REVIEW

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The role of gut microbiota in human development

Rola mikrobioty jelitowej w rozwoju człowieka

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Abstract:

The gut microbiota constitutes a complex ecosystem of microorganisms. Its development may begin as early as the prenatal period and is particularly intensive during the first three years of life. Key determinants of its composition include the mode of delivery, ~~the~~ feeding method, and exposure to antibiotics. Vaginal delivery ensures optimal colonization by bacteria from the genera *Bifidobacterium* and *Lactobacillus*, whereas cesarean section promotes the dominance of hospital flora. This may increase the risk of metabolic and immunological diseases. Breastfeeding, due to the presence of human milk oligosaccharides (HMOs), selectively supports the growth of beneficial symbionts and the synthesis of short-chain fatty acids (SCFA), which are essential for intestinal barrier maturation and immune system development. The article also analyzes the influence of the gut-brain axis on neurological development, indicating that dysbiosis in early childhood may be associated with disorders such as ASD or ADHD. Understanding the mechanisms of microbiota transmission and stabilization remains crucial for the prevention of lifestyle diseases and the implementation of modern probiotic therapies.

Keywords: gut microbiota, gut – brain axis, delivery, breastfeeding, dysbiosis, probiotics.

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Streszczenie:

Mikrobiota jelitowa stanowi złożony ekosystem drobnoustrojów. Jego kształtowanie może rozpoczynać się już w życiu płodowym i jest niezwykle intensywne do 3 roku życia. Kluczowe determinanty jej składu to metoda porodu, sposób karmienia oraz ekspozycja na antybiotyki. Poród siłami natury zapewnia optymalną kolonizację bakteriami z rodzajów *Bifidobacterium* i *Lactobacillus*, podczas gdy cesarskie cięcie sprzyja dominacji flory szpitalnej. Może to zwiększać ryzyko chorób metabolicznych i immunologicznych. Karmienie piersią, dzięki obecności oligosacharydów (HMOs), selektywnie wspiera wzrost pożytecznych symbiontów i syntezę krótkołańcuchowych kwasów tłuszczowych (SCFA), które są niezbędne dla dojrzewania bariery jelitowej oraz układu odpornościowego. Artykuł analizuje również wpływ osi jelito-mózg na rozwój neurologiczny, wskazując, że dysbioza we wczesnym dzieciństwie może być powiązana z zaburzeniami takimi jak ASD czy ADHD. Zrozumienie mechanizmów transmisji i stabilizacji mikrobioty może być kluczowe dla prewencji schorzeń cywilizacyjnych oraz wdrażania nowoczesnych terapii probiotycznych.

Słowa kluczowe: mikrobiota jelitowa, oś jelito-mózg, poród, karmienie piersią, dysbioza, probiotyki.

Introduction

The gut microbiota is a highly complex biological ecosystem. It comprises trillions of microorganisms, including bacteria, viruses, fungi, and archaea, that colonize the human body [1-2]. The number of microbial cells in the intestines is estimated to exceed that of host cells, while their collective genome, referred to as the microbiome, contains over 150 times more genes than the human genome [3-4]. Bacteria from the phyla *Firmicutes* and *Bacteroidetes* predominate, constituting up to approximately 90% of the gut microbiota; however, other less abundant groups, such as *Verrucomicrobia* and *Actinobacteria,* are also significant [1, 5]. These microorganisms, whose importance has long been underestimated, not only participate in digestion and vitamin synthesis, but also contribute to immune function, metabolic regulation, and neurological processes via the gut-brain axis [2, 4].

