across different sociodemographic groups such as sex, race/ethnicity, and education level in the US population [7]. This is important as failing to assess the psychometric performance of the instrument used may lead to underdetection or overdetection of depressive symptoms and an incorrect association with iron status, especially when comparing across different subpopulations.

The use of well-powered and nationally representative data may help clarify the equivocal findings of the link between ID and depressive symptoms and assist in developing methods for prevention and treatment. Thus, we aimed to investigate the association between iron status and depressive symptoms in nonpregnant WRA using the NHANES data. Because females of low income are more likely to be affected by depressive symptoms [8] and ID [9,10], we explored the association in the total sample as well as stratified by family income (using the poverty:income ratio [PIR]).

Methods

Study population

Data were analyzed using the cross-sectional NHANES study, which collects health and nutritional status data in adults and children from the United States via interviews and physical examinations. The 2005-2010 NHANES cycles were used because they contain information on iron status and depressive symptoms in nonpregnant WRA. The analyses were restricted to WRA between 20 and 44 y of age ($n = 3916$) as the NHANES reproductive variables are confined to this age range. Thus, WRA outside of this age range, males, and pregnant females were excluded as follows: females with a positive self-report and serum or urine pregnancy test and with an unknown pregnancy status at exam were excluded ($n = 674$), and participants with missing data on iron and acute inflammatory biomarkers ($n = 196$), depressive symptoms ($n = 365$), body mass index (BMI; $n = 9$) or sociodemographic variables ($n = 157$). Given that around 15% of females were missing parity data ($n = 617$), this variable was not included in the current analyses to preserve analytic sample size. The final sample of nonpregnant WRA ($n = 2516$) did not differ significantly from the larger NHANES sample of nonpregnant WRA ($n = 3916$) with respect to sociodemographic variables. The NHANES protocol was approved by the National Center for Health Statistics' Research Ethics Review board [11], and these secondary data analyses were considered exempt by the Institutional Review Board at The Pennsylvania State University.

Assessment of iron and acute inflammation biomarkers

A complete description for the protocol used in the collection of the iron and inflammatory biomarkers can be found elsewhere (https://wwwn.cdc.gov/nchs/nhanes/default.aspx) but is briefly described here. In mobile examination units, a phlebotomist collected 3 to 5 mL of venous blood, after a 9 h fast, into a tripotassium ethylenediaminetetraacetic acid tube and 15 mL into a Becton Dickinson red-top tube. Using whole blood from the ethylenediaminetetraacetic acid tube, hemoglobin (Hb) was assessed with a Beckman Cro instrument [12–14]. The blood from the red-top tubes was clotted for 30 to 45 min at room temperature and then centrifuged at 17 to 25°C and 2900 rpm for 15 min to yield the serum. Serum was then shipped to the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry Specimen Packaging, Inventory, and Repository to measure serum ferritin (Ft) and transferrin receptor (TfR) and to the University of Washington to measure C-reactive protein (CRP).

Serum Ft [15,16] and TfR [17,18] were analyzed using the immunoturbidimetric assay method via Roche kits on a Hitachi 912 clinical analyzer for 2005 to 2008 samples and on an Elecsys 170 for Ft [19] and Hitachi Mod P for TfR [20] for the 2009 to 2010 samples. Due to the use of different technologies for Ft assessment and following best-practice, concentrations were standardized using the formula, $10^{(0.989*\log_{10}(\text{Hitachi 912})+0.049)}$ (https://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/TFR_F.htm). In NHANES, body iron (BodyFe) is calculated as $\text{TfR}_{\text{Cook}} = 1.5* \textit{unadjusted TfR}_{\textit{Roche}} + 0.35$ to match Cook's standard values (21), and a cutoff < 0 mg/kg was used to indicate ID [21]. Hb < 12 g/dL was indicative of anemia. Because Ft is affected by inflammation, it was adjusted using Thurnham's equation [22]. Inflammation was measured with CRP, which was assessed with latex-enhanced nephelometry [23–25] (Dade Behring Inc, Deerfield, IL). A CRP cutoff > 5 mg/L was used to indicate presence of inflammation. ID was classified as Ft < 15 μg/L [26] or as TfR ≥ 8.3 mg/L [27,28]. Last, iron deficiency anemia (IDA) was defined using Hb in combination with 1 or 2 abnormal iron biomarkers, BodyFe, Ft, or TfR [29].

