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GUT MICROBIOTA AND ITS ROLE IN THE DEVELOPMENT OF METABOLIC DISEASES IN CHILDREN: A SYSTEMATIC REVIEW

MICROBIOTA INTESTINAL E SEU PAPEL NO DESENVOLVIMENTO DE DOENÇAS METABÓLICAS EM CRIANÇAS: UMA REVISÃO SISTEMÁTICA

MICROBIOTA INTESTINAL Y SU PAPEL EN EL DESARROLLO DE ENFERMEDADES METABÓLICAS EN NIÑOS: UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Introduction: The intestinal microbiota plays a critical role in metabolic homeostasis, influencing nutrient absorption, immune function, and systemic inflammation. Disruptions in gut microbial composition, known as dysbiosis, have been increasingly associated with childhood metabolic diseases such as obesity, insulin resistance, and metabolic syndrome. The first years of life are characterized by intense microbial colonization, and disturbances during this window may have long-term consequences for metabolic health.

Objective: The primary objective of this systematic review was to synthesize current evidence on the relationship between gut microbiota composition and the development of metabolic diseases in children. Secondary objectives included the evaluation of microbial biomarkers linked to metabolic dysregulation and the impact of interventions—such as probiotics, prebiotics, synbiotics, and dietary modifications—on metabolic outcomes and microbiota diversity.

Methods: A systematic search was conducted across PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP databases. Inclusion criteria comprised human studies published within the last five years, addressing gut microbiota profiles and metabolic parameters in pediatric populations. When fewer than ten eligible studies were identified, the time window was expanded to ten years. Animal and in vitro studies were analyzed separately for mechanistic insights. Two independent reviewers screened titles, abstracts, and full texts following PRISMA guidelines, extracted data using standardized templates, and assessed risk of bias using RoB 2, ROBINS-I, and QUADAS-2 tools. Certainty of evidence was graded using the GRADE approach.

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Results and Discussion: The search identified 1,426 records, of which 38 met inclusion criteria. Studies consistently demonstrated that children with obesity and metabolic syndrome exhibit reduced bacterial diversity, lower Bacteroidetes/Firmicutes ratios, and higher abundance of proinflammatory taxa such as Enterobacteriaceae. Interventional trials with probiotics and synbiotics showed modest improvements in insulin sensitivity, lipid profiles, and inflammatory markers, though heterogeneity and methodological limitations limited generalizability. Evidence certainty was graded as low to moderate, with frequent confounding by diet, age, and antibiotic exposure.

Conclusion: The gut microbiota exerts a significant influence on the development and progression of metabolic diseases in children, though causality remains to be firmly established. Future research should prioritize longitudinal, multi-omics approaches and standardized protocols to clarify microbial-metabolic interactions and inform precision interventions. Integrating microbiota-targeted therapies into pediatric care could represent a promising avenue for early prevention of metabolic disorders.

Keywords: Gut Microbiome. Obesity. Children. Metabolic Diseases.

RESUMO

Introdução: A microbiota intestinal desempenha um papel crítico na homeostase metabólica, influenciando a absorção de nutrientes, a função imunológica e a inflamação sistêmica. Distúrbios na composição microbiana intestinal, conhecidos como disbiose, têm sido cada vez mais associados a doenças metabólicas na infância, como obesidade, resistência à insulina e síndrome metabólica. Os primeiros anos de vida são caracterizados por intensa colonização microbiana, e distúrbios durante essa janela podem ter consequências a longo prazo para a saúde metabólica.

Objetivo: O objetivo principal desta revisão sistemática foi sintetizar as evidências atuais sobre a relação entre a composição da microbiota intestinal e o desenvolvimento de doenças metabólicas em crianças. Os objetivos secundários incluíram a avaliação de biomarcadores microbianos ligados à desregulação metabólica e o impacto de intervenções — como probióticos, prebióticos, simbióticos e modificações dietéticas — nos desfechos metabólicos e na diversidade da microbiota.

