Review

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Influence of gut microbiota on the pediatric endocrine system and associated disorders

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Abstract

The microbiota, a complex assembly of microorganisms residing in various body systems, including the gastrointestinal tract, plays a crucial role in influencing various physiological processes in the human body. The dynamic nature of gut microbiota is especially pronounced in children and is influenced by factors like breastfeeding and antibiotic use. Dysbiosis, characterized by alterations in microbiota composition or function, is associated with several pediatric endocrine disorders, such as precocious puberty, polycystic ovarian syndrome, and diabetes mellitus. This review focuses on the intricate relationship between gut microbiota and the pediatric endocrine system. The aim of this narrative review is to critically examine the existing literature to elucidate the impact of gut microbiota on the pediatric endocrine system and associated disorders. Additionally, potential interventions, such as probiotics and current gaps in knowledge, will be discussed. Despite emerging treatments like probiotics, further research is needed to understand and validate their effectiveness in treating pediatric endocrine disorders associated with dysbiosis.

Keywords: dysbiosis, endocrine, gut microbiota, obesity, prebiotics, probiotics, synbiotics

Introduction

The microbiota is an assortment of microbial species inhabiting a community, while the microbiome encompasses the collective genetic material, or metagenome, contributed by the entire community[1]. In general, the microbiota exhibits a 10-fold greater abundance than the somatic and germ line cells of the human body, while the microbiome exceeds the size of the human genome by an estimated 150 times[2,3]. As environmental factors and host attributes, such as sex and age, act as crucial determinants influencing the composition of gut microbiota and the metabolites they generate, everyone possesses a distinct microbiome composition. The human gut comprises 150–170 predominant bacterial species, which derive benefits from the warm, nutrient-rich environment of the gut and perform various metabolic, structural, and protective functions within the body[1,2]. The human gut contains over a trillion microbes, including bacteria, viruses, and fungi. These microbes interact in complex ways within the gut environment. They produce various metabolites, which are substances that can significantly affect the host's physiology and bodily functions. The human microbiota is the focus of one of the most dynamic research fields

HIGHLIGHTS

- The gut microbiota significantly influences child health and may contribute to various diseases, including obesity, diabetes mellitus, and polycystic ovary syndrome (PCOS).
- Changes in gut microbiota begin before birth, with several maternal factors – such as smoking and antibiotic use – impacting the infant's gut microbiome.
- An infant's early life experiences contribute to gut microbiota variability, as the type of nutrition (breastfeeding versus formula feeding) and antibiotic exposure can lead to distinct microbial profiles.
- Some environmental factors such as air pollutants are not well studied yet in the context of gut microbiota in the pediatric population.
- Understanding the factors that can alter a child's gut microbiota can help health care professionals manage and mitigate these known influences.
- While existing studies on prebiotics primarily examine diabetes and obesity in children concerning gut microbiota, there is a notable lack of research focusing on PCOS in adolescents, indicating a need for further investigation in this area.
- Interventions like prebiotics, probiotics, and synbiotics have been shown to improve gut microbiota; however, their optimal doses and potential side effects in children require further exploration.

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of our time, and most efforts are directed at the gastrointestinal tract (GIT), which harbors most of our microbes[4]. The establishment of microbial communities in the GIT begins at birth, with maternal vaginal, gut, and skin microbiota serving as significant sources of bacterial colonization[3]. The development of the gut microbiota is most dynamic in early life, with notable shifts in composition continuing until the child reaches 2–3 years of age[5-7]. However, achieving an adult-level diversity in gut microbial communities may extend beyond 5 years of age[5]. Multiple factors, including the mode of delivery, gestational age, birth weight, early life antibiotic usage, the presence of pets in the household, and dietary habits, have been proposed as influential determinants shaping the diversity and colonization patterns of the gut microbiota in early life[8,9]. Differences in microbiota composition between males and females become evident only postpuberty and are linked with variations in their respective sex hormone levels[10].

Over the preceding decade, increased attention has been directed toward the gut microbiota due to a substantial shift in our conceptual framework; the microbiota is now recognized not as a passive aggregate of microbes residing in the gut but as an integral component of the body, which contributes essential functions to the host[11]. These functions encompass various endocrine, metabolic, and immunological activities within the human body. A detailed understanding of the gut microbiota has led to targeted therapeutic advancements with notable health benefits. For instance, prebiotics enhance gut health by promoting beneficial bacterial growth, while probiotics restore microbiota balance and aid in managing conditions like irritable bowel syndrome and inflammatory bowel disease (IBD). Pharmaceuticals targeting the microbiome, such as specific antibiotics and novel microbiome-modulating drugs, have improved treatments for infections and metabolic disorders. Additionally, fecal microbiome transplantation (FMT) has proven effective for recurrent *Clostridium difficile* infections and is being explored for other conditions. These strategies highlight how microbiota insights have translated into improved health outcomes through precise microbiome modulation[12].

The gut microbiome has been implicated in various physiological and pathological facets of the endocrine system, primarily through its modulation of entero-endocrine secretions, hypothalamic–pituitary–adrenal (HPA) axis, gut–brain axis, gut–kidney axis, gut–sex hormone axis, gut microbiota–bile acid–vitamin D axis, and bone growth[13,14]. Recently, a growing body of evidence also indicates its potential involvement in various conditions associated with the endocrine system, such as thyroid cancer development, diabetes, precocious puberty, polycystic ovarian syndrome (PCOS), and obesity[15-21]. Furthermore, dysbiosis, characterized by an imbalance in gut microbial communities, can disrupt host health and contribute to various disease states, including endocrine system disorders. The serum levels of metabolites produced by gut microbiota can influence the development of endocrine disorders[22]. The advent of pharmacotherapies focused on modulating host–microbiota interactions introduces a new dimension for managing endocrine diseases and emphasizes the significance of this reciprocal relationship. The present study aims to comprehensively review the existing scientific literature and elucidate the effects of microbiota on the pathophysiology of various physiological processes through their modulation of the endocrine system.

Method

We conducted a literature search using search terms and Medical Subject Headings (MeSH) along with Boolean operators ("AND," "OR," and "NOT") and appropriate filters on PubMed from the year 1998 to 2023. The search terms include gut/gastrointestinal, microbiota/microbiome, probiotics, endocrine system, hormone, and pediatric/child. The search strategy was adapted for EMBASE database and Google Scholar to retrieve more results, and references from selected articles were screened for inclusion. In total, we identified 762 original articles through this search process. Following a thorough screening of titles and abstracts based on predefined inclusion and exclusion criteria, 54 articles were selected for detailed review. Authors screened the articles based on title and abstract, and those matching the inclusion and exclusion criteria were selected for the review. We included articles that were published in English or translated into English, were conducted with pediatric participants (age <18 years), and explored the interplay between gut microbiota and endocrinal system function and/or pathology. All types of articles focusing on skin or respiratory microbiome and those with only adult populations were excluded. The following article types were also excluded: editorials, commentaries, special topics, letters to the editor, opinion pieces, and personal correspondence.

Factor influencing gut microbiota in pediatric populations

It is crucial to have a better understanding of the intricate interplay between the microbial community and the factors that influence the diversity and composition of gut microbiota in pediatric groups (Fig. 1). This would enable us to unravel its implications on the health outcomes of children.

