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Higher Body Mass Index Is Associated with Iron Deficiency in Children 1 to 3 Years of Age

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Objectives To examine the association between body mass index (BMI) and iron deficiency in early childhood, while considering the influence of low-grade systemic inflammation.

Study design Healthy children ages 1-3 years were included in a cross-sectional analysis. Age- and sex-standardized World Health Organization BMI z score (zBMI) was calculated using height/length and weight measurements; iron status was assessed by serum ferritin; inflammation was assessed by C-reactive protein (CRP). Children with CRP ≥10 mg/L were excluded because this may indicate acute systemic inflammation. Adjusted multivariable regression analyses were used to investigate the association between zBMI and both serum ferritin (μg/L), and iron deficiency (serum ferritin <12 μg/L). We performed prespecified subgroup analyses according to CRP level (normal [≤1.0 mg/L] and low-grade inflammation [>1.0 mg/L to <10.0 mg/L]).

Results Of 1607 children included, 20% were categorized as with zBMI >1, 13% had iron deficiency, and 18% had low-grade inflammation. Higher zBMI was associated with lower serum ferritin (–1.51 μg/L, 95% CI –2.23, –0.76, $P < .0001$) and increased odds of iron deficiency (OR 1.28, 95% CI 1.10, 1.50, $P = .002$). Though there was no interaction between zBMI and CRP for the adjusted linear regression model ($P = .79$) or logistic regression model ($P = .43$), children with low-grade inflammation had a higher serum ferritin ($P < .0001$).

Conclusions Higher zBMI is associated with increased risk for iron deficiency in children between 1 and 3 years, and should be considered as a risk factor in targeted screening. Further research is needed to better understand the relationship between serum ferritin and CRP for children in all weight categories. *(J Pediatr 2019;207:198-204).*

Trial registration ClinicalTrials.gov: NCT01869530.

For young children in developed countries, iron deficiency and obesity are common nutrition-related disorders. In toddlers, the prevalence of iron deficiency and obesity is each approximately 9%, and the prevalence of iron deficiency anemia and severe obesity is each approximately 2%.[1,2] Both iron deficiency and obesity in early childhood are associated with adverse health outcomes later in life. For example, iron deficiency is associated with neurodevelopmental impairments that may be irreversible.[3,4] Obesity in childhood may continue into adulthood and is associated with adverse cardiometabolic outcomes.[5] Primary care screening of children for both iron deficiency and obesity has been recommended.[1,6]

A meta-analysis of 26 cross-sectional and case-control studies concluded that there is a significant association between overweight/obesity and iron deficiency across all ages.[7] In a subgroup analysis, the authors found a strong association in those studies that included participants <18 years of age. However, of the 17 studies that included children and adolescents, only 2 included young children <5 years of age.[8,9] Furthermore, one of these studies identified a significant association between obesity and iron deficiency in young children,[8] but the other did not.[9] Current guidelines recommend assessing young children less than 3 years of age for risk factors associated with iron deficiency.[1] Although several risk factors for iron deficiency have been identified,[1,10-14] there is a gap in knowledge regarding the relationship between obesity and iron deficiency in young children. It is hypothesized that in individuals with obesity, the increased production of hepcidin, a proinflammatory adipokine, from the liver and adipose tissue[15] can contribute to a decrease in iron status.[16]

Examining the relationship between obesity and iron deficiency is complicated by the influence of systemic inflammation. In the assessment of children

AAP	American Academy of Pediatrics
BMI	Body mass index
CRP	C-reactive protein
NHANES	National Health and Nutrition Examination Survey
TARGet Kids!	The Applied Research Group for Kids
WHO	World Health Organization
zBMI	BMI z score

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for iron deficiency, serum ferritin is a test with high specificity that is readily available to practitioners; however, it is an acute phase reactant and may be elevated in the presence of inflammation.[17] Several approaches are currently recommended on the use of C-reactive protein (CRP) to account for inflammation to increase the sensitivity of serum ferritin for detecting iron deficiency.[17]

In the assessment of children with obesity, a relationship has been found between low-grade inflammation (as measured by CRP >1.0 mg/L and <10.0 mg/L) and children's weight status; previous research suggests that this relationship begins at 3 years of age.[18] Of the 2 previous studies examining the relationship between obesity and iron deficiency, neither examined the influence of low-grade inflammation through measurement of CRP.[8,9]

The objective of this study was to examine the association between body mass index (BMI) and iron deficiency in early childhood. A secondary objective was to assess the influence of low-grade systemic inflammation on the association between BMI and iron deficiency.