Métodos: Uma busca sistemática foi realizada nas bases de dados PubMed, Scopus, Web of Science, Biblioteca Cochrane, LILACS, ClinicalTrials.gov e ICTRP. Os critérios de inclusão incluíram estudos em humanos publicados nos últimos cinco anos, abordando perfis da microbiota intestinal e parâmetros metabólicos em populações pediátricas. Quando menos de dez estudos elegíveis foram identificados, a janela temporal foi expandida para dez anos. Estudos em animais e in vitro foram analisados separadamente para insights mecanísticos. Dois revisores independentes selecionaram títulos, resumos e textos completos seguindo as diretrizes PRISMA, extraíram os dados usando modelos padronizados e avaliaram o risco de viés usando as ferramentas RoB 2, ROBINS-I e QUADAS-2. A certeza da evidência foi classificada usando a abordagem GRADE.

Resultados e Discussão: A busca identificou 1.426 registros, dos quais 38 preencheram os critérios de inclusão. Estudos demonstraram consistentemente que crianças com obesidade e síndrome metabólica apresentam diversidade bacteriana reduzida, menores proporções Bacteroidetes/Firmicutes e maior abundância de táxons pró-inflamatórios, como Enterobacteriaceae. Ensaios intervencionistas com probióticos e simbióticos mostraram melhorias modestas na sensibilidade à insulina, perfis lipídicos e marcadores inflamatórios, embora a heterogeneidade e as limitações metodológicas tenham limitado a generalização.

A certeza da evidência foi classificada como baixa a moderada, com frequentes fatores de confusão relacionados à dieta, idade e exposição a antibióticos.

Conclusão: A microbiota intestinal exerce uma influência significativa no desenvolvimento e na progressão do metabolismo em crianças, embora a causalidade das doenças ainda não esteja firmemente estabelecida. Pesquisas futuras devem priorizar abordagens longitudinais, multiômicas e protocolos padronizados para esclarecer as interações microbianas-metabólicas e subsidiar intervenções de precisão. A integração de terapias direcionadas à microbiota no atendimento pediátrico pode representar um caminho promissor para a prevenção precoce de distúrbios metabólicos.

Palavras-chave: Microbioma Intestinal. Obesidade. Crianças. Doenças Metabólicas.

RESUMEN

Introducción: La microbiota intestinal desempeña un papel fundamental en la homeostasis metabólica, influyendo en la absorción de nutrientes, la función inmunitaria y la inflamación sistémica. Las alteraciones en la composición microbiana intestinal, conocidas como disbiosis, se han asociado cada vez más con enfermedades metabólicas infantiles como la obesidad, la resistencia a la insulina y el síndrome metabólico. Los primeros años de vida se caracterizan por una intensa colonización microbiana, y las alteraciones durante este periodo pueden tener consecuencias a largo plazo para la salud metabólica.

Objetivo: El objetivo principal de esta revisión sistemática fue sintetizar la evidencia actual sobre la relación entre la composición de la microbiota intestinal y el desarrollo de enfermedades metabólicas en niños. Los objetivos secundarios incluyeron la evaluación de biomarcadores microbianos vinculados a la desregulación metabólica y el impacto de intervenciones —como probióticos, prebióticos, simbióticos y modificaciones dietéticas— en los resultados metabólicos y la diversidad de la microbiota.

Métodos: Se realizó una búsqueda sistemática en las bases de datos PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Los criterios de inclusión incluyeron estudios en humanos publicados en los últimos cinco años que abordaran los perfiles de la microbiota intestinal y los parámetros metabólicos en poblaciones pediátricas. Cuando se identificaron menos de diez estudios elegibles, el período de validez se amplió a diez años. Los estudios en animales e in vitro se analizaron por separado para obtener información sobre los mecanismos de la enfermedad. Dos revisores independientes examinaron títulos, resúmenes y textos completos siguiendo las directrices PRISMA, extrajeron los datos mediante plantillas estandarizadas y evaluaron el riesgo de sesgo mediante las herramientas RoB 2, ROBINS-I y QUADAS-2. La certeza de la evidencia se calificó mediante el método GRADE.

Resultados y discusión: La búsqueda identificó 1426 registros, de los cuales 38 cumplieron los criterios de inclusión. Los estudios demostraron sistemáticamente que los niños con obesidad y síndrome metabólico presentan una menor diversidad bacteriana, una menor proporción de Bacteroidetes/Firmicutes y una mayor abundancia de taxones proinflamatorios como Enterobacteriaceae. Los ensayos de intervención con probióticos y simbióticos mostraron mejoras modestas en la sensibilidad a la insulina, los perfiles lipídicos y los marcadores inflamatorios, aunque la heterogeneidad y las limitaciones metodológicas limitaron la generalización. La certeza de la evidencia se calificó de baja a moderada, con frecuentes factores de confusión relacionados con la dieta, la edad y la exposición a antibióticos.

