

REVIEW ARTICLE

Relationship Between Obesity and Iron Deficiency Among Children: A Scoping Review

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ABSTRACT

Obesity, the fifth leading cause of global mortality, is a low-grade inflammatory chronic illness that linked to conditions such as iron deficiency (ID). A higher prevalence of ID may be found in children with obesity. This review aimed to examine the relationship between obesity and ID in children. A systematic search was conducted in PubMed, Scopus, and Google Scholar, following PRISMA-ScR guidelines. From 2057 articles identified, 11 relevant studies were included. Findings indicate that children with higher Body Mass Index (BMI) are at increased risk for ID. Elevated serum ferritin and hepcidin levels were noted in obese children due to inflammatory responses. A higher prevalence of iron deficiency was found in children with obesity, and overweight and obese children were at higher risk of iron deficient as compared to normal weight and underweight children. Further research is necessary to elucidate the underlying mechanisms connecting obesity and ID.

Malaysian Journal of Medicine and Health Sciences (2025) 21(5): 337-344. doi:10.47836/mjmhs.21.5.37

Keywords: Obesity, Iron-deficiency, Children, Hepcidin, Inflammation

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INTRODUCTION

Obesity, which ranked as the fifth leading cause of mortality worldwide, is a low-grade inflammatory chronic illness that negatively affects public health (1). According to World Health Organization (2), obesity is defined as an abnormal or excessive fat accumulation that presents a risk to public health. The body weight status for children under the age of five and children aged 5-19 can be classified based on the WHO Growth Standard 2006 and WHO Growth Reference 2007, respectively (2). Other growth references, including United States Centers for Disease Control and Prevention (CDC) Growth Reference can also be recommended for children aged 2-20, where overweight is >85th to <95th percentile and obesity is ≥95th percentile based on CDC growth charts (3). Generally, obesity occurs due to an imbalance between energy expenditure and consumption; with an increase in positive energy balance that has been strongly associated with dietary preferences and lifestyle choices (4).

Since 1980, the prevalence of obesity has doubled in more than 70 nations and has continued to rise, approaching epidemic levels (5). Over 650 million people and 124 million children and adolescents (6% of girls and 8% of boys) between the ages of 5 and 19 were obese in 2016 (2). The prevalence of obesity

among children in 2016 was highest (>30%) in many Pacific Island nations and was high (>20%) in several countries in the Middle East, Micronesia (region of the western Pacific), Polynesia (subregion of Oceania), north Africa, the Caribbean, as well as in the USA (6). In just 40 years, childhood obesity has doubled as compared to adult obesity (7). It is estimated that there would be 206 million children and adolescents aged 5–19 years living with obesity in 2025, and 254 million in 2030 (8). The increased prevalence of childhood overweight and obesity is associated with the emergence of comorbidities, including obstructive sleep apnea, hypertension, type 2 diabetes mellitus, hypertension, and non-alcoholic fatty liver disease (9). Obese children are more likely to become obese adults and have higher risk on developing other non-communicable diseases (NCDs), which eventually contribute to mortality and premature death (10). Thus, prevention of childhood obesity is considered a crucial approach in order to promote future health and well-being (1).

While obesity is undoubtedly a condition, it also leads to the onset of new ones and aggravates ones that already exist, including iron deficiency (ID) (11). Iron deficiency (ID) is the most common nutritional deficiency found in children, which cause them to have iron deficiency anemia (IDA) (12). As a worldwide health known issue, iron deficiency (ID) is characterised by plasma ferritin levels <12 µg/L without any adjustment for inflammation or infection, or can be defined as serum ferritin <15 µg/L or transferrin saturation (TS) <10% (13). The typical clinical presentation of moderate to severe iron deficiency includes pallor and fatigue, which are

typical anaemia symptoms (14).

Globally, ID is the most common nutrient deficiency affecting 2 billion people worldwide, primarily pregnant women and children under five residing in developing countries (15). ID affects up to 39% of children under the age of five and 48% of children aged 5-14 in non-industrialized countries, as compared to 20% in the children under five and 5.9% in children aged 5-14 in industrialised countries (12). Since iron is crucial for the growth and development of the central nervous system among children, ID has been linked to delayed brain development as well as long-term behavioural and cognitive impairment in children due to their rapid growth and high iron requirements in childhood (16).