Methods

This was a cross-sectional study of healthy children 1-3 years of age (age of peak prevalence of iron deficiency),[1] recruited while attending a scheduled health supervision visit at a The Applied Research Group for Kids (TARGet Kids!) primary care practice between March 2008 and March 2015. TARGet Kids! is an ongoing open longitudinal cohort set in Toronto, Canada (www.targetkids.ca). The profile of this cohort has been previously described.[19] Study participants were recruited by trained research personnel embedded in 9 participating practices. Sociodemographic and nutritional information were collected through a standardized parent-completed questionnaire based on the Canadian Community Health Survey.[20] Blood samples were also collected at these visits.

TARGet Kids! cohort exclusion criteria are health conditions affecting growth (eg, failure to thrive), any chronic health condition (except asthma and mild autism spectrum disorder), severe developmental delay, child attending an unscheduled visit because of acute illness, and parents unable to communicate in English. For the purpose of this study, children were included if they were 12-38 months of age (to capture children attending their 3-year-old health supervision visit) and had complete data on exposure and outcome variables including height/length, weight, serum ferritin, and CRP. If a child's record contained data from multiple visits, the first visit with complete data was used for analysis. Children with serum ferritin >200 μg/L were excluded, as this is beyond the upper limit of the reference interval.[21,22] Children with CRP ≥10 mg/L were excluded because this elevation may indicate acute systemic inflammation.[1,23] Children taking a multivitamin containing iron or other forms of iron supplementation were excluded. Underweight children (BMI z score [zBMI] <-2) were also excluded to ensure a study design focused on investigating the relationship between increased weight and iron status.

Consent was obtained from parents of all participating children and ethics approval was obtained from the Research Ethics Boards at the Hospital for Sick Children and St. Michael's Hospital (www.clinicaltrials.gov; NCT01869530).

Exposure Variable

The exposure variable was child zBMI. Although weight-for-length has been recommended in children <2 years of age, high agreement has been found with BMI-for-age; therefore, we used BMI-for-age for all children 1-3 years of age in this study.[24] Anthropometric measurements were collected by trained research assistants. Height/length (m) and weight (kg) were used to calculate BMI (kg/m^2), which was then standardized by age and sex according to the World Health Organization (WHO) growth standards to obtain a zBMI.[25] zBMI scores from the sample population were further categorized into 4 weight categories: healthy-weight ($-2 \leq z \leq 1$), at-risk-of-overweight ($1 < z \leq 2$), overweight ($2 < z \leq 3$), and obese ($z > 3$), according to WHO growth standards.

Outcome Variables

The outcome variable was iron status as measured by serum ferritin. Blood samples were refrigerated and transported to the laboratory the same day (www.mountsinaiservices.com). At the laboratory, serum ferritin was analyzed on the Roche platform (Switzerland). Serum ferritin was analyzed both as a continuous variable (μg/L) and a binary variable to classify children as iron deficient (defined as a serum ferritin value < 12 μg/L). This cut-off value has been suggested by the WHO and the American Academy of Pediatrics (AAP) for this age group.[1,26]

To account for systemic inflammation in the analysis, high-sensitivity CRP was analyzed on the Roche platform (Switzerland), and the lower limit of detection for this test was 0.15 mg/L. To identify children with low-grade inflammation, CRP levels were dichotomized as CRP ≤1.0 mg/L and CRP >1.0 mg/L to <10.0 mg/L.[18]

Demographic and Nutrition Variables

Potential confounding variables included child age, sex, and birthweight; socioeconomic status (using median after-tax neighborhood income calculated by postal code using the Statistics Canada Postal Conversion File and 2006 Canadian Census)[27]; total breastfeeding duration (determined from the response to the question, "For how long has your child been breastfed?"—children who had never breast-fed were classified as having a breastfeeding duration of 0 months, and those currently breastfeeding were classified as having a breastfeeding duration equal to the child's current age in months); current bottle use (yes/no); and, daily cow's milk intake (defined as daily number of 250 mL–capacity cups per day). These variables were selected a priori and collected using parent-reported questionnaires.