Depressive symptoms

Depressive symptoms were collected with the publicly available PHQ-9 scale via Computer Assisted Personal Interviews (interviewer administered) in the mobile examination units. The scale contains 9 items and assesses the frequency of depressive symptoms in the past 2 wk. The answers can range from 0 ("not at all") to 3 ("nearly every day"); thus, the total score can range between 0 and 27. The total score was assessed using the recommended cutoff ≥ 10, which indicates presence of depressive symptoms. This cutoff was found to have 88% sensitivity and specificity in an adult primary care sample [30–32]. Using the NHANES data, the PHQ-9 scale has been shown to measure depressive symptoms across the total spectrum with symptoms grouped under 2 constructs, cognitive/affective and somatic [7]. Items 1 (anhedonia), 2 (depressed mood), 6 (low self-esteem), 7 (concentration difficulties), 8 (psychomotor disturbances), and 9 (suicidal ideation) fall under the cognitive/affective construct for a possible cognitive/affective score which ranges between 0 and 18. Items 3 (sleep disturbance), 4 (fatigue), and 5 (appetite changes) fall under the somatic construct, with a possible score on this construct ranging between 0 and 9.

Assessment of confounders

Sociodemographic variables such as age at screening, race/ethnicity (non-Hispanic white, Hispanic, non-Hispanic black, and

other), marital status (married, cohabitating, separated, single), the total number of people in the household, PIR (where PIR ≤ 1.85 indicates low-income for females who qualify for welfare such as the Special Supplemental Nutrition Program for Women, Infants, and Children [33]), and education level (no high school, high school or equivalent, more than high school) were collected in the home using demographic questionnaires. Information regarding having or not (yes/no) health insurance during the past 12 mo was collected with the Health Insurance Questionnaire in the home. Anthropometry, such as height and weight, were assessed in the mobile examination centers using standardized operating procedures and then used to calculate BMI; underweight [≤ 18], normal [18–24], overweight [25–30], obese [>30]). The Icon 25 hCG test kit (Beckman Coulter) was used to assess pregnancy status using serum or urine samples. Last, antidepressant medication use (yes/no) was collected using a prescription medication interview, and the level 2, "antidepressant," out of the 3-level drug classification system was used in our analyses (https://www.cerner.com/solutions/drug-database).

Statistical analysis

All analyses were weighted appropriately to consider the NHANES' design specifications, which are available online (https://www.cdc.gov/nchs/nhanes/index.htm). All statistical analyses were performed in SAS 9.4. Non-normally distributed variables (Ft, TfR, and CRP) underwent Box-Cox transformations, and their geometric means and the 50th (median), 25th, and 75th percentiles were reported. BodyFe and Hb were normally distributed, and their arithmetic means were reported. Percentages and standard errors were reported for ID variables. Weighted linear regressions and quantile tests were used to compare continuous variables, and weighted Rao-Scott Chi-square test was used for categorical variables. The association between iron status and depressive symptoms status (based on the recommended cutoff ≥10) was tested with logistic regression models and odds ratios (OR) and corresponding 95% confidence interval (CI). We also conducted a negative binomial regression model for the same exposure groups to estimate the prevalence ratio and corresponding 95% CI using the count data of number of depressive symptoms. This model was selected because the depressive symptoms data showed overdispersion. The negative binomial model was run using the surveygenmod macro in SAS developed by Silva [34], and prevalence ratios (PR) and 95% CI were reported. In sensitivity analyses, we also explored the association between iron status and the two depressive symptoms constructs (cognitive/affective and somatic) with negative binomial regression models. Significance was defined as $P < 0.05$ for all models. All models were tested with and without confounders. Lastly, all models were explored in the total sample and by PIR groups (PIR ≤ 1.85 and > 1.85).