A higher prevalence of ID may be found in children with obesity, where Hamed et al. (17) reported that lower hemoglobin and ferritin levels and higher hepcidin level was observed among obese children. While obesity acts as emerging risk factor for ID, the exact processes behind this association remain unclear (11). There is little evidence on the relationship between obesity and ID among children as most of the studies only examined on the association among adults, or such associations only assessed on specific hematological and biochemical markers, including serum iron, ferritin, hemoglobin and haematocrit to examine iron status (18, 19, 20). Hence, this review aimed to examine the relationship between obesity and ID among children, by including not only basic iron biomarkers, but also inflammatory markers and serum hepcidin, which play a crucial role in iron homeostasis to indicate ID.

MATERIAL AND METHODS

The research question of this scoping review is: "What is the relationship between obesity and ID among children?" This review of relationship between obesity and ID among children was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) guidelines (21). The Population, Concept, and Context (PCC) framework developed by the Joanna Briggs Institute (JBI) for scoping review was utilised to identify studies relevant to this review (22). It is advised to use the PCC framework (population, concept, and context) as a guide to create precise and significant goals and qualifying standards for a scoping review (23). The PCC framework supports our goal to scope a broader literature by adhering to our search plan. Hence, the inclusion should meet the PCC as follows:

Population: children aged under 18 years

Concept: Relationship between obesity (BMI) and iron-deficiency (serum ferritin, transferrin saturation, serum iron, TIBC, inflammation markers, hepcidin)

Context: There is no limitation on the geographical origin of the study, racial background, and gender of participants.

Search Strategies

A systematic search was conducted in PubMed, Scopus and Google Scholar databases to identify potential literatures related to obesity and ID among children for the past ten years up to May 2024 using the search terms "obesity", "overweight", "weight change", "iron-deficiency", "iron insufficiency" and "children". The BOOLEAN operators "OR" and "AND" were used to combine the keywords or controlled vocabulary within and between PCC elements, respectively. By searching the reference lists of the included research and studies that would be relevant to the present review, backward reference list checking was performed. Additionally, forward reference list checking was performed to identify studies that cited the included studies using Google Scholar's "cited by" feature. A total of additional 13 publications were found through forward and backward search of the references and citations. The search was limited to studies involving humans, specifically focusing on children, and included only literature published in English.

Eligibility Criteria

This review included published study on the relationship between obesity and ID among children. The articles for this review were selected based on the following inclusion criteria: (1) published in the English language and was open accessed; (2) publications for the period from 2014 to 2024; (3) the term child was defined based on the Conventions on the Rights of the Child (CRC) (24), which refers to individuals under the age of 18 years and (4) the articles had explored relationship between obesity and ID among children. The maximum sample size was unrestricted. The exclusion criteria were articles with other age ranges instead of children and informal narrative or reviews on obesity and ID.

Selection Process

The articles that were acquired during the identifying process were then subjected to screening. Duplicated articles were first being removed based on title and abstracts were examined to identify articles that were relevant to the review research question. Relevant and shortlisted studies were then read in full text for inclusion. Reasons were recorded for excluded studies that did not fit the inclusion criteria.

Data Extraction, Synthesis and Charting

The data from the included studies was extracted using a standardised electronic data extraction form. Microsoft Excel spreadsheet was utilized to develop the form in order to extract relevant information from each study. The relevant information extracted included: the study characteristics (titles, author of the studies/year of publication and study designs), population characteristics (children age range, sample size) and the outcome (relationship between obesity and ID among children). The data was then descriptively reported according to

the study characteristics, and the relationship between obesity and ID among children was also identified.

RESULTS

Study Results

The study search retrieved 2057 articles by using the search engines mentioned (Pubmed= 1039, Scopus= 558, Google Scholar= 460) and the keywords. After removing the irrelevant research (n=853) and duplicates (n=508), 696 articles were then underwent title and abstract screening. This procedure resulted in 40 full-text articles that were reviewed for inclusion in the final review, and 29 articles were excluded with reasons, including non-open access (n=10), not published in English language (n=6), review articles (n=7) and study population >18 age (n=6). Finally, 11 articles that met the eligibility criteria were included in this review. The summarization of the study identification process was shown in Figure 1.

