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Excess adiposity and iron-deficient status in Colombian women of reproductive age

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Abstract

Objective: Information about excess adiposity markers different from BMI and iron status is limited and more so about the shape of these associations. This study evaluated the relationship between three adiposity markers and iron-deficient status in reproductive-age women.

Methods: Cross-sectional analysis in 6357 non-pregnant women from the Colombian nutritional health survey (ENSIN) 2010. Exposures were the following: waist circumference (WC), waist-to-height ratio (W-HtR), BMI, and WC > 80 cm, W-HtR > 0.5, and BMI ≥ 25 and ≥30. Outcomes were the following: iron deficiency (ID) as serum ferritin <15 μg/L, ID as ferritin <30 μg/L, anemia, and continuous values of ferritin and hemoglobin. Logistic and linear regressions adjusted for socio-demographic/inflammation covariates were conducted.

Results: All the adiposity markers, continuous or categorical, were inversely and significantly associated with both ID thresholds in fully adjusted models ($p < 0.05$). W-HtR reported stronger effect estimates for ID (odds ratios < 0.5) and for prediction of log-ferritin levels (fully adjusted β-coefficient [95% confidence interval] 0.61 [0.39–0.82], $p < 0.01$) and was also inversely associated with anemia ($p < 0.05$). In cubic splines analyses, W-HtR, WC, and BMI were linearly associated with ID from values closer to international thresholds of general or central obesity, and the patterns of WC and BMI tended toward flatness. A significant decline in the likelihood of anemia was steeper by increasing W-HtR than by increasing BMI. After exclusion of women with C reactive protein > 5 mg/L or adjustment for C reactive protein, adiposity markers remained significantly related to ferritin levels and W-HtR with anemia.

Conclusions: Women with higher adiposity were less likely to have an iron-deficient status. W-HtR was the strongest and most consistently associated marker. Inflammation would not be involved in the associations found.

INTRODUCTION

Prevention and management of obesity is still complex due to its multi-etiological nature and interaction of diverse factors, including biological, behavioral, cultural, and social factors [1]. Obesity in turn is a well-risk factor for many noncommunicable chronic diseases, and metabolic alterations under obesity condition might be beyond the misbalance of lipid and glucose levels [2]. Obesity can be related to

minerals and vitamins deficiency, and this is known as a double burden of malnutrition [3].

Particularly, the impact of obesity on iron status has been evaluated in several studies with conflicting findings. It has been reported that obesity and overweight have a negative impact on iron metabolism [4, 5]. This pattern appears to be related to a reduction of both iron intestinal absorption and iron distribution/availability throughout body tissues triggered by excess adiposity-induced chronic and subclinical inflammation [6]. On the other hand, body iron stores, estimated as serum ferritin, have been broadly associated with insulin resistance [7], a highly prevalent condition in individuals affected by overweight and obesity in whom another group of studies have found higher serum ferritin levels [8, 9].

In Colombia, one out each two individuals in urban areas are affected by overweight (57.6%) according to evaluations in five major cities of the country [10]. The Colombian National Survey of Nutritional Situation (ENSIN by its name in Spanish) prioritizes data collection on anthropometrical measures and micronutrients status in groups such as women of reproductive age. In fact, there are gender inequalities reflected in trends of higher prevalence of overweight and obesity and anemia in women in comparison with men [11]. Currently, excess adiposity is estimated via a variety of surrogate anthropometrical measures and indexes that reflects general or located adiposity, and the evaluation of these in regard to iron status is pertinent. Moreover, the shape of the association between excess adiposity measures and iron status has not been explored yet. Therefore, we conducted research to study the pattern and shape of the relationship between three different adiposity markers and iron-deficient status in Colombian women of reproductive age using data from the ENSIN 2010.

Study Importance

What is already known?

- The pattern of association between excess adiposity and iron-deficient status is still inconclusive on the basis of studies reporting both positive and inverse associations. The shape of the association has not been previously explored, and a multivariable approach or adjustment for inflammatory markers has not been considered.

What does this study add?

- An inverse association between several excess adiposity markers and iron-deficient status was found in 6357 premenopausal women, including waist-to-height ratio (W-HtR), the marker most strongly and consistently associated with iron deficiency (ID) and or anemia. A cubic splines analysis showed that W-HtR and BMI were linearly associated with ID from values of approximately 0.5 and 33, respectively. Adjustment for the plasma levels of the inflammatory marker C reactive protein did not substantially change this pattern.

How might these results change the direction of research or the focus of clinical practice?

- Current findings indicate W-HtR as an index with higher potential to capture a link between adiposity and iron status and that iron status is not necessarily expected to be negatively impacted by excess adiposity. However, further studies comparing excess adiposity measures with prospective design and repeated measurements of exposure and outcomes are specifically needed.

METHODS

Study population

The 2010 ENSIN is a cross-sectional survey that evaluates the nutritional situation in the Colombian population and covers individuals from birth to 64 years old in 258 municipalities located in either urban or rural areas. Participants were randomly sampled from the national census of 2005. Details on the methodological design and sampling strategy of 2010 ENSIN have been previously reported [12]. The study was a secondary analysis of the 2010 ENSIN in a subsample of non-underweight and non-pregnant reproductive-age women (18–53 years) with available biochemical and anthropometrical evaluation ($N = 6974$). Underweight was an exclusion criterion because it might bias biochemical markers in terms of potential undernutrition and susceptibility to infectious or inflammatory conditions. After further exclusion of cases with missing values for outcome and exposure variables, the final sample consisted of 6357 women. Details on exclusions and identification of the sample are provided in Figure S1. ENSIN survey protocol was approved by the ethics committee of the National Heath Institute.

Anthropometrical and exposure/independent variables

The anthropometrical markers used were body mass index (BMI), waist circumference (WC), and waist-to-height ratio (W-HtR). In ENSIN 2010, weight and height were measured by using standard techniques [13, 14]. WC was measured from the midpoint between the lateral iliac crest and the lowest rib using a flexible steel tape measure [14]. Values of the above variables were used to calculate BMI (weight/height^2) [15] and W-HtR. Exposure variables were then defined: increased WC as values ≥ 80 cm according to the suggested cut-off of abdominal obesity for Latin American populations from the harmonized definition of metabolic syndrome [16]; increased W-HtR was defined as values >0.5 [17]; and overweight and obesity was defined as BMI ≥ 25 and ≥30, respectively [18]. The anthropometrical markers were additionally used as tertiles to compare lowest and highest values with regard the outcome variables.

Biochemical and outcome/dependent variables

Serum levels of ferritin and hemoglobin levels were used as biochemical variables in this analysis. Ferritin concentration was estimated using a chemiluminescent immunoassay (ADVIA Centaur), and hemoglobin levels were measured by azidam methemoglobin method in portable photometer (Hemocue AB and 201). From these markers outcomes were defined: iron deficiency (ID) as ferritin < 15 μg/L as suggested by World Health Organization [19]; ID as ferritin < 30 μg/L, a threshold suggested for mild ID [20]; and anemia as hemoglobin levels <12 g/dL. Continuous values of ferritin and hemoglobin levels were additionally used as outcomes.

C reactive protein (CRP) levels, an inflammatory marker, was measured via immunoturbidimetric assay. In this analysis, it was used as covariate because inflammation triggers increased synthesis of ferritin. Adjusting the associations for CRP levels was also useful to test if the effect of excess adiposity on iron status was independent of the inflammatory state derived from adipose tissue.