The gut microbiota is a dynamic rather than static system. At birth, the human organism is relatively uncolonized; however, initial microbial exposure occurs during delivery, initiating a process of microbial succession that progresses toward relative stability by approximately three years of age [4, 6]. Key factors influencing its development include the mode of delivery, feeding practices, diet, and pharmacological exposure. Infants delivered vaginally are typically colonized by microbial communities resembling the maternal vaginal microbiota, whereas cesarean section is associated with increased colonization by skin – and hospital-associated bacteria. Breastfeeding provides oligosaccharides that may stimulate the growth of *Bifidobacterium* [5-6]. Increased dietary fiber intake supports bacterial taxa that use fiber as a substrate for the production of short-chain fatty acids (SCFA), whereas a diet rich in simple sugars and saturated fats has been associated with an increased abundance of pro-inflammatory species [2, 7]. Antibiotic therapies, although sometimes unavoidable, have been shown to reduce gut microbiota diversity by up to 30%, while simultaneously increasing susceptibility to infections [1, 5]. In older individuals, a decrease in *Bifidobacterium* and an increase in *Proteobacteria* are observed, and these changes are correlated with a weakened immune response and increased susceptibility to infections [6]. Exposure to environmental toxins, low physical activity, and high levels of stress may disrupt microbial homeostasis [5].

The gut microbiota performs multiple functions that extend beyond digestive processes. These include metabolic functions, such as the fermentation of dietary fiber into short-chain fatty acids (SCFA), including butyrate, propionate, and acetate, which serve as a major energy source for colonocytes. These metabolites contribute to maintaining intestinal barrier integrity and modulating inflammatory responses [2, 7]. It synthesizes vitamin K, essential for blood clotting, as well as B vitamins [4, 6]. It contributes to host defense against pathogens by competing for adhesion receptors and nutrients, a phenomenon referred to as colonization resistance [7]. It also produces bacteriocins that inhibit the growth of *Salmonella* or *E. coli* [1]. Regarding immunity, SCFA have been shown to stimulate the differentiation of regulatory T lymphocytes (Treg), which modulate excessive immune reactions [2, 7]. Moreover, they promote the expression of proteins such as occludin, which are involved in maintaining intestinal barrier integrity, thereby preventing the translocation of pathogens [7].

The gut – brain axis is also an important component in this context, given that a substantial proportion of serotonin, a neurotransmitter involved in mood regulation, is produced in the gastrointestinal tract through mechanisms influenced by microbial activity, including bacteria of the genera Lactobacillus and Bifidobacterium [4]. Intestinal melatonin, whose concentration is 400 times higher than in the pineal gland, protects the intestinal epithelium against oxidative stress and may exert a regulatory influence on the circadian rhythms [1].

Dysbiosis defined as, disturbances in the balance of the gut microbiota, is associated with a broad spectrum of disorders, such as metabolic diseases, inflammatory bowel diseases, neurodegenerative diseases, as well as mental disorders. In obese individuals, an increased *Firmicutes* to *Bacteroidetes* ratio is observed, which has been associated with increased energy harvest from the diet [2, 7]. In contrast, in individuals with type 2 diabetes, the abundance of *Akkermansia muciniphila* – a species associated with improved insulin sensitivity – decreases [5]. A reduction in Faecalibacterium prausnitzii, and consequently in butyrate production, together with overgrowth of E. coli, may exacerbate inflammatory processes through activation of NF – κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) [1, 7]. Dysbiosis has been associated with increased intestinal permeability, which allows the penetration of bacterial amyloids and lipopolysaccharides (LPS), which may contribute to neuroinflammatory processes in Alzheimer's and Parkinson's diseases [1, 4]. Deficiency of SCFA and GABA has been linked to depressive symptoms and anxiety, whereas elevated levels of pro-inflammatory cytokines (e.g., IL-6 and TNF-α) have been implicated in hippocampal dysfunction [4, 7].

The gut microbiota is a highly dynamic ecosystem. Its balance has a profound impact on physical and mental health. Microbiota disturbances lead to a cascade of disorders, from insulin resistance to neurodegeneration. Innovative therapies, such as personalized probiotics or epigenetic modulation using SCFA, open new possibilities for precision medicine. However, the greatest challenge remains understanding the individual variability of the microbiota and the long – term effects of interventions [1, 5].

This article integrates current knowledge from a range of disciplines, such as microbiology, immunology, and neurology. Drawing on numerous scientific studies, this review aims to examine how early – life factors shape the establishment of a favorable gut microbiota and how dysbiosis may be prevented.