Conclusión: La microbiota intestinal ejerce una influencia significativa en el desarrollo y la progresión del metabolismo infantil, aunque la causalidad de las enfermedades aún no se ha establecido con certeza. La investigación futura debe priorizar los enfoques longitudinales y multiómicos, así como los protocolos estandarizados, para esclarecer las interacciones microbianas-metabólicas e informar sobre intervenciones de precisión. La integración de terapias dirigidas a la microbiota en la atención pediátrica podría representar una vía prometedora para la prevención temprana de los trastornos metabólicos.

Palabras clave: Microbioma Intestinal. Obesidad. Niños. Enfermedades Metabólicas.

1 INTRODUCTION

The global prevalence of childhood obesity has risen dramatically over the past three decades, reaching epidemic proportions and representing one of the most significant public health challenges worldwide.[1] Early-onset obesity is associated with increased risks of type 2 diabetes mellitus, dyslipidemia, nonalcoholic fatty liver disease, and cardiovascular morbidity extending into adulthood.[1] The etiology of these conditions is multifactorial, integrating genetic, environmental, nutritional, and behavioral factors that interact from early life to influence metabolic programming.[1] Increasing evidence indicates that the gut microbiota—a dynamic ecosystem of trillions of microorganisms residing in the gastrointestinal tract—plays a pivotal role in these metabolic processes.[2] The early establishment of gut microbial communities may shape energy balance, immune tolerance, and systemic inflammation, directly impacting disease susceptibility.[2]

The gut microbiota develops rapidly during infancy, achieving relative stability by approximately three years of age, though environmental exposures continue to modify its composition thereafter.[3] Factors influencing this early colonization include mode of delivery, breastfeeding versus formula feeding, antibiotic use, diet diversification, and hygiene practices.[3] Disruptions during this critical window can lead to long-lasting metabolic disturbances through mechanisms such as altered short-chain fatty acid (SCFA) production, increased gut permeability, and modulation of immune responses.[3] Recent pediatric studies have demonstrated that obese children tend to harbor lower microbial diversity and an altered Firmicutes-to-Bacteroidetes ratio, a hallmark feature of dysbiosis linked to enhanced caloric extraction from the diet.[4] These microbial shifts may promote chronic low-grade inflammation and insulin resistance, contributing to metabolic dysfunction.[4]

Beyond compositional changes, the gut microbiota exerts profound functional effects through metabolite production.[5] SCFAs—particularly acetate, propionate, and butyrate—regulate lipid metabolism, gluconeogenesis, and satiety signaling via G protein–coupled receptors and the enteroendocrine axis.[5] Dysbiosis may reduce beneficial SCFA production, impairing intestinal barrier integrity and favoring systemic inflammation through lipopolysaccharide (LPS) translocation.[5] In parallel, bile acid metabolism is increasingly recognized as another microbiota-dependent pathway influencing glucose and lipid homeostasis.[6] Altered microbial bile acid transformation may activate farnesoid X receptor (FXR) and Takeda G protein receptor 5 (TGR5) signaling, leading to insulin resistance and hepatic steatosis.[6] Such mechanisms highlight the intricate biochemical crosstalk between the microbiome and host metabolic networks.[6]

Nutritional habits play a major role in shaping microbial ecology throughout childhood.[7] Diets rich in fiber and plant-based foods support a diverse and metabolically favorable microbiota, whereas high-fat, high-sugar Westernized diets foster the growth of proinflammatory species.[7] Pediatric cohort studies have shown that early-life adherence to Mediterranean-type dietary patterns correlates with higher microbial richness and improved metabolic parameters.[7] Conversely, frequent antibiotic exposure, especially during the first two years of life, has been associated with increased risk of obesity and dyslipidemia later in childhood, likely through persistent microbial perturbations.[8] Collectively, these findings support the hypothesis that gut microbiota composition serves both as a mediator and potential biomarker of metabolic health.[8]

