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# Major clinical and metabolomic approaches to childhood obesity: a systematic review

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## Abstract

**Introduction:** In the context of childhood obesity, of children under 5 years of age in Brazil, 7% are overweight and 3% meet the criteria for obesity. Globally, according to a report from the World Health Organization (WHO), it is estimated that the total number of overweight and obese children in the world could reach 75 million by the year 2025. Objective: It was to carry out a systematic review to present the main approaches to clinical and metabolomics of childhood obesity. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from September to October 2024 in the Scopus, PubMed, Science Direct, Scielo and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 110 articles were recruited for the initial evaluation. A total of 41 articles were evaluated and 19 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 28 studies that did not meet GRADE. Most studies showed homogeneity in their results, with $X^2$=89.7%>50%. It was concluded that miRNAs are potential biomarkers for the development of pathologies, such as obesity. A heterogeneous group of these molecules was found to be associated with obesity in children. miR-15b-5p, miR-486-5p and hsa-miR-122-5p were considered good candidates for childhood obesity biomarkers. MiRNA-dependent mechanisms regulate up to 60% of all human genes. MiRNAs influence multiple pathways, including insulin signaling, immunemediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and regulation of food intake.

**Keywords:** Child obesity. Comorbidities. Meta-inflammation. MicroRNAs. Gene expression.

## Introduction

In the context of chronic non-communicable diseases (NCDs), obesity stands out as a multifactorial disease affecting approximately 30% of the world

population. It is estimated that more than 60% of the world population will be severely obese by 2030 [1]. Furthermore, according to data from the National Study of Child Nutrition and Feeding (ENANI-2019), among children under 5 years of age in Brazil, 7% are overweight and 3% meet the criteria for obesity [2,3]. Globally, according to a report by the World Health Organization (WHO), it is estimated that the total number of overweight and obese children in the world could reach 75 million by 2025 [4]. In this context, it is essential to understand that childhood obesity is not an isolated pathology, but rather the manifestation of several pathological changes, which can culminate in dysfunctional physiological changes [5].

Among these, damage to the respiratory system can be highlighted, with a possible reduction in its performance. In this context, it is observed that the accumulation of body fat in childhood is associated with respiratory changes that include, among many changes, reduced lung expansion, increased airway responsiveness, and reduced lung compliance [6]. Furthermore, an unbalanced diet, as well as obesity, causes damage to the development and maintenance of the immune system, predisposing to illness and a worse prognosis of diseases [7].

As a potential aggravating factor, the emergence of the new coronavirus (SARS-CoV-2), which causes COVID-19, has led to the worsening of obesity comorbidities [8]. It is necessary to understand the mechanisms by which obese patients are at greater risk of developing severe forms of the disease, even death. In this sense, immunity plays a decisive role in SARS-CoV-2 infection. The lack of regulation and the excessive immune response to viral stimuli produce pro-inflammatory cytokines in an exacerbated manner (cytokine storm), reaching a state of hyperinflammation, with consequent damage to various tissues in obese individuals [8]. In this context, molecules such as microRNAs (miRNAs) regulate gene expression by binding to a complementary mRNA sequence. MiRNA-dependent mechanisms regulate up to 60% of all human genes. MiRNAs influence multiple pathways, including insulin signaling, immune-mediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and food intake regulation. Disorders in miRNA expression affect gene expression and, therefore, cellular tissue function in the pathological process. The development of new ways to identify the progression of obesity to inflammation in the early stages will help to understand the different mechanisms that regulate this process [9].

Therefore, the occurrence of immune dysfunction, increased predisposition to infection, and mortality from sepsis is a reality. Obesity has been correlated with high leukocyte and lymphocyte counts (except for NK, suppressor T, and cytotoxic T cells), with suppression of lymphocyte proliferation of T and B lymphocytes, and with higher rates of oxidative activity and phagocytosis by monocytes and granulocytes, demonstrating the consequences of this pathology on the immune system [10].

In addition to these changes, it is known that obesity initially favors the development of inflammation in adipose tissue, through increased production of pro-inflammatory adipokines, such as IL-6 and TNF-α. Thus, the proportion between pro-inflammatory and anti-inflammatory cytokines becomes unbalanced [11]. Consequently, damage occurs to the vascular system, promoting endothelial dysfunction, characterized by decreased nitric oxide production and increased synthesis of reactive oxygen species, which establishes an inflammatory state and oxidative stress. Regarding innate immunity, in obese patients, there is a modification of the immune environment in adipose tissue [12].