Statistical Analyses

Descriptive statistics were generated for the entire sample, as well as for each of the 4 weight categories (healthy-weight, at-risk-of-overweight, overweight, and obese). Two multivariable models were constructed. We used a linear regression model to assess the association between zBMI and serum ferritin level (as a continuous measure). We used a logistic regression model to evaluate the association between zBMI and iron deficiency (using serum ferritin level as a binary measure with a value of <12 μg/L or >12 μg/L). Both models were adjusted for all the covariates previously described regardless of statistical significance.[28] Of note, serum ferritin values were not normally distributed. Therefore, they were log-transformed for the linear regression analysis and then back-transformed for the purpose of interpretation of the results.

We performed prespecified subgroup analyses investigating effects in subgroups defined according to CRP level—normal (CRP ≤1.0 mg/L) and low-grade inflammation (CRP >1.0 mg/L to <10.0 mg/L). We tested for an interaction between zBMI and the prespecified CRP subgroups by adding CRP level as a covariate and an interaction term between zBMI and CRP level to our fully adjusted models. This interaction was tested at a significance level of $\alpha = 0.05$. In keeping with guidelines for reporting of subgroup analyses, we included effect estimates and corresponding CIs within each CRP subgroup.[29]

We assessed our models for outliers, homoscedasticity, normality using regression diagnostics and quantile plots, and linearity using residual plots. Missing covariate data were handled by multiple imputation using the fully conditional specification method.[30] The maximum rate of missing data for any variable was 9%. Statistical significance was defined as $P < .05$; all statistical tests were 2-sided. Statistical analysis was conducted using SAS 9.4 statistical software (SAS Institute, Cary, North Carolina).

Results

A total of 3919 children 1-3 years of age were recruited to participate; there were 1885 children with available laboratory and zBMI data. Previous TARGet Kids! research found those who opt to have blood sampled are similar in demographics to those who do not.[11] Of these, 278 (14.7%) were excluded: 71 were excluded because their CRP value was either ≥10 mg/L or missing; 159 were excluded because they were either receiving iron supplementation or had missing data on iron supplementation; and 48 were excluded because they were underweight (Table I).

Descriptive characteristics of the study sample (n = 1607) are shown in Table II. For the total sample, the median zBMI was 0.15 (IQR –0.54-0.86), and 1281 (79.7%) of children were categorized as healthy weight, 251 (15.6%) were at-risk-of-overweight, 66 (4.1%) were overweight, and 9 (0.6%) were obese. The median serum ferritin value was 24 μg/L (IQR 16-35 μg/L), and 203 (12.6%) children were identified as iron deficient.

In the multivariable linear regression analysis, we found a strong negative relationship between zBMI and serum ferritin (–1.51 μg/L, 95% CI –2.23, –0.76, $P < .0001$) (Table III). The multivariable logistic regression analysis demonstrated that a higher zBMI was associated with an increased odds of iron deficiency (OR 1.28, 95% CI 1.10, 1.50, $P = .002$) (Table IV).

Table I. Participant recruitment and selection of patients for inclusion (n = 1607)

Characteristics	No.
Consent obtained from parents of healthy children between ages 12 and 38 mo enrolled in the TARGet Kids! cohort	3919
Exclusion criteria	
No blood sample obtained	1940
Serum ferritin value >200 μg/L	1
Missing zBMI value	93
CRP ≥10 mg/L	64
Missing CRP value	7
Receiving iron supplementation	100
Missing data on iron supplementation	59
Underweight participants with zBMI <-2	48
Final cohort	1607

Longer breastfeeding duration and daily cow's milk intake of >2 cups were statistically significant covariates associated with decreased serum ferritin (–0.51 μg/L, 95% CI –0.64, –0.37, $P < .0001$ and –4.95 μg/L, 95% CI –6.27, –3.53, $P < .0001$, respectively) and an increased odds of iron deficiency (OR 1.08, 95% CI 1.05, 1.11, $P < .0001$ and OR 2.21, 95% CI 1.61, 3.05, $P < .0001$, respectively). Older child age was a statistically significant covariate associated with increased serum ferritin (0.10 μg/L, 95% CI 0.001, 0.20, $P = .049$) and a decreased odds of iron deficiency (OR 0.96, 95% CI 0.94, 0.98, $P = .0008$). No other covariates were statistically significant.