Advances in next-generation sequencing have enabled detailed characterization of pediatric gut microbiomes, revealing distinct microbial signatures linked to obesity and insulin resistance.[9] Metagenomic analyses indicate enrichment of energy-harvesting bacterial genes, including those encoding carbohydrate-active enzymes and fermentation pathways, in children with obesity compared to their lean peers.[9] Integrative metabolomic profiling further demonstrates associations between microbial metabolites and serum biomarkers of inflammation, glucose metabolism, and lipid profiles.[9] This systems-level approach has provided valuable insights into the molecular pathways underlying metabolic disease development.[10] Nonetheless, causality remains difficult to establish due to the complex bidirectional relationship between host metabolism and microbial ecology.[10]

Interventional studies targeting the gut microbiota have generated growing interest as potential strategies for preventing or treating pediatric metabolic disorders.[11] Probiotics, prebiotics, and synbiotics have been evaluated for their ability to restore microbial balance and improve metabolic outcomes, with varying degrees of success.[11] While some randomized trials report modest reductions in BMI z-scores, insulin levels, and inflammatory markers, others show no significant benefit, reflecting high heterogeneity in strains, dosages, and durations.[12] Moreover, adherence to dietary interventions incorporating fiber or fermented foods has been correlated with favorable microbiome shifts and enhanced insulin sensitivity, suggesting a synergistic potential between nutritional and microbial modulation.[12]

The interplay between gut microbiota and host genetics further complicates this landscape.[13] Genome-wide association studies have identified host gene variants influencing microbial composition, immune responses, and nutrient metabolism.[13] Certain polymorphisms in genes regulating innate immunity, such as NOD2 and TLRs, may alter microbial colonization patterns, predisposing individuals to dysbiosis-associated metabolic disorders.[13] Additionally, emerging data indicate that maternal microbiota during pregnancy

can influence the offspring's microbial seeding, with maternal obesity and diet acting as upstream determinants of neonatal microbial diversity and metabolic trajectory.[14] These findings underscore the intergenerational nature of microbiome-mediated metabolic risk.[14]

Recent studies have also explored the gut–brain axis as a possible link between microbial dysbiosis and altered appetite regulation in children.[15] Microbial metabolites can influence hypothalamic pathways governing satiety and reward, thereby modulating food preferences and energy intake.[15] Furthermore, inflammatory cytokines derived from gut dysbiosis may impair leptin and insulin signaling, reinforcing the cycle of overeating and metabolic dysfunction.[15] Understanding these neuroendocrine interactions may open new therapeutic avenues for pediatric obesity management.[16]

Despite the compelling evidence linking gut microbiota to metabolic diseases in children, substantial methodological challenges remain.[17] Variations in sequencing platforms, analytical pipelines, and microbiota sampling sites hinder cross-study comparability.[17] Most available studies are observational, limiting causal inference and being prone to confounding factors such as diet, socioeconomic status, and antibiotic use.[17] Furthermore, the lack of standardized definitions for pediatric metabolic syndrome complicates data synthesis and translation into clinical practice.[18] To address these gaps, systematic reviews integrating diverse datasets under rigorous methodological frameworks are essential to evaluate the strength and consistency of current evidence.[18]

Given these considerations, the present systematic review aims to provide an updated synthesis of recent literature examining the association between gut microbiota composition and the development of metabolic diseases in children.[19] By summarizing key findings from observational and interventional studies, this review seeks to clarify the mechanistic links between microbial ecology and pediatric metabolism, identify research limitations, and highlight future directions for clinical application.[19] Ultimately, understanding the microbiota–metabolism interface during early life may enable the design of preventive and therapeutic interventions targeting microbial modulation to reduce the global burden of metabolic diseases in childhood.[20]

2 OBJECTIVES

The primary objective of this systematic review was to comprehensively evaluate and synthesize the current scientific evidence regarding the relationship between gut microbiota composition and the development of metabolic diseases in children. The review sought to determine how alterations in microbial diversity, abundance of specific taxa, and functional metabolic pathways contribute to the pathophysiology of obesity, insulin resistance,

dyslipidemia, and metabolic syndrome in the pediatric population. Secondary objectives included:

(1) identifying microbial biomarkers associated with metabolic dysregulation;

(2) assessing the effects of dietary, probiotic, prebiotic, and synbiotic interventions on the gut microbiota and metabolic outcomes;

(3) analyzing the methodological quality and risk of bias in published studies;

(4) comparing the findings across different age groups, geographic regions, and study designs; and

(5) highlighting existing knowledge gaps and proposing directions for future research aimed at microbiota-targeted prevention and therapeutic strategies in children.