Covariates

Along with CRP levels, sociodemographic and food security variables were used as adjustment variables given their potential to confuse or modify the associations. ENSIN 2010 used a structured questionnaire to collect information on sociodemographic variables. These variables were used as covariates because their potential influence on either adiposity and/or iron status, and were the following: age [years]; sex (male [reference], female); ethnicity (general population [reference]/Indigenous/Afro-descendant); employment (employed [reference]/unemployed/student/other); wealth index quintiles (lowest quintile as reference); health status (excellent [reference], very good, good, regular, bad); number of people in the household (1, 2–4, 5–6, ≥7); food security (safe [reference], slightly unsafe, middle unsafe, severely unsafe); area of residence (urban [reference], rural); geographical region of the country (Bogotá capital city [reference], Atlantic, East, Central, Pacific, Orinoco, and Amazon).

Ethnicity was defined according to the autoperception of belonging to a collective according to his or her identity and ways of interacting in and with the world. The categories in this variable were the following: (1) general population: formed by people who did not perceive themselves as part of a specific ethnic group, (2) Indigenous, characterized by belonging to an indigenous people who share ancestral ties with the land and the natural resources of the territory in which they live, (3) Afro-descendants, including the Black, Black-White, Afro-Colombian, Afro-descendant, Palenquero de San Basilio, or Raizales denominations.

The wealth index was estimated using the Staveteig and Mallick methodology [21], based on variables that incorporate three components: asset ownership (e.g., owning refrigerator, washing machine, television, computer), household access to public services (e.g., drinking water, sewerage, electric power, garbage collection), housing conditions (e.g., floor and wall material, number of rooms) [21], quintiles of the score are used to obtain the categorical classification: very low (quintile 1), low (quintile 2), medium (quintile 3), medium-high (quintile 4), high (quintile 5).

Food security was measured and classified based on the Food and Nutrition Security Scale in the original study.

In the original survey, health status was categorized according to answer to questions related to health and social security such as if the individuals were affiliated to a health security entity, covered their medical costs, have had hospitalizations, have been diagnosed with any disease last year, and so forth.

Data analysis

The study variables were described according to their nature. All continuous variables were described as median and its interquartile range independently of their distribution, normal or nonnormal. The reason for this approach was to have a single center trend measure for all the continuous variables. In this way, if a variable had normal distribution, the median is equal or close to the arithmetic mean. Categorical variables were described as number and percentage. The study variables were described by groups of ID (yes/no), and differences by groups were estimated via Mann–Whitney U for continuous variables and χ^2 test for categorical variables.

We evaluated associations between the adiposity markers, as either continuous and categorical (international thresholds and tertiles) variables, with ID and anemia, through three logistic regression models: age adjusted, adjusted for age plus sociodemographic covariates (model 1), and model 2 (model 1 plus CRP levels). The reason for the progression of the adjustments of the above models was to observe the influence of inflammation on the associations apart of the of the rest of covariates because inflammation might lead to higher ferritin levels not representative of reliable body iron stores.

Additionally, linear regression analyses were conducted to test whether changes in continuous values of the adiposity markers were significantly related to changes in ferritin and hemoglobin levels, applying the same adjustments as in logistic regressions. In these analyses, continuous variables with skewed distributions, ferritin and CRP levels, were used after log-normalization of their distributions.

We also examined the shape of the association between each adiposity marker and iron-deficient statuses through cubic splines method with three knots at percentiles 10, 50, and 90, and this analysis was adjusted for covariates as well.

Because ENSIN 2010 lacked variables to exclude individuals with chronic, inflammatory, and infectious diseases, a sensitivity analysis was additionally conducted by re-running the previously mentioned association analyses after excluding women with moderate increased CRP levels (>5 mg/L or 0.5 mg/dL), which might be suggestive of inflammatory and/or /infectious disease that affect ferritin levels [22, 23]. We also conducted a supplementary analysis by age groups, ≤35 years and >35 years old, to examine or detect possible differences in the direction of the associations between women closer to and far from menopausal status.

TABLE 1 Description of study population (2010 ENSIN)

Variables	*n* for variables	All	ID (ferritin <15 μg/L)		*p* value
			No (*n* = 4970)	Yes (*n* = 1387)	
Age (years)*	6357	32 (25–41)	32 (25–41)	34 (26–41)	0.013
Serum ferritin (μg/L)*	6357	30.7 (16.3-54.6)	40.5 (25.8–63.9)	8.1 (5.2–11.8)	<0.001
Hemoglobin (g/L)*	6357	137 (126-147)	139.7 (130.1–149.4)	128.3 (116.9–139.5)	<0.001
C reactive protein (mg/dL)*	6357	0.02 (0.02-0.48)	0.02 (0.02–0.52)	0.02 (0.02–0.34)	<0.001
Anemia, %	6357	13.4	8.4	29.9	<0.001
WC* (cm)	6357	81.9 (75–89.9)	82.1 (75.3–90.2)	80.8 (74.2–89)	<0.001
W-HtR*	6357	0.53 (0.48–0.58)	0.53 (0.48–0.58)	0.52 (0.48–0.58)	<0.001
BMI * (kg/m^2)	6357	25.1 (22.5–28.5)	25.2 (22.5–28.6)	24.7 (22.2–28.4)	<0.001
WC ≥ 80 cm, %		57	58	53.9	0.006
W-HtR > 0.5, %		64.9	65.9	61.6	0.003
Weight status, %					
Normal weight		48.4	47.4	51.6	0.011
Overweight		34.3	35	32.1	
Obesity		17.3	17.6	16.3	
Ethnicity, %	6282				
General population		85.7	86	84.5	
Indigenous		4.1	4.0	4.4	
Afro-descendant		10.2	9.9	11.1	0.350
Employment, %	6310				
Employed		48.5	48	50.2	
Unemployed		2.7	2.7	2.6	
Student		6.6	6.6	6.5	
Other		42.3	42.7	40.8	0.149
Wealth index quintiles, %	6357				
1		16.2	16.6	14.9	
2		19.9	20.2	19.1	
3		22	22.2	21.4	
4		22.4	22.4	22.4	
5		19.4	18.6	22.1	0.004
Health status, %	6357				
Excellent		7.8	7.9	7.6	
Very good		8.8	8.4	10	
Good		56	56.6	53.8	
Regular		25.7	25.4	26.6	
Bad		1.8	1.7	2.0	0.821
Number of people in the household, %	6356				
1		1.5	1.4	1.6	
2–4		53.6	53.9	52.7	
5–6		30.1	30.2	29.6	
≥7		14.8	14.4	16.1	0.260
Food security, %	6356				
Safe		39.4	39.1	40.6	
Low unsafeness		38.8	39	38.1	
Middle unsafeness		14.7	15.1	13.2	
Severe unsafeness		7.1	6.8	8.0	0.749

TABLE 1 (Continued)

Variables	*n* for variables	All	ID (ferritin <15 μg/L)		*p* value
			No (*n* = 4970)	Yes (*n* = 1387)	
Area, %	6356				
Urban		78.8	78.2	80.8	
Rural		21.2	21.7	19.2	0.038
Region, %	6356				
Atlantic		18.3	18.3	21.6	
East		17.8	19.2	13.1	
Central		25.6	25.9	24.6	
Pacific		17.2	16.6	19.3	
Bogotá		18.9	18.6	19.7	
Orinoco and Amazon		2.2	2.3	1.7	<0.001

*Data are median (interquartile range). Continuous and categorical variables are described on the basis of weighted values. Samples sizes are shown as unweighted.

