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LITERATURE REVIEW
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# Occurrence of Obesity and Its Relation to Fe Deficiency in School-Age Children: A Systematic Review

## *Kejadian Obesitas dan Hubungannya dengan Defisiensi Fe pada Anak Usia Sekolah: Tinjauan Sistematis*

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**ABSTRACT**

**Background:** The problem of nutritional health in society is a crucial topic widely reported in developed and developing countries. The incidence of Fe deficiency in children is associated with obesity, including overweight, but the relationship between the two is still being identified further.
**Objectives:** To identify the relationship between obesity in school-aged children (7-19 years) and Fe deficiency and the specific parameters used through a systematic review.
**Methods:** This research was conducted with a systematic review using PubMed, Scopus, and ScienceDirect databases. The literature search strategy was carried out through evidence software by entering predefined inclusion and exclusion criteria. Five kinds of literature were selected from 2015 to 2021.
**Discussions:** Fe deficiency is defined as the presence of two or more abnormal values of the following parameters: (i) serum ferritin (SF) <15µg/L (ii) serum iron (SI) <10.7 µmol/l; (iii) Total iron Binding Capacity (TIBC) >62.7 µmol/l; dan (iv) %transferrin saturation (%Tsat) <15%. Fe deficiency in obese conditions occurs through an increase in proinflammatory mechanisms and the role of leptin which can reduce the availability and absorption of Fe in the body. Parameters soluble transferrin receptor (sTfR) is the best parameter to identify Fe deficiency in obese individuals. At the same time, serum ferritin (SF) has limitations as an indicator of iron status in obese children.
**Conclusions:** These findings indicate that the incidence of obesity in children may lead to an increased risk of iron deficiency. The problem of iron deficiency and obesity is a public health problem that has detrimental short and long-term health effects, especially for school-age children in a phase of cognitive growth and development. The sTfR parameter is not significantly affected by inflammation due to adiposity, so it can differentiate iron deficiency from inflammatory hypoferremia.

## INTRODUCTION

Health problems related to nutrition in society are crucial topics widely reported in developed and developing countries. Many nutritional problems occur in obesity and Fe deficiency; previous studies have shown a relationship between Fe deficiency in individuals who are overweight to obesity[1,2]. Fe deficiency is a health problem in children with normal nutritional status and obese conditions[2,3]. Obesity is characterized by low-grade chronic inflammation, increased hepcidin, and decreased absorption of Fe and sometimes systematically causes iron deficiency and/or reduced formation of erythropoiesis[4,5].

"Healthy Growth Study" involved children aged 9-13 years, showing that as many as 42% were overweight or obese. The prevalence of iron deficiency increases to 29% in obese children compared to 15% in children with normal weight. The possibility of Fe deficiency is adjusted to the factors confounding (diet, knowledge, puberty) showed significantly higher results in the obese group compared to the normal weight group (odds ratio [OR] = 2.5 in males and 2.1 in females)[6]. The results of the NHANES III survey (*National Health and Nutrition Examination Survey*) involved 9700 American children aged 2-16 years, 24% of whom were overweight or obese[6]. Fe deficiency can decrease serum ferritin plasma concentrations or transferrin saturation and increase erythrocyte protoporphyrin[7].

The reason behind the high incidence of Fe deficiency in the obese group is still being debated. Among the obese and non-obese groups, it was indeed more common in the risk group. However, several previous dietary surveys found little to no difference in nutritional intake between the two[7], and whether



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nutrients or anti-nutrients such as phytates interfere with Fe absorption. The potential findings that support the relationship between obesity and the incidence of Fe deficiency are dilutional *hypoferremia*, low intake of sources of Fe, and increased demand for Fe to impaired absorption of Fe in individuals with obesity[8]. On the other hand, many previous findings explained an increase in hepcidin due to chronic inflammation from obesity, which induced the decreased absorption of Fe in the small intestine and the reticuloendothelial system[7,9]. Iron deficiency in children is associated with adverse long-term outcomes such as impaired growth and cognitive dysfunction. Hence, prevention and early detection of iron deficiency are very important[6]. This study aimed to identify the relationship between the incidence of obesity and iron deficiency in school-age children (7-19 years) and the specific parameters used.