Microbiota of the pregnant woman

The maternal microbiota undergoes changes during pregnancy, which are associated with modulation of immune and metabolic systems required to sustain pregnancy. Studies have shown that the third trimester of pregnancy is associated with an increased abundance of bacteria from the genera *Bifidobacterium* and *Bacteroides*. These changes are adaptive responses of the maternal organism to support fetal development and to facilitate microbiota transmission during childbirth [8]. There is growing evidence to suggest that microbial colonization may begin during fetal life. The presence of bacteria from the genera *Staphylococcus*, *Lactobacillus*, and *Bifidobacterium* has been detected in the amniotic fluid, placenta, and chorionic villi of healthy newborns, challenging the traditional view of the intrauterine environment as a sterile site. This early exposure may play a significant role in the development of the fetal immune system [9].

During vaginal delivery, the newborn is exposed to the maternal microbiota through contact with the vaginal microbiota rich in *Lactobacillus spp*., the maternal intestinal microbiota (perianal area), and the maternal skin microbiota. High-resolution metagenomic studies have demonstrated that the primary source of bacteria colonizing the newborn intestine is the maternal gastrointestinal tract. Phylogenetic analyses have shown that vertical transmission of the intestinal microbiota is dominated by bacteria from the phyla *Bacteroidetes* and *Actinobacteria*. Key species transmitted during vaginal delivery include: *Bifidobacterium breve, Bifidobacterium longum subsp. infantis, Bifidobacterium bifidum, Bacteroides vulgatus, Bacteroides thetaiotaomicron, Bacteroides dorei* and *Bacteroides uniformis*. The aforementioned bacteria demonstrate the ability to metabolize human milk oligosaccharides; therefore, colonization by these species may be important for early microbial and metabolic development. Importantly, most of these bacteria originating from the maternal intestines persist long-term in the child's intestines, with as many as 20 of 21 species persisting over time [8].

In newborns delivered vaginally, rapid colonization of the gastrointestinal tract by maternal bacteria is observed. In the first days of life, the following are predominant: *Bifidobacterium spp.* (particularly in breastfed infants), *Bacteroides spp.*, *Escherichia coli*, and other *Enterobacteriaceae*, *Streptococcus spp.* and *Enterococcus spp*. During the first month of life, a gradual increase in microbial diversity occurs, with a marked rise in the abundance of *Bacteroides* and *Bifidobacterium* [8, 10]. In breastfed infants, *Bifidobacterium* may constitute up to 60-90% of the entire gut microbiota, which is associated with the presence of oligosaccharides in maternal milk that selectively stimulate the growth of these bacteria [8-9].

Delivery by cesarean section (CS) is associated with significant disruption of the natural process of microbial transmission. Newborns delivered by CS do not pass through the birth canal, and therefore, are not exposed to the maternal vaginal and intestinal microbiota. They are colonized primarily by bacteria from the hospital environment and the skin of medical personnel. Moreover, they are often exposed to perioperative antibiotic therapy. Metagenomic studies have shown that the microbiota of newborns after CS is characterized by a significantly lower abundance of *Bifidobacterium* and *Bacteroides,* and a higher abundance of potentially pathogenic bacteria from the genera: *Enterococcus, Klebsiella, Clostridium, Staphylococcus,* and *Streptococcus* [8, 10]. Importantly, these differences persist for several months, and full convergence of microbiota composition compared with children born vaginally may take 3–5 years [10]. Sources of microbiota in newborns after cesarean section include the mother's skin and oral cavity, the hospital environment, as well as maternal milk (if the child is breastfed). In contrast to vaginal delivery, bacteria originating from the maternal intestines constitute a much smaller proportion of the newborn's microbiota after cesarean section, which may have important implications for immune system development [8].

Differences in microbiota colonization between children born vaginally and by CS may have important health implications. Observational and clinical studies have linked cesarean section delivery with an increased risk of: allergic diseases (asthma, atopic dermatitis), autoimmune diseases (type 1 diabetes, Crohn's disease), obesity, and metabolic disorders, infections (particularly of the gastrointestinal and respiratory systems), and neurodevelopmental disorders [8-10]. Studies in animal models have demonstrated that microbial antigens induce immune tolerance only within a specific time frame in the first weeks of life. Exposure to the same antigens outside this period has been associated with loss of tolerance and a pro-inflammatory response [8]. This suggests the existence of a critical developmental window in humans during which key interactions between the immune system and microorganisms occur.