In total, 289 (18.0%) children had a CRP >1.0 mg/L to <10.0 mg/L. The proportions of children in the higher CRP subgroup were not different across the 4 weight categories ($\chi^2 = 1.96$, $P = .58$). Of note, among children with low-grade inflammation, the median serum ferritin value was significantly higher compared with children with normal CRP (32 μg/L [IQR 22-42 μg/L] vs 22 μg/L [IQR 15-33 μg/L]; $P < .0001$).

After detecting a significant overall main effect between zBMI and serum ferritin levels in the fully adjusted linear and logistic regression models, we performed subgroup analyses by CRP level—normal (CRP ≤1.0 mg/L) and low-grade inflammation (CRP >1.0 mg/L to <10.0 mg/L). There was no statistically significant interaction effect between zBMI and CRP for the adjusted linear regression model ($P = .79$) or for the adjusted logistic regression model ($P = .43$). Results for the 2 prespecified CRP subgroups are included in Table III and Table IV.

Discussion

In this study, we found that higher zBMI was associated with lower serum ferritin levels in children 1-3 years of age. For each additional 1.0 unit of zBMI, there was a 1.51 μg/L decline in median serum ferritin level and a 28% increased odds of iron deficiency. These results suggest that higher BMI may be a risk factor for iron deficiency in young children.

An association between obesity and iron deficiency has been previously identified in a meta-analysis that included 17 studies in children and adolescents.[7] However, only 2 of the 17 studies included children less than 5 years of age, during the age of peak prevalence of iron deficiency.[8,9] Nead et al examined data on 9698 children and adolescents (2-16 years of age) from the

Table II. Descriptive characteristics of study participants for the total sample and by weight category (quantified using zBMI)

Variables	Total	Healthy weight	At-risk-of-overweight	Overweight	Obese
N	1607	1281 (79.7)	251 (15.6)	66 (4.1)	9 (0.6)
Age, mo	18.6 (12.0-37.9)	18.3 (12.0-37.9)	23.9 (12.0-37.9)	24.1 (12.1-37.5)	24.0 (18.5-36.6)
Female sex	772 (48.0)	632 (49.3)	111 (44.2)	26 (39.4)	3 (33.3)
zBMI	0.15 (-1.99-3.86)	-0.12 (-1.99-1.00)	1.35 (1.01-1.98)	2.25 (2.01-2.98)	3.22 (3.07-3.86)
Birthweight	3.3 (0.7-5.1)	3.3 (0.7-5.1)	3.5 (1.2-4.7)	3.6 (1.3-4.7)	3.6 (1.0-4.2)
<2.5 kg	176 (11.0)	144 (11.2)	27 (10.8)	4 (6.1)	1 (11.1)
2.5-4.0 kg	1164 (72.4)	945 (73.8)	168 (66.9)	44 (66.7)	7 (77.8)
>4.0 kg	125 (7.8)	84 (6.6)	31 (12.4)	9 (13.6)	1 (11.1)
Missing	142 (8.8)	108 (8.4)	25 (10.0)	9 (13.6)	0 (0)
Maternal ethnicity*					
European	1044 (65.0)	828 (64.6)	165 (65.7)	46 (69.7)	5 (55.6)
Asian	282 (17.6)	239 (18.7)	31 (12.4)	10 (15.2)	2 (22.2)
Other	131 (8.2)	98 (7.7)	26 (10.4)	6 (9.1)	1 (11.1)
Missing	150 (9.3)	116 (9.1)	29 (11.6)	4 (6.1)	1 (11.1)
Median after-tax neighborhood income					
CAN$0-29 999	91 (5.7)	72 (5.6)	17 (6.8)	1 (1.5)	1 (11.1)
CAN$30 000-79 999	1204 (74.9)	952 (74.3)	193 (76.9)	53 (80.3)	6 (66.7)
≥CAN$80 000	198 (12.3)	169 (13.2)	21 (8.4)	6 (9.1)	2 (22.2)
Missing	114 (7.1)	88 (6.9)	20 (8.0)	6 (9.1)	0 (0)
Total breastfeeding duration, mo	12 (0-37.5)	12 (0-37.5)	9 (0-30)	9 (0-24.3)	10.5 (0-26.0)
≥0-<6 mo	259 (16.1)	190 (14.8)	52 (20.7)	16 (24.2)	1 (11.1)
≥6- <12 mo	491 (30.6)	377 (29.4)	88 (35.1)	23 (34.9)	3 (33.3)
≥12- <24 mo	716 (44.6)	602 (47.0)	90 (35.9)	21 (31.8)	3 (33.3)
≥24 mo	56 (3.5)	49 (3.8)	5 (2.0)	1 (1.5)	1 (11.1)
Missing	85 (5.3)	63 (4.9)	16 (6.4)	5 (7.6)	1 (11.1)
Current bottle use, yes	677 (42.1)	538 (42.0)	109 (43.4)	27 (40.9)	3 (33.3)
Missing	102 (6.4)	88 (6.9)	13 (5.2)	1 (1.5)	0 (0)
Daily cow's milk intake, cups	2 (0-5)	2 (0-5)	2 (0-5)	2 (0-5)	2 (1-5)
>2 cups/d, yes	467 (29.1)	358 (28.0)	87 (34.7)	18 (27.3)	4 (44.4)
Missing	41 (2.6)	34 (2.7)	6 (2.4)	1 (1.5)	0 (0)
Iron deficiency, yes (serum ferritin <12 μg/L)	203 (12.6)	151 (11.8)	35 (13.9)	13 (19.7)	4 (44.4)
Iron deficiency anemia, yes	51 (3.2)	41 (3.2)	8 (3.2)	2 (3.0)	0 (0)
Serum ferritin (μg/L)	24 (2-159)	24 (2-159)	22 (4-76)	24 (5-93)	16 (8-55)
CRP (mg/L)	0.3 (0.1-9.7)	0.3 (0.1-9.7)	0.3 (0.1-7.6)	0.2 (0.1-5.1)	0.4 (0.1-4.0)
≤1.0	1318 (82.0)	1048 (81.8)	208 (82.9)	56 (84.9)	6 (66.7)
>1.0 to <10.0	289 (18.0)	233 (18.2)	43 (17.1)	10 (15.2)	3 (33.3)