## METHODS

This research was conducted with a systematic review using three databases, namely PubMed, Scopus, and ScienceDirect in 2015-2021range with keywords ('obesity' or 'obese' or 'overweight' or 'adipose' or 'adiposity' or 'body size') and ('iron' or 'anemia' or 'anemia' or 'ferritin' or 'transferrin' or (sTfR)). The literature in this study referred to predetermined inclusion and exclusion criteria. The following are some of the inclusion criteria in this study: (i) the study which identified a relationship between Fe status and overweight/obesity; (ii) research that included groups overweight/obese and normal weight groups and (iii) studies reporting the mean and standard deviation (SD) or median and sums for several Fe biomarkers: serum iron, transferrin saturation presentation (TS%), serum ferritin or transferrin receptor (sTfR). In this study, researchers used parameters overweight obesity in children with age- and sex-adjusted BMI (body mass index) (BMI- (body mass index) for age), IMT-standard deviation score (IMT-SDS), or BMI Z-score. While the exclusion criteria in this study: (i) the study did not use a diagnosis of overweight or obesity as a category standard; (ii) studies involving obese patients undergoing bariatric surgery; (iii) research involving participants with other co-morbidities such as metabolic syndrome, diabetes, hypertension, cancer and others and (iv) research conducted on experimental animals or cell level and (vi) not original articles, unpublished articles and articles duplication. Two investigators conducted an assisted literature search for Covidence software to facilitate the extraction of articles. The researcher limited the literature to English, and the PRISMA diagram of the literature search strategy used in this study is presented in Figure 1.

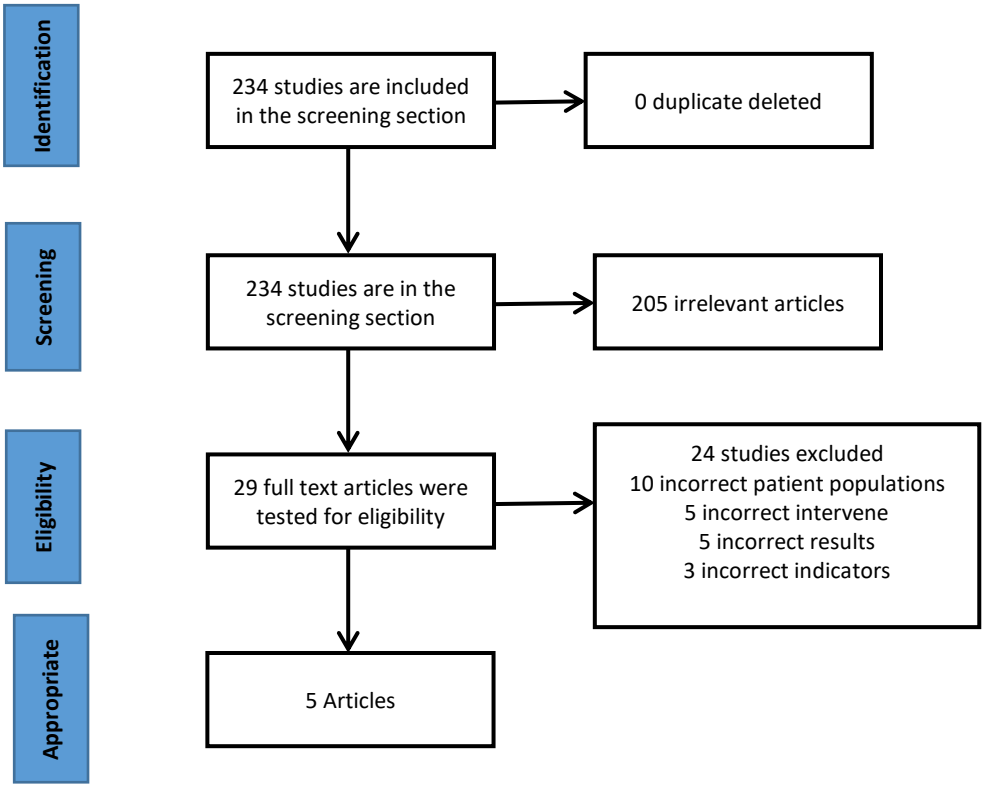


**Figure 1. Literature search strategy**

The following data were taken from each selected literature: basic information (title, author's name, and year of publication); research characteristics (study name, research design, and geographic location); participant characteristics (sample size, number of cases, and non-cases, age, gender); standard diagnosis overweight or



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obesity. When a study employs several adjustment models for confounding factors, the most adjusted confounding variable is used to determine the risk estimation.

**DISCUSSION**

Based on the search and results of literature selection through three databases, 234 kinds of literature are potentially relevant. In the screening process, by selecting titles and abstracts, the researcher determined 29 types for further evaluation and as many as 205 irrelevant kinds of literature. Five kinds of literature met the inclusion criteria, while 24 types of literature were excluded due to inappropriate samples, interventions, outcomes, and indications.

The five kinds of literature involve the subject of school-age children aged 6 to 17 years who are overweight or obese. The diagnosis to determine the nutritional status of obesity uses BMI, BMI Z-Score, and BMI-SDS, while the parameter of Fe deficiency uses (SF: serum ferritin); (SI: serum iron); (TIBC: total iron binding capacity); (%Tsat: %transferrin saturation); (sTfR: soluble transferrin receptor).

