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THE GUT-BRAIN-MICROBIOME AXIS IN CHILDHOOD OBESITY: MECHANISMS AND CLINICAL IMPLICATIONS

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Abstract

Background: Childhood obesity has become a global health crisis affecting 188 million children aged 5–19 years worldwide, with serious metabolic complications. The gut–brain–microbiome axis has emerged as a key mechanistic link and therapeutic target for obesity in children.
Methods: A narrative literature review was conducted using PubMed, Scopus, and Google Scholar and included studies published up to December 2025. Search terms, used in various combinations, included “childhood obesity,” “gut microbiota,” “gut–brain axis,” “targeted interventions,” “probiotic,” and “prebiotic”.
Results: Childhood obesity is associated with early-life gut dysbiosis characterized by reduced diversity, higher Firmicutes/Bacteroidetes ratios, and shifts in key taxa, driven by prenatal, postnatal, and lifestyle factors. This dysbiotic microbiota enhances energy harvest, promotes low-grade inflammation and barrier dysfunction, and disrupts gut–brain axis signaling via altered short-chain fatty acids, neurotransmitter, and gut hormone profiles, thereby impairing appetite regulation and favoring positive energy balance. Emerging evidence indicates that targeting the gut microbiota–brain axis with probiotics, prebiotics, synbiotics, and fecal microbiota transplantation may improve metabolic outcomes and body composition in children with obesity.
Conclusion: Gut microbiota dysbiosis contributes to childhood obesity via altered metabolism, inflammation, and gut–brain axis–mediated appetite regulation.

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Keywords: childhood obesity, gut microbiota, gut–brain axis, probiotic

Introduction

Childhood obesity is currently a global health crisis, with the prevalence rising significantly in the past few decades. Globally in 2025, over 35 million children under age 5 were overweight, and for the first time in history, obesity has surpassed underweight as the most common form of malnutrition among school-age children and adolescents worldwide, affecting 188 million (one in 10) children aged 5-19 years.[1] From 2000 to 2022, the global prevalence of childhood overweight and obesity increased from 5.4% to 5.7%, with Asia harboring over 18 million affected children (48%) and Africa more than 10 million (27%).[2] Childhood obesity is associated with serious metabolic complications, including type 2 diabetes, nonalcoholic fatty liver disease, hypertension, dyslipidemia, and increased cardiovascular risk later in life.[3, 4]

The gut-brain axis (GBA) has emerged as a key mechanistic link between gut microbiota and metabolic regulation in childhood obesity. This bidirectional network integrates neural, endocrine, and immune signaling pathways that influence appetite control, energy homeostasis, and obesity-related behaviors.[5] Alterations in gut microbial composition early in life have been consistently associated with weight status, with obese children showing reduced microbial diversity and impaired gut stability,[6] highlighting gut microbiota as a promising target for therapeutic intervention.[7, 8]

This review synthesizes current evidence on the gut–brain–microbiome axis in childhood obesity, summarizing signaling mechanisms and bacterial strains linked to metabolic risk or protection, and discussing emerging emerging microbiota-targeted therapeutic strategies.

Method

A literature search was performed using major databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant studies published up to December 2025. Reference lists of key articles and existing systematic reviews were also manually reviewed to identify additional studies not captured in the initial search.

Search terms, used in various combinations, included “childhood obesity,” “gut microbiota,” “gut–brain axis,” “targeted interventions,” “probiotic,” and “prebiotic.” Eligible studies were peer-reviewed articles published in English that involved children and adolescents aged 0–18 years and examined either the relationship between gut microbiota and obesity or microbiota-targeted interventions affecting metabolic or weight-related outcomes. Included study designs comprised original research, clinical trials, systematic reviews, and meta-analyses. Non-English publications, non-peer-reviewed articles, case reports, and unpublished studies were excluded. Potential publication bias related to the exclusion of unpublished data should be considered when interpreting the findings.