However, cesarean section is sometimes unavoidable; therefore, a range of microbiota – modulating interventions is available after such a procedure. Commonly used probiotic strains include *B. breve, B. longum, B. infantis, B. lactis,* as well as *L. rhamnosus,* and *L. reuteri*. Studies have shown that probiotic supplementation at doses ranging from 2×10^6 to 9×10^11 CFU/day may shorten the time required to achieve a more mature microbiota profile [9]. Prebiotics, particularly human milk oligosaccharides, may stimulate the proliferation of *Bifidobacterium* in the newborn's intestine. Vaginal seeding, a method involving swabbing the newborn with gauze previously exposed to the maternal vaginal microbiota, has also been proposed. However, to date, studies have not demonstrated significant effectiveness of this method in restoring gut microbiota composition of newborns after CS [10]. Importantly, interventions initiated in the first days of life are significantly more effective than those initiated later, which underscores the importance of the critical time window for colonization [9]. Moreover, the effects of interventions often persist after the end of supplementation, suggesting a lasting modification of the microbial ecosystem.

Method of delivery and the development of the gut microbiota

Early colonization of the newborn intestine by microorganisms plays an important role in the development of the immune and metabolic systems. The composition of the microbiota in the first days of life is strongly dependent on the mode of delivery and on antibiotic therapy used during this period, especially in the context of prophylaxis against group B streptococcal (GBS) infections [11-13]. Infants delivered vaginally typically acquire a microbiota resembling the maternal birth canal microbiota, with a predominance of *Bifidobacterium, Bacteroides,* and *Lactobacillus* [11, 13]. In contrast, in infants delivered by cesarean section, an increased abundance of environmental bacteria, such as *Staphylococcus, Clostridium,* and *Enterococcus* is observed, resulting from contact with the mother's skin and hospital microflora [12-14]. A study by Liu et al. (2019) showed that cesarean section significantly reduces the abundance of *Bifidobacterium* ($p = 0.028$) in favor of *Klebsiella* and *Veillonella* [11]. The use of antibiotics for GBS prophylaxis is common; however, it may disrupt early intestinal colonization. Antibiotics reduce the abundance of beneficial bacteria, such as *Bifidobacterium* or *Lactobacillus*, while simultaneously promoting the growth of potentially pathogenic *Proteobacteria* [11-12, 15]. Although some studies have not demonstrated a lasting impact of short – term antibiotic exposure [11], others emphasize the risk of horizontal transfer of resistance genes, which may have long – term consequences for the child's health [15]. A study by Metz et al. (2020) did not confirm an association between antibiotic therapy in GBS prophylaxis and body mass index (BMI) in later childhood [16]; however, animal models indicate that even short – term antibiotic therapy significantly reduces the density of intestinal bacteria [17].

Studies indicate that mode of delivery is an important determinant of early gut microbiota development in newborns. Vaginal delivery is associated with colonization by beneficial bacterial taxa such as *Bifidobacterium*, *Bacteroides*, and *Lactobacillus*, which originate from the mother's birth canal and play an important role in immune system development. In turn, cesarean section is associated with disruption of this process, leading to the dominance of environmental bacteria, including *Staphylococcus*, *Clostridium*, and *Enterococcus*, which may increase the risk of dysbiosis and related health complications. The use of antibiotics in prophylaxis against group B streptococcus (GBS) constitutes an additional factor that may disrupt early intestinal colonization patterns, although some studies do not confirm its lasting effect on microbiota composition. Study results suggest that even short – term exposure to antibiotics may lead to a reduction in the abundance of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, with a simultaneous increase in potentially pathogenic *Proteobacteria.*