In this context, obesity induces a change in the macrophage profile, increasing the M1 (pro-inflammatory) phenotype. This effect corresponds to an upregulation of inflammatory genes and a downregulation of anti-inflammatory genes [13]. However, this change in cells of the innate immune system does not only occur in adipose tissue. Thus, authors have demonstrated that circulating mononuclear cells of obese individuals are also in a pro-inflammatory state, with an increase in intranuclear factor κB (NF-κB) and, consequently, with an increase in the transcription of pro-inflammatory genes regulated by it [14].

As a corollary, the innate immune response in patients with obesity is altered, resulting in an imbalance in the line of defense against infections, an increase in the inflammatory response, and an abnormal activation of T lymphocytes. Furthermore, the primary increase in the inflammatory response in obese patients is a predictor for the hyperinflammatory state observed in COVID-19. Therefore, this primary increase can be amplified by SARS-CoV-2 infection, increasing the production of cytokines such as TNF-α, IL-1, and IL-6 [8].

Therefore, the present study performed a systematic review to present the main clinical and metabolomic approaches to childhood obesity.

## Methods

### Study Design

This study followed the international systematic review model, following the PRISMA (preferred

reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/12/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 09/12/2024.

### Search Strategy and Search Sources

The literature search process was carried out from September to October 2024 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS /MeSH Terms) were used: "Child obesity. Comorbidities. Meta-inflammation. MicroRNAs. Gene expression", and using the Boolean "and" between MeSH terms and "or" between historical findings.

### Study Quality and Risk of Bias

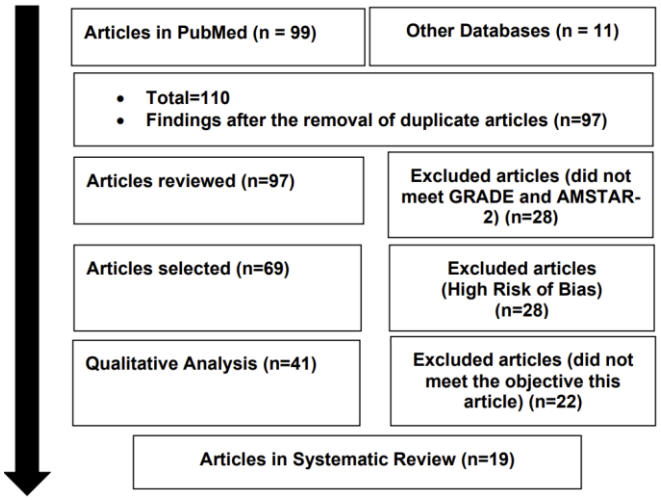
The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

## Results and Discussion

### Summary of Findings

As a corollary of the literary search system, a total of 110 articles were found that were subjected to eligibility analysis and, then, 19 of the 41 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with $X^2$=89.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 28 studies with a high risk of bias and 28 studies that did not meet GRADE and AMSTAR-2.

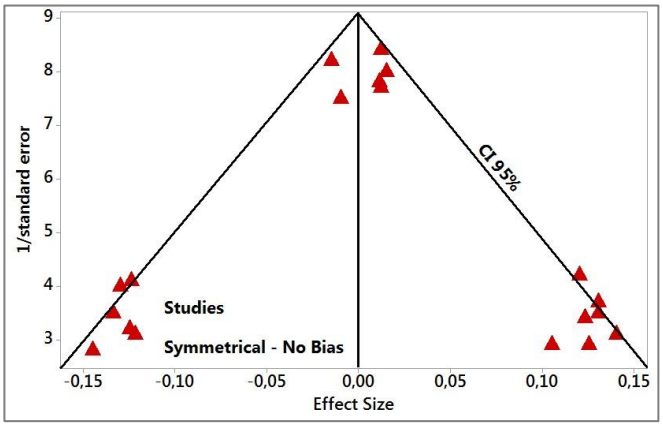
Figure 1. Flowchart showing the article selection process.




Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=19 studies).




Source: Own authorship.

### Main Clinical and Metabolomic Approaches to Childhood Obesity

After the process of selection and interpretation of the articles, it was observed that there is an association between miRNA expression and childhood obesity. Some authors have postulated a group of miRNAs as

biomarkers to identify the risk of early obesity. miR15b-5p, miR-486-5p and hsa-miR-122-5p were considered good candidates for obesity biomarkers [15-17].