Study Characteristics

Among the 11 studies included in this review, there were only 1 cohort study, 4 case-control studies, and 6 cross-sectional surveys. The age group of children in these studies ranged from 12 months to 18 years, and the

number of participants in each study ranged from 90 to 5295 children. The study participants were from Egypt, Saudi Arabia, Iran, Canada, Spain, Palestine, Turkey, China and Thailand. Apart from measuring ID among obese children using serum ferritin as main indicators, some studies also examined ID using other iron biomarkers, such as transferrin saturation, serum iron and serum hepcidin. Table I shows the summarization of the included study characteristics.

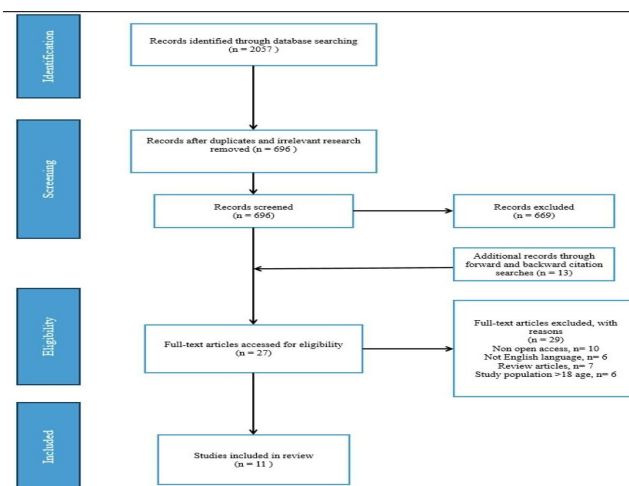


Figure 1: PRISMA flow chart illustrating the selection process of articles for the scoping review.

Table I: Overall characteristics of included studies on the relationship between obesity and ID among children

References & Author (s), Year	Primary Objective	Study Characteristics	Outcome Measurements	Main Results
(30) Abd-El Wahed et al., 2014	To assess iron profile in primary school-aged obese Egyptian children in El-Giza Governorate.	Design: Case-control Setting: Children in El-Giza Governorate (Dokki Sector), Egypt Subjects: 120 children Age: 6-12 years	Iron status: SI, TIBC, and SF *ID was defined if: MCV is 76 fl or less, Serum TS 15% or less, SF <10 µg/ml (The presence of at least 2 abnormal iron status parameters of iron status indicate impaired iron status)	<ul style="list-style-type: none"> • A higher prevalence of ID was shown among obese children (68.3%) as compared to non-obese children (25%). • Obese children showed statistically highly significant lower SI, and TS, and increased TIBC than control group. • Obese children showed statistically significant higher rate of ID when compared with the control group (OR: 7.09, 95% CI: 3.16–15.92).
(7) Aloufi et al., 2018	To evaluate the association between the obesity and iron deficiency anemia among children in Al-Taif Region Kingdom of Saudi Arabia and to increase the awareness about the hazards of obesity on the general health.	Design: Cross-sectional Setting: Children in Al-Taif Region Kingdom of Saudi Arabia Subjects: 200 children Age: 5-12 years	Iron status: hemoglobin level, SI, serum iron saturation, *ID was defined as TS <16%	<ul style="list-style-type: none"> • A negative significant correlation was found between BMI and SI levels (r -0.429 p value 0.017).
(25) Atrushi et al., 2022	To examine the association between obesity and iron status and the presence of iron deficiency anemia in children.	Design: Case-control Setting: Children in Zakho General Hospital, Iraq Subjects: 100 children Age: 2-14 years	Iron status: SI, ferritin, TIBC and TS * ID is defined as TS <16%	<ul style="list-style-type: none"> • Obese children have higher level of ferritin (P = 0.5) and TIBC (P = 0.449) but lower levels of SI (P = 0.234) and TS (P = 0.45) but with no statistical significance.
(26) Borkhoff et al., 2023	To examine the association between body mass index and iron deficiency in early childhood.	Design: Cross-sectional Setting: Toronto, Canada Subjects: 1953 children Age: 12-29 months	Iron status: SF, hemoglobin, CRP	<ul style="list-style-type: none"> • Higher zBMI was associated with lower SF (change in median SF -1.31 µg/L, 95% CI -1.93, -0.68, p < 0.001). • Higher zBMI was associated with a higher odds of ID (OR 1.14, 95% CI 1.00, 1.30, p = 0.04).

CONTINUE

Table 1: Overall characteristics of included studies on the relationship between obesity and ID among children (CONT.)