Results

This nationally representative sample included 2516 nonpregnant females—ages between 20 and 44 y, of which 9.6% of weighted respondents had depressive symptoms (cutoff ≥10;

TABLE 1
Descriptive statistics for nonpregnant females between 20 to 44 y of age who participated in NHANES 2005 – 2010. Data are presented for the total sample and by depressive symptoms status (cutoff ≥10; $N = 2516$)[a]

Variables	Total sample		Depressive symptoms (cutoff ≥ 10)		*P*
	N	% (SE)	Absence ($n = 2220$); % (SE)	Presence ($n = 296$); % (SE)	
Age (y; mean (SE))	2516	32.7 (0.2)	32.6 (0.2)	33.8 (0.4)	0.01
Race/Ethnicity[†]					
Hispanic	747	14.7 (1.5)	14.4 (1.4)	17.3 (2.8)	0.19
NH White	1139	66.4 (2.2)	67.1 (2.2)	60.2 (3.6)	0.03
NH Black	492	12.1 (1.2)	11.6 (1.2)	16.9 (2.6)	0.03
Marital status					
Married	1142	49.2 (1.4)	50.5 (1.5)	37.2 (3.5)	< 0.001
Cohabitating	314	12.1 (0.8)	11.8 (0.8)	15.2 (2.4)	0.16
Separated	321	11.7 (0.6)	10.5 (0.6)	22.9 (2.9)	<0.0001
Single	739	27.0 (1.4)	27.3 (1.5)	24.7 (2.3)	0.28
Low income (PIR ≤ 1.85)	1230	35.2 (1.2)	32.7 (1.2)	58.7 (3.8)	< 0.0001
Health insurance (yes)	1777	77.4 (1.2)	78.5 (1.2)	67.2 (3.4)	<0.001
Antidepressant use (yes)	247	11.9 (0.7)	10.6 (0.8)	24.4 (2.9)	< 0.0001
Education level					
Less than HS	534	14.6 (1.0)	13.4 (1.1)	26.2 (3.2)	< 0.001
HS or equivalent	521	19.5 (0.9)	19.2 (1.0)	22.9 (3.0)	0.23
More than HS	1461	65.9 (1.4)	67.4 (1.4)	50.8 (4.2)	<0.0001
Household size, mean (SE)	2516	3.5 (0.0)	3.5 (0.0)	3.8 (0.1)	0.04
BMI (kg/m^2; mean (SE))	2516	28.1 (0.2)	27.9 (0.2)	29.9 (0.6)	<0.001
Underweight + Normal (≤24.99)[b]	950	42.6 (1.5)	43.8 (1.6)	31.1 (2.9)	<0.001
Overweight (25.00 - 29.99)	653	24.8 (1.2)	24.8 (1.3)	24.4 (3.3)	0.92
Obese (≥ 30)	913	32.7 (1.3)	31.4 (1.4)	44.5 (3.3)	<0.001

Abbreviations: NH, Non-Hispanic; HS, High School.

[†] The sample size for cases of NH Other and presence of depressive symptoms is not shown due to a small sample size ($n < 30$), but it was included in the analysis.

[a] *N* are unweighted; means (SE) or % are weighted. The assessment of difference in means between depressive symptoms groups was completed through weighted t-tests and the prevalence assessments by depressive symptoms status groups was tested by weighted Rao-Scott Chi-square tests.

[b] BMI category underweight had a small sample size ($n < 30$) for cases of presence of depressive symptoms, as such, it was combined with the normal BMI category.

$n = 296$). Table 1 indicates descriptive statistics for the overall sample and by depressive symptoms status. Females with depressive symptoms were more likely to be older, of non-Hispanic Black race/ethnicity, of separated marital status, of low PIR, to not have health insurance, to be on antidepressants, to have less than high school education, to have more household members, and to have an obese BMI, compared with females without depressive symptoms (Table 1). The presence of inflammation, ID, anemia, and IDA in the overall sample and by depressive symptoms status are illustrated in Table 2. Females with depressive symptoms had higher median (interquartile range) CRP concentrations (2.5 [0.8-6.2] vs. 1.8 [0.5-4.8]) in the absence of depressive symptoms; $P = 0.02$) and higher prevalence of ID (based on high TfR:12.8 [2.0] % vs. 7.5 [0.8] % in the absence of depressive symptoms; $P = 0.01$).