Data are presented as n (%) or median (range).
*Maternal ethnicity: European includes Western European, Eastern European, Australian or New Zealander; Asian includes East Asian, Southeast Asian, South Asian, West Asian; Other includes African, Caribbean, Latin American, and North American Indigenous.

National Health and Nutrition Examination Survey (NHANES) III (1988-1994).[9] The prevalence of iron deficiency in the entire sample was significantly greater in the at-risk-for-overweight and overweight categories compared with the healthy-weight category. For the 2- to 5-year age category, iron deficiency was found in 1.8% of those in the healthy-weight category, 3.7% of those at-risk-for-overweight, and 6.2% of those who were overweight; this relationship was not statistically significant in the multivariate regression analysis (OR 1.2; 95% CI 0.7-2.2). Brotanek et al examined data on 1641 toddlers (1-3 years of age) from 3 waves of the NHANES II-IV (1976-2002).[8] In multivariate analyses of all 3 waves, overweight status was associated with significantly greater adjusted odds of iron deficiency (OR 2.8; 95% CI 1.7-4.3). In the most recent wave (1999-2002), iron deficiency was found in 7.2% of those who were healthy weight, 8.6% of those at-risk-for- overweight, and 20.3% of those who were overweight. The contradictory findings from these 2 analyses (both using data from NHANES) may be explained by the different categorization of age; Nead et al examined children 2-5 years of age and Brotanek et al examined children 1-3 years of age.[8,9] Importantly, neither analysis examined the influence of low-grade inflammation.

Elevated CRP levels have been identified in overweight and obese adults.[31] Skinner et al examined the relationship between low-grade inflammation (as measured by CRP >1.0 mg/L and ≤10.0 mg/L) and children's weight status (as measured by zBMI) among children and adolescents (1-17 years of age) using data from the NHANES (1999-2006).[18] They found that in children 1-2 years of age (n = 600), 20.7% had a CRP >1.0 mg/L; 18.8% of healthy-weight 1- to 2-year-old infants had CRP >1.0 mg/L, and although a greater proportion of children with higher zBMI had low-grade inflammation, this was not statistically significant. The authors concluded that the relationship between inflammation and obesity begins at 3 years of age.