Breastfeeding

Diet has a critical role in influencing the composition of the gut microbiota. In pediatric populations, breastfeeding, the introduction of solid foods, and a range of macro and micronutrients all play a pivotal role in the functionality of the gut microbiota[23,24]. Breast milk is enriched with various nutritional elements, including complex microbiota, oligosaccharides, and proteins that collectively regulate the colonization of the infant's gut with microorganisms. This was presented in a study that showed there was a positive correlation observed between the populations of *Staphylococcus, Enterococcus, Bacteroides, Lactobacillus*, and *Rothia* in maternal breast milk and the infant's GIT[25]. Notably, proteins, sialylated oligosaccharides, and prebiotics from breast milk traverse the GIT partially undigested, carefully sculpting the gut microbiome[26]. Two primary sialylated oligosaccharides in breastmilk, 3′-sialyllactose and 6′-sialyllactose, play an important role in shaping the infant's gut microbiome. Another study found that the four main proteins in breast milk – casein, lactalbumin, osteopontin (OPN), and secretory immunoglobulin A – were positively correlated with the flourishing intestinal microorganisms population[27]. Among these proteins, OPN, a glycosylated bioactive phosphoprotein, demonstrated an abundance of *P. distasonis*, which is regarded as a "second-generation probiotic" and is one of the fundamental microorganisms that maintain intestinal health integrity[28,29].

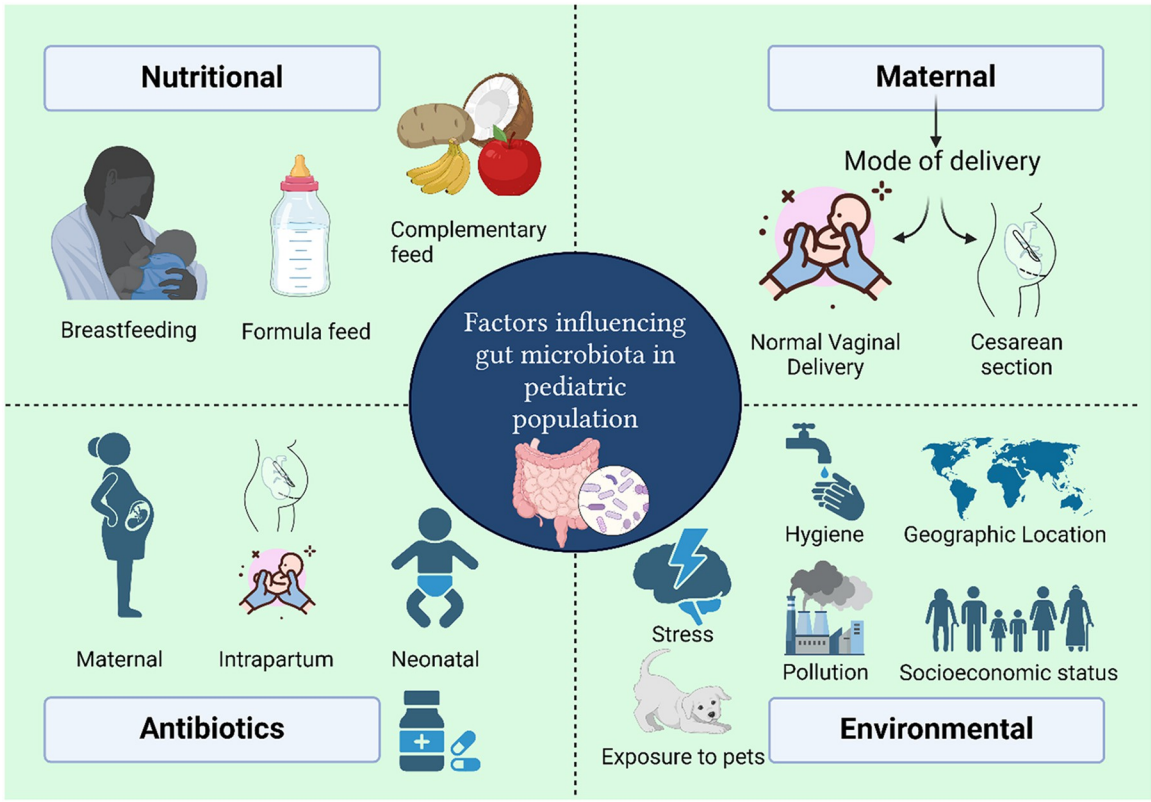

Figure 1. Figure illustrates various internal and external factors that affect the composition and function of gut microbiota in children (created with biorender.com).

α- and β-diversity are two parameters used to assess the diversity of the microbiome. α-diversity refers to the variety of microbial species present within an individual. On the other hand, β-diversity refers to the variation in microbial composition between different individuals. A study has shown that as opposed to formula-fed infants, breastfed infants exhibit an altered β-diversity (diversity between communities) and diminished α-diversity (diversity within the community) of the gut bacterial community in their initial year of life[30]. Lower α-diversity (within an individual) in breastfed infants may suggest a more specialized microbiome, which can be beneficial early in life as it is dominated by protective, health-promoting bacteria like *Bifidobacteria*. In contrast, formula-fed infants often have higher α-diversity, which could expose them to a broader range of microbes, some of which may be harmful. Whereas altered β-diversity (between individuals) in breastfed infants, with more uniform microbial communities, may contribute to a more consistent immune response and gut health. This may reduce the risk of infections, allergies, and chronic conditions like obesity and autoimmune diseases later in life, highlighting the protective role of breastfeeding on infant gut health development[31-33].

Moreover, higher levels of certain beneficial bacteria, primarily *Bifidobacteria*, and *Bacteroidetes*, have been associated with breastfeeding[26]. Furthermore, studies have shown that breast milk consumption results in a substantial reduction in a newborn's susceptibility to necrotizing enterocolitis (NEC), with gut microbiota playing an important role in its pathophysiology. The potential risk reduction can be up to 10-fold compared to infants who are fed formula milk[33].

Pediatric gut ecology is known to change when solid food regimes are introduced. According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), the ideal age for weaning of breast milk or formula feeding should be no sooner than 17 weeks of age and not more than 26 weeks[34]. In a study involving 605 children, infants transitioning from exclusive breastfeeding to solid foods were monitored for 4 weeks. Results revealed that following weaning, *Bifidobacterium*, the *Clostridium coccoides* group, and *Bacteroides* became more prominent in the altered gut microbiota. Notably, variations in the overall microbiome were observed between formula-fed and breastfed groups, with breastfed infants exhibiting lower levels of *Bacteroides* compared to *Bifidobacteria* before the introduction of solid foods[35]. A case study explored the impact of introducing solid foods like peas to an exclusively breastfed infant, noting a significant shift in the colonic microbiome between days 170 and 290[35].