The results of literature extraction show that being overweight or obese is associated with the risk of Fe deficiency. Four of the five kinds of literature found by the researchers used SF (serum ferritin) as a parameter of iron deficiency. Previous research has shown a tendency for lower serum ferritin levels in obese conditions, and it is referred to as the main protein in storing iron[10]. Compared to the standard group, the %Tsat was significantly different from the overweight or obese[11]. The numbers are much lower in adolescents with overweight or obese. Fe serum concentration significantly decreased in the group overweight and obese. In addition, the researchers also identified different sTfR concentrations between the group overweight or obese and normal. Assessment related to the quality of the literature was carried out by two research members using the Center for Evidence-Based Management (CEBMa)[12] for cross-sectional research design. The results of this assessment are presented in Table 1 with the moderate quality category. This assessment aims to identify the quality of the research methodology and determine the extent to which the research controls possible design, implementation, and analysis biases. At the same time, the summary related to the characteristics of the research can be seen in Table 2.

Fe deficiency is characterized by low levels of iron in the blood due to decreased intake, increased loss, or decreased absorption[13] as well as marked the presence of two or more abnormal values of the following parameters: (i) SF<15 µg/ml; (ii) SI<10.7 µmol/l; (iii) TIBC>62.7 µmol/l; and (iv) %Tsat<15%[14]. Meanwhile, to identify the relationship between iron deficiency and obesity, BMI is measured by calculating body weight (kilograms) divided by height squared (meters), while the category of obesity (>+2), *overweight* (>+1 and <+2), normal (>-2) and thin (<-2) according to the BMI Z-Score from WHO 2007[15]. BMI SDS uses WHO growth reference data for children aged 5-19 years with categories overweight ≥+1 SD while obesity ≥+2 SD. Fe is found in many foods, especially red meat. These nutrients are needed to help optimize physical activity and cognitive development, especially at school age[16]. A person's body contains two to four grams of Fe. About two-thirds are stored in hemoglobin, and the rest (30-40%) is found in iron-binding proteins, namely ferritin and transferrin[17]. When the body needs Fe, the transport protein ferroportin increases to increase Fe absorption and vice versa[18]. Ferroportin is a Fe transporter on the surface of intestinal enterocytes, hepatocytes, macrophages, and placental cells, all of which release Fe into the plasma[19]. Most ferroportin concentrations are influenced by hepcidin levels, and hepcidin itself is an amino acid peptide hormone with a key role as a regulator of Fe in the body. One of the roles of hepcidin is as a negative regulator of iron absorption in the small intestine. When hepcidin binds to ferroportin on the target cell membrane, this condition will inhibit iron absorption in the gastrointestinal tract[20]. Increased inflammation or leptin levels in obese individuals can reduce satiety sensitivity. In addition, adipose tissue itself can produce hepcidin[20]. In a meta-analytic study by Zhao L et al. comparing individuals with normal weight and obesity, the serum ferritin and CRP were higher as the BMI category increased, while the serum Fe and transferrin saturation were lower[21].

Serum ferritin is an acute phase protein that can increase in adiposity-mediated inflammatory conditions[20]. Previous research by Alshwaiyat et al. stated that obese children are more susceptible to hepcidin-mediated Fe deficiency. Besides, the presentation parameters of circulating transferrin and hepcidin saturation are higher than the normal weight group[22].



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**Table 1.** Literature quality assessment - CEBMa

| Questions Assessment | Author, year | | | | |
|---|---|---|---|---|---|
| | Hao Zheng et al., 2020 | Suteerojntrakool et al., 2021 | Huang et al., 2015 | Ferrari et al., 2015 | Panichsillaphakit et al., 2021 |
| | 23 | 24 | 1 | 25 | 11 |
| Did the study address a focused question/issue clearly? | Y | Y | Y | Y | Y |
| Is the research method (study design) appropriate for answering the research question? | Y | Y | Y | Y | Y |
| Is the method of selection of the subjects (employees, teams, divisions, organizations) clearly described? | Y | Y | Y | Y | Y |
| Could the way the sample was obtained introduce (selection)bias? | Y | Y | Y | Y | Y |
| Was the sample of the subject representative of the population to which the findings will be referred? | Y | Y | Y | Y | Y |
| Was the sample size based on pre-study considerations of statistical power? | N | Y | N | Y | N |
| Was a satisfactory response rate achieved? | C | Y | C | C | Y |
| Are the measurements (questionnaires) likely to be valid and reliable? | Y | C | C | C | C |
| Was the statistical significance assessed? | Y | Y | Y | Y | Y |
| Are confidence intervals given for the main results? | Y | Y | Y | Y | Y |
| Could there be confounding factors that have not been accounted for? | Y | Y | Y | Y | Y |
| Can the results be applied to your organization? | Y | Y | Y | Y | Y |
| Quality | M | M | M | M | M |