References & Author (s), Year	Primary Objective	Study Characteristics	Outcome Measurements	Main Results
(44) Cabacas Pujadas et al., 2022	To evaluate the association between changes in obesity status between 4 and 9 years of age and iron deficiency.	Design: Cohort Setting: Madrid, Spain Subjects: 1347 children Age: 4-9 years	Iron status: SF, TS	<ul style="list-style-type: none"> The prevalence of ID in the stable general obesity (GO) and abdominal obesity (AO) groups was 38.2% and 41.2%, versus 23.6% and 23.4% in the stable without obesity groups, respectively. The ORs for iron deficiency were 1.85 (95% CI: 1.03-3.32) in the stable GO group and 2.34 (95% CI: 1.29-4.24) in the stable AO group.
(27) Doğan et al., 2016	To investigate the associations between iron parameters, pro-hepcidin and soluble transferrin receptor levels in obese children.	Design: Case-control Setting: Turkey Subjects: 110 children Age: 6-16 years	Iron status: hemoglobin, SI, IBC, ferritin level, sTfR and pro-hepcidin *ID was defined as SF <12 ng/mL and TSI <16%	The correlation analysis of BMI and the iron parameters showed a negative correlation between BMI and iron level and TSI (R=-0.252, P=0.008 and R=-0.280, P=0.003, respectively).
(28) Panichsilaphakit et al., 2021	To assess iron status and serum hepcidin-25 in Thai children and adolescents with obesity and investigate their relationships with body mass index-standard deviation score (BMI-SDS).	Design: Cross-sectional Setting: Children from the King Chulalongkorn Memorial Hospital and local communities Subjects: 90 children Age: 5-15 years	Iron status: Complete blood count, SI, ferritin, TS, TIBC and serum-hepcidin *ID was defined when TS was 15% and below	<ul style="list-style-type: none"> A positive correlation was found between BMI-SDS and hepcidin-25 ($r=0.28, p=0.001$). Thai children and adolescents with obesity had a higher prevalence of ID (42.9%) and higher serum hepcidin-25 than children of normal weight.
(29) Sal et al., 2018	To investigate the associations between iron parameters, leptin, hepcidin and adiponectin levels in obese children.	Design: Case-control Setting: Palestine Subjects: 237 children Age: 5-18 years	Iron status: complete blood count, iron, IBC, TS, ferritin values and hepcidin	<ul style="list-style-type: none"> White blood cell and platelet count, IBC, high-sensitive CRP, leptin and hepcidin values in the obese group were higher than the control group ($p<0.001, p=0.002, p<0.001, p<0.001, p<0.001$ and $p<0.001$, respectively). The rate of subjects with a TS below 15% was 39.8% in obese children, compared to 22.8% in the control group.
(31) Suteerajtrakool et al., 2021	To investigate the association between different indices of iron status and anthropometric measurements in Thai children.	Design: Cross-sectional Setting: Thailand Subjects: 336 children Age: 6-12 years	Iron status: SI, SF, transferrin, TIBC, and sTfR *ID was defined using two or more of the following: (1) % TS <16%; (2) SF <15 µg/mL; and (3) sTfR >5 mg/L	<ul style="list-style-type: none"> The prevalence of ID among overweight/obese group was higher as compared to normal-weight group (ID: 6.1% vs. 5%). The number of participants with sTfR more than 5 mg/L in the overweight/obesity group was nearly twice as high as in the normal-weight group (31.3% vs. 14.9%, $p=0.002$).
(45) Sypes et al., 2019	To examine the association between body mass index (BMI) and iron deficiency in early childhood.	Design: Cross-sectional Setting: Toronto, Canada Subjects: 3919 children Age: 1-3 years	Iron status: SF *ID is defined as a SF value <12 µg/L	<ul style="list-style-type: none"> A strong negative relationship was found between zBMI and SF (-1.51 µg/L, 95% CI -2.23, -0.76, $P<.0001$). A higher zBMI was associated with an increased odds of ID (OR 1.28, 95% CI 1.10, 1.50, $P=.002$).
(46) Zheng et al., 2020	To assess the status of Fe metabolism parameters, the prevalence of anaemia, Fe deficiency (ID) and Fe-deficiency anaemia (IDA), and the associations of these variables with obesity in Chinese schoolchildren.	Design: Cross-sectional Setting: Guangzhou City, China Subjects: 5295 children Age: 7-11 years	Iron status: Hb, SF, SI, TIBC and TS *ID was defined following a multiple-index model, proposed by the Chinese Medical Association in 2010: presence of two or more of the following four abnormal values: (i) SF <15 ng/ml; (ii) SI <10.7 µmol/l; (iii) TIBC >62.7 µmol/l; and (iv) TS <15 %	<ul style="list-style-type: none"> Prevalence of ID was progressively higher with increasing BMI, being highest in children with obesity (8.4 %). Obesity was positively associated with ID (adjusted OR = 1.808; 95 % CI 1.146, 2.853).