Maternal factors that impact the infant's gut microbiota

Mode of delivery

Some maternal factors considerably impact the gut microbiota composition of an infant. The mode of delivery has several effects on the primary colonization and subsequent growth of the gut microbiota in infants. Vaginally delivered infants exhibit initial colonization by the microbiota of the birth canal, predominantly composed of *lactobacillus* and *Bacteroides* species, instituting a resilient gut microbiota[36]. Previous studies have

suggested that cesarean section (C-section) delivered infants display an altered microbial community, often characterized by a lower diversity and decreased abundance of beneficial bacteria, potentially impacting immune development and metabolic pathways[37]. The microbiota of infants delivered via C-section is established by acquiring microbes from the hospital atmosphere, the hospital staff, wards, and other patients[38]. It is commonly acknowledged that babies delivered via C-section lack exposure to the mother's vaginal and fecal microbiota, despite some theories suggesting that colonization of the baby's gut arises due to the amniotic fluid ingestion in the utero[39].

In a study conducted in the Netherlands with 1000 participants, the results revealed that infants delivered via C-section exhibited significantly lower levels of *Bifidobacteria* and *Bacteroides fragilis*, with a concurrent 100-fold higher concentration of *C. difficile* in their colonic microbiota[40]. Another study focused on 3-day-old infants highlighted the substantial impact of delivery mode on the infant microbiota. Specifically, vaginally delivered infants showed elevated levels of *Bifidobacteria* and lower levels of *C. difficile*[41]. However, few studies evaluated the possibility of a confounding variable of antibiotic use which is imminent in C-section infants. Subsequently, although delivery mode may influence changes in the microbiome in infancy, it is frequently complicated by the mother's exposure to antibiotics during labor and delivery[42].

Use of antibiotics

The deleterious effects of antibiotics can be categorized as the ones arising from maternal exposure to antibiotics and the introduction of antibiotics into a neonate's treatment regime for any postnatal condition that may ensue.

The use of intrapartum antibiotic prophylaxis (IAP) antibiotics. Maternal antibiotics can enter the fetus's bloodstream through the umbilical cord, and they stay there for up to 10 hours post-infusion. Maternal antibiotics can also change the microbiome of the mother's gut and vagina, which can affect newborn immunity and transmission of microbes during labor via exposure to the microbial community of the birth canal[43]. Approximately 40% of women who undergo elective and emergency C-sections are administered IAP. Additionally, IAP is frequently prescribed to GBS-colonized (Group B Streptococcus (GBS), *Streptococcus agalactiae*) women as well[44]. A multicenter study revealed significant differences in the composition of neonate intestinal microbiota, primarily influenced by factors such as the administration of intrapartum antibiotics like penicillin and cefazolin. Notably, intrapartum antibiotic use was associated with decreased populations of *Bifidobacterium longum, Parabacteroides distasonis, Bacteroides vulgatus*, and *Escherichia coli* in the infant stool microbiome[42]. A prospective cohort study investigated the impact of intrapartum antibiotic administration on infant gut microbiota and revealed that infants exposed to antibiotics exhibited lower α-diversity, decreased populations of *Actinobacteria*, specifically *Bifidobacteriaceae*, and a notable increase in the abundance of *Proteobacteria*[45]. Moreover, another such study found an increased abundance of beta-lactamase-encoding genes in the gut microbiota of antibiotic-exposed infants, which promotes antibiotic resistance. The gut microbiota that encodes for beta-lactamase genes primarily includes various species of bacteria, particularly those within the *Enterobacteriaceae* family, such as *E. coli* and *Klebsiella pneumoniae*. These bacteria can acquire and express beta-lactamase genes, which provide resistance to beta-lactam antibiotics, including penicillins and cephalosporins. Additionally, other gut commensals, such as certain strains of *Bacteroides* and *Enterococcus*, may also harbor these resistance genes, contributing to the overall antibiotic resistance landscape in the gut microbiome[46].

The use of antibiotics in pediatric population. Many studies have indicated that antibiotic exposure during the early years of life is a major perturbing factor in causing dysbiosis of the gut microbial communities, which can have both immediate and long-term repercussions on the well-being of the growing neonate[47]. The population of *Lactobacillus* and *Bifidobacterium* colonies substantially decreases when antibiotics are administered for managing newborn illnesses, which renders the host defenseless to colonization of unwanted pathogenic microorganisms. This exerts a negative impact on the gut microbiota due to the role of these bacterial species in enhancing gut homeostasis[48].

A study of 26 infants treated with cephalexin for the first 4 postnatal days showed a substantial and prolonged decrease in the proportion of *Bifidobacteria* in their microbiome, persisting for at least 1 month after the initiation of treatment[48]. *Bifidobacteria* plays a critical role in the growth and maintenance of healthy gut microbiota. They are considered the most significant agents for the catabolism of human milk oligosaccharides to ensure their digestion in infants[49]. Moreover, two studies indicated that a reduction in *Bifidibacter* titers in the gut microbiome increased susceptibility to atopic conditions, such as asthma, in infants[50,51]. A study by Fouhy *et al* (2012) demonstrated that infants treated with broad-spectrum antibiotics exhibited reduced levels of *Bifidobacteria* and increased levels of potentially harmful bacteria like *Enterobacteriaceae*[52].

A study was conducted that highlighted the adverse effects of the use of parenteral antibiotics, such as ampicillin and gentamicin, on the gut microbiota. The use of antibiotics during the early years elicited short-term repercussions like gastritis, diarrhea, glossitis, and gastrointestinal discomfort[53]. The proliferation of antibiotic-resistant bacteria in the gut poses significant risks to health, complicating the treatment of various diseases later in life. This resistance can undermine the effectiveness of antibiotics, leading to more severe infections and limited treatment options.

Another study was conducted by Tanaka *et al* (2009) which revealed that the use of antibiotics in the early postnatal period could disrupt the natural acquisition of *Bifidobacteria*, impacting the infant's gut microbiome composition long-term[54]. In a study, the effects of clavulanic acid and amoxicillin for 13 days, followed by a second antibiotic course (trimethoprim and sulfamethoxazole) for 12 days, were assessed on neonates. The results showed notable instability in colonic microbiota, particularly an increase in *E. coli*, and a significant reduction in gut *Bifidobacteria* populations in infants exposed to the antibiotic regimen until the age of 1 month[55].

Environmental factors

The effects of the environment on pediatric gut microbiota include a wide range of variables that extend beyond nutrition and medical interventions. These include, but are not limited to,

geographic region, socioeconomic standing, exposure to pets, standards of hygiene, chronic stress, air pollution, and many more[56]. The geographic region has a lasting influence on biodiversity, contributing to the resilience of the gastrointestinal microbial community and the associated fetal well-being[57].

Recent research investigated pediatric gut microbiota alterations with respect to the family's socioeconomic status (SES). The abundance and diversity of microorganisms in the infant gut microbiomes were correlated with familial SES, with the children belonging to a higher SES and more educated parents exhibiting higher latent microbiome factor scores, indicating a potential association between education level and the composition or characteristics of their gut microbiome. The findings of the study showed that individuals belonging to higher SES have lower levels of *Bacteroides* and a greater variety of *Eubacterium, Anaerostipes, Lachnospiraceae*, and *Faecalibacterium*. Notably, SES correlated most strongly with the *Faecalibacterium* species, which is regarded as a crucial indicator of pediatric gastrointestinal health[58]. It has been frequently observed that one of the primary sources of butyrate in the intestine is *Faecalibacterium prausnitzii*. In terms of host health and intestinal physiology, it serves as the primary source of nourishment for colonocytes and offers defense against IBD and colorectal cancer[59]. Another study confirmed the correlation between a greater relative abundance of *Faecalibacterium* and a higher SES, consequently demonstrating that infants with higher SES had an adequately functioning pediatric gut[60].