Results and Discussion

Gut microbiota profile in childhood obesity: A focus on the gut-brain axis

The early-life gut microbiome is shaped by multiple interconnected factors during critical developmental windows, with perturbations during this period having lasting consequences for metabolic health.[9, 10] Maternal and prenatal factors such as maternal diet, obesity, smoking, and antibiotic exposure during pregnancy significantly influence the initial composition and development of the infant gut microbiota.[11] Postnatal determinants

including mode of delivery, type of feeding (breastfeeding versus formula feeding), and the specific composition of breast milk or formula further shape early intestinal colonization and microbial diversity.[12-14]

Children with obesity commonly exhibit a higher *Firmicutes*/*Bacteroidetes* ratio compared to children of healthy weight.[15-17] This microbial imbalance contributes to inflammatory processes, enhanced energy extraction, adipose tissue accumulation, and compromised intestinal barrier function.[18] However, it is important to note that this marker remains controversial due to heterogeneity across studies.[15-17] Multiple determinants shape gut microbiome composition, including diet, age, ethnicity, antibiotic exposure, metabolic profiles, and environmental influences.[19] The metabolic activities of specific bacterial taxa also depend heavily on individual characteristics including age, dietary patterns, and concurrent health conditions.[20]

Several studies have investigated the gut microbiota profile in children with obesity. A systematic review by Nóbrega et al[21] analyzed 70 studies (23 clinical trials and 47 cross-sectional studies) and found that certain bacterial genera consistently emerged as being associated with obesity-related traits in pediatric populations. Specifically, *Akkermansia, Bifidobacterium, Blautia*, and *Faecalibacterium* were frequently identified as key players in obesity development, though the exact nature of their associations varied across studies.[21] A systematic review by Morgado et al also highlighted that gut microbiome profiles in obese children typically show compromised bacterial diversity.[22] Overweight and obese children showed reduced alpha diversity Specifically, obese children had significantly lower species richness and alpha diversity indices (e.g., Chao1, Shannon, observed OTUs) in several studies,

indicating a less diverse and potentially less stable gut microbial community.[22]

The gut-brain axis represents a bidirectional communication network linking the gastrointestinal tract with the central nervous system, with gut microbiota serving as a critical regulatory component.[5] This intricate system operates through multiple interconnected pathways: neural signaling via the enteric nervous system and vagus nerve, endocrine modulation through the hypothalamic-pituitary-adrenal (HPA) axis, and immunological mechanisms involving inflammatory mediators.[5, 23]

Gut microbiota exert profound influence on brain function and behavior by producing or stimulating the synthesis of neurotransmitters, including serotonin, dopamine, gamma-aminobutyric acid (GABA), and tryptophan metabolites. These neuroactive compounds can impact hypothalamic circuits governing appetite regulation, energy homeostasis, and feeding behavior.[24] For instance, GABA produced by *Levilactobacillus brevis* and *Bifidobacterium dentium* can cross the blood-brain barrier and directly modulate neuronal activity.[25, 26]

In the context of childhood obesity, microbial dysbiosis disrupts the normal functioning of the gut-brain axis through several mechanisms. Reduced production of short-chain fatty acids (SCFAs), particularly by depleted *Bifidobacteri-um* and *Bacteroides* species, compromises both gut barrier integrity and blood-brain barrier function.[27] This facilitates translocation of bacterial lipopolysaccharide, triggering systemic low-grade inflammation and neuroinflammation that can impair hypothalamic circuits controlling satiety and energy expenditure.[28] SCFAs act on specific G protein-coupled receptors on enteroendocrine cells that initiate hormonal cascades involving direct Glucagon-Like Peptide-1 (GLP-1) and Peptide YY (PYY) induction plus indirect ghrelin regulation, which collectively mediate eating behavior

through satiety signaling, hunger perception, and appetite control pathways.[29]

The vagus nerve serves as a major conduit for gut-to-brain signaling, conveying information about nutrient availability, microbial metabolites, and gut hormones to the nucleus tractus solitarius in the brainstem.[23] High-fat diet consumption and obesity-associated microbiota alterations can diminish vagal afferent sensitivity, potentially contributing to dysregulated appetite control and overconsumption. Furthermore, disrupted gut microbiota composition has been linked to alterations in glucagon-like peptide-1 secretion, a critical gut hormone that regulates satiety and glucose metabolism through both peripheral and central mechanisms.[30]