Abbreviations: ENSIN, Colombian National Survey of Nutritional Situation; WC, waist circumference; W-HtR, waist-to-height ratio.

We avoid addressing missing values via imputation because women with missing values for exposure/outcome variables were only 616 among the group with both anthropometrical and biochemical evaluation ($n = 6974$). Similarly, the *n* for valid values for each covariate was closer to the final sample of 6357 reproductive-age women.

All the analyses were run applying ENSIN survey weights and were conducted by using STATA 14.2. software (Statistics/Data Analysis, Stata Corporation, College Station, Texas).

RESULTS

Description of study population

Variables of the study population are described for the whole sample and by ID status (yes/no) in Table 1. In the whole sample, prevalence of ID (ferritin < 15 μg/L), mild ID (ferritin <30 μg/L), and anemia were 23%, 48.6%, and 13.4%, respectively. The proportion of women with excess adiposity by any marker was above half (57% high WC, 64.9% by high W-HtR, and 51.6% BMI-based overweight or obesity). Among women with obesity, 73.9% had type 1 obesity (BMI < 35), 19.3% type 2 obesity (BMI 35 to <40), and 6.8% severe obesity (BMI ≥ 40). Women with ID were older and had lower values of hemoglobin levels, WC, W-HtR, and BMI than women without ID (Table 1). On the other hand, slightly higher proportions of women with wealthiest status and urban residence were found in the group of ID versus non-ID status. Women with ID tended to reside more in coastal regions (Atlantic and Pacific) and less in regions of flat and jungle geography (east and Orinoco/Amazon) when compared with non-ID women.

A total of 6.9% of women had both ferritin levels lower than 15 μg/L and anemia, and 9.2% had either ferritin levels lower than 30 μg/L and anemia. According to unadjusted proportions, prevalence of any kind of ID tended to be lower in women with higher values of the adiposity markers (international thresholds; Table S1). Prevalence of anemia was slightly higher in increased WC versus normal and slightly lower in increased W-HtR (vs. W-HtR ≤ 0.5) and overweight (vs. BMI < 25; Table S1).

Likelihood of ID and anemia according to continuous values and international thresholds of excess adiposity

By approaching adiposity markers as continuous variables, all three markers were inversely and significantly associated with both thresholds of ID in fully adjusted models (Table 2), W-HtR was the marker with the strongest association, showing a reduction of 79% and 82% in the likelihood of ferritin levels <15 and <30 μg/L, respectively, by increasing values of this marker. In regard to anemia, W-HtR was significantly and inversely associated after adjustments and with a similar effect estimate than that reported for its relationship with ID (Table 3). BMI and WC showed a nonsignificant trend for association with anemia in fully adjusted models (Table 3).

When adiposity markers were used as categorical variables, all the international cut-off points had a significant and inverse association with both ID thresholds, and with comparable effect estimates (Table 3). Among the three adiposity markers, only W-HtR > 0.5 was significantly linked to lower likelihood of anemia, whereas WC ≥ 80 cm and BMI ≥ 30 kg/m^2 reported marginal trends for odds of anemia (Table 3).

By comparing age-adjusted associations, partially adjusted associations, and fully adjusted associations, including the inflammatory marker, CRP, levels as s covariate, the effect estimates did not substantially change. The same occurred for statistical significances with the only exception of associations between continuous BMI and anemia, in which a significant *p* value turned into marginal (0.054) after introducing additional adjustment for CRP levels.

The cubic splines analyses to evaluate the shape of the associations (Figure 1) showed that W-HtR and was linearly associated with

TABLE 2 Likelihood of ID and anemia by international cut-points of the adiposity markers

	Age adjusted		Model 1 adjusted		Model 2 adjusted	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
ID (ferritin levels < 15 μg/L)						
Waist circumference (cm)	0.98 (0.97–0.99)	0.001	0.98 (0.97–0.99)	0.002	0.99 (0.98–0.99)	0.040
Waist-to-height ratio	0.1 (0.03–0.32)	<0.001	0.11 (0.03–0.38)	<0.001	0.21 (0.06–0.71)	0.012
BMI (kg/m^2)	0.96 (0.95–0.98)	<0.001	0.96 (0.95–0.98)	<0.001	0.97 (0.95–0.99)	0.014
Waist circumference						
<80 cm	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
≥80 cm	0.77 (0.65–0.91)	0.002	0.78 (0.66–0.92)	0.004	0.82 (0.69–0.97)	0.028
Waist-to-height ratio						
≤0.5	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
>0.5	0.74 (0.62–0.88)	0.001	0.76 (0.64–0.91)	0.003	0.80 (0.67–0.96)	0.019
BMI						
Normal weight <25	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
Overweight ≥25 and <30	0.80 (0.65–0.97)	0.050	0.79 (0.66–0.94)	0.010	0.81 (0.68–0.97)	0.026
Obesity ≥30	0.75 (0.58–0.96)	0.127	0.77 (0.59–0.99)	0.030	0.85 (0.67–1.08)	0.210
ID (ferritin levels < 30 μg/L)						
Waist circumference (cm)	0.98 (0.98–0.99)	<0.001	0.98 (0.97–0.99)	<0.001	0.98 (0.98–0.99)	0.002
Waist-to-height ratio	0.10 (0.03–0.32)	<0.001	0.10 (0.03–0.27)	<0.001	0.18 (0.06–0.50)	0.001
BMI	0.97 (0.95–0.98)	<0.001	0.97 (0.95–0.98)	<0.001	0.98 (0.96–0.99)	0.013
Waist circumference						
<80 cm	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
≥80 cm	0.75 (0.65–0.91)	<0.001	0.74 (0.65–0.85)	<0.001	0.78 (0.68–0.90)	<0.001
Waist-to-height ratio						
≤0.5	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
>0.5	0.73 (0.64–0.85)	<0.001	0.74 (0.64–0.85)	<0.001	0.78 (0.67–0.90)	0.001
BMI						
Normal weight <25	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
Overweight ≥25 and <30	0.76 (0.66–0.88)	<0.001	0.75 (0.66–0.87)	<0.001	0.78 (0.67–0.90)	0.026
Obesity ≥30	0.73 (0.61–0.88)	0.001	0.71 (0.59–0.86)	<0.001	0.79 (0.65–0.96)	0.019

Note: Model 1: adjusted for age (years), ethnicity (general population [reference], Indigenous, Afro-descendant), employment (employed [reference], unemployed, student, other), wealth index quintiles (lowest quintile as reference), health status (excellent [reference], very good, good, regular, bad), number of people in the household (1, 2–4, 5–6, ≥7), food security (safe [reference], slightly unsafe, middle unsafe, severely unsafe), area of residence (urban [reference], rural), geographical region of the country (Bogotá capital city [reference], Atlantic, East, Central, Pacific, and Orinoco and Amazon). Model 2: adjusted for Model 1 plus CRP levels.

Abbreviations: CRP, C reactive protein; ID, iron deficiency; OR, odds ratio.

both cut-offs of ID from values of ∼0.5 (Figure 1C,E). The association between WC and BMI with ID starts from values lower than cut-offs of 80 cm and 25 kg/m^2, respectively, but tending toward flatness (Figure 1A,D,C,F). The significant declination in the likelihood of anemia was steeper throughout increasing values of W-HtR than throughout BMI values (Figure 1H,I). WC values only reached a marginal relationship with anemia between a narrow range of 100 to 100 cm, approximately.