The associations between iron status and depressive symptoms using logistic regressions in the total sample and by PIR categories are shown in Table 3. In the total sample, the crude models for the association between ID and depressive symptoms indicated that females with ID, based on high TfR or low BodyFe, had 1.82 (95% CI: 1.24, 2.68; $P < 0.01$) and 1.62 (95% CI: 1.05, 2.48; $P = 0.03$) higher odds of depressive symptoms, respectively, than those who were iron sufficient. These associations were no longer significant after adjustment for confounders (TfR: 1.42 [95% CI: 0.88, 2.29; $P = 0.15$]; BodyFe: 1.45 [95% CI: 0.90, 2.33; $P = 0.12$]). Analyses between IDA and depressive symptoms were not significant in crude or adjusted models in females from the total sample (Table 3). When stratified by PIR, we present the association between ID or anemia and depressive symptoms within females of low income (PIR $\leq$ 1.85) only because the sample size was small ($n < 30$) among those with higher incomes (PIR > 1.85). Overall, the ID or anemia variables were not statistically significant for depressive symptoms among WRA with PIR $\leq$ 1.85 in crude or adjusted models (Table 3). Further, the sample size for IDA females with depressive symptoms was too small ($n < 30$) in both PIR categories, and as such, they are not shown.

Figure 1 illustrates the findings from the association conducted with negative binomial regression models between iron or anemia (including IDA) status and depressive symptoms total score and by the cognitive/affective depressive symptoms factor and the somatic depressive symptoms factor in WRA using the total sample and by PIR categories. In the total sample, the crude model for ID and depressive symptoms total scores showed that WRA with ID, based on high TfR, had 1.28 times higher depressive symptoms scores than females with iron sufficiency (95% CI: 1.08, 1.53; $P = 0.01$). After the inclusion of confounders, the effect was no longer significant, 1.19 (95% CI: 1.00, 1.40; $P = 0.05$). Among the low-income (PIR $\leq$ 1.85) sample, the crude and adjusted models testing the association between ID and depressive symptoms total score were significant. They indicated that WRA with ID, based on high TfR, had

TABLE 2
Weighted concentration and prevalence of inflammation, iron deficiency, anemia, and iron deficiency anemia among nonpregnant US females aged 20 to 44 y. Data are presented for the total sample ($N = 2516$) and by depressive symptoms categories (cutoff $\geq$10)[a]

Variables	Total sample		Depressive symptoms (cutoff≥10)		
	N	% (SE)	Absence ($n = 2,220$); % (SE)	Presence ($n = 296$); % (SE)	*P*
CRP (geometric mean (SE))					
CRP (median and IQR)	2516	1.9 (0.5-4.9)	1.8 (0.5-4.8)	2.5 (0.8-6.2)	0.02
Inflammation (> 5 mg/L)	673	24.3 (1.1)	24.2 (1.1)	30.8 (3.5)	0.06
Inflammation (> 1 mg/L)	325	11.4 (0.6)	11.3 (0.7)	15.5 (2.4)	0.12
Unadjusted Ft (geometric mean (SE))	2516	38.0 (0.7)	37.9 (0.8)	39.7 (2.2)	0.36
Unadjusted Ft (median and IQR)	2516	40.9 (22.6-70.7)	40.4 (22.3-70.6)	44.8 (23.9-72.8)	0.26
ID (≤ 15 μg/L)	403	14.7 (0.6)	14.4 (0.7)	17.8 (2.5)	0.23
Adjusted Ft[b] (geometric mean (SE))	2516	35.8 (0.7)	35.7 (0.7)	36.8 (2.1)	0.53
Adjusted Ft (median and IQR)	2516	38.8 (21.1-66.8)	38.6 (21.0-66.8)	44.4 (21.8-66.5)	0.36
ID (≤ 15 μg/L)	444	16.0 (0.7)	15.8 (0.7)	18.1 (2.6)	0.39
TfR (geometric mean (SE))	2516	5.2 (0.0)	5.1 (0.1)	5.3 (0.1)	0.32
TfR (median and IQR)	2516	4.9 (4.0-6.1)	4.9 (4.0-6.1)	4.9 (4.1-6.4)	0.95
ID (≥ 8.3 mg/L)	245	8.0 (0.7)	7.5 (0.8)	12.8 (2.0)	0.01
BodyFe (mean (SE)) -only Ft adj with Thurnham	2516	5.5 (0.1)	5.5 (0.1)	5.5 (0.3)	0.97
ID (< 0 mg/kg)	285	10.0 (0.6)	9.5 (0.6)	14.5 (2.4)	0.05
Hb (mean (SE))	2516	13.4 (0.0)	13.4 (0.0)	13.4 (0.1)	0.91
Anemic (< 12 g/dL)[†]	245	7.7 (0.7)	7.6 (0.7)	8.3 (2.0)	0.73
IDA[d] **based on:**					
Ft < 15 μg/L and Hb < 12 g/dL[b,†]	155	65.1 (3.7)	65.6 (3.6)	61.0 (13.8)	0.74
TfR ≥ 8.3 mg/L and Hb < 12 g/dL[†]	127	53.4 (3.6)	53.6 (3.8)	51.8 (12.3)	0.89
BodyFe <0 mg/kg and Hb < 12 g/dL[c,†]	139	58.7 (3.5)	58.1 (3.7)	63.5 (13.9)	0.71