*MCV: mean corpuscular volume; TIBC: total iron-binding capacity; TS: transferrin saturation; IBC: iron-binding capacity; TSI: transferrin saturation index, SI: serum iron; SF: serum ferritin, sTfR: soluble transferrin receptor

Relationship between Obesity and ID among Children

Most of the studies (90%) reported that obese children had higher risk of iron deficiency as compared to non-obese children. However, there was a case-control study found that although obese children had lower serum iron level and transferrin saturation, there was no statistically difference with non-obese children and was not associated with iron deficiency (25). Serum ferritin is

the most common iron biomarker used to indicate iron deficiency in all studies, while inflammatory markers such as CRP and serum hepcidin, which play crucial roles in iron metabolism was also accounted to indicate iron deficiency in four studies (26-29). Overall, it was reported that children with obesity had lower serum iron, transferrin saturation but higher serum hepcidin level, indicating higher risk of ID despite no association

found between obesity and ID among children in a case control study (25).

DISCUSSION

This scoping review highlights the relationship between obesity and ID among children, which contributes to the burden of iron-deficiency anemia in this population. It is essential to recognize that this review adds to the growing body of literature exploring the connection between obesity and ID among children globally. Despite the limited number of studies examining this relationship using various iron biomarkers, our review serves as a critical resource for healthcare professionals, researchers, and policymakers, providing insights into the implications of obesity-related ID across diverse contexts. In this review, we aimed to summarize the existing data on ID among obese children, and its relationship with obesity between 2014 -2024. Based on the eligibility criteria, we were able to identify 11 studies and the findings revealed significant insights from the available research evidence.

The majority of studies (8 out of 11) employed both serum ferritin and transferrin saturation as indicators of ID among children. According to Mantadakis et al. (12), these biomarkers are emphasized in clinical guidelines as primary parameters for defining and treating ID. Previous research has indicated that obese children tend to have lower serum ferritin levels and transferrin saturation compared to their non-obese counterparts, contributing to a heightened risk of ID (26, 45). The low serum ferritin levels observed in these children may result from the depletion of iron stored in ferritin molecules within cells (32). Conversely, during ID, low iron stores can lead to increased transferrin production due to less iron available for binding (33).

However, some findings contradict this trend, reporting that obese children exhibited higher serum ferritin levels. This discrepancy may be attributed to the inflammatory conditions commonly associated with obesity (25, 27, 31). While serum ferritin is typically regarded as a reliable indicator for assessing ID prevalence, it also functions as an acute-phase reactant that can be elevated during inflammatory states, potentially masking true ID (13). Inflammatory cytokines such as interleukin-1 β and tumour necrosis factor- α can stimulate ferritin production in various cells (34). Consequently, the increased serum ferritin levels observed in overweight and obese children might obscure the actual extent of ID within this population (35). Previous studies have suggested that relying solely on serum ferritin may underestimate the prevalence of ID compared to using transferrin saturation as a diagnostic marker (12). Therefore, it is suggested to combine serum ferritin measurements with assessments of acute phase proteins (APPs) to accurately identify inflammation and its potential impact on elevating ferritin levels (13).

Three studies (25, 29-30) reported that obese children had higher total iron-binding capacity (TIBC), which contributes to an increased risk of ID. These findings contrast with previous research indicating no changes in TIBC with increasing BMI (36). The current review's findings could be explained by two potential mechanisms: first, chronic low-grade inflammation associated with obesity may elevate inflammatory cytokines that stimulate the liver to produce more transferrin, resulting in higher TIBC levels (37). Second, obese individuals often possess a greater total blood volume than their non-obese counterparts, leading to an increase in TIBC due to a proportional rise in transferrin concentration (38). Since TIBC reflects the maximum amount of iron transferrin can bind, a larger blood volume correlates with an increased TIBC (39). In iron deficiency, there is a decrease in the body's iron stores (37). As a compensatory mechanism, the body increases the production of transferrin to capture more iron from the diet and distribute it to tissues, resulting in higher TIBC (37).