Moreover, a study evaluating the potential effects of domestic pets on the neonatal gut microbiome found that two primary bacteria, *Ruminococcus* and *Oscillospira*, which have been adversely attributed to a higher-than-normal BMI in childhood and atopy, appeared to be more prevalent among individuals who were subjected to pets[61].

The association between Ambient Air Pollution (AAP) and adults' gut microbial community has been investigated in several epidemiological studies, but this correlation has not been widely studied in the pediatric demographic. A study was conducted that examined the effects of AAP exposure 6 months postnatal and the impact it portrayed on the neonatal's microbial population and diversity of GIT. The concentration of particulate matter, PM2.5 and PM10, and nitrogen dioxide (NO_2) was investigated. Exposure to PM2.5 had a significant positive correlation with *Actinomyces*, whereas exposure to PM10 was positively correlated with *Dialister, Dorea, Acinetobacter*, and *Campylobacter*. Additionally, the pollutant NO_2 exhibited a statistically significant association with the presence *of Actinomyces, Enterococcus, Clostridium*, and *Eubacterium* in the infant gut microbiota[62].

Moreover, a pooled analysis of three prospective study cohorts demonstrated the effects of maternal smoking habits and pediatric gut microbial flora. Neonates born from mothers who were smokers exhibited higher levels of *Bacteroides* and *Staphylococcus*. This, along with other factors, contributed to childhood obesity at 1–3 years of age[63]. Although the complex processes that connect these variables to gut microbiota are still being studied, research indicates that environmental factors may affect the diversity and composition of microorganisms.

Effect of GIT disorders on gut microbiota

The gut microbiome is significantly influenced by GIT diseases, which affect the microbiome through various mechanisms. In the case of noninfectious disorders, the predominant mechanism involves immune-mediated inflammation of the GIT. The specific pathogenesis and triggers of these diseases vary, leading to distinct impacts on the composition and function of the gut microbiome. Celiac disease, which is frequently associated with various endocrine disorders, has been shown in numerous studies to exhibit alterations in the gut microbiome compared to healthy children. Notably, an increased prevalence of *Bacteroides* and *Proteobacteria* species has been observed in patients with celiac disease. However, even a positive HLA-DQ genotype is found to be associated with difference in gut microbiome with relative abundance of *Firmicutes* and *Proteobacteria* and reduced *Bacteroidetes* and *Actinobacteria* compared to normal infants[64,65]. Several studies have revealed a lower level of gut microbiome maturity in children with IBD compared to age-matched healthy controls[66,67]. In children with ulcerative colitis associated with primary sclerosing cholangitis have demonstrated the reduction of commensal microorganisms like *Akkermansia, Bacteroides, Parabacteroides*, etc. and an increase in pathogenic gut microbes like *Streptococcus, Saccharomyces*, and *Debaryomyces*[68]. In necrotizing enterocolitis, due to necrosis of the gut, a wide range of changes in gut microbiome, like a relative decrease in Firmicutes and a relative increase in *Proteobacteria*, have been noted[69]. In a prospective study, an increase in *Enterobacteriaceae* and decrease in *Clostridiales* was noted in food protein induced allergic proctocolitis, which is often an early sign of food allergy in children[70]. Some differences in gut microbiome may be seen even before the onset of symptoms. In a prospective cohort, it was noted that patients with cystic fibrosis have similar diversity of gut microbiome compared to normal children upto 2 years of age, after which the growth of the former plateaus. With progressing age, the microbiota progresses toward the healthy-like compostion except for *Akkermansia*, which decreases with age, and *Blautia*, which increases with age[71]. In children with gastroesophageal reflux disease, the dominant bacteria are found to be *Proteobacteria* and *Bacteroidota* which are seen in close relation with different metabolic pathways particularly involving arachidonic acid, tyrosine, glutathione, and caffeine metabolism[72]. Certain genus-level markers like *Blautia, Anaerostipes, Veillonella, Lachnospira*, and *Haemophilus* have been identified in patients with Henoch–Schönlein purpura with gastrointenstinal involvement[73]. Increase in pathogenic *Proteobacteria* and a decrease in beneficial *Lactobacilli* and *Bifidobacteria* have been noted in functional GIT-like infantile colic and functional constipation[74]. Finally, an abundance of methanogenic gut bacteria has been identified in children with small intestinal bacterial overgrowth syndrome[75]. While these examples are described as effects of GIT disorders, they may play a role in the pathogenesis of the diseases themselves.

In infectious gastrointestinal diseases like acute gastroenteritis, alteration in gut microbiome may be temporary and the composition greatly varies upon the specific infectious agent. For example, specific alterations in gut microbiota have been observed in various gastrointestinal infections. *Proteobacteria* are found to be more abundant in cases of Salmonella-induced acute gastroenteritis[76]. In children infected with *Giardia duodenalis*, an increased bacterial species diversity and a reduced total bacterial count have been noted[77]. In Shigella infections, there is an expansion of species known to promote gastrointestinal health and restore microbiota homeostasis[78]. Rotavirus-induced diarrhea in children has been associated with an increased abundance of the *Actinobacteria*

phylum, as well as *Bifidobacterium, Streptococcus, Enterococcus*, and *Lactobacillus* species. Similarly, diarrhea caused by Norwalk virus is associated with increased Fusobacteria and Cyanobacteria phyla, along with *Enterococcus* and *Streptococcus* species[79]. Finally, significant reductions in the abundance of normal gut microbes have been observed in infections caused by *Helicobacter pylori*[80]. It is important to note that the composition of gut microbiome species varies significantly depending on the site of sampling, whether from the duodenum or the distal small intestine, the latter of which closely resembles colonic microbiota.

Gut microbiota in pediatric endocrinology

The influence of the microbiota extends to organs beyond the gut, affecting disease processes in various systems such as central nervous system and reproductive system[63]. The term "endocrine organ" is used to describe the gut microbiota because it releases bioactive molecules, such as metabolites and signaling compounds, into the bloodstream[63,81,82]. These microbial products can travel to distant organs and influence their function, highlighting the bidirectional communication between the gut and various physiological systems. A summary of studies on the effect of microbiota on the pediatric endocrine system has been mentioned in Table 1.

Effect of gut microbiota on the reproductive system

Gut microbiota is an important regulator of Ca^{2+} levels in the reproductive system[83]. The modulating effect of the microbiota on the calcium salt status either promotes or inhibits the survival and motility status of sperm[85]. Disturbance in the gut microbiota can also alter the balance of hormones involved in ovarian steroidogenesis, potentially influencing ovarian follicle development. Failure in ovarian follicle development can lead to various reproductive challenges, including infertility. This concept underscores the intricate connection of the gut microbiota with various physiological systems, including those related to reproductive health in women[86].