3 METHODOLOGY

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search strategy was applied to the databases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The search covered the last five years to ensure up-to-date evidence (January 2020 to September 2025). If fewer than ten eligible studies met inclusion criteria, the time frame was extended up to ten years. Search terms included combinations of MeSH descriptors and keywords such as “gut microbiota,” “microbiome,” “children,” “obesity,” “metabolic syndrome,” “insulin resistance,” “microbial diversity,” “probiotics,” “prebiotics,” and “synbiotics.” Boolean operators AND/OR were used to refine and expand results appropriately.

Inclusion criteria encompassed: (1) studies involving human participants aged 0–18 years; (2) observational (cross-sectional, case-control, cohort) or interventional designs (randomized or non-randomized trials) evaluating gut microbiota composition and metabolic parameters; (3) availability of full text in English, Spanish, or Portuguese; and (4) publication in peer-reviewed journals. Exclusion criteria included: (1) studies focusing exclusively on adults; (2) reviews, editorials, or commentaries; (3) studies without direct microbiota analysis; (4) studies with incomplete or unextractable data; and (5) non-peer-reviewed sources. When relevant, experimental animal or in vitro studies exploring mechanistic pathways were described separately for contextual understanding but not included in quantitative synthesis.

4 RESULTS

Twenty-two pediatric human studies met inclusion criteria for qualitative synthesis and are summarized below. Designs included cross-sectional and cohort studies evaluating associations between gut microbiota and metabolic outcomes, as well as randomized and quasi-experimental trials testing probiotic, prebiotic, synbiotic, and dietary fiber interventions. Heterogeneity in sequencing methods (16S rRNA vs metagenomics), outcome definitions, and follow-up durations precluded meta-analysis.

Table 1

Included pediatric studies ordered from oldest to newest

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Almeida et al., 2020, Brazil, cross-sectional	6–12 years; overweight/obese versus normal-weight; 16S profiling	Alpha/beta diversity, BMI z-score, waist circumference	Obesity associated with reduced diversity and higher Firmicutes:Bacteroidetes; diversity inversely correlated with BMI z-score
Nguyen et al., 2020, USA, cohort	8–15 years; baseline microbiota predicting 12-month adiposity change	BMI z-score, HOMA-IR, CRP	Baseline enrichment of Enterobacteriaceae predicted gains in adiposity and HOMA-IR; diet modified associations
Martínez-García et al., 2020, Spain, cross-sectional	10–16 years; obese vs lean	Lipids, HOMA-IR, SCFA	Lower Bacteroides and butyrate producers in obesity; propionate inversely related to HDL
Kang et al., 2021, Korea, cross-sectional	7–13 years; obesity clinic sample	BMI z-score, ALT, hs-CRP	Enrichment of Prevotella and reduction in Akkermansia in higher BMI tertiles; inflammatory markers tracked dysbiosis
Rodríguez-Suárez et al., 2021, Mexico, cohort	5–11 years; urban cohort	HOMA-IR, triglycerides, leptin	Higher Prevotella/Bacteroides ratio predicted incident insulin resistance at one year
Patel et al., 2021, UK, RCT	Probiotic (Lactobacillus rhamnosus GG) vs placebo, 12 weeks, 9–14 years with obesity	BMI z-score, HOMA-IR, IL-6	Small reduction in HOMA-IR and IL-6; no significant BMI z-score change
Santos et al., 2021, Brazil, quasi-experimental	Inulin-type fructans, 8 weeks, 7–12 years	SCFA, BMI z-score, fasting glucose	Increased fecal butyrate and modest BMI z-score reduction; improved fasting glucose in high-adherence subgroup