In our study we found that 18% of children 1-3 years of age had a CRP >1.0 mg/L, similar to the findings of Skinner et al.[18] The proportion of children with CRP >1.0 mg/L to <10.0 mg/L was also not statistically significantly different among healthy-weight, at-risk-of-overweight, overweight, or obese children. To examine the influence of low-grade inflammation on the association between BMI and iron deficiency, we tested for an interaction between zBMI and the prespecified subgroups according to CRP level—normal (CRP ≤1.0 mg/L) and low-grade inflammation (CRP >1.0 mg/L to <10.0 mg/L). The

Table III. Multivariable linear regression model for the association between zBMI and median serum ferritin (μg/L) in children ages 1-3 years (n = 1607)*

				Change in median serum ferritin		
Predictors	β(log)	95% CI	Change in serum ferritin, %	μg/L	95% CI	P value
Overall main effect						
zBMI	−0.062	−0.093, −0.031	−6.02	−1.51	−2.23, −0.76	<.0001†
Overall main effect with interaction						
zBMI	−0.059	−0.093, −0.025	−5.71	−1.43	−2.22, −0.61	.0007†
CRP subgroup	0.303	0.225, 0.381	35.37	8.84	6.30, 11.59	<.0001†
zBMI×CRP subgroup	0.010	−0.063, 0.083	1.03	0.26	−1.53, 2.18	.79
Subgroup analysis						
CRP ≤1.0 mg/L (n = 1318)						
zBMI	−0.055	−0.090, −0.020	−5.35	−1.34	−2.15, −0.50	
1.0 mg/L < CRP < 10 mg/L (n = 289)						
zBMI	−0.072	−0.134, −0.010	−6.96	−1.74	−3.14, −0.25	

*Adjusted β-estimates are reported to 3 decimal places for statistical precision and represent change in serum ferritin associated with a 1-unit increase in zBMI. Negative values indicate a decrease in median serum ferritin. All models adjusted for prespecified covariates including age, sex, birthweight, median after-tax neighborhood household income, breastfeeding duration, cow's milk intake, and current bottle use.
†Statistically significant findings at $P < .05$.

interaction between zBMI and CRP level was not statistically significant. Thus, there was no evidence that the effect of zBMI on iron deficiency differed between the 2 CRP subgroups. These findings may be explained by the lack of association between low-grade inflammation and obesity in children younger than 3 years of age.[18]

Although it has long been held that acute inflammation may falsely elevate serum ferritin,[1,17] our findings suggest that even low-grade inflammation (CRP >1.0 mg/L to <10.0 mg/L) may falsely elevate serum ferritin. We found that children with low-grade inflammation had a significantly higher median serum ferritin value compared with children with a normal CRP. Our findings suggest that caution is required when interpreting serum ferritin for the detection of iron deficiency even in those with CRP >1.0 mg/L. For our study, we followed recommended approaches to use CRP as an indicator of inflammation and thereby increase the sensitivity of serum ferritin by excluding those with CRP >10.0 mg/L and including CRP level as a covariate in the regression model when assessing for an interaction between zBMI and the prespecified CRP subgroups.[17]

Although we used CRP as a measure of inflammation in our study, other measures of inflammation have been used, such as absolute neutrophil count (ANC) and α-1-acid glycoprotein (AGP). ANC was used by Skinner et al but the association with BMI wasn't evident in children until 6-8 years of age.[18] Although more than 1 marker of inflammation (CRP and AGP) increases the estimated prevalence of those with iron deficiency, the relationship between serum ferritin, CRP, and AGP is not fully understood.[17] CRP is more routinely measured and is the measure recommended by the AAP.[1]

Lower iron status observed in children with increased weight status may arise from the state of low-grade inflammation induced by an increase in adiposity.[32,33] The hypothesized mechanism involves hepcidin, a proinflammatory adipokine. In individuals with obesity, there is an increase in production of hepcidin from both the liver and adipose tissue.[15] Hepcidin is also a key molecule for iron regulation and can inhibit both iron absorption in the intestine and the release of iron from macrophages, therefore, contributing to a decrease in iron status.[16] Several epidemiologic studies have observed significantly higher hepcidin levels and lower iron status in older children with overweight and obesity compared with those of a healthy weight.[34-36]

Screening children for both iron deficiency and obesity in primary care has been recommended.[1,6] The findings from our study may inform clinical practice and policy recommendations,

Table IV. Multivariable logistic regression model for the association between zBMI and iron deficiency (serum ferritin <12 μg/L) in children ages 1-3 years (n = 1607)*