Ruminococcus and *Faecalibacterium* species, affiliated with the *Ruminococcaceae* and *Ruminococcus* families, exert influence over host sex hormone levels and have demonstrated the capacity to impact puberty onset[15,84]. Specifically, their impact on estrogen metabolism, particularly through β-glucuronidase activity, is noteworthy[87]. *Bacteroides* species' β-glucuronidase enzymes can metabolize only estrone, while both estrone and estradiol can be cleaved by *Ruminococcus* and *Faecalibacterium* enzymes. The abundance of *Ruminococcus* exhibits a positive correlation with the estrone–estrogen metabolite ratio in urine, whereas *Bacteroides* spp. show an inverse correlation[82-88]. These findings imply that the gut microbiota's estrogen metabolism might play a role in regulating the initiation of puberty.

The diversity of gut microbiota also plays an important role in the development of secondary sexual characters in children through the production of sex hormones. There is a direct association between the diversity of gut microbiota and the level of sex steroid hormones[82]. Gut microbiota can influence estrogen metabolism by increasing α-glucuronidase activity, which deconjugates estrogen metabolites and potentially leads to higher circulating levels of estrogen.

The human body runs a very closely monitored endocrine-reproductive system. Hydroxysteroid dehydrogenases (HSD) play a major role in modulating the equilibrium between steroids and non-steroid hormones in the body, which is essential to maintain the levels of estrogen and progesterone in the blood, which in turn leads to the development of secondary sexual characteristics, such as breasts, facial/body hair, and the emergence of puberty. *Actinobacteria, Proteobacteria*, and *Firmicutes* are the three main bacterial phyla that are known

Table 1

A summary of studies on the effect of microbiota on the pediatric endocrine system.

Author(s)	Type of study	Target	Main findings
Calcaterra *et al*, 2022[15]	Review	Reproductive system	*Faecalibacterium* species, affiliated with the *Ruminococcaceae* and *Ruminococcus* families, influence host sex hormones and regulate estrogen metabolism via their β-glucuronidase activity.
Sui *et al*, 2021[70]	Review	Reproductive system	The gut microbiota's β-glucuronidase regulates estrogen metabolism
Qinyu *et al*, 2021[65]	Review	Reproductive system	The gut microbiota secretes β-glucuronidase, which plays a role in the metabolism of estrogen to estrone. This affects the circulating levels of estrogen mediating various effects on reproductive health
Hussain *et al*, 2021[72]	Review	Reproductive system	The difference in gut microbiota composition between males and females at puberty, along with the identification of bacterial species associated with sex hormone metabolism, have proposed the role of gut microbiota in puberty and various reproductive diseases
Yue *et al*, 2024[75]	Review	Reproductive system	Preliminary studies suggest the role of metabolites of gut microbiota in a reversal of central precocious puberty, suggesting an association between gut microbiota and the onset of puberty
Jobira *et al*, 2020[79]	Case–control study	Reproductive system	Obese adolescents with PCOS show differences in gut microbiota compared to those without PCOS, which serve as markers of metabolic disease and testosterone levels
Amelio *et al*, 2017[66]	Review	Bone health	Gut microbiota modulates the immune system and inflammation by altering calcium absorption and regulating gut serotonin and hence affects bone turnover and bone health, especially among elderly and postmenopausal females
Sjögren *et al*, 2008[82]	*In vivo*	Bone health	The gut microbiota exerts a regulatory influence on the bone mass of mice through modifications in immune status within the bone, subsequently affecting osteoclast-mediated bone resorption
Koskinen *et al*, 2023[83]	Cohort study	HPA axis	Abundance of specific genera of gut microbiota may be associated with chronic HPA axis activity in young children
Brown *et al*, 2011[84]	*In vitro*	Diabetes mellitus	Development of Autoimmunity in Type 1 diabetes mellitus may be attributed to gut microbiota-induced mucin production and subsequent increase in tight junctions

to manufacture HSD enzymes. An abundance of bacteria that produce HSD is what keeps the gastrointestinal flora in order[89]. Moreover, it was illustrated in Fig. 1 of this study, highlighting various other effects of gut microbiota on the endocrine–reproductive axis; the increase in the bioavailability of androgens and progesterone, conversion of dietary polyphenols into metabolites that are estrogen mimics, and transforming inactive steroids to active estrogen, all of which aid in secondary sexual characteristics development[89]. Dysbiosis-induced inflammation and immune activation may contribute to a decrease in serum testosterone levels[90]. Gut microbiotas are responsible for the synthesis of many metabolites like 5-hydroxytryptamine, gamma-aminobutyric acid, dopamine, nitric oxide, carbon monoxide, hydrogen sulfide, and sulphur dioxide that play roles in regulating sex steroid levels within the reproductive system. These signaling molecules and metabolites are closely associated. Dong *et al* conducted a study elucidating variations in the gut microbiota between individuals with idiopathic central precocious puberty (ICPP) (n = 25) and healthy females (n = 23)[91]. Notably, *Rumicoccus bromii, Ruminococcus gnavus*, and *Ruminococcus leptum* exhibited higher prevalence in females with ICPP when considering microbial species levels. The investigation also explored the relationship between gut microbiota (GM) and three clinical biomarkers – insulin resistance, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Dong *et al* identified a negative association between LH and Romboutsia, positive correlations between FSH and *Fusobacterium*, and *Gemmiger* and ICPP in girls. An increasing number of studies have suggested that disruption of the gut microbiota may play an integral role in precocious puberty in children. For instance, an observational study conducted in China enrolled 27 girls with central precocious puberty (CPP), 24 overweight girls, and 22 healthy controls, the findings of this research demonstrated significant changes in the composition of gut microbiota across the groups. Additionally, the gut microbiota of the CPP girls showed heightened α-diversity more than the physiological amount although no specific measures or range of α-diversity is defined, and further research is needed to quantify the threshold value. This study also revealed a significantly higher abundance of bacteria such as *Sutterella, Klebsiella*, and *Alistipes*[92]. These three bacterial species are notoriously known to be vital biomarkers in various neurological disorders[93]. Gut microbiota may influence the early onset of puberty by secreting neurotransmitter-related metabolites, such as serotonin and dopamine, which activate the hypothalamic–pituitary–gonadal axis. This suggests that specific gut bacteria might trigger precocious puberty through these compounds. Further research is needed to validate these findings and understand the mechanisms involved[15]. According to a study, a high-fat diet may modulate the early activation of the hypothalamic–pituitary–gonadal axis, potentially leading to the premature onset of puberty[94]. In a recent rodent experimental model, Bo *et al* demonstrated that the interaction between gut microbiota and hormones influences the impact of a high-fat diet on early puberty[95]. Postweaning, high-fat diet elevated blood levels of Gonadotropin-releasing hormone (GnRH), leptin, deoxycholic acid, and Pancreatic polypeptide (PP) in the hypothalamus. *Desulfovibrio, Lachnoclostridium, GCA-900066575, Streptococcus, Anaerotruncus*, and *Bifidobacterium* exhibited a favorable correlation with GnRH, suggesting a potential role for these bacteria in promoting sexual development[95]. Additionally, the study noted that "high-fat diet-microbiota" transplantation increased the preputial separation of mice, supporting the idea that GM influences systemic and local sex hormone levels, contributing to premature puberty[95]. The complete composition of the microbial community and the α-diversity undergo substantial alterations in the gut microbiota of adolescents with PCOS[96]. Given that these modifications are observed in individuals typically aged between 14 and 16 years, it suggests that the microbiota may play a significant role in the metabolic disorders affecting obese female adolescents with PCOS[96]. Conversely, an in-depth exploration of the levels of short-chain fatty acids (SCFAs), their respective species, and their associations with PCOS remains a topic for future investigations.