Y=yes; C=Can't tell; N=no; N/A=not applicable; M=Moderate overall quality; L=Low overall quality



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**Table 2.** Characteristics of research

| Authors | Year | Country | Study Design | Participant and sample size | Diagnose weight | Fe deficiency parameters | Finding |
|---|---|---|---|---|---|---|---|
| Hao Zheng et al.23 | 2020 | China | A cross-sectional study | 5295/7-11 years | BMI | (i) SF<15 µg/ml;<br>(ii) SI<10.7 µmol/l;<br>(iii) TIBC>62.7µmol/l<br>(iv) %Tsat<15 % | Obesity is significantly associated with the risk of iron deficiency (adjustedOR = 1.808; 95 % CI 1.146, 2.853) |
| Suteerojntrakool et al.24 | 2021 | Thailand | A cross-sectional study | 315/6-12 years | BMI-SDS | (i) %Tsat<16%;<br>(ii) SF<15 µg/ml;<br>(iii) sTfR>5mg/L | Obesity is significantly associated with iron deficiency (sTfR, r: 0.209, p <0.001; SF, r: 0.214, p <0.001) |
| Huang et al.1 | 2015 | Taiwan | A cross-sectional study | 2099/12-16 years | BMI | (i) SF<15 µg/L;<br>(ii) SI<60 µg/dL | Obesity is significantly associated with Fe deficiency (SI <60 µg/dL with an OR (95%) of 1.78 (1.34-2.37) |
| Ferrari et al.25 | 2015 | Europe | A cross-sectional study | 876/12-17 years | BMI Z-score | (i) SF<15 µg/ml;<br>(ii) sTfR>8.5mg/L | Obesity is significantly associated with iron deficiency |
| Panichsillaphakit et al.11 | 2021 | Thailand | A cross-sectional study | 90/9-13 years | BMI-SDS | (i) %Tsat< 5%<br>(ii) TIBC>62.7µmol/l | Obesity is significantly associated with Fe deficiency through an increase in hepcidin 14,070.8 ± 7213.5 vs. 8419.1 ± 4826.1 pg/mLc |

(SF: serum ferritin); (SI: Serum Fe); (TIBC: Fe-Binding Capacity); (%Tsat: %Transferrin Saturatin); (sTfR: Soluble Transferrin Receptor



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The findings of this study indicate Fe deficiency in obese conditions using parameters (SF: serum ferritin); (SI: Serum Fe); (TIBC: Fe-Binding Capacity); (%Tsat: %Transferrin Saturation); (sTfR: Soluble Transferrin Receptor). Obesity shows a significant relationship to the incidence of Fe deficiency by measuring the % Tsat, SF, and sTfR levels[24]. Plasma ferritin and serum Fe levels were also used to identify Fe deficiency in obese children aged 12 to 16 years in Taiwan[26]. The condition of obesity is associated with subclinical inflammation. In contrast, SF is an acute phase protein, so sTfR is probably the best clinical benchmark in someone who is overweight[25]. sTfR increases because cell expression of transferrin receptors is upregulated to increase circulating Fe uptake, especially in marrow precursors of red blood cells. sTfR concentration is not significantly affected by inflammation, and therefore, it is helpful to distinguish iron deficiency from inflammatory hypoferromie[19,27]. Research by Sierpinski et al. showed that the sTfR examination was able to accurately describe depleted iron stores in the bone marrow[28]. Thus, in obese children with Fe deficiency, the sTfR and SF may differ due to confounding inflammatory effects. Apart from adiposity conditions, SF has limitations as an indicator of iron status in obese children.

The weakness in this study is the status of Fe deficiency which can be influenced by several confounding factors, including the content of food consumed before sample examination, drugs that may be consumed, inflammation, or infectious conditions. However, this study had low heterogeneity because researchers only used one research design, and the sample used was uniform, namely school-age children. Significant differences in hematological biomarkers and risk of Fe deficiency persisted across most subgroups, suggesting that the pooled results are likely reliable.

## CONCLUSIONS

These findings indicate that the incidence of obesity in children may lead to an increased risk of iron deficiency. The problem of iron deficiency and obesity is a public health problem that has detrimental short and long-term health effects, especially for school-age children in a phase of cognitive growth and development. The sTfR parameter was not significantly affected by inflammation due to adiposity to differentiate iron deficiency from inflammatory hypoferremia. Researchers recommend checking the nutritional status of children periodically through the school health unit and periodically checking the Fe status, considering that some children may already have latent Fe deficiency. Further research is needed regarding the modulation of obesity-associated inflammation and the effect on Fe deficiency status.

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**Conflict of Interest and Funding Disclosure**

All researchers involved declare no conflict of interest with this article. Sources of funding come from researchers.

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