An association between iron levels and obesity has been observed in both children and adults. However, the exact mechanism underlying this link is not yet fully understood. A new theory suggests that ID in obese children may be linked to inflammation triggered by excessive body fat (40). Specifically, obese individuals often exhibit elevated levels of inflammatory cytokines, which have been linked to lower serum iron levels, and this was in accordance to studies in Egypt, Saudi Arabia and Turkey which reported that children with obesity had lower serum iron level (6, 27, 30). In many obese individuals, fat tissue starts to produce inflammatory adipokines (41). Macrophages within fat tissue mainly produce interleukin (IL)-6, IL-1, IL-8, and tumour necrosis factor (TNF)- α , while adipocytes contribute primarily to leptin production (41). For instance, IL-6 and TNF- α are responsible for inducing the liver to produce proteins associated with acute inflammation, such as CRP, α -1 acid glycoprotein (AGP), ferritin, and hepcidin (42). The unbalanced in adipokines production contributes to a persistent, low-grade inflammatory state that lead to comorbidities associated with obesity, such as ID (42). Hepcidin levels were significantly higher in obese children as compared to those of normal weight, reflecting disruptions in iron metabolism (28). However, the lack of correlation between hepcidin and inflammatory markers and iron status indicators (e.g. transferrin saturation and ferritin) in obese individuals suggests that other factors, such as leptin may contribute to obesity-associated ID (29).

The findings and conclusion of this review suggest a connection between obesity and ID among children which is highly significant for clinical practice and implementation. Besides, this review emphasizes the importance of well-designed randomized clinical trials adjusted for important confounders with various iron

biomarkers to examine and perform in-depth analysis on the causal relationship between obesity and ID. Due to the different definitions and guideline recommendations regarding ID, there are various laboratory parameters used for diagnosing ID, and there is no universal consensus on its definition and treatment. Weight loss achieved through calorie restriction or physical activity could potentially alleviate obesity-related low iron levels and restore iron balance in obese population (43).

Strength and Limitation

To the best of our knowledge, this is the first scoping review that has investigated the relationship between obesity and ID among children. A comprehensive search was performed and the studies were carefully chosen for the inclusion. The data was systematically extracted in order to obtain information on the relationship between obesity and ID among children. This review is able to provide a generalised result as there is no restriction in terms of the study location. Also, inflammation markers and serum hepcidin, which have important roles in iron metabolism, were also included for indicating ID, and this is able to provide a more comprehensive and better understanding on the relationship between obesity and ID among children. However, there were few limitations in this review. Firstly, bias and quality assessments of the included studies were not performed. Second, only three search engines were being used for searching the articles, which limited the data obtained in this review. Furthermore, the review was only limited to English language and excluded the unpublished papers.

Recommendations for Future Research

This review urges more recognition of ID among children as an essential public health concern in worldwide. It is recommended to include additional biochemical markers such as soluble transferrin receptor and hepcidin for a more accurate assessment of iron status. While hepcidin may provide useful insights into iron regulation, its exact role in obesity-related ID remains complex, which requires further investigation. Also, it is important to account for potential interference from increased inflammation when examining iron status in obese individual by measuring acute phase proteins such as CRP or avoid iron testing during periods of suspected infection. A more comprehensive epidemiological study is recommended to be conducted in the future in order to reduce the comorbidities among obese children effectively. With this, healthcare professionals and policymakers are able to develop public health strategies or effective programmes specific to children to manage obesity-related ID.

CONCLUSION

A higher prevalence of ID was found in children with obesity, and overweight and obese children were at higher risk of iron deficient as compared to normal weight and underweight children. Hepcidin, a key regulator of

iron homeostasis, is proposed as a potential mediator in the relationship between obesity and ID. However, the inconsistent relationship between hepcidin and inflammation or iron status in obese children suggests that other factors, such as leptin, might also be involved in the disruptions of iron metabolism. Future longitudinal studies are recommended to establish a causal relationship between obesity and iron deficiency, as understanding this connection is crucial for effective intervention strategies. The insights gained from this review can inform health policymakers and planners, emphasizing the need for targeted health interventions, such as weight management programs, to improve iron status among obese children. Addressing both obesity and ID concurrently could enhance health outcomes and reduce the long-term risks associated with these conditions in obese children.

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