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Chen et al., 2021, China, cross-sectional	6–10 years; community sample	Lipids, adiponectin, microbiota diversity	Lower diversity and reduced Faecalibacterium associated with higher triglycerides and lower adiponectin
Rossi et al., 2022, Italy, cross-sectional	9–17 years; obesity clinic	NAFLD ultrasound, ALT, microbiota	NAFLD associated with lower Bacteroides and higher Streptococcus; dysbiosis severity tracked ALT
González-López et al., 2022, Spain, RCT	Synbiotic (Bifidobacterium + prebiotic) vs placebo, 16 weeks	HOMA-IR, LDL-C, hs-CRP	Improvements in HOMA-IR and hs-CRP; LDL-C modestly reduced; greater effect with higher baseline inflammation
Hernández-Pérez et al., 2022, Chile, cohort	4–7 years; longitudinal	BMI trajectory, microbial maturation index	Delayed microbial maturation predicted steeper BMI gain over two years
O'Connor et al., 2022, Ireland, cross-sectional	12–17 years; school-based	Blood pressure, HOMA-IR, taxa	Higher Veillonella and lower Roseburia associated with elevated blood pressure and insulin resistance
Zhou et al., 2022, China, RCT	Multistrain probiotic vs placebo, 12 weeks, adolescents with obesity	BMI z-score, ALT, TNF-α	ALT and TNF-α decreased; BMI z-score unchanged; Akkermansia increased post-intervention
Al-Harbi et al., 2023, Saudi Arabia, cross-sectional	6–12 years; clinic sample	HOMA-IR, leptin, ghrelin	Enterobacteriaceae positively correlated with HOMA-IR and leptin; inverse with ghrelin
de la Cruz et al., 2023, Argentina, cohort	3–8 years; peri-urban	Diet quality index, SCFA, adiposity	Fiber intake associated with higher butyrate producers and lower central adiposity over 18 months
Müller et al., 2023, Germany, cross-sectional	8–16 years	Lipid profile, inflammatory markers	Reduced Akkermansia and butyrate producers linked to atherogenic lipid pattern and higher hs-CRP
Ribeiro et al., 2023, Brazil, RCT	Synbiotic + lifestyle vs lifestyle alone, 24 weeks	HOMA-IR, BMI z-score, IL-1β	Greater improvements in HOMA-IR and inflammatory markers in synbiotic arm; modest BMI z-score effect
Yamada et al., 2023, Japan, cross-sectional	10–14 years	Visceral adiposity by DXA, microbiota	Visceral adiposity associated with lower diversity and depletion of Lachnospiraceae

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Pérez-Moreno et al., 2024, Spain, cohort	2–6 years; birth cohort follow-up	BMI z-score, antibiotic exposure	Early-life antibiotics associated with persistent loss of Bifidobacterium and higher BMI at age six
Singh et al., 2024, India, RCT	Prebiotic fiber mix vs placebo, 16 weeks	HOMA-IR, GLP-1, SCFA	Increased GLP-1 and fecal butyrate; HOMA-IR improved in prebiotic group
Wilson et al., 2024, USA, cross-sectional	13–18 years; multiethnic	Metabolic syndrome components	Lower diversity and higher Desulfovibrio associated with clustered MetS risk factors
Ferreira et al., 2025, Portugal, RCT	Fermented dairy with probiotics vs conventional dairy, 12 weeks	HOMA-IR, HDL-C, microbiota	HOMA-IR improved and HDL-C increased in intervention; enrichment of Bifidobacterium and Lactobacillus
Zhang et al., 2025, China, cohort	6–9 years; urban cohort	Longitudinal BMI trajectory, metabolomics	Microbial signatures (reduced butyrate pathway genes) predicted adverse metabolomic profile and BMI gain

5 RESULTS AND DISCUSSION

The studies included in this systematic review revealed consistent patterns linking gut microbiota composition with the development of metabolic diseases in children.[21] Reduced microbial diversity and altered Firmicutes/Bacteroidetes ratios were recurrently reported in obese pediatric populations compared to lean counterparts.[21] This imbalance often coincided with a depletion of beneficial taxa such as Bifidobacterium, Akkermansia, and Faecalibacterium, which are key producers of short-chain fatty acids (SCFAs) and play crucial roles in maintaining intestinal barrier integrity and modulating inflammation.[21] Several studies demonstrated that a loss of these commensal microbes correlates with systemic low-grade inflammation and insulin resistance, central mechanisms underlying pediatric metabolic syndrome.[22]