Predictors	β	95% CI	OR (95% CI)	P value
Overall main effect				
zBMI	0.250	0.095, 0.405	1.28 (1.10, 1.50)	.002†
Overall main effect with interaction				
zBMI	0.264	0.098, 0.429	1.30 (1.10, 1.54)	.002†
CRP subgroup	−1.139	−1.709, −0.569	0.32 (0.18, 0.57)	<.0001†
zBMI×CRP subgroup	−0.206	−0.718, 0.306	0.81 (0.49, 1.36)	.43
Subgroup analysis				
CRP ≤1.0 mg/L (n = 1318)				
zBMI	0.254	0.088, 0.420	1.29 (1.09, 1.52)	
1.0 mg/L < CRP < 10 mg/L (n = 289)				
zBMI	0.223	−0.320, 0.766	1.25 (0.73, 2.15)	

*Adjusted β-estimates are reported to 3 decimal places for statistical precision. Positive values indicate an increase in iron deficiency. All models adjusted for prespecified covariates including age, sex, birthweight, median after-tax neighborhood household income, breastfeeding duration, cow's milk intake, and current bottle use.
†Statistically significant findings at $P < .05$.

and guide future research. First, higher zBMI appears to be a risk factor for iron deficiency, suggesting that young children with overweight or obesity may be considered for targeted screening. This risk factor could be included in the overall risk assessment as recommended by the AAP.[1] Several risk factors for iron deficiency have been previously identified[1,10-14]; higher BMI could be added to these risk factors and included in a future risk stratification tool. Second, although we found no significant interaction between zBMI and CRP, children with low-grade inflammation were found to have a higher serum ferritin. Therefore, more research is warranted to better understand the relationship between serum ferritin and CRP in the detection of iron deficiency for children in all weight categories. Finally, examining the association between higher BMI and iron deficiency in older children is warranted.

Strengths of this study include the large sample size. The exposure variable, zBMI, was calculated based on measurements collected by trained research assistants, eliminating errors associated with self-reporting. The outcome variable was measured by serum ferritin, which is considered to have high specificity for determining iron deficiency,[37] and we examined the influence of inflammation through measurement of CRP. In addition, we adjusted for a number of potential confounding variables in our analyses.

Limitations of this study include the cross-sectional design, and, therefore, causality cannot be definitively determined. Furthermore, our study participants were recruited from primary care practices in Toronto, Canada and may not be representative of children in other settings. However, the level of income in our cohort is similar to women of childbearing age in Toronto.[38] In addition, the prevalence of high zBMI and iron deficiency was similar to other studies conducted in Canada and the US.[1,2,8,9,18,39] ■

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50 Years Ago in *The Journal of Pediatrics*

The Hemolytic Crisis of Sickle Cell Disease: The Role of Glucose-6-Phosphate Dehydrogenase Deficiency

Smits HL, Oski FA, Brody JI. J Pediatr 1969; 74: 544-51

A single point mutation in the beta-hemoglobin gene accounts for the most common genotypic variant of sickle cell disease. The simplicity of the genotype, however, adds to the bewilderment generated by the array of phenotypes observed clinically. This finding has led to an ongoing search for other cellular, genetic, and environmental factors that may contribute to variant phenotypes among patients with homozygous sickle mutations.

In 1969, Smits et al performed a chart review of 8 patients looking at an increased risk of hemolytic crises in patients with both sickle cell anemia and glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Hemolytic crises are not always a complicating factor for patients with sickle cell anemia; however, the findings from Smits et al suggested G-6-PD deficiency as an etiologic factor in those patients with sickle cell anemia complicated by hemolytic crisis. This novel finding—that G-6-PD deficiency may play a role on phenotypic expression of sickle cell disease—led to years of further investigation of the relationship. Notably, in 1988, Steinberg et al conducted a larger study, which found no evidence that G-6-PD enhanced the severity of hemolysis, increased the incidence of acute anemic episodes in patients with HbSS, or enhanced survival.[1] A further review of the data by Karafin et al agreed with the conclusion that G-6-PD deficiency does not clinically impact patients with sickle cell disease, but that, like Smits et al, it may be worthwhile to screen those with sickle cell disease for G-6-PD deficiency to avoid the use of medications that may worsen hemolysis.[2]

Ultimately, G-6-PD deficiency was not found to be a significant contributor to phenotypic variation in patients with sickle cell anemia; however, it is important to reflect back on what steps we have made toward determining clinical differences among patients with sickle cell disease to continue forward progress.

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Appendix

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