Feeding

Colonization of the gut microbiota in the newborn begins immediately after birth and is intensively shaped by early environmental factors – one of the most significant being the method of feeding. Breast milk not only nourishes the infant but also serves as a biologically active source of commensal bacteria and substances that promote their proliferation in the gastrointestinal tract [18-19]. Breast milk plays a central role in the colonization of the infant gastrointestinal tract by beneficial microorganisms, mainly bacteria of the genera *Bifidobacterium* and *Lactobacillus* [18]. Exclusively breastfed infants have a characteristic microbiome dominated by *Bifidobacterium*, whose presence is associated with immune system maturation, reduced inflammation, and enhanced intestinal barrier integrity [18-19]. These bacteria produce short-chain fatty acids (SCFA), which exert anti-inflammatory effects and modulate the host immune response. The predominance of *Bifidobacterium* in breastfed infants is regarded as a physiological, protective pattern of the infant microbiota [18]. Breast milk is a dynamic biological fluid; its composition changes depending on the stage of lactation, the time of day, and the mother's health status. Thus, it provides the infant with bacteria and bioactive factors that support microbiota development across different stages of early life. Breastfeeding also promotes "skin-to-skin" contact, which additionally enhances the transmission of microorganisms from mother to child, supporting colonization already within first hours after delivery [19-20].

Human milk is not only a source of nutrients but also a complex biological fluid containing numerous compounds with immunological, metabolic, and microbiological activity. One of the most important groups of compounds influencing the microbiota is human milk oligosaccharides (HMOs – Human Milk Oligosaccharides), which are present in breast milk in high concentrations and with substantial structural diversity [19]. Although the infant is unable to digest them, HMOs function as selective prebiotics, serving as substrates for specific strains of commensal bacteria, mainly of the genus *Bifidobacterium*. Through this interaction between milk composition and microorganisms, the infant microbiota develops toward a stable, low-diversity but functionally favorable microbial community that supports immune system maturation and the maintenance of intestinal homeostasis. Fermentation of HMOs leads to the production of short-chain fatty acids (SCFA), such as acetate, propionate, and butyrate. These compounds have a range of beneficial properties: they exert anti-inflammatory effects, regulate the pH of the intestinal environment, strengthen intestinal barrier integrity, and influence immune system maturation [18-19]. Breastfed infants exhibit higher concentrations of SCFA in stool, reflecting active microbial metabolism that promotes protection against pathogens and allergens.

In addition to HMOs, breast milk contains other bioactive components that affect the microbiota. Lactoferrin is an iron-binding protein that limits its availability to pathogens while simultaneously supporting the growth of symbiotic bacteria. Studies have shown that lactoferrin may act bacteriostatically against pathogenic strains while promoting the proliferation of beneficial microorganisms [19]. Immunoglobulins of the IgA class, naturally present in milk, provide protective functions not only at the level of the overall immune system but also through the modulation of the microbiota. IgA can neutralize pathogenic microorganisms and limit their adhesion to the intestinal epithelium, without disrupting the presence of commensal bacteria [20]. In this way, breast milk supports selective tolerance toward beneficial microorganisms, which is essential for the development of the gut-immune axis. Human milk also contains cytokines, hormones, and microRNA present in exosomes, whose profiles change depending on the mother's diet and the stage of lactation. Studies indicate that microRNA contained in breast milk may modulate gene expression in the infant's intestinal epithelial cells, influencing the maturation of the intestinal barrier and local immune reactions. Although the direct effect of microRNA on intestinal microorganisms has not yet been unequivocally confirmed, an indirect effect has been proposed, through the shaping of the intestinal environment, including regulation of immune and epithelial processes that favor colonization by beneficial bacteria.

Increasing evidence indicates that the microbiota of breast milk is strongly correlated with the infant gut microbiota, which underscores the multidirectional nature of interactions between milk components and the development of the child's microbiome [21-23]. Breastfeeding is of particular importance in newborns belonging to high – risk groups, such as preterm infants, children born with very low birth weight (VLBW), or infants hospitalized in intensive care units. In these cases, the development of the gut microbiota may be delayed, disrupted, and susceptible to unfavorable environmental changes, including contact with hospital pathogens, antibiotic therapy, or a lack of contact with the natural maternal flora. Preterm infants have an immature immune system and intestinal barrier, which makes them more susceptible to dysbiosis – disturbance of microbiota balance – which may lead to serious health consequences such as necrotizing enterocolitis (NEC), sepsis, or chronic inflammation. In this context, breast milk serves not only a nutritional but also a potentially therapeutic function. The commensal bacteria, immunoglobulins, lactoferrin, and oligosaccharides contained in it support the development of a protective microbiota, strengthen the intestinal barrier, and reduce inflammatory responses [20].