The analysis by age groups, younger and older, showed the same trend for an inverse association between excess adiposity and iron-deficient statuses in both groups, and again W-HtR was the most consistent associated marker (Tables S3–S5). Women older than 35 years old ($n = 2563$) had higher proportions of cases with both excess adiposity and iron-deficient statuses in comparison with younger women ($n = 3794$) (Table S2).

Likelihood of ID/anemia according to tertiles of adiposity markers and prediction of continuous values of ferritin and hemoglobin by adiposity markers

By comparing extreme values in the distribution of the adiposity markers (highest vs. lowest tertiles), the pattern of inverse association with ID was replicated (Table 4). The significant association between

TABLE 3 Likelihood of anemia by each unit and international cut-points of the adiposity markers

	Age adjusted		Model 1 adjusted		Model 2 adjusted	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Waist circumference (cm)	0.99 (0.98–1.00)	0.383	0.99 (0.98–1.00)	0.066	0.99 (0.98–1.00)	0.075
Waist-to-height ratio	0.30 (0.07–1.27)	0.105	0.14 (0.03–0.63)	0.010	0.14 (0.03–0.66)	0.013
BMI (kg/m^2)	0.98 (0.96–1.00)	0.184	0.97 (0.95–0.99)	0.031	0.97 (0.95–1.00)	0.054
Waist circumference						
<80 cm	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
≥80 cm	0.99 (0.80–1.22)	0.974	0.89 (0.72–1.09)	0.266	0.90 (0.72–1.12)	0.366
Waist-to-height ratio						
≤0.5	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
>0.5	0.82 (0.66–1.03)	0.091	0.74 (0.59–092)	0.007	0.75 (0.60–0.95)	0.018
BMI						
Normal weight <25	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
Overweight ≥25 and <30	0.86 (0.68–1.09)	0.236	0.82 (0.66–1.03)	0.094	0.85 (0.67–1.08)	0.191
Obesity ≥30	0.87 (0.68–1.09)	0.326	077 (0.59–1.02)	0.075	0.77 (0.58–1.03)	0.088

Note: Model 1: Adjusted for age (years), ethnicity (general population [reference], Indigenous, Afro-descendant), employment (employed [reference], unemployed, student, other), wealth index quintiles (lowest quintile as reference), health status (excellent [reference], very good, good, regular, bad), number of people in the household (1, 2–4, 5–6, ≥7), Food security (safe [reference], slightly unsafe, middle unsafe, severely unsafe), area of residence (urban [reference], rural), geographical region of the country (Bogotá capital city [reference], Atlantic, East, Central, Pacific, and Orinoco and Amazon). Model 2: adjusted for Model 1 plus CRP levels.

Abbreviations: CRP, C reactive protein; ID, iron deficiency; OR, odds ratio.

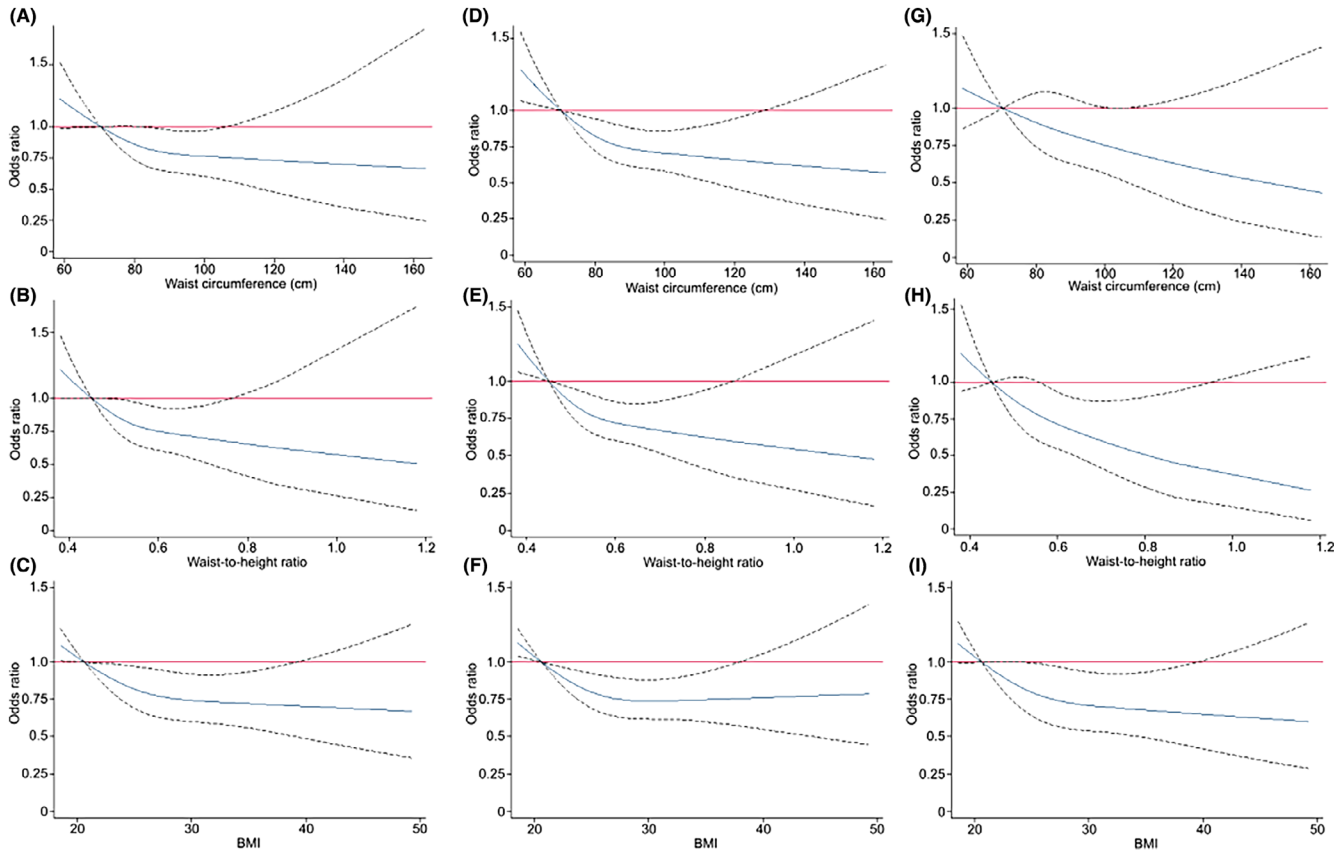

FIGURE 1 Cubic spline analyses for the association between the adiposity markers and (A–C) iron deficiency (ferritin levels <15 μg/L), (D–F) iron deficiency (ferritin levels <30 μg/L), and (G–I) anemia.