Emerging evidence suggests that early-life gut microbiota disruptions may have lasting consequences for neurodevelopment and behavior in children. Dysbiotic microbial communities have been associated with various neurodevelopmental and behavioral disorders, including autism spectrum disorder, attention deficit hyperactivity disorder, and anxiety. In the context of obesity, these alterations may contribute not only to metabolic dysfunction but also to mood disturbances and cognitive impairments that further perpetuate unhealthy eating patterns.[31]

The role of gut microbiota in childhood obesity: A focus on the gut-brain axis

Gut Microbiota: Energy Harvest and Nutrient Handling

Classical animal studies showed that microbiota from obese donors confer an “obese phenotype” to germ-free recipients, with increased adiposity despite identical caloric intake.[32] Turnbaugh et al demonstrated that obese ob/ob mice harbor a higher proportion of genes for polysaccharide degradation and transport, with greater capacity to metabolize starch, sucrose

and other indigestible carbohydrates into SCFAs.[32, 33] In children, multiple studies report higher *Firmicutes/Bacteroidetes* ratios or enrichment of specific *Firmicutes* (e.g. *Lachnospiraceae*, *Ruminococcaceae*) in obesity, taxa associated with enhanced fermentation and caloric salvage.[15, 34, 35]

SCFAs (acetate, propionate, butyrate) provide up to 10% of daily energy, but also act as signaling molecules via G-protein–coupled receptors (GPR41/43) on enteroendocrine and immune cells.[36, 37] In pediatric obesity, altered SCFA profiles have been linked to increased hepatic de novo lipogenesis, enhanced adipogenesis, and impaired insulin sensitivity.[38] Acetate may stimulate parasympathetic activity and ghrelin secretion, whereas propionate and butyrate can modulate intestinal gluconeogenesis and satiety hormone release, indicating that a shift in SCFA balance may favor positive energy balance.[39, 40] Furthermore, gut microbes influence metabolic pathways by modulating bile acid metabolism, affecting lipid absorption and glucose homeostasis, and by regulating the expression of genes involved in fatty acid oxidation and lipogenesis.[41]

Gut Microbiota: Low-Grade Inflammation and Barrier Dysfunction

Pediatric obesity is characterized by chronic low-grade inflammation driven largely by gut dysbiosis, compromising tight junction integrity and increasing intestinal permeability.[1,2,15] The resulting "leaky gut" allows translocation of lipopolysaccharide (LPS) and other microbial molecular patterns into the circulation, producing metabolic endotoxemia.[42] LPS activates Toll-Like Receptor 4 (TLR4) on adipocytes, macrophages, and hepatocytes, triggering NF-κB signaling and secretion of pro-inflammatory cytokines that impair insulin signaling and promote adipose tissue expansion.[42] In pediatric, elevated LPS and LPS-binding protein

correlate with BMI, insulin resistance, and metabolic dysfunction markers, while NLRP3 inflammasome activation by microbial products further amplifies IL-1β and IL-18 production, linking gut dysbiosis to systemic metabolic inflammation.[43-45]

Gut Microbiota: Interaction With the Gut–Brain Axis

Microbial metabolites (SCFAs, bile acids, tryptophan catabolites), immune mediators, and vagal afferent signaling converge on hypothalamic and brainstem nuclei that control appetite and energy expenditure.[5] Dysbiosis can blunt anorexigenic signals (e.g. GLP-1, PYY) and modify orexigenic pathways (e.g. ghrelin), altering central energy-balance set points.[23, 46] In children, imaging and hormonal studies suggest that obese individuals exhibit altered hypothalamic responses to nutrient and hormonal cues, and the microbiota is increasingly recognized as a key upstream modulator of these changes.[5, 46]

The Mechanism of the Gut-Brain Axis on Appetite Regulation

In childhood obesity, dysbiosis perturbs multiple gut-brain axis components that regulate appetite and feeding behavior. Enteroendocrine cells in the gut lining detect SCFAs produced by the gut microbiota through activation of G protein–coupled receptors GPR41 and GPR43. In response, these cells release satiety hormones including GLP-1, PYY, and cholecystokinin, which enter the circulation and act on neurons in the arcuate nucleus of the hypothalamus. There, these hormones stimulate anorexigenic POMC/CART neurons that suppress appetite while simultaneously inhibiting orexigenic NPY/AgRP neurons that promote hunger, thereby shifting the balance toward reduced hunger and increased satiety to regulate energy intake and overall energy balance.[5] However, in obese children, dysbiosis attenuates GLP-1 and PYY responses while microbial-driven inflammation induces central leptin and

insulin resistance, biasing the system toward increased orexigenic drive and elevated body weight set points.[5] The vagus nerve serves as the primary neural conduit, transmitting gut signals to the nucleus tractus solitarius and reward centers; experimental evidence demonstrates that dysbiotic microbiota can alter vagal activity, dopamine signaling, and appetitive behavior even when diet is controlled, while chronic inflammation may desensitize vagal afferents and blunt satiety signaling in obesity.[5]