Effect of gut microbiota on bone health

The gut microbiota plays a crucial role in supporting the body's ability to absorb calcium and produce vitamin K and amino acids necessary for maintaining strong and healthy bones. If these processes are impaired due to alterations in the gut microbiota, it can negatively impact musculoskeletal health, potentially leading to conditions characterized by weakened bones and insufficient mineralization, such as nutritional rickets[97]. The presence or activity of *Bifidobacteria* and *Lactobacillus* in the gut can influence calcium absorption efficiency from food[83]. Other intestinal microbes can regulate serotonin, vitamin D, and sex steroids through metabolites such as SCFAs[83,98]. SCFAs, particularly in the colon, regulate calcium levels by influencing the formation of calcium phosphate and promoting calcium absorption. SCFAs can influence the synthesis of serotonin, which modulates calcium absorption, osteoblast proliferation, and bone calcium formation[99]. A visual presentation of a summary of the effect of gut microbiota on reproduction, cognitive, metabolic, and bone health is shown in Fig. 2.

Effect of gut microbiota on HPA Axis

The HPA axis is a critical component of the body's neuroendocrine system, playing a central role in the response to stress. Cortisol, often referred to as the stress hormone, is the product of HPA axis activity[100]. Cortisol can be converted to its inactive form, cortisone, by the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). This enzyme plays a role in regulating the balance between active and inactive forms of cortisol. Metabolites produced by gut microbiota can act as inhibitors of 11β-HSD2[101].

Another parameter of HPA axis activity was indicated in a study measuring the concentration of cortisol/cortisone and dehydroepiandrosterone (DHEA) in 3 cm segments of hair follicles acquired from healthy 2.5-year-old toddlers. The results of this study concluded, in preadolescent children, there is a direct association between *ruminococci* in the gut and hair cortisol ratios, indicating that hair cortisol levels are also affected by the gut microbiota composition[100]. Furthermore, different genera within the phyla *Firmicutes, Actinobacteria, Bacteroidetes*, and *Proteobacteria* – part of gut microbiota showed associations with cortisol and DHEA levels in hair. Hair DHEA is associated with cognitive flexibility in kindergarten children[102].

Effect of gut microbiota on diabetes mellitus (DM) and obesity

Dysbiosis is associated with several metabolic health issues, including Type 2 diabetes mellitus, disruptions in insulin

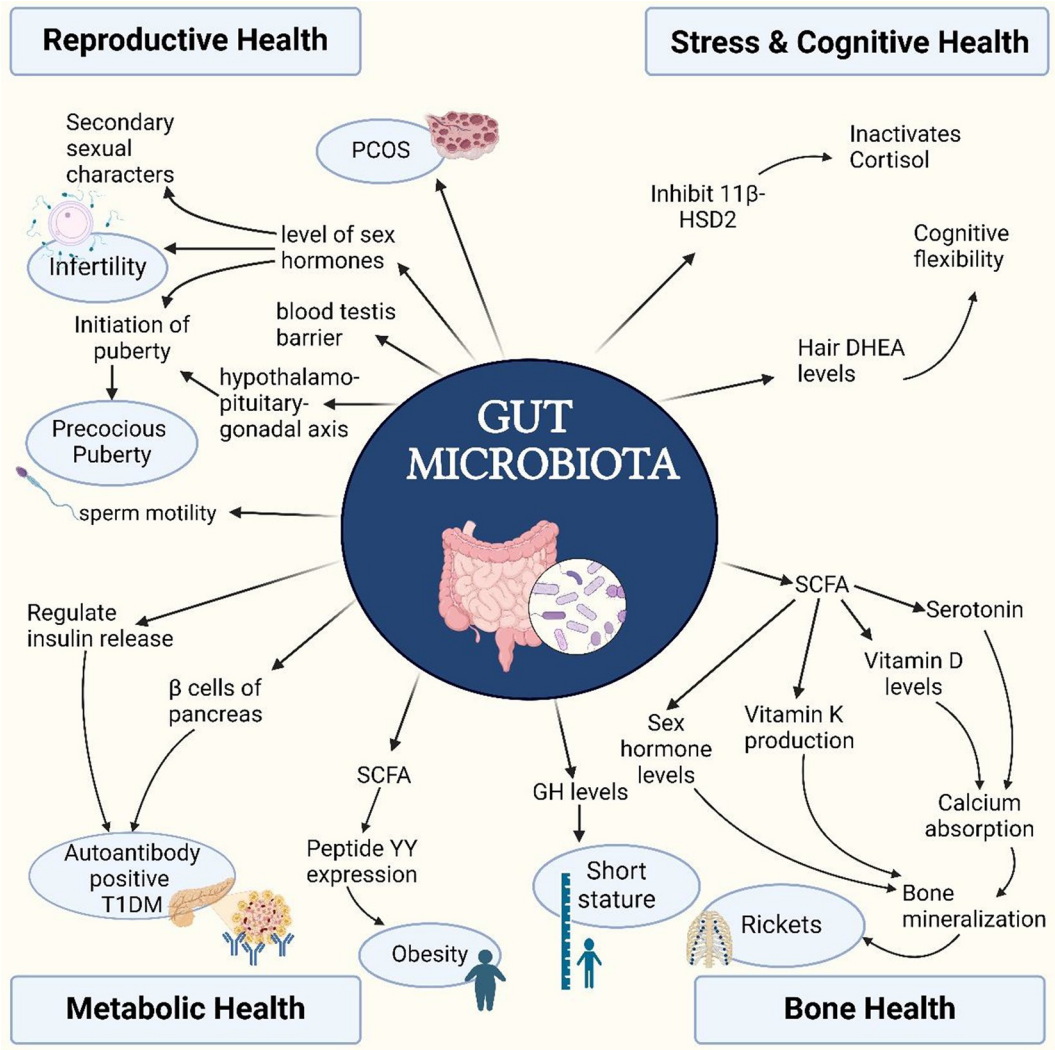

Figure 2. Overview of how gut microbiota influences various aspects of reproduction, cognitive, metabolic, and bone health (created with biorender.com). PCOS, polycystic ovarian syndrome; T1DM: Type 1 diabetes mellitus; SCFA, short-chain fatty acids; GH, growth hormone; DHEA, dehydroepiandrosterone; 11β-HSD2, 11 β-hydroxysteroid dehydrogenase type 2.

release, obesity, and alterations in the numbers and function of insulin-secreting β-cells. Several studies have indicated alterations in the gut microbiota among individuals with Type 1 diabetes[103,104]. It has been discovered that children with Type 1 diabetes who are autoantibody-positive have a greater risk of *Bacteroides* spp. colonization than children who are autoantibody-negative[104,105]. This suggests a possible association between Type 1 diabetes and gut microbiota. Moreover, research on animals has suggested that Toll-like receptors have a regulatory function in how microbes contribute to the development of Type 1 diabetes[106].