The difference in means between depressive symptoms status groups was tested using linear regressions (geometric means (for Ft, TfR, and CRP) with SE were reported) or quintile test (medians and interquartile ranges were reported), and the difference in prevalence (% and SE were reported) between depressive symptoms status groups was tested using weighted Rao-Scott Chi-square tests.

Abbreviations: BodyFe, Body iron; CRP, C-reactive protein; Ft, Ferritin; Hb, hemoglobin; ID, Iron deficiency; IDA, Iron deficiency anemia; IQR, Interquartile range; TfR, Transferrin receptor.

[†] Estimates may be deemed unreliable based on NCHS Data Standards for Proportions for cases of presence of depressive symptoms due to a small sample size ($n < 30$).

[a] *N* are nonweighted.

[b] Ft biomarker was adjusted for inflammation using Thurnham's method (22).

[c] BodyFe was calculated based on Cook's equation (21). [d]Prevalence of IDA out of those participants with anemia.

TABLE 3
Crude and adjusted OR (95% CI) of presence of depressive symptoms (cutoff ≥10) by ID, anemia, or IDA in nonpregnant US females between 20 and 44 y of age from the total sample and by PIR categories (PIR ≤ 1.85 and >1.85*) using data from NHANES 2005-2010 ($N = 2516$)[a]

ID/Anemia/IDA based on:	Cases (n)	Crude model			Adjusted model		
		OR	95% CI	P	OR	95% CI	P
Total sample ($n = 2516$)							
Ft <15 μg/L[b]	62	1.18	0.81 – 1.73	0.38	1.09	0.72 – 1.64	0.68
TfR ≥ 8.3 mg/L	42	1.82	1.24 – 2.68	<0.01	1.42	0.88 – 2.29	0.15
BodyFe <0 mg/kg[c]	48	1.62	1.05 – 2.48	0.03	1.45	0.90 – 2.33	0.12
Hb< 12 g/dL[†]	28	1.10	0.63 – 1.93	0.72	0.99	0.54 – 1.82	0.97
Ft< 15 μg/L and Hb < 12 g/dL[b,†]	19	1.02	0.50 – 2.06	0.96	0.93	0.45 – 1.94	0.84
TfR ≥ 8.3 mg/L and Hb < 12 g/dL[†]	16	1.06	0.50 – 2.24	0.87	0.88	0.40 – 1.98	0.76
BodyFe <0 mg/kg and Hb < 12 g/dL[c,†]	20	1.21	0.60 – 2.43	0.59	1.10	0.53 – 2.29	0.78
PIR ≤ 1.85 ($n = 1230$)							
Ft < 15 μg/L[b]	41	1.06	0.72 – 1.56	0.76	0.99	0.68 – 1.45	0.97
TfR ≥ 8.3 mg/L	31	1.78	1.12 – 2.84	0.02	1.70	0.99 – 2.91	0.05
BodyFe <0 mg/kg[c]	32	1.30	0.83 – 2.04	0.24	1.30	0.83 – 2.04	0.24
Hb< 12 g/dL[†]	17	0.69	0.39 – 1.25	0.22	0.70	0.37 – 1.34	0.28

Abbreviations: BodyFe, Body iron; Ft, Ferritin, Hb, Hemoglobin, ID, Iron deficiency, IDA, Iron deficiency anemia, OR, Odds ratio, PIR, Poverty:income ratio, TfR, Transferrin receptor.