Dysbiosis profoundly affects neurotransmitter systems governing appetite, mood, and impulse control. Approximately 90–95% of the body's serotonin is synthesized in the gastrointestinal tract under strong regulation by the gut microbiota, while dysbiosis can redirect tryptophan metabolism toward the kynurenine pathway via immune activation, increasing neuroactive kynurenines that influence prefrontal and limbic circuits involved in mood, stress responsivity, and reward-related eating behavior in obese children.[47, 48] Similarly, GABA-producing bacteria such as *Lactobaci-llus* and *Bifidobacterium* can modulate central GABAergic signaling via vagus-dependent gut–brain communication, and dysbiosis-related changes in microbial GABA production and GABA receptor expression are proposed to weaken prefrontal inhibitory control over hedonic eating circuits, thereby increasing vulnerability to overeating and loss-of-control eating, particularly in stressful contexts.[49, 50] The mesocorticolimbic dopamine system (ventral tegmental area, nucleus accumbens, prefrontal cortex) controls food reward and motivation. In parallel, gut microbiota can modify dopaminergic and opioid receptor signaling in these regions, while dysbiosis-driven neuroinflammation changes dopamine availability and reward sensitivity, making hedonic circuits more responsive to palatable foods and weakening satiety-based control of eating.[51-

[53] Neuroimaging studies in obese youth confirm heightened striatal activation to food cues and patterns consistent with "food addiction-like" behaviors.[54, 55] Collectively, this integrated gut-brain axis dysfunction provides a mechanistic framework explaining how gut microbiota alterations foster emotional eating, impaired satiety, and reward-driven overconsumption in childhood obesity.

Therapeutic strategies targeting gut microbiota in childhood obesity

Interventions aimed at modulating the gut microbiota have shown potential as complementary approaches in the treatment of childhood obesity.[56] Table 1 summarizes therapeutic strategies that may modulate gut microbiota dysbiosis and improve metabolic profile in childhood obesity.

Probiotics, prebiotics, and synbiotics show potential in modulating inflammatory pathways and improving metabolic profiles in obese children. Probiotics consist of living microbes that provide health advantages when consumed in sufficient quantities, while prebiotics comprise indigestible dietary fibers that selectively stimulate the proliferation and metabolic activity of health-promoting intestinal bacteria, especially *Bifidobacterium* and *Lactobacillus* species.[57] Synbiotics represent strategic combinations of both components designed to work together for amplified health benefits.[58]

Randomized clinical trials have demonstrated that probiotic administration for 12 weeks in obese children significantly improved lipid metabolism potentially through increased *Lactobacillus* spp. and *B. animalis*,[59] while probiotic-prebiotic mixtures decreased body fat and increased fecal *Bifidobacterium* levels.[60-62] The BIFI-OBESE trial showed that an 8-week supplementation with *Bifidobacterium breve* BR03 and B632, alongside a calorie-restricted

diet, modestly enhanced insulin sensitivity and slightly favored weight-related improvements in children and adolescents with obesity and insulin resistance.[63]

Prebiotic supplementation is increasingly being adopted as a routine treatment for children due to its benefits in modulating gut microbiome composition.[64] A recent study demonstrated that inulin supplementation exhibits increased muscle mass via gut microbiota modulation and anti-inflammatory effects, with *Bifidobac-terium* metabolites rich in SCFAs downregulating key inflammatory gene expression including TNF-α and IL-6.[65] The effect of inulin also extend beyond inflammatory markers to modulating appetite-regulating hormones and improving eating behaviors.[66]

Table 1. Summary of therapeutic interventions of the gut-brain axis via gut microbiota