The reviewed studies suggested that modified microRNAs may be involved in the regulation of pathways related to the development of pathologies, and they can predict the presence of obesity during childhood. MicroRNAs (miRNAs) are factors that regulate gene expression through binding to a complementary mRNA sequence [9].

A systematic review study analyzed the association between miRNA expression with overweight and obesity in children. A total of seven studies (684 children) were included. A total of 361 children were obese/overweight and 323 were normal weight. 40.64% (278) of the children were boys. The classification of obesity was inconsistent among studies with various classifications used. A total of 65 miRNAs were reported to be associated with obesity and overweight; at least two studies reported miR-122, miR-122-5p, miR-15b, miR15b-5p, miR191-5p, miR-222, miR-222-3p, miR 486, miR-486-3p, and miR-486-17h. Pathway analysis of the repeat miRNAs showed that they were involved in the regulation of metabolic and signaling pathways, including fatty acid metabolism. Therefore, miRNAs are potential biomarkers for the development of pathologies, such as obesity. A heterogeneous group of these molecules was found to be associated with obesity in children. miR-15b-5p, miR-486-5p, and hsa-miR-122-5p have been considered good candidates for obesity biomarkers [18]. Furthermore, the lipid gene perilipin 1 (PLIN1) is involved in the regulation of lipolysis and therefore represents a viable candidate mechanism for genetic research on obesity in children. Furthermore, the regulation of gene expression by circulating microRNAs (miRNAs) offers a new research venue for diagnostic innovation. Thus, a study reported new findings on associations between circulating miRNAs, PLIN1 gene regulation, and susceptibility to childhood obesity. In a sample of 135 unrelated individuals, 35 children with obesity (aged 3–13 years) and 100 healthy controls (aged 4–16 years), we examined the expression levels of four candidate miRNAs (hsa-miR-4777-3p, hsa-miR-642b-3p, hsamiR-3671-1, and hsa-miR-551b-2) targeting PLIN1 as measured by real-time polymerase chain reaction in whole blood samples. The full genetic model including the four candidate miRNAs and the PLIN1 gene was found to explain a statistically significant 12.7% of the variance in childhood obesity risk ($p = 0.0034$). The four miRNAs together explained 10.1% of the risk ($p = 0.008$). The percentage of variation in childhood obesity risk explained by hsa-miR-642b-3p and age was 19%. In line with the biological polarity of the observed association, for example, hsa-miR-642b-3p was upregulated, while PLIN1 expression was decreased in obese participants compared to healthy controls [19].

Thus, obesity, determined by the accumulation of adipose tissue in the human body, is considered a chronic disease with multifactorial etiology [2,3]. In the pediatric population, the identification and diagnosis of this pathology involve the correlation between several data that must be stratified according to the sex and age group of each individual. To obtain more accurate data, it is recommended to use complementary methods to the physical examination that assesses, in short, weight, height, abdominal circumference, and skin folds [5].

In terms of population assessment and classification, the body mass index (BMI), calculated based on the child's weight and height, is globally accepted. According to WHO data, the diagnosis is established when the values exceed the 99.9th percentile in children aged 0 to 5 years and above the 97th percentile in those aged 5 to 20 years. In these, there is also the classification of severe obesity when they exceed the 99.9th percentile and the Z+3 score [1].

It is important to emphasize that weight, as well as BMI, does not reflect an individual's body composition and, therefore, should not be used as isolated methods. This is because children and adolescents may manifest pathophysiological changes due to the accumulation of body fat, even if they have a normal weight [2]. For complementary assessment to BMI, skin folds, bioelectrical impedance (BIA), as well as more complex methods such as hydrostatic weight and computed tomography (CT) may be useful to differentiate the amount of body fat from other fat-free components such as muscle tissue, bone mass and the amount of total body water [5].

In this regard, the circulating level of cytokines and acute phase proteins associated with inflammation is elevated in patients with obesity. Thus, adipocytes secrete several cytokines and acute-phase proteins that increase the production and circulation of factors related to inflammation. The inflammatory process may be due to resistance to the action of insulin and other disorders associated with obesity, such as hyperlipidemia and metabolic syndrome [10]. Thus, the association between obesity and inflammatory disease is highlighted. There are three possibilities, the first reflects the production and release from organs other than adipose tissue, mainly the liver (and immune cells). The second explanation is that white adipose tissue secretes factors that stimulate the production of inflammatory markers by the liver and other organs. The third possibility is that adipocytes themselves are an immediate source of some, or several, of these inflammatory markers [10,11].