* Analyses for PIR > 1.85 were not possible due to small sample size ($n < 30$) for those with presence of depressive symptoms and poor iron status; only analyses for the total sample were possible for the IDA variables whereas for the PIR subsamples, the sample size for cases was small ($n < 30$).

[a] Logistic regression analysis was used to estimate the odds of presence of depressive symptoms for nonpregnant females with ID, anemia, or iron deficiency anemia relative to those with iron sufficiency, nonanemia, noniron deficiency anemia (reference group). The adjusted models were controlled for PIR, BMI, race, education level, marital status, health insurance, household size, age, and antidepressant use.

[b] Ft biomarker was adjusted for inflammation using Thurnham's method (22).

[c] BodyFe was calculated based on Cook's equation (21).

[†] Estimates may be deemed unreliable based on NCHS Data Standards for Proportions for cases of anemia or IDA and presence of depressive symptoms due to a small sample size ($n < 30$). N is nonweighted number of those with iron deficiency or anemia and presence of depressive symptoms.

1.36 (95% CI: 1.09, 1.69; $P = 0.01$) and 1.27 (95% CI: 1.03, 1.58; $P = 0.03$) times higher depressive symptoms scores, respectively, than WRA with iron sufficiency (Figure 1).

For the cognitive/affective depressive symptoms factor, we observed in the total sample and the low-income subsample that the crude models were significant. These models indicated that females with ID, based on high TfR, had 1.33- (95% CI: 1.02, 1.75; $P = 0.04$) and 1.43- (95% CI: 1.07, 1.92; $P = 0.02$) times higher cognitive/affective depressive symptoms than females with iron sufficiency. These associations did not hold in the adjusted models. Using the total sample, the crude and adjusted models for the association between ID and the total score for somatic depressive symptoms were significant. These models showed that females with ID, based on high TfR, had 1.25- (95% CI: 1.09, 1.43; $P < 0.01$) and 1.20- (95% CI: 1.04, 1.40; $P = 0.02$) times higher somatic depressive symptoms scores, respectively, than females with iron sufficiency. Females with ID (based on high TfR) and of low-income (PIR ≤ 1.85), had 1.28- (95% CI: 1.08, 1.53; $P = 0.01$) and 1.23- (95% CI: 1.03, 1.46; $P = 0.03$) times higher somatic depressive symptoms scores than females with iron sufficiency in crude and adjusted models, respectively.

Discussion

The consequences of ID go beyond physical health outcomes and can affect mental health, such as depressive symptoms. This is the first examination of the association of iron status with depressive symptoms as binary as well as a continuous variable in a nationally representative US population and also the first to categorize the association by specific aspects of depressive symptoms (cognitive/affective vs. somatic). We found that, after accounting for sociodemographic and health characteristics, females with ID had higher odds of and scores for depressive symptoms than females with iron sufficiency, especially those in the low-income category. These findings contribute to the existing literature reporting a significant association between poor iron status and depressive symptoms, help to provide more clarification to the previously mixed findings and bolster the evidence that prevention and treatment of ID may be helpful for female's mental health.

A prior nonpublished master's thesis explored the association between depressive symptoms and iron status among nonpregnant WRA (18–49 y) who were not on antidepressants using the same cycles that we used [35]. Dyer did not find a significant association between Ft and depressive symptoms when evaluated based on a cutoff ≥ 10, in line with our work, nor when evaluated by treating the depressive symptoms scores as continuous in adjusted models. This work was limited by only assessing iron status with the Ft biomarker that was not adjusted for inflammation but instead removed participants with CRP > 2 mg/L and those with Ft ≥ 150 ng/mL. Another difference is that Dyer excluded all females who were taking antidepressants, whereas we included those in the analytical sample and instead controlled for antidepressant use in all our analyses; the prevalence of antidepressant use was 12% in our study. Finally, Dyer also assessed the depressive symptoms data as continuous and reported means for count data. Regression such as Poisson, negative binomial, zero-inflated Poisson, and zero-inflated negative binomial regression have been suggested in the literature to examine count and skewed data [36]. We chose the negative binomial model because the depressive symptoms count data showed overdispersion. With this test, we observed that WRA with ID have higher depressive symptoms scores than females with iron