Therapeutic strategy	Main approach	Proposed effects on gut microbiota	Potential metabolic benefits	Ref.
Probiotics	Single (*Lactobacillus* spp.) and multi-strain probiotics (*Bifidobacterium breve* BR03 and B632; multi-species combinations)	Increases beneficial bacteria (*Bifidobacterium*, *Lactobacillus*);[59] reduces pathogenic bacteria (*E. coli*, *Enterobacteriaceae*);[63] improves microbial diversity; reshapes obesity-related gut dysbiosis	Reduces BMI z-score, waist circumference; lowers serum total cholesterol, LDL-C, TNF-α, leptin; increases adiponectin and HDL-C;[59] improves fasting glucose and insulin sensitivity; improves working memory and reduces neuroinflammatory markers[67]	59, 63, 67, 68
Prebiotics	Inulin; oligofructose, high-fiber supplements	Increases beneficial and SCFA-producing bacteria; enhances gut microbial diversity	Improves body composition (reduces fat mass index and trunk fat mass index); increases fat-free mass; lowers IL-6 and triglycerides; reduces ghrelin levels; improves glucose regulation; modulates appetite and improves eating behaviours (when	65, 66, 69, 70

Therapeutic strategy	Main approach	Proposed effects on gut microbiota	Potential metabolic benefits	Ref.
			combined with dietary and lifestyle advice)	
Synbiotics	Multispecies synbiotics combining probiotics (*Lacticaseibacillus rhamnosus*, *L. acidophilus*, *B. longum*, *B. bifidum*) with prebiotics (fructooligosaccha-rides)	Combines probiotic and prebiotic effects; promotes probiotic survival in GI tract; increases *Bifidobacteriu m*levels; reduces dysbiosis	Significant decrease in BMI z-score, body weight, waist circumference, waist-to-height ratio; improves glucose and lipid parameters; reduces systolic blood pressure	60-62
Fecal microbiota transplan-tation (FMT)	Single-course oral encapsulated FMT from lean donors	Shifts overall gut microbiome composition toward donor profile; increases microbial diversity; sustained changes in community composition up to 12-26 weeks	Reduces android-to-gynoid fat ratio (abdominal adiposity); resolution of metabolic syndrome in participants with baseline condition; transient improvements in insulin sensitivity at 6 weeks; sustained metabolic benefits at 4-year follow-up; no significant effect on BMI or total body weight	71, 72

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TNF-α, tumor necrosis factor alpha; SCFA, short-chain fatty acids; IL-6, interleukin-6; GI tract, gastrointestinal tract

Fecal microbiota transplantation (FMT) represents a novel therapeutic approach for childhood obesity that involves transferring gut microbiota from lean donors to recipients with obesity to reshape the gut microbial community toward a healthier metabolic profile. The landmark "Gut Bugs" randomized controlled trial enrolled 87 adolescents with obesity and evaluated single-course oral encapsulated FMT from lean donors. While FMT did not lead to significant reductions in body mass index or total body weight at 6 weeks in the initial trial, it produced a clinically meaningful reduction in android-to-gynoid fat ratio (A/G ratio), a measure of abdominal adiposity, which was sustained for at least 26 weeks. This effect was particularly pronounced in female adolescents, suggesting potential sex-based differences in

response to FMT. The 4-year follow-up study revealed sustained and even enhanced metabolic benefits, with FMT recipients demonstrating significantly smaller waist circumference (-10.0 cm, *p* = 0.026), lower total body fat (-4.8%, p = 0.024), reduced metabolic syndrome severity score, and markedly decreased systemic inflammation as measured by high-sensitivity C-reactive protein (-68% mg/dL, p = 0.002) compared to placebo recipients. [71, 72]

Conclusion

The gut microbiota is increasingly recognized as a contributor to fat accumulation, weight gain, and insulin resistance. Dysbiosis may promote childhood obesity through disrupted energy metabolism, inflammation, endocrine alterations, and impaired gut–brain axis signaling that regulates appetite and satiety. The gut–brain axis operates via bidirectional neural, immune, and endocrine pathways. Microbiota-targeted interventions, including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation, show therapeutic potential for obesity; however, further well-designed studies are needed to establish their safety, efficacy, and clinical applicability.

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Conflict of Interest

There is no conflict interest of this publication.

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