TABLE 4 Likelihood of ID throughout tertiles of values of adiposity markers

	ID (ferritin levels <15 μg/L)						ID (ferritin levels <30 μg/L)					
	Age adjusted		Model 1–adjusted		Model 2–adjusted		Age adjusted		Model 1–adjusted		Model 2–adjusted	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Waist circumference (cm)												
Tertile 1 (≤78)	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
Tertile 2 (>78 to ≤87.4)	0.84 (0.70–1.02)	0.082	0.86 (0.71–1.05)	0.151	0.89 (0.73–1.08)	0.240	0.80 (0.68–0.93)	0.006	0.80 (0.68–0.94)	0.008	0.82 (0.70–0.97)	0.022
Tertile 3 (≥87.5)	0.71 (0.58–0.87)	<0.001	0.72 (0.58–0.89)	0.002	0.78 (0.63–0.97)	0.027	0.68 (0.57–0.80)	<0.001	0.68 (0.57–0.80)	<0.001	0.74 (0.62–0.88)	<0.001
Waist-to-height ratio												
Tertile 1 (≤0.5)	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
Tertile 2 (>0.5–0.56)	0.78 (0.64–0.94)	0.012	0.80 (0.66–0.97)	0.028	0.82 (0.67–1.00)	0.051	0.79 (0.67–0.93)	0.005	0.80 (0.68–0.94)	0.007	0.82 (0.69–0.96)	0.017
Tertile 3 (>0.56)	0.69 (0.56–0.85)	0.001	0.71 (0.57–0.88)	0.002	0.78 (0.62–0.97)	0.026	0.66 (0.56–0.79)	<0.001	0.66 (0.55–0.78)	<0.001	0.72 (0.60–0.86)	<0.001
BMI (kg/m^2)												
Tertile 1 (≤23.5)	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)	
Tertile 2 (>23.5–27.3)	0.70 (0.58–0.84)	0.423	0.71 (0.59–0.86)	0.001	0.72 (0.60–0.88)	0.001	0.79 (0.68–0.92)	0.004	0.81 (0.69–0.94)	0.009	0.84 (0.70–0.96)	0.017
Tertile 3 (>27.3)	0.70 (0.58–0.86)	0.001	0.71 (0.58–0.86)	0.001	0.76 (0.62–0.94)	0.012	0.71 (0.61–0.84)	<0.001	0.72 (0.61–0.85)	<0.001	0.78 (0.65–0.92)	0.004

Note: Model 1: adjusted for age (years), ethnicity (general population [reference], Indigenous, Afro-descendant), employment (employed [reference], unemployed, student, other), wealth index quintiles (lowest quintile as reference), health status (excellent [reference], very good, good, regular, bad), number of people in the household (1, 2–4, 5–6, ≥7), food security (safe [reference], slightly unsafe, middle unsafe, severely unsafe), area of residence (urban [reference], rural), geographical region of the country (Bogotá capital city [reference], Atlantic, East, Central, Pacific, and Orinoco and Amazon). Model 2: adjusted for Model 1 plus CRP levels.

Abbreviations: CRP, C reactive protein; ID, iron deficiency; OR, odds ratio.

TABLE 5 Likelihood of anemia throughout tertiles of adiposity markers

	Whole sample ($n = 6357$)						Women with CRP levels ≤ 5 mg/L ($n = 4794$)		
	Age adjusted		Model 1 adjusted		Model 2 adjusted		Model 2 adjusted		
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	Tertile	OR (95% CI)	*p* value
Waist circumference (cm)									
Tertile 1 (≤78)	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		Tertile 1 (≤77)	1.0 (Ref.)	
Tertile 2 (>78 to ≤87.4)	0.97 (0.77–1.20)	0.805	0.91 (0.72–1.15)	0.499	0.90 (0.71–1.14)	0.423	Tertile 2 (>77 to ≤85.8)	0.78 (0.59–1.03)	0.087
Tertile 3 (≥87.5)	0.83 (0.64–1.07)	0.152	0.74 (0.57–0.96)	0.025	0.72 (0.55–0.95)	0.021	Tertile 3 (≥85.9)	0.75 (0.56–1.02)	0.068
Waist-to-height ratio									
Tertile 1 (≤0.5)	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		Tertile 1 (≤0.49)	1.0 (Ref.)	
Tertile 2 (>0.5–0.56)	0.84 (0.67–1.07)	0.169	0.80 (0.63–1.01)	0.070	0.79 (0.62–1.01)	0.063	Tertile 2 (≥0.5–0.55)	0.74 (0.55–0.98)	0.038
Tertile 3 (>0.56)	0.75 (0.57–0.98)	0.035	0.66 (0.51–0.86)	0.003	0.65 (0.49–0.85)	0.002	Tertile 3 (>0.55)	0.65 (0.48–0.8)	0.006
BMI (kg/m^2)									
Tertile 1 (≤23.5)	1.0 (Ref.)		1.0 (Ref.)		1.0 (Ref.)		Tertile 1 (≤23.1)	1.0 (Ref.)	
Tertile 2 (>23.5–27.3)	0.85 (0.68–1.08)	0.194	0.86 (0.68–1.08)	0.216	0.85 (0.68–1.08)	0.206	Tertile 2 (>23.1–26.7)	0.76 (0.58–1.01)	0.061
Tertile 3 (>27.3)	0.81 (0.63–1.03)	0.099	0.75 (0.58–0.97)	0.030	0.74 (0.57–0.96)	0.026	Tertile 3 (>26.7)	0.89 (0.66–1.19)	0.442

Note: Model 1: Adjusted for age (years), ethnicity (general population [reference], Indigenous, Afro-descendant), employment (employed [reference], unemployed, student, other), wealth index quintiles (lowest quintile as reference), health status (excellent [reference], very good, good, regular, bad), number of people in the household (1, 2–4, 5–6, ≥7), food security (safe [reference], slightly unsafe, middle unsafe, severely unsafe), area of residence (urban [reference], rural), geographical region of the country (Bogotá capital city [reference], Atlantic, East, Central, Pacific, and Orinoco and Amazon). Model 2: Adjusted for Model 1 plus CRP levels.

Abbreviations: CRP, C reactive protein; OR, odds ratio.

TABLE 6 Linear regression between values of adiposity markers, serum ferritin levels, and hemoglobin concentration

	Whole sample ($n = 6357$)						Women with CRP levels ≤5 mg/L ($n = 4794$)	
	Age adjusted		Model 1 adjusted		Model 2 adjusted		Model 2 adjusted	
	β coefficient (95% CI)	*p* value	β coefficient (95% CI)	*p* value	β coefficient (95% CI)	*p* value	β coefficient (95% CI)	*p* value
Log-ferritin (μg/L)								
Waist circumference (cm)	0.004 (0.003 to 0.005)	<0.001	0.004 (0.003 to 0.005)	<0.001	0.003 (0.002 to 0.005)	<0.001	0.003 (0.001 to 0.005)	<0.001
Waist-to-height ratio	0.72 (0.52 to 0.92)	<0.001	0.71 (0.51 to 0.91)	<0.001	0.61 (0.39 to 0.82)	<0.001	0.57 (0.31 to 0.83)	<0.001
BMI (kg/m^2)	0.009 (0.006 to 0.012)	<0.001	0.009 (0.006 to 0.12)	<0.001	0.007 (0.004 to 0.010)	<0.001	0.007 (0.003 to 0.011)	0.001
Hemoglobin (g/L)								
Waist circumference (cm)	0.04 (−5.95 to 10.2)	0.979	0.03 (−0.01 to 0.08)	0.219	0.03 (−0.02 to 0.08)	0.236	0.03 (−0.03 to 0.10)	0.355
Waist-to-height ratio	2.16 (−0.56 to 10.2)	0.601	7.52 (−0.36 to 15.4)	0.062	7.7 (−0.55 to 16.1)	0.067	7.52 (2.84 to 17.86)	0.155
BMI (kg/m^2)	0.04 (−0.07 to 0.17)	0.451	0.11 (−0.007 to 0.23)	0.065	0.11 (−0 to 009 to 0.248)	0.069	0.11 (−0.05 to 0.27)	0.186

Note: Model 1: Adjusted for age (years), ethnicity (general population [reference], Indigenous, Afro-descendant), employment (employed [reference], unemployed, student, other), wealth index quintiles (lowest quintile as reference), health status (excellent [reference], very good, good, regular, bad), number of people in the household (1, 2–4, 5–6, ≥7), food security (safe [reference], slightly unsafe, middle unsafe, severely unsafe), area of residence (urban [reference], rural), geographical region of the country (Bogotá capital city [reference], Atlantic, East, Central, Pacific, and Orinoco and Amazon). Model 2: adjusted for Model 1 plus log-transformed CRP levels.
Abbreviation: CRP, C reactive protein.