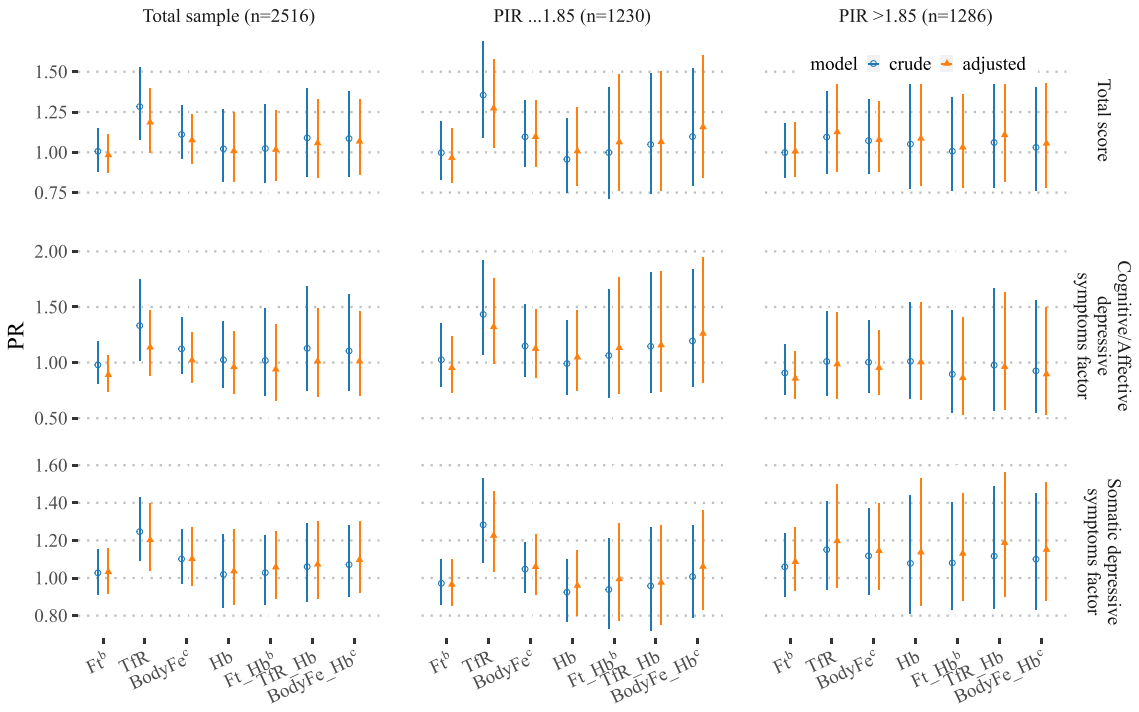

FIGURE 1. Crude and adjusted PR (95% CIs) of depressive symptoms total score and by cognitive/affective and somatic factors for iron deficient, anemic, or iron deficient anemic nonpregnant US females ages 20 to 44 y who participated in NHANES 2005 – 2010. Data are presented for the total sample and by PIR categories (n = 2516).[a]

[a]Negative binomial regression was used to estimate the prevalence ratio (and 95% CIs) of depressive symptoms (count data) for nonpregnant females with ID, anemia, or ID anemia relative to their corresponding reference group, iron sufficiency, nonanemia, or non-ID anemia. The adjusted models were controlled for PIR, BMI, race, education level, marital status, health insurance, household size, age, and antidepressant use. [b]Ft biomarker was adjusted for inflammation using Thurnham's method (22). [c]BodyFe was calculated based on Cook's equation (21). *N* is the unweighted number of those with ID, anemia, or ID with anemia.

Abbreviations: BodyFe=Body iron, BodyFe_Hb=Body iron and hemoglobin, Ft=Ferritin, Ft_Hb=Ferritin and hemoglobin, ID, Iron deficiency; IDA, Iron deficiency anemia; PIR, Poverty:income ratio; PR, Prevalence ratio; TfR, Transferrin receptor; TfR_Hb, Transferrin receptor and hemoglobin.

sufficiency in the total and the low-income samples. To our knowledge, this approach has not been applied in prior literature where this association was tested [37–48].