Effects as sensors of energy balance have been attributed to cytokines. Among all adipokines related to inflammatory processes, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), leptin, and adiponectin stand out.5 In this context, some studies have shown low concentrations of the anti-inflammatory adipokine (adiponectin) associated with the occurrence of several types of cancer and high concentrations with inhibition of tumor growth [8-12]. Adiponectin and leptin are the most abundant adipokines synthesized by adipose tissue, although there are others such as TNF-α, IL-6, IL-1, CC-chemokine ligand 2 (CCL2), a visceral adipose-tissue-derived serine protease inhibitor (vaspin) and retinolbinding protein 4 (RBP4) [8].

Finally, excess adipose tissue increases the production of several adipokines that have a major impact on several bodily functions. In this case, the most important is control of food intake and energy balance, the immune system, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism, and body homeostasis, situations strongly correlated with cardiovascular disease [13]. Adipokines with anti-inflammatory action include IL-1 receptor antagonist (IL-1ra), transforming growth factor-β (TGF-β), those produced by Th2 cells (IL-4, IL-5, and IL-10), and adiponectin. An imbalance between pro- and anti-inflammatory cytokines can induce inflammatory or hypersensitivity responses. Furthermore, high plasma concentrations of adiponectin are associated with a reduced risk of myocardial infarction in men. Adipokine is inversely proportional to the concentration of C-reactive protein (CRP). It can negatively regulate CRP gene expression in adipocytes [8].

## Conclusion

It was concluded that miRNAs are potential biomarkers for the development of pathologies, such as obesity. A heterogeneous group of these molecules was found to be associated with obesity in children. miR-15b-5p, miR-486-5p, and hsa-miR-122-5p were considered good candidates for childhood obesity biomarkers. MiRNA-dependent mechanisms regulate up to 60% of all human genes. MiRNAs influence multiple pathways, including insulin signaling, immune-mediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and food intake regulation.

## CRediT

Author contributions: **Conceptualization -** Iuri Sanzio Souto, Rafael Tinoco Alves, Deangelo Cláudio Gomes de Lima, Jose Manuel Torres Garcia, Karlla Vieira Campos Ricatto, Luciene Pereira de Oliveira, Renatto Souza Nunes Cabral; **Data curation-** Iuri Sanzio Souto, Rafael Tinoco Alves, Deangelo Cláudio Gomes de Lima, Jose Manuel Torres Garcia, Karlla Vieira Campos Ricatto, Luciene Pereira de Oliveira, Renatto Souza Nunes Cabral, Celso Alexandre Alves; **Formal Analysis -** Iuri Sanzio Souto, Rafael Tinoco Alves, Deangelo Cláudio Gomes de Lima, Jose Manuel Torres Garcia, Karlla Vieira Campos Ricatto, Luciene Pereira de Oliveira, Renatto Souza Nunes Cabral, Celso Alexandre Alves, Natashira Soares Torres, Jussara Santos Sousa; **Investigation-** Iuri Sanzio Souto; **Methodology-** Iuri Sanzio Souto; **Project administration-** Iuri Sanzio Souto; **Supervision-** Iuri Sanzio Souto, Deangelo Cláudio Gomes de Lima; **Writing - original draft-** Iuri Sanzio Souto, Rafael Tinoco Alves, Deangelo Cláudio Gomes de Lima, Jose Manuel Torres Garcia, Karlla Vieira Campos Ricatto, Luciene Pereira de Oliveira, Renatto Souza Nunes Cabral, Celso Alexandre Alves, Natashira Soares Torres, Jussara Santos Sousa ; **Writing-review & editing-** Iuri Sanzio Souto, Rafael Tinoco Alves, Deangelo Cláudio Gomes de Lima, Jose Manuel Torres Garcia, Karlla Vieira Campos Ricatto, Luciene Pereira de Oliveira, Renatto Souza Nunes Cabral, Celso Alexandre Alves, Natashira Soares Torres, Jussara Santos Sousa.

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No additional data are available.

## Conflict of Interest

The authors declare no conflict of interest.

## Similarity Check

It was applied by Ithenticate®.

## Peer Review Process

It was performed.