W-HtR and anemia remained and was even stronger across all of the adjustment models than by using the cut-off of 0.5. The marginal statistical significance of the associations between WC, BMI, and anemia previously observed in Table 3 did not improve by comparing their values in the lowest and highest tertiles (Table 5).

All of the adiposity variables predicted positively and significantly continuous values of ferritin in the linear regression approach. With increasing W-HtR there was an increase of 0.72 log-transformed units in levels of ferritin (μg/L). WC and BMI had weaker relationships with ferritin levels as continuous variable (Table 6). Unlike its significant association with the categorical outcome of anemia, W-HtR as continuous variable did not achieve statistical significance in predicting changes in hemoglobin concentration units.

Sensitivity analysis including only women with CRP levels ≤5 mg/L (0.5 mg/dL; $n = 4794$)

After excluding women with potential inflammatory and/or infectious disease, the association patterns previously described for outcomes of ID (ferritin levels < 30 μg/L) and anemia remained similar (Tables S6–S8). Moreover, the statistically significant linear relationships between the adiposity variables and continuous values of ferritin seen in the whole sample persisted, with practically identical regression coefficients, in the subgroup with CRP levels ≤ 5 mg/L (Table 6). The effects estimates for the associations between the adiposity markers and ferritin < 15 μg/L remained comparable to those observed in the whole sample, but their statistical significance was attenuated presumably because of reduced statistical power (Table S6).

DISCUSSION

This research evaluated the association between three measures of adiposity and iron-deficient status. Women with higher adiposity were less likely to have ID, a W-HtR was the marker of adiposity most strongly and consistently related to lower odds of presenting iron-deficient status outcomes. Apparently, inflammation would not be involved in the associations found.

The association pattern between iron status and excess adiposity is not totally clear throughout the findings provided by several studies carried out in vulnerable populations such as women and children or adolescents (Table 7). There is a trend for positive associations (more adiposity, more odds of ID), with most of the studies with this kind of report having ID definitions directly or indirectly based on low serum iron. Unadjusted analyses appear to be common in studies on adiposity and iron status. Haidari et al. evaluated difference in concentration for several iron markers across categories of body weight in heathy women aged 18 to 35 years [24]. They did not find differences in values of total iron binding capacity, transferrin, and ferritin levels, and only serum iron as well as hemoglobin levels were significantly lower in women affected by overweight and obesity. This trend for

TABLE 7 Findings on adiposity and ID or anemia in selected studies

Authors	Sample *n*	Age range or mean age (years)		Exclusion criteria	Adiposity markers	ID definition	Anemia definition	Iron markers	Findings on adiposity-ID/anemia association			Covariates
		Children	Women						Positive association-higher likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	Inverse association-lower likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	No association	
Kordas et al. 2013 [33]	3267		13–49	Pregnancy Age below or above the age range	Categories of weight status in terms on BMI non-overweight (overweight/ obesity)	Ferritin <12 μg/L	<120 g/L	Ferritin Hb		Less likelihood of anemia by overweight/ obesity vs. non-overweight	No significant association between ID and weight status	Age, region of country, visit to doctor last year, age of head household, children <5 y old in household, persons in household, marital status, and employed/ working (yes/no)
Eckhardt et al. 2008 [34]	Multicentric study 6841 (Egypt) 5078 (Peru) 11,965 (Mexico)		18–49 years	Pregnancy Age below or above the age range	Categories of weight status in terms on BMI non-overweight (overweight/ obesity)	-	<120 mg/L	Hb		Less likelihood of anemia by overweight/ obesity vs. non-overweight in Egyptian and Peruvian women	No significant association between anemia and weight status in Mexican women	Age, parity, education (years), socioeconomic status, and region (urban/ rural)
Haidari et al. 2020 [24]	170		18–35 years	Chronic disease, irregular menstrual cycle, participation in weight-loss regimens or professional sports program during the previous 6 months, vitamin/ mineral	BMI WHR BF%s	-	-	Iron Ferritin Transferrin TIBC Hb	Lower Hb levels with higher BMI values Higher transferrin levels with higher W-HtR values	-	-	Not adjusted analysis but intakes were measured, and no differences were found

(Continues)

TABLE 7 (Continued)

Authors	Sample *n*	Age range or mean age (years)		Exclusion criteria	Adiposity markers	ID definition	Anemia definition	Iron markers	Findings on adiposity-ID/anemia association			Covariates
		Children	Women						Positive association-higher likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	Inverse association-lower likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	No association	
				treatment, laxative use, or hormone medications at least 6 months before sampling								
Al Sabbah 2020 [25]	251		23 ± 5.3	NOT DESCRIBED	Total body fat	-	<120 mg/L	-	Total body fat % was found to be the highest (38·9%) among students with anemia ($p < 0.05$)	-	-	Not adjusted analysis
Cepeda-Lopez et al. 2011 [27]	1174 children 621 women	5–12	18–50	Underweight women (BMI < 18.5) and children (BMI *z* score ≤ −2 SD)	BMI BMI *z* score	Low serum iron (<60 μg/dL) or elevated TIBC (>0.360 μg/dL) and low %TSAT (<20%) values	Hb used a continuous variable	TS TIBC Serum iron	-	-	No differences by obesity status in Hb or ID or iron markers in children and women. Except ID in women only in terms of low serum iron	Age, sex, area (rural or urban), geographic region, caregiver education, and iron intake
Zhang et al. 2021 [42]	20,172	7–14		NOT DESCRIBED	Obesity according to BMI IOTF definition WC W-HtR	-	(1) For children aged 7–9 years, ≥115 g/L normal, 110–114 g/L mild anemia, 80–109	-	The prevalence of anemia increased with the severity of thinness and obesity	-	-	Not adjusted

TABLE 7 (Continued)

Authors	Sample *n*	Age range or mean age (years)		Exclusion criteria	Adiposity markers	ID definition	Anemia definition	Iron markers	Findings on adiposity-ID/anemia association			Covariates
		Children	Women						Positive association-higher likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	Inverse association-lower likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	No association	
							moderate anemia, and <80 g/L severe anemia; (2) for children aged 12–14 years, ≥120 g/L normal, 110–119 g/L mild anemia, 80–109 moderate anemia, and <80 g/L severe anemia					
Manios 2013 [28]	2492	9–13	-	Thalassemia minor	BMI IOTF	TSAT <16%	< 12 g/dL	TSAT	Higher likelihood of ID by having obesity in both boys (OR 2.83 [1.65–4.85]) and girls (OR 2.03 [1.08–3.81])	-	-	Dietary iron, calcium, vitamin C and fiber, paternal educational level, and menarche (girls only)
Jeong et al. 2022 [26]	10,231	13–21		Menstruation at the time of examination	BMI 2017 Child Growth and Development Table	-	<11.5 g/dL (age 10–11 years) < 12 g/dL (age 12–14 years) For age ≥15 <12 g/dL in women and <13 g/dL in men	-	Only in the subgroup of 10–13 years the risk of anemia was significantly higher (adjusted OR, 2.88; 95% CI, 1.20–6.95) in the obesity group	-	Compared with the non-obesity group, the adjusted odds ratio for anemia 1.00 95% CI (0.66–1.50) in the obesity group	Sociodemographic factors (sex, age, and household income). Model 3: Model 2 plus adjusted for menarche

(Continues)

TABLE 7 (Continued)

Authors	Sample *n*	Age range or mean age (years)		Exclusion criteria	Adiposity markers	ID definition	Anemia definition	Iron markers	Findings on adiposity-ID/anemia association			Covariates
		Children	Women						Positive association-higher likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	Inverse association-lower likelihood/ proportion/ prevalence of ID and anemia by excess adiposity	No association	
Aguree et al. 2023 [29]	2442		20–49	BMI < 18.5 CRP > 6 mg/L	Categories of weight status in terms of BMI non-overweight (overweight/ obesity)	(1) 2 of 3 abnormal values in SF, TS, and EPP. (2) 2 of 3 abnormal values in MCV, TS, and EPP. (3) ID based on low body iron. <6.5 μg/L	<12 g/dL	Ferritin TS EPP	Higher prevalence of ID (any definition) and anemia in women with and obesity	-	-	Age, race, and Hispanic origin, educational attainment, BMI, and family poverty-to-income ratio

Abbreviations: BF, body fat; CRP, C reactive protein; EPP, erythrocyte protoporphyrin; Hb, hemoglobin; ID, iron deficiency; IOTF, International Obesity Task Force; MCV, mean corpuscular volume; OR, odds ratio; SF, serum ferritin; TIBC, total iron binding capacity; TSAT or TS, transferrin saturation; WC, waist circumference; WHR, waist-hip ratio; W-HtR, waist-to-height ratio.

anemia in obesity was also observed in 251 female university students from Dubai, in which those with anemia also presented a higher mean of total body fat percentage (38.9%) [25]. Meanwhile, Jeong et al. did not find an association between obesity and anemia in adolescents aged 10.21 years adjusting for sex, age, household income, and menarche, although in a subgroup analysis they found a positive association in the group of 10 to 13 years old [26]. Cepeda-Lopez et al. did not find a significant relationship between BMI as continuous variable or BMI cut-points for obesity with hemoglobin levels, values of transferrin saturation or total iron binding capacity in women of reproductive age and children (5–12 years old) from the 1999 Mexican nutrition survey, in unadjusted and adjusted (age, area [rural/Urban], geographic region, parity, and iron intake) regression models [27]. As occurred in the previously mentioned non-adjusted analysis by Haidari et al., Cepeda-Lopez et al. only found a significant inverse association between BMI and serum iron in either unadjusted or adjusted regression models (crude β coefficient −9.78, 95% CI:−16.5 to −3.06; adjusted β coefficient −9.56, 95% CI: −16.8 to −2.35) [27]. Unlike the negative findings in Mexican children from the Cepeda-Lopez et al. study, in Greek children and adolescents (9–13 years old) from the Healthy Growth Study, the likelihood of ID estimated as transferrin saturation < 16% in participants with obesity was twice that of children and adolescents with normal weight in crude models and adjusting for covariates for dietary iron, calcium, vitamin C, fiber, paternal educational level, and menarche [28]. In this study conducted by Manios et al., serum ferritin was significantly higher, and hemoglobin level significantly lower in individuals with obesity versus individuals with normal weight [28]. More recently, Aguree et al. described higher prevalence of ID and anemia in women affected by overweight and obesity (vs. normal weight) from NHANES 2001-2006. These authors used three definitions of ID based on combinations of different markers (e.g., low ferritin, low transferrin saturation, or high erythrocyte protoporphyrin; low mean corpuscular volume, low transferrin saturation, or high erythrocyte protoporphyrin) [29].

Our finding of higher adiposity related to less likelihood of iron-deficient status is discrepant with the studies above described with use of ID definitions based on iron markers other than serum ferritin, and with reports suggesting higher likelihood of ID and/or anemia in excess adiposity context. A possible reason for this discrepancy might rely on how other iron markers different from ferritin could be directly or indirectly influenced by subclinical and clinical inflammation at some extent, and lack of adjustment for inflammatory markers in previous studies. Admittedly, serum ferritin as previously mentioned is widely influenced by inflammation because ferritin is also a phase acute reactant, and thus its capability to detect ID is limited under inflammatory contexts [30]. However, definitions of ID based on other iron markers are also prone to be biased by inflammation. For instance, low serum iron concentrations do not truly represent ID independent of inflammation. Serum iron is a measure of the circulating metal in blood serum, and although it is not an iron protein whose synthesis is up or downregulated via cytokines or inflammatory mediators, its availability in circulation and body redistribution does depend on iron proteins. In fact, serum iron levels have been found markedly reduced during early stages of inflammation [31]. If ferritin is increased in acute phase, intracellular iron will tend to be retained in the form of storage, with poor release to blood mainstream and decreasing the apparent blood serum iron content. Similar indirect alterations of serum iron via inflammation in terms of transferrin levels can be expected. Transferrin is downregulated in acute phase causing circulating iron to be reduced [30]. In this way, markers such as total iron binding capacity and transferrin saturation, which are dependent on serum iron content and/or transferrin synthesis, might indirectly be altered by inflammation. However, Aguree et al., who described higher prevalence of anemia and ID in US women from the NHANES 2001-2006 and used transferrin saturation as part of their ID definitions, restricted the analysis to women with CRP levels ≤ 6 mg/L, reducing the chance of findings biased by inflammation/infection [29]. Marked differences in BMI values and ethnicity might account for the opposite findings between Aguree et al.'s study and our study, although via unclear mechanisms. The proportion of women with BMI ≥ 30 in NHANES is almost two-fold the proportion in the Colombian women (31.2% vs. 17.3%), and severity of the obesity could influence association patterns. Most of the ENSIN women with obesity had type 1 obesity (BMI < 35), and proportions of types of obesity were not reported by Aguree et al. Future meta-analyses on the topic should consider categories of obesity for subgroup analyses and meta-regression. The vast majority of our sample belonged to the general population known as mestizo (mixed Indigenous-Spanish ancestry) in comparison with 66.7% of Non-Hispanic White women in NHANES. Several studies have reported differences in iron metabolism-related genetic variants according to ethnicity [32]. Particularly, African American ethnicity appears to have lower hemoglobin levels, and association patterns with other ethnicities are not fully conclusive [32]. Additionally, neither Aguree et al.'s study nor our study included dietary characterization, which might fully or partially explain lower and higher odds of ID and anemia by excess adiposity.

On the other hand, as us, other authors have reported inverse associations between adiposity and iron status. In an analysis also conducted in Colombian population by Kordas et al. using data from 2005 ENSIN survey, ID (ferritin < 12 μg/L) or anemia were less frequent in women of reproductive age with BMI ≥ 30 [33]. Moreover, Eckhardt et al. also found lower odds for anemia in women from Egypt and Peru affected by overweight or obesity (vs. non-overweight) using data of nationally representative surveys [34]. Excess adipose tissue is known for an increasing activity in releasing of pro-inflammatory cytokines and other inflammatory mediators, which might trigger increased ferritin concentration not truly related to iron status [6]. However, in our study, the associations found were not affected when inflammation was part of the adjustment model. Similarly, when women with CRP levels >5 mg/L were excluded, the adiposity markers persisted as significant positive predictors of ferritin levels. Moreover, the trend of inverse association between adiposity and iron status was also seen when anemia was the outcome, with higher adiposity being associated with lower odds for anemia, and this finding was also replicated in women with CRP levels ≤5 mg/L. These observations discard a pattern of ID anemia with high serum ferritin

derived from adiposity-induced inflammation but with lower hemoglobin levels as a result of iron cellular sequestration triggered by inflammation. Therefore, other mechanisms would be behind the inverse associations between adiposity and iron-deficient status.

One possible explanation for the association pattern we found might lay in the relationship between insulin resistance and ferritin level. Many *in vitro* studies have shown pro-oxidant deleterious effect of iron excess on insulin signaling, and from those findings, a large amount of epidemiological studies have evaluated and found serum ferritin as predictor of type 2 diabetes and metabolic syndrome [7, 35, 36]. Although iron excess is a plausible risk factor for insulin resistance and cardiometabolic disease, its relationship with this risk might not be causal. Iron metabolism could be disturbed in initial stages of risk along with other cardiometabolic risk markers. Similarly, the consistently reported positive association between ferritin levels and metabolic syndrome and its components is evidence of how ferritin behaves in line with biochemical and clinical alterations related to insulin resistance [37]. Serum ferritin synthesis may largely be increased in the context of a proxy of an insulin-resistant state such as excess adiposity. Particularly, the genetic expression of ferritin in terms of their messenger RNA has been reported to be increased with worsened insulin resistance in adipose tissue extracted from individuals affected by morbid obesity [38], and this could be linked to higher levels of soluble fraction of ferritin in mainstream blood in excess adiposity. However, this disturbing impact of adiposity and insulin resistance on iron proteins such as ferritin, although it is not reflecting iron status, apparently would not be affecting iron distribution because, based on the women from our study, hemoglobin levels were higher with more adiposity.

Another reason for the nature of our associations could be the menstrual cycle of the women in our study. Women affected by obesity are more prone to have longer and irregular menstrual cycles that lead to less blood loss and higher iron storage than women with normal weight status [39]. Moreover, insulin resistance might be a mediating factor between obesity and menstrual irregularity because the strong association between these variables is markedly attenuated toward null effect when the association is adjusted for insulin resistance [40]. Unfortunately, the 2010 ENSIN study did not have variables on the regularity of menstrual cycle of the women to adjust the associations between the anthropometric and iron markers.

Additionally, women with a higher caloric intake might have an acceptable iron status with simultaneous excess adiposity and this might lead to a pattern of inverse association between adiposity and iron-deficient status. However, we could not adjust our analysis for dietary variables because missing values for these covariates extremely reduced the statistical power of the study to a sample of around 351 women. An analysis in children with data from the 2015 ENSIN survey, found that red meat and egg intakes were determinants of serum ferritin levels, although no correlations with adiposity were aimed in that study [41]. Further studies should examine in detail the effect of dietary variables on the adiposity-iron status association.

Whatever it is the kind of mechanism or context mediating the link between excess adiposity and lower odds of iron-deficient status, W-HtR seems to be a better associated and consistent marker for that association pattern. Comparative studies on WC, BMI, and W-HtR in respect to iron status are very limited to contrast our findings. Zhang et al., who also compared the three anthropometric marker, found that anemia was more prevalent in both the lowest and highest values of three anthropometric markers, but their study population was exclusively pediatric (7–14 years old) and the analysis was unadjusted (Table 6) [42]. Meanwhile, several systematic reviews and meta-analyses have found W-HtR as a better predictor than BMI or WC for highly relevant outcomes such as cardiometabolic risk, which, as mentioned before, is a physio-pathological state that might be involved in the adiposity-iron metabolism link. Ashwell and Gibson reported, in a systematic review and meta-analysis involving more than 300,000 individuals, a better discriminating power of W-HtR than WC and BMI for distinguishing people with hypertension, type-2 diabetes, dyslipidemia, metabolic syndrome, and general cardiovascular outcomes [43]. Another meta-analysis by Savva et al. described stronger associations between W-HtR and diabetes and metabolic syndrome than those when BMI was the exposure variable [44]. In this way, it appears that comparing waist with height would better capture excess adiposity and, in turn, outcomes derived from this adiposity. In our study, the widely used cut-off to establish a relationship with cardiometabolic risk, in terms of having a waist measure higher than the half of the height, was shown to be an inflection point from which the inverse association between W-HtR and iron-deficient statuses started to be linear and significant.

Several limitations need to be acknowledged. As previously mentioned, this study lacked information on the menstrual cycle of the women, which would have represented a potential mediating variable for the association pattern described herein. Additionally, having available a broad set of different iron makers would have allowed us to obtain a better characterization of iron status in the population, but 2010 ENSIN only collected data on serum ferritin and hemoglobin levels. There was also a large amount of missing data for relevant covariates of dietary intake, use of supplements, and physical activity, and thus, these variables were not used to avoid affecting statistical power. However, in the few studies revised with adjusted analyses, iron intake and physical activity did not affect association patterns between excess adiposity and iron status. The 2010 ENSIN lacked data on variables of status for diabetes and other chronic diseases or infectious diseases such as malaria in which inflammation and/or hematological alterations can bias iron markers. This limitation was attenuated by conducting a sensitivity analysis in which the effect estimates for the associations were recalculated after excluding women with potential inflammation or infection on the basis of high CRP levels, and this did not substantially affect the associations initially found. Similarly, the finding on lower prevalence of anemia in excess adiposity seems to discard the effect of subclinical or clinical inflammation on iron status in this sample of women. The Pacific

littoral of Colombia tends to report more cases of malaria, but only 4% of women in this 2010 ENSIN analysis were from this subregion. Parity was an additional covariate not available for this analysis, and multiple gestations have been found to be positively related to both obesity and ID [45, 46]. However, its effects as a non-measured confounder appear to be null because the association between excess adiposity and iron-deficient status we found was inverse. Our findings apply for this Colombian population and their generalizability requires further validation in other populations by using similar methodological approaches.

To the best of our knowledge, this is the first study analyzing the relationship between excess adiposity and iron status by comparing three different adiposity markers in multivariate models and exploring the shape of the associations. Additionally, this study used nationally representative data with a considerable large sample size.

In summary, women with higher adiposity were less likely to have an iron-deficient status. W-HtR was the marker of adiposity most strongly and consistently related to lower likelihood of iron-deficient status. Apparently, inflammation would not be involved in the associations found.O

AUTHOR CONTRIBUTIONS

Milton Fabián Suarez-Ortegón conceived the study design, analyzed data, and drafted the manuscript. Jenny Elizabeth Ordoñez-Betancourth conceived the data analysis design and analyzed data. Ana Yibby Forero analyzed data. José Guillermo Ortega-Ávila reviewed/edited the manuscript. José Manuel Fernández-Real reviewed/edited the manuscript and contributed to the discussion.

CONFLICT OF INTEREST DISCLOSURE

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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