Studies show that the breast milk microbiota exhibits high concordance with the gut microbiota of naturally fed preterm infants, suggesting a direct contribution of milk to gastrointestinal colonization [19-20]. In infants fed breast milk, an increased presence of *Bifidobacterium* and a reduced amount of potentially pathogenic bacteria from the *Enterobacteriaceae* family are observed compared with infants fed formula [18, 20]. Such a microbial profile supports the maturation of the intestinal barrier and limits the risk of bacterial translocation into the systemic circulation. In high-risk groups, breast milk also contributes to a shorter time to colonization by desired strains and more rapid stabilization of the gut microbiota, which is important for further metabolic and immunological development. Importantly, even donor milk, despite thermal processing, exhibits beneficial microbiological properties and may be a valuable alternative when the mother's own milk is unavailable [20]. Breastfeeding plays an significant role in shaping a favorable microbiota profile, particularly after a cesarean section. Studies have shown that in breastfed infants, differences in microbiota composition between vaginal delivery and cesarean section are less pronounced than in infants fed infant formula [10]. However, women who undergo cesarean section are less likely to initiate or continue breastfeeding, which further exacerbates dysbiosis in these newborns [9].

Environmental factors shaping the gut microbiota in infants

After the neonatal period, the composition of the child's gut microbiota is influenced by environmental factors, such as the place of residence, contact with animals, and the presence of older siblings. It has been shown that microbiome diversity in the first months of life may affect the risk of developing allergies, obesity, and autoimmune diseases [13-14, 24]. Children raised in rural areas tend to exhibit a richer and more diverse microbiota than their urban peers. In their intestines, bacteria of the genera *Prevotella* and *Ruminococcus predominate*, which are associated with a high-fiber diet and contact with the natural environment [14, 24]. In contrast, in urban infants, an increased abundance of *Proteobacteria* is more frequently observed, potentially increasing the risk of inflammation-related conditions and allergies [11, 24]. A study by Tun et al. (2017) showed that the presence of animals in the home increases the diversity of the infant gut microbiota, with a particular increase in the abundance of *Ruminococcus* and *Oscillospira*. Importantly, this effect was most pronounced in children delivered by cesarean section, suggesting that contact with animals may partially mitigate differences in early colonization patterns [13-14]. Furthermore, infants raised with older siblings have a more diverse gut microbiota, which is associated with a lower risk of allergies and autoimmune diseases [11, 14]. This mechanism may result from early exposure to diverse microorganisms transmitted by other children.

After the neonatal period, environmental factors begin to exert a significant influence on the composition of the child's gut microbiota, potentially modifying earlier differences resulting from the mode of delivery. It has been shown that children raised in a rural environment are characterized by a more diverse microbiome, which likely results from greater exposure to natural microorganisms and may constitute a protective factor against the development of allergies and autoimmune diseases. Contact with pets appears to be another important element promoting microbiota diversity, particularly in children delivered by cesarean section. The presence of older siblings may also promote greater microbiota diversity, probably through early exposure to diverse microorganisms transmitted by other children. All these environmental factors appear to play an a crucial role in shaping the gut microbiota and may modify the risk of developing diseases associated with microbiota disturbances.

Impact of pharmaceuticals on the human gut microbiota

Antibiotic exposure has been shown to reduce the species diversity of the gut microbiota, which may persist for months or even years after treatment completion. In particular, clindamycin treatment has been associated with long – term depletion of species from the genera *Bifidobacterium* and *Bacteroide,* and an increase in the number of *Enterobacteriaceae* [25]. A shift in dominant enterotypes occurs, from *Bacteroides* to *Prevotella*, which may affect host metabolism and has been associated with an increased risk of metabolic diseases. Antibiotics also disrupt SCFA production, which may lead to inflammation and increased permeability of the intestinal barrier [26]. Treatment with vancomycin reduces levels of secondary bile acids, which play a key role in protection against *Clostridioides difficile*, leading to changes in metabolism [25]. A decrease in the number of butyrate – producing bacteria, such as *Faecalibacterium prausnitzii*, may weaken anti-inflammatory mechanisms in the intestine through the loss of fermentative capacity [26]. Antibiotic exposure may promote the emergence and spread of resistant bacterial strains through horizontal gene transfer (HGT). Antibiotic therapies induce HGT processes, such as conjugation, transduction, and transformation, which accelerate the spread of resistance genes. The reduction in protective bacteria may favor the expansion of resistant pathogens, such as *Enterococcus faecium* (VRE) [25].

With regard to short-and medium-term effects after antibiotic therapy, the following can be distinguished: antibiotic – associated diarrhea related to the loss of protective bacteria such as *Bifidobacterium* and *Lactobacillus*, which occurs in 5-35% of patients; *Clostridi-*

oides difficile infection, caused particularly by broad – spectrum antibiotics; and infection with Helicobacter pylori, whose eradication with antibiotics may lead to an increase in bacteria from the phylum *Firmicutes* and an increased risk of metabolic disturbances. Long-term consequences have been linked to an increased risk of autoimmune diseases, obesity, and metabolic disorders, as well as allergies and asthma. Such long-term consequences are most commonly observed when antibiotics are administrated in childhood or earlier, because the microbiota is still developing during this period and may therefore be more susceptible to disruption [25-26].

The composition of the human microbiota differs depending on age, diet, environmental factors, and medications used. The microbiota plays an important role in nutrient metabolism, SCFA production, modulation of the immune system, and protection against pathogens. Vaccines may also modulate the microbiota through various mechanisms [30]. mRNA vaccines, similarly to other immunological interventions, may affect the gut microbiota indirectly through modulation of the host immune response. In recent years, it has been shown that gut microbiota composition correlates with the strength of the immune response after vaccination against SARS-CoV-2. The presence of bacteria producing short-chain fatty acids (SCFA), which can enhance the humoral response, is particularly important. Studies have shown that in individuals vaccinated with mRNA preparations (e.g., mRNA-1273), a higher abundance of SCFA – producing bacteria is associated with a stronger antibody response, whereas predominance of potentially pro-inflammatory bacteria may weaken this response. These findings suggest that the microbiota may modulate the immune response to mRNA vaccines and that individual differences in its composition may affect vaccine efficacy [28-30].

Neurodevelopmental disorders and the gut microbiota

In recent years, increasing interest has been observed in the influence of the gut microbiota on nervous system development, particularly in the context of neurodevelopmental disorders such as autism spectrum disorder (ASD) and ADHD. A growing body of research indicates that the microbiota is not merely a passive participant in physiological processes but may actively participate in the regulation of neurological and immunological functions from the earliest stages of life. The concept of the microbiota-gut-brain axis – a bidirectional communication network between the gastrointestinal tract and the brain – is supported by both preclinical and clinical studies. Already during pregnancy and immediately after birth, the maternal microbiota – shaped by diet, health status, vaginal microbiota, mode of delivery, and antibiotic use – may substantially influence the composition of the newborn's microbiota. Studies suggest that these factors may influence subsequent neurodevelopmental outcomes. Children of women with disrupted gut microbiota, in whom dysbiosis occurs, may exhibit an increased risk of neurodevelopmental disorders, probably as a result of the action of pro-inflammatory cytokines, bacterial metabolites, or changes in immune system functioning already during fetal life [27]. The mode of delivery is also important; infants delivered vaginally generally exhibit a distinct and more diverse microbiota composition than those delivered by cesarean section.

Animal studies provide further evidence for an association between the microbiota and brain function. Experiments conducted on mice have shown that the disruption of microbial composition in early life may lead to persistent changes in behavior and brain structure, such as increased anxiety levels, impaired myelination, or difficulties in social interactions [4]. In mice devoid of intestinal flora (so-called germ-free), disturbances in the development of neurons and microglial cells were observed, supporting the view that intestinal bacteria are essential for normal nervous system development. One of the mechanisms through which the microbiota influences the brain is the production of neuroactive substances, such as short – chain fatty acids (SCFA), GABA, serotonin, and dopamine. These compounds act on neurons directly or indirectly via the immune system. Of particular interest are findings indicating that certain bacteria are capable of producing neurotransmitters or influencing their levels in the body, which may be relevant to the etiology of autism spectrum disorders.

An increasing amount of evidence also comes from studies conducted in humans. Already in early life, in infants at risk of developing autism, differences in intestinal flora composition have been identified. For example, a reduced presence of beneficial bacteria of the genus *Bifidobacterium* was noted, along with a greater proportion of potentially pro – inflammatory bacteria such as *Clostridioides* [27]. Importantly, these changes preceded the appearance of visible clinical symptoms, suggesting that the microbiota may serve not only as an indicator but also as a risk factor. However, establishing causality remains challenging. Many variables are involved, such as study methodology, timing, and interactions with genetic or environmental factors. Nevertheless, the number of findings indicating that disturbances in microbiological balance in the first years of life may contribute to the development of neurodevelopmental disorders or increase their severity is growing. In this context, microbiota based interventions, such as the use of probiotics, prebiotics, or fecal microbiota transplants (FMT), are of considerable interest. Although these are still experimental methods, intensive research is being conducted on their safety and potential efficacy. In the future, they may become components of therapeutic strategies supporting the development of children with autism spectrum disorders or ADHD.

One of the main problems in research on the role of the microbiota in developmental disorders is the difficulty in determining cause and effect. Increasing attention has been given to the possibility of a bidirectional relationship. Changes in the gut microbiota may influence neurological symptoms, but the symptoms themselves, as well as treatment and lifestyle, may in turn alter the microbiota. For example, children with autism often have a restricted diet resulting from strong sensory preferences. Selective eating patterns are common, which leads to a decrease in intestinal microbial diversity. A diet low in fiber and fresh products and rich in processed foods promotes the growth of opportunistic bacteria that may intensify inflammation and exacerbate neurological symptoms [25]. Another factor influencing the microbiota is psychotropic medication. Some of these drugs, particularly antipsychotics and antidepressants, may alter the composition of bacterial flora. Certain antipsychotic drugs exhibit antibacterial activity that reduces the abundance of beneficial bacteria such as *Akkermansia* or *Faecalibacterium*, which may lead to intensified inflammation and further dysregulation of the gut – brain axis [1]. Clinical observations also indicate that children with ASD frequently present with gastrointestinal symptoms, including constipation, diarrhea, and abdominal pain. Such disturbances promote the development of inflammatory states and further changes in the microbiota, potentially creating a self – perpetuating cycle. Alterations in gut microbiota composition may influence neurological symptoms, which in turn worsen gastrointestinal function. Psychological factors also affect the microbiota. Chronic stress, tension, and sleep disturbances, frequently occurring in individuals with neurodevelopmental disorders, disrupt the functioning of the hypothalamic – pituitary – adrenal (HPA) axis, leading to increased cortisol levels and enhanced intestinal permeability. This, in turn, facilitates the translocation of bacterial toxins into the bloodstream and the intensification of inflammatory responses [27].

In addition, children with ASD often live in greater social isolation, are less physically active, and have limited contact with a diverse environment, all of which may influence microbiota composition. Lifestyle, level of activity, diet, and stress are factors that together create an environment that may support or disrupt gut microbiota homeostasis. Moreover, non – pharmacological methods of support, such as sensory therapy, psychotherapy, and behavioral interventions, by reducing stress and improving sleep quality, they may indirectly influence gut microbiota composition as well. Although research in this area is still at an early stage, initial results suggest that an improvement in psychological well – being may be accompanied by changes in microbiota composition or function.

Table 1. Factors of dysbiosis and associated clinical outcomes

Factor of dysbiosis	Associated clinical outcomes
Premature birth	Disrupted microbial colonization and hospital associated microbiota exposure Increased risk of necrotizing enterocolitis (NEC), sepsis, immune dysregulation, and infections.
Cesarean section	Altered initial microbial colonization and impaired immune maturation Increased risk of metabolic disorders, allergic diseases, autoimmune diseases, neurodevelopmental disorders, infections, and obesity.
Lack of breastfeeding	Impaired immune maturation and reduced gut barrier function Increased risk of metabolic disorders, allergic diseases, and infections.
Antibiotic exposure	Decreased microbial diversity ~30%Increased risk of metabolic