Although it has been established that the composition of gut microbiota in the pediatric population plays an instrumental role in the onset and progression of obesity, it is crucial to acknowledge that obesity is the result of a complex interaction between a number of factors, including genetics, nutrition, physical activity, insulin resistance and environmental effects[107]. In humans and animals, antibiotics alter the makeup of the gut microbiota in a way that promotes obesity[108]. A long-term study of these negative antibiotic effects is necessary, particularly in populations that are more susceptible, such as children, newborns, and pregnant women. In addition to many gastrointestinal hormones, enzymes, and microbial metabolites, the microbiome also influences the digestion and absorption of nutrients as well as the function of the digestive tract. For instance, the production of peptide YY is caused by gut-derived metabolites, such as SCFAs, binding to and activating GPR41. Hepatic lipogenesis is enhanced, intestinal transit is suppressed, and nutrient-based energy harvesting is expanded when peptide YY is expressed[109]. The ratio of *Bacteroidetes* to *Firmicutes* is linked to fat accumulation and the extraction of energy from indigestible meals. Furthermore, there is a considerable correlation between weight and the makeup of the gut flora. A long-term investigation has shown that fecal samples from infants who weigh normally had higher amounts of *Bifidobacterium*. On the other hand, a stool sample from infants showed a larger quantity of *Staphylococcus aureus* in overweight (BMI ≥95th percentile) children[110]. Additional research demonstrates an

inverse relationship between *Bifidobacterium* quantity and lipopolysaccharides (LPS) level, BMI, and glucose intolerance[111,112]. A longitudinal cohort study of 909 newborns found further evidence that the presence of *B. fragilis* at 1 month of age was substantially linked with higher BMI *z*-scores in children up to 10 years old[113]. The BMI *z*-score represents children's normal growth and is based on the WHO growth standards, which establish uniform measures of body fat in children based on gender and age. They are used to determine whether a child is underweight, overweight, obese, or within a healthy weight range[114]. One of the primary causes of the rising rates of obesity in both children and adults is the interplay between gut microbiota and low-grade inflammation. For instance, research conducted in 2007 by Cani *et al* revealed that high-fat meals were associated with increased circulation of plasma LPS levels and metabolic inflammation. Increased obesity and insulin resistance result from this[115]. It has been demonstrated that prebiotic and probiotic bacteria, together with FMT, can restore the gut microbiota and lessen the metabolic consequences of obesity[116].

Effect of gut microbiota on thyroid hormone

Iodine is a trace element, which is reduced to iodide in the gut. Iodide is almost entirely absorbed in the stomach and the duodenum. The gut microbiota has been identified as a crucial factor in thyroid physiology and pathology[117]. Microbes regulate thyroid hormone levels by modulating iodine uptake, degradation, enterohepatic cycling, and the bioavailability of levothyroxine(L-thyroxine). Dysbiosis may disrupt the absorption of key micronutrients essential for thyroid function, such as iron, vitamin D, and selenium, potentially leading to thyroid dysfunction[118]. Deiodination is the biochemical process enabling both the activation and inactivation of hormones. Deiodination plays a key role in thyroid metabolism, and animal studies have indicated that residual bacteria colonizing the gut can inhibit deiodinase activity, which contains selenium as an essential component, potentially linking gut microbiota to thyroid disorders[118]. Several studies have reported differences in the gut microbiota between individuals with thyroid disorders and those who are healthy. For instance, patients with hyperthyroidism showed a significant reduction in *Bifidobacteria* and *lactobacilli*, accompanied by an increase in enterococci[119]. Another study found variations in bacterial species like *Veillonella, Paraprevotella, Neisseria*, and *Rheinheimera*[120]. Owing to molecular mimicry, Lactobacillus spp. and *Bifidobacterium* spp. may induce antibodies cross-reacting with thyroperoxidase and thyroglobulin[121]. Emerging research suggests that the gut microbiome might play a significant role in the development and progression of autoimmune thyroid disorders such as Hashimoto's thyroiditis and Graves' disease[117].

A study by Ishaq *et al* suggests that alterations in gut microbiota may significantly contribute to the development and progression of clinical symptoms in Graves' disease. A symptom seen in 20–40% of patients with Graves' disease is Graves' orbitopathy, which is the deposition of fat tissue around the eyes[122]. The results of an experimental study on mice published in 2018 were able to demonstrate a relation between gut dysbiosis and Graves' orbitopathy. The study showed a positive correlation between the presence of *Firmicutes* and Graves' orbitopathy, and a negative correlation between *Intestinimonas* and Graves' orbitopathy[123]. The results from the INDIGO Multicentre European study in 2023 were further able to demonstrate the relation between gut microbiota changes and thyroid disease in human beings. A significantly higher *Firmicutes/Bacteroidetes* ratio (F:B ratio) and high levels of Fusicatenibacter species was seen in individuals with hyperthyroidism compared to the healthy cohort[124].

Similarly, a research by Zhao *et al* highlighted an increased F:B ratio, a marker of gut balance, in patients with Hashimoto's thyroiditis[125]. However, no studies have yet focused on the pediatric population. The microbiota can also affect the metabolism of thyroid medications. For instance, in hypothyroidism, increased stomach pH, often due to *H. pylori*, may reduce L-thyroxine absorption, which requires an acidic environment. Similarly, in hyperthyroidism, bacterial enzymes can metabolize propylthiouracil, potentially leading to subtherapeutic levels compared to methimazole. High levels of *Clostridiales* species were noted in Graves' disease patients resistant to anti-thyroid drug therapy compared to controls in the INDIGO study.

Effect of gut microbiota on growth hormone (GH)

Children's growth and development are significantly influenced by the stability of their gut microbiota[82]. The pivotal elements in the growth and development regulatory pathway are GH and insulin-like growth factor-1 (IGF-1)[126]. Gut microbiota modulates the secretion of GH. They mediate signal transduction via the intestinal–brain axis and influence the secretion of GH-releasing peptide, somatostatin, and leptin, all of which regulate the GH/IGF-1 axis[91,95,127-130]. Understanding the underlying role of microbiota and hormonal factors affecting the IGF system is crucial for diagnosing and managing cases of dwarfism and targeted therapies, such as recombinant human insulin-like growth factor-1 or recombinant human GH. Li *et al* discovered a robust positive correlation between the standard deviation score (SDS) for height and IGF-1 SDS in children with idiopathic short stature, with a notable association with intestinal *Clostridium* and *Eubacterium*. Their investigation into significant alterations in the gut microbiota of these patients led them to propose that a potential cause might be the diminished production of IGF-1 by *Clostridium* and *Eubacterium*, likely influenced by SCFAs[131].