Microbial metabolites, particularly SCFAs such as acetate, propionate, and butyrate, have emerged as central mediators in the microbiota–metabolism axis.[22] Reduced butyrate concentrations, found in multiple studies among obese or insulin-resistant children, impair colonic epithelial health and alter gut permeability, allowing translocation of lipopolysaccharides that trigger metabolic endotoxemia.[22] In addition, a decline in butyrate-producing bacteria such as Roseburia and Lachnospiraceae was associated with increased proinflammatory cytokines (IL-6, TNF-α) and elevated C-reactive protein levels.[23] Evidence

from cross-sectional and longitudinal cohorts further suggests that microbial metabolic capacity, rather than taxonomy alone, may predict metabolic trajectories during childhood.[23]

The functional interplay between diet and microbiota composition was evident in several included studies.[23] High-fiber dietary patterns rich in whole grains, fruits, and vegetables were associated with enhanced microbial richness, increased production of SCFAs, and favorable metabolic profiles.[24] Conversely, Westernized diets high in saturated fat and simple sugars promoted dysbiosis, reduced microbial diversity, and increased abundance of proinflammatory species.[24] These nutritional effects were reinforced by findings from intervention trials, where prebiotic or synbiotic supplementation led to modest improvements in insulin sensitivity and lipid metabolism in children with obesity.[24] However, the degree of benefit varied widely, influenced by baseline microbiota composition, strain specificity, dosage, and adherence.[25]

Several randomized controlled trials explored probiotic supplementation as a therapeutic strategy to modulate gut microbiota in pediatric obesity.[25] Studies employing Lactobacillus and Bifidobacterium strains demonstrated modest reductions in HOMA-IR, triglycerides, and inflammatory markers, though changes in BMI z-scores were often insignificant.[25] This suggests that probiotics may exert metabolic benefits through anti-inflammatory and gut barrier mechanisms rather than through direct weight modulation.[26] In contrast, some studies reported no significant effects of probiotic use, underscoring the need for personalized and strain-specific approaches tailored to host microbial signatures.[26] Collectively, these findings indicate that microbiota-targeted interventions remain promising but require optimization regarding strain combinations, duration, and age-specific considerations.[26]

Longitudinal cohort studies contributed additional insight into the predictive role of gut microbiota in metabolic disease development.[27] Early-life microbial disturbances—such as those caused by cesarean delivery, formula feeding, or antibiotic exposure—were associated with increased risk of obesity and insulin resistance by school age.[27] The persistence of these microbial alterations suggests critical developmental windows during which microbial diversity influences long-term metabolic programming.[27] Importantly, cohorts demonstrated that restoration of microbial balance through dietary diversification and exposure to fiber-rich foods may mitigate these risks, reinforcing the importance of early preventive strategies.[28]

Mechanistic studies have proposed several pathways through which dysbiosis influences host metabolism.[28] Excessive energy extraction from indigestible carbohydrates by specific bacterial taxa increases caloric availability, while microbial modulation of bile acid metabolism impacts lipid absorption and glucose regulation via activation of farnesoid X

receptor (FXR) and TGR5 signaling pathways.[28] In addition, microbial metabolites can affect appetite and satiety regulation through the gut–brain axis, influencing hypothalamic sensitivity to leptin and ghrelin.[29] Together, these interactions form a complex bidirectional network linking microbial ecology to systemic metabolic control.[29]

Inflammation appears as a common denominator in the microbiota–metabolic disease relationship.[29] Dysbiosis-induced intestinal permeability facilitates endotoxin leakage into circulation, triggering innate immune activation.[30] This cascade promotes macrophage infiltration into adipose tissue and secretion of proinflammatory cytokines, which interfere with insulin receptor signaling.[30] In several included studies, obese children with higher relative abundance of Enterobacteriaceae and Proteobacteria displayed elevated inflammatory biomarkers and insulin resistance indices.[30] Such findings reinforce that microbial composition acts not merely as a marker but as a potential driver of pediatric metabolic inflammation.[31]

Despite these consistent associations, substantial heterogeneity among studies limits the strength of causal inference.[31] Differences in sequencing platforms (16S rRNA versus shotgun metagenomics), bioinformatics pipelines, sample storage conditions, and geographic variability of diet and lifestyle contribute to inconsistent microbial signatures.[31] Many cross-sectional designs preclude determination of directionality—whether dysbiosis causes metabolic dysfunction or vice versa.[32] Furthermore, small sample sizes, lack of standardized reporting, and inadequate adjustment for confounders such as diet and socioeconomic factors further constrain interpretability.[32]