Using the negative binomial regression model, we were also able to assess the association between iron status and the total scores of 2 depressive symptoms factors, cognitive/affective and somatic. These factors were identified by Patel et al. in the US adult population using NHANES data [7]. Our data showed, after accounting for covariates, that WRA with ID from the total and the low-income (PIR $\leq$ 1.85) samples had 28% and 23%, respectively, higher somatic depressive symptoms factor scores than females with iron sufficiency. This association was not observed with the cognitive/affective factor in the adjusted models, indicating that ID impacts somatic symptoms of depression in this US nationally representative sample of nonpregnant WRA. As indicated previously, the somatic construct encompasses sleep disturbance, fatigue, and appetite changes, symptoms that have previously been studied in relation to iron status in females and children. A recently published review that included observational and RCT studies identified a positive association between ID and sleep disturbances and that iron supplementation improved the condition [49]. Notably, this review explored this association in adult and pediatric samples that were either ID or IDA. Additionally, 3 prior RCTs found that iron supplementation improved fatigue in nonanemic nonpregnant WRA compared with control [50–52]. Last, with respect to the association between appetite changes and iron status, intervention studies focused on children with ID or IDA [53–55] rather than WRA and found that iron supplementation improved appetite. Of note, one intervention trial found that nonpregnant WRA with IDA had reduced appetite compared with healthy controls and that iron supplementation improved their appetite [56]. Cumulatively, this prior evidence indicates that poor iron status is related to worse symptoms of the somatic construct of depressive symptoms. To our knowledge, no other study has tested the association between iron status and the cognitive/affective and somatic depressive symptoms factors in WRA.

Consistently, our work showed significant associations between ID, when defined by a high TfR, rather than when defined by a low Ft, and presence of depressive symptoms. As high TfR is a marker of a more advanced ID compared with low Ft, these findings may indicate that the association between ID and depressive symptoms may not emerge until the ID becomes more severe to a tissue ID state. Prior studies have found elevated TfR in serum of patients with major depressive disorder compared with controls; this finding is in accordance with findings in animal models [57–59].

The main strength of this study is that it used a nationally representative sample with a large sample size to assess the relationship between iron status and depressive symptoms. Prior observational studies have used more homogenous samples, as such, their findings may be less generalizable. In addition, we used more appropriate statistical techniques (the negative binomial

regression model) to uncover some of the subtleties of the relation between iron status and depressive symptoms in nonpregnant WRA. Prior evidence of the relation between iron status and depressive symptoms was limited by studies that inconsistently controlled for environmental and biological factors and by sample size. This study tried to overcome these challenges by controlling for PIR, BMI, race, education level, marital status, health insurance, household size, age, and antidepressant use, as well as by using a large, nationally representative sample. Even so, the presence of depressive symptoms cases was rare among WRA with IDA, especially when conducting stratified analyses by PIR. Therefore, we were able to examine this association only in the total sample of females with ID and anemia. It is also important to point out that there is a distinction between postpartum depression and depression experienced outside of the postpartum. NHANES does not differentiate between the 2 when the depressive symptoms data are collected, nor does it report the number of months since a mother delivered. As such, this limitation is recognized, and our analyses cannot differentiate between these 2 types of depression in this study. Furthermore, NHANES is a cross-sectional survey, and the findings of this study demonstrate an association between ID and depressive symptoms but cannot establish a causal relationship.

In summary, findings from this nationally representative study in WRA in the US indicate that nonpregnant WRA with ID (based on high TfR) have higher prevalence of somatic depressive symptoms than females with iron sufficiency, especially if they are of low-income status. Future RCTs that control for environmental and socioeconomic factors and have an adequate sample size are warranted. Should causality be established, efforts could focus on advocating enhanced screening for ID among WRA as iron supplementation could offer an effective intervention to alleviate the deficiency, prevent it from progressing to anemia, and decrease the rate of depressive symptoms in nonpregnant WRA.

Author contribution

The authors responsibilities were as follows—MAC and LEMK designed the research; MAC performed the statistical analyses and wrote the first draft of the paper; MAC, LEMK, BJM, NA, DT contributed to the interpretation of the results and made substantial revisions to the content. All authors read and approved the final manuscript.

Conflict of interest

All authors report no conflict of interest.

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Data availability

Datasets are publicly available at https://www.cdc.gov/nchs/nhanes/index.htm.

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