## References


1. WHO- World Health Organization. Available at: https://www.sbcbm.org.br/endoscopia-e-obesidade/ Accessed on: October 18, 2024.
2. Brazilian Association for the Study of Obesity and Metabolic Syndrome. Brazilian Obesity Guidelines 2016. 4th ed. São Paulo: ABESO, 2016. Available at: https://abeso.org.br/ Accessed on October 19, 2024.
3. Silva AAMD. Methodological aspects of the Brazilian National Survey on Child Nutrition (ENANI-2019). Cad Saude Publica. 2021 Aug 30;37(8):e00172121. English, Portuguese, Spanish. doi: 10.1590/0102-311X00172121.
4. UNICEF/WHO. United Nations Children's Fund, World Health Organization, The World Bank Group. Global Database on Child Growth and Malnutrition. Joint child malnutrition estimates - Levels and trends (2019 edition). New York: UNICEF; 2021. 32p.
5. Nutrologia pediátrica: prática baseada em evidências, manuele 2016.
6. Rodrigues MMP et al. "A obesidade como fator predisponente de alterações respiratórias na infância: revisão da literatura." ANAIS CONGREGA MIC-ISBN 978-65-86471-05-2 (2017): 561-562. http://ediurcamp.urcamp.edu.br/index.php/congregaanaismic/article/view/1436
7. Nutrologia Pediátrica: Temas da Atualidade em Nutrologia Pediátrica - 2021. / Sociedade Brasileira de Pediatria. Departamento Científico de Nutrologia. São Paulo: SBP, 2021.
8. Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. Lancet [Internet]. 30 abr 2020 [capturado 8 jun 2020]; 395(10236):1544-1545. DOI 10.1016/ S0140-6736(20)31024- 2. Disponível em: https://www.thelancet.com/journals/lancet/article/ PIIS0140-6736(20)31024-2/fulltext.
9. Cui X, You L, Zhu L, et al. Change in circulating microRNA profile of obese children indicates future risk of adult diabetes. Metabolism 2018; 78: 95-105. http://dx.doi.org/10.1016/j.metabol.2017.09.006.
10. Schetz M, De Jong A, Deane AM, et al. Obesity in the critically ill: a narrative review. Intensive Care Med. 2019;45(6):757-769. doi:10.1007/s00134-019-05594-1.
11. Apovian CM. Obesity: definition, comorbidities, causes, and burden. Am J Manag Care. 2016;22(7 Suppl):s176-s185.
12. Andolfi C, Fisichella PM. Epidemiology of Obesity and Associated Comorbidities. J Laparoendosc Adv Surg Tech A. 2018;28(8):919-924. doi:10.1089/lap.2018.0380.
13. Ghanim H, Aljada A, Hofmeyer D, Syed T, Mohanty P, Dandona P. Circulating Mononuclear Cells in the Obese Are in a Proinflammatory State. Circulation [Internet]. 21 set 2004 [capturado 8 jun 2020]; 110(12):1564-1571. DOI 10.1161/01.CIR.0000142055.53122.FA. Disponível em: https://www.ahajournals.org/doi/10.1161/01.cir.0000142055.53122.fa.
14. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet [Internet]. 02 maio 2020 [capturado 7 jun 2020]; 395(10234):1417-1418. DOI 10.1016/S0140-6736(20)30937-5. Disponível em: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30937-5/fulltext.
15. Can U, Buyukinan M, Yerlikaya FH. The investigation of circulating microRNAs associated with lipid metabolism in childhood obesity. Pediatr Obes 2016; 11(3): 228-34. [http://dx.doi.org/10.1111/ijpo.12050.
16. Prats-Puig A, Ortega FJ, Mercader JM, et al. Changes in circulating microRNAs are associated with childhood obesity. J Clin Endocrinol Metab 2013; 98(10): E165560. [http://dx.doi.org/10.1210/jc.2013-1496].
17. Carolan E, Hogan AE, Corrigan M, et al. The impact of childhood obesity on inflammation, innate immune cell frequency, and metabolic microRNA expression. J Clin Endocrinol Metab 2014; 99(3): E474-8.
18. Flórez CAR, García-Perdomo HA, Escudero MM. MicroRNAs Associated with Overweight and Obesity in Childhood: A Systematic Review. Microrna. 2020;9(4):255-265. doi: 10.2174/2211536609666191209152721.
19. Görücü Yılmaz Ş, Bozkurt H, Ndadza A, Thomford NE, Karaoğlan M, Keskin M, Benlier N, Dandara C. Childhood Obesity Risk in Relationship to Perilipin 1 (PLIN1) Gene Regulation by Circulating microRNAs. OMICS. 2020 Jan;24(1):43-50. doi: 10.1089/omi.2019.0150.


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