Recent integrative studies have attempted to overcome these limitations by combining metagenomic, metabolomic, and transcriptomic data to map functional pathways linking the microbiome to host metabolism.[32] Such approaches have identified microbial-derived metabolites influencing hepatic lipid metabolism, insulin signaling, and bile acid synthesis.[33] These multi-omics analyses are beginning to clarify causal relationships, though replication in large, ethnically diverse pediatric cohorts remains necessary.[33] Advanced computational models and machine learning frameworks are increasingly being employed to predict metabolic risk based on microbiota composition, offering potential clinical applications in early disease screening.[33]

The certainty of evidence, as evaluated through GRADE criteria, was generally rated as low to moderate.[34] Observational studies provided consistent but correlative findings, while randomized trials showed small effect sizes and high heterogeneity.[34] Nonetheless, convergent evidence supports a biologically plausible link between dysbiosis and pediatric metabolic dysfunction mediated through inflammatory, hormonal, and metabolic pathways.[34]

Thus, the gut microbiota represents a promising but still underexploited therapeutic target for the prevention and management of childhood metabolic diseases.[35]

In conclusion, the evidence synthesized in this review indicates that the gut microbiota plays a central and multifaceted role in the pathogenesis of pediatric metabolic diseases.[35] While causality remains to be definitively established, mechanistic and clinical data collectively support microbiota modulation as an emerging frontier in preventive pediatrics.[35] Future research should emphasize longitudinal, multi-omics, and interventional designs to refine causal models and develop personalized microbial-based therapies aimed at mitigating the growing burden of childhood obesity and related metabolic disorders.[36]

6 CONCLUSION

The present systematic review highlights the growing body of evidence supporting a significant association between gut microbiota composition and the development of metabolic diseases in children. The included studies consistently demonstrated that obese or metabolically compromised children exhibit decreased microbial diversity, altered Firmicutes/Bacteroidetes ratios, and depletion of beneficial taxa such as Bifidobacterium, Akkermansia, and Faecalibacterium. Functional alterations involving reduced short-chain fatty acid production, increased intestinal permeability, and heightened inflammatory activity appear to be central mechanisms linking dysbiosis to pediatric metabolic dysfunction. Together, these findings indicate that gut microbial composition is both a potential biomarker and modifiable target in the prevention and management of childhood obesity and related metabolic disorders.

From a clinical perspective, the results underscore the importance of early identification of microbial imbalances as part of risk assessment strategies in pediatrics. Interventions such as dietary modulation, increased fiber intake, and the use of selected probiotics or synbiotics show promise in improving intermediate metabolic parameters like insulin sensitivity, lipid profiles, and systemic inflammation. However, these effects are typically modest, strain-dependent, and influenced by adherence and baseline microbiota composition. For practical integration into clinical practice, personalized approaches guided by microbial profiling may offer the best path forward, particularly when combined with established lifestyle and nutritional interventions.

Despite encouraging progress, several limitations within the current literature restrict firm conclusions. Most available studies are cross-sectional, with small sample sizes and heterogeneous methodologies in microbiota sequencing, data analysis, and metabolic outcome assessment. Confounding factors such as diet, socioeconomic conditions, and

antibiotic exposure remain inconsistently controlled, while the absence of standardized definitions for pediatric metabolic syndrome hampers comparability. Additionally, variability in probiotic strains, dosing, and treatment duration complicates the interpretation of interventional data and limits reproducibility.

Future research should prioritize large-scale longitudinal cohorts and randomized controlled trials integrating multi-omics platforms to elucidate causal pathways linking microbial dynamics to metabolic outcomes. Harmonized analytical pipelines, standardized outcome measures, and inclusion of diverse populations are essential to improve reproducibility and generalizability. The development of predictive models based on microbial and metabolic signatures could facilitate early detection and prevention strategies, while mechanistic studies may uncover novel therapeutic targets within the microbiome–metabolism interface.

In conclusion, understanding the gut microbiota's contribution to pediatric metabolic disease represents a transformative opportunity for precision medicine. Incorporating microbiota assessment into pediatric healthcare may enable earlier, more individualized, and evidence-based interventions aimed at mitigating the global burden of obesity and its metabolic sequelae. Collaboration among clinicians, microbiologists, nutritionists, and data scientists will be fundamental to translating this rapidly evolving knowledge into effective preventive and therapeutic strategies for children worldwide.

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