Clinical implications

Gut microbiota can be modified using prebiotics, probiotics, synbiotics, FMT, and gut microbiota metabolite supplementation[132-134]. The gut microbiome has been implicated in various endocrine diseases affecting children, such as Type 1 diabetes mellitus (T1DM), PCOS, and obesity. Given its significant role, clinically altering the gut microbiota presents a promising avenue for intervening in these conditions, offering a potential disease management and prevention strategy. A 2021 trial studied the role of metformin in altering microbiota in obesity and found that there was a reduction in *Actinobacteria*, suggesting that it may have some role in microbiota alteration therapy in childhood obesity[135]. This reduction suggests that metformin may help rebalance the gut microbiome, offering potential benefits such as reduced inflammation, improved insulin sensitivity, and better metabolic outcomes[136]. Obesity and diabetes are known to cause low-grade intestinal inflammation and metabolic dysfunction. Some studies suggest that fat-enriched diet and obesity can cause

increased permeability of the gut by disruption in gene expression of proteins, such as tight junction proteins ZO-1 and occludins, which, in turn, allows reabsorption of LPS, a major component found on the outer membrane of gram-negative disease-causing bacteria such as *Actinobacteria*[137]. Metformin is an anti-diabetic medication that promotes weight loss by decreasing hepatic gluconeogenesis, enhancing glycolysis, and facilitating glucose uptake by peripheral cells. As a result, it helps reduce obesity and the reabsorption of LPS in patients with Type 2 diabetes[138].

Role of prebiotics

Prebiotics are nonliving compounds in food that enhance health by supporting the growth of beneficial gut bacteria, thereby positively affecting the gut microbiome[139]. In a study conducted in Canada, obese children were given oligo fructose-enriched inulin as a probiotic for 4 months. The results showed a significant decrease in body weight, body fat percentage, and truncal fat compared to the placebo group. Additionally, there was an increase in *Bifidobacterium* and a decrease in *B. vulgatus*[130].

A 2021 quadruple-blinded trial in Italy investigated the impact of butyrate on BMI in children with obesity. The study revealed a greater reduction in BMI among those receiving butyrate supplementation. The researchers also identified specific gut microbiome signatures associated with a therapeutic response[131]. Another study reported a protective effect of SCFAs, a gut microbiota metabolite, in early onset T1DM. Children at high risk of T1DM showed a deficiency in SCFA-producing bacteria[140].

In 2022, a trial focused on adults with T1DM using the acetylated and butylated high amylose maize-resistant starch (HAMSAB) showed changes in gut microbiota. Although no study on HAMSAB and childhood T1DM has been published, a 2023 US study protocol aims to investigate its effects on youth with T1DM[132]. There have been multiple studies on the positive effect of prebiotics on adult PCOS; however, no such studies have been conducted on adolescent PCOS[133].

Role of probiotics

Probiotics are beneficial bacteria that, when taken in the right amounts, can help maintain or improve health[139]. In a 2021 cross-over double-blinded trial, obese children were supplemented with the probiotic *Bifidobacterium breve* BR03 and B632 strains, resulting in a significant decrease in BMI in the treatment group[141]. Another 2021 trial focused on children with new-onset T1DM and assessed the impact of daily administration of a multi-strain probiotic for 3 months. The study showed a significant reduction in hemoglobin A1c (HbA1c) and total insulin dose compared to the control group, indicating improved glycemic control when probiotics were added to the standard treatment for T1DM[142]. HbA1c, or glycosylated hemoglobin, measures the average blood glucose levels over the past 2–3 months. Higher HbA1c levels suggest poor blood sugar control and a higher risk of diabetes-related complications.

In 2019, a study conducted in China investigated the effects of the probiotic *Bifidobacterium lactis V9* on PCOS, revealing a decrease in LH and LH/FSH ratio, along with an increase in sex hormones and intestinal SCFAs[143].

Role of synbiotics

When prebiotics and probiotics are combined, they form what is known as synbiotics[139]. In 2020, a double-blind clinical trial in Iran investigated the impact of an 8-week synbiotic supplementation containing Lactobacillus sporogenes, fructo-oligosaccharide, and maltodextrin on children with T1DM. The study revealed a significant decrease in HbA1c levels, fasting blood sugar (FBS), and markers of oxidative stress[144]. A similar outcome was observed in a 2023 Iranian study that used synbiotics for 12 weeks, showing a decrease in HbA1c and FBS[145]. However, additional research is needed to determine the optimal duration of synbiotic therapy in childhood T1DM before it can be incorporated into T1DM treatment.

In a 2022 Chinese study, adults with PCOS receiving synbiotics (high-fiber diet, prebiotics) and acarbose experienced a decrease in insulin resistance and hyperandrogenism[146].

Role of fecal microbiome transfer (FMT)

In a 2020 trial conducted in New Zealand, the impact of FMT on obese adolescent females was investigated. While there was no significant decrease in overall weight, there was a notable reduction in abdominal adiposity. This suggested a potential therapeutic effect of FMT on metabolic syndrome[147]. In a 2022 experimental study in China, FMT was performed for a year on two adolescent patients with T1DM. The study reported the effectiveness of FMT in treating autoimmune T1DM in both patients[148]. Although no FMT trials for PCOS have been conducted in humans as of now, a positive outcome was observed in a 2016 study involving PCOS-induced rats[149].

Moreover, studies have suggested that the gut microbiota and/or its metabolites have the potential to serve as biomarkers for identifying high-risk patients with various endocrine disorders in children. Obesogenic gut microbiota and their associated metabolites can potentially serve as predictors for pediatric obesity risk. A 2021 Korean study combining microbiota and metabolites in childhood obesity showed elevated urine myristic acid levels post-lifestyle intervention, suggesting it is a potential target for treatment[150]. A study conducted in 2018 explored gut microbiota as a predictor for T1DM development, revealing a mild association between microbiota stability and T1DM onset[150]. A study conducted in Sweden in 2023, from the All Babies in Southeast Sweden (ABIS) cohort identified gut microbiota biomarkers up to 20 years before T1DM diagnosis in infants, with higher levels of *Porphyromonas* and lower levels of *Flavonifractor, Alistipes*, and *Ruminococcaceae* UBA1819 in those who later developed T1DM[140].

Most studies conducted are reviews; however, case–control studies could provide more information about the risk of endocrine disorders in the context of alterations in gut microbiota. Some environmental factors, such as air pollutants, are not yet well studied in relation to gut microbiota in the pediatric population. While existing research on prebiotics primarily examines diabetes and obesity in children concerning gut microbiota, there is a notable lack of studies focusing on PCOS in adolescents, indicating a need for further investigation in this area. Additionally, interventions like prebiotics, probiotics, and synbiotics have shown potential in improving gut microbiota; however, their optimal doses and potential side effects in children require further exploration.

Conclusion

In summary, gut microbiota significantly influences endocrine function and health, impacting various aspects such as reproductive health, bone health, growth, and the HPA axis. Environmental factors, particularly, in pediatric populations, play a crucial role in shaping gut microbiota composition. Dysregulation of gut microbiota is associated with several endocrine disorders, including precocious puberty, PCOS, and DM. While emerging treatments targeting gut microbiota, such as probiotics, prebiotics, synbiotics, and FMT, have shown potential, their effectiveness is still not fully established across various endocrine disorders. Therefore, further research is essential to better understand these mechanisms and improve treatment outcomes.

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Ethics approval was not required for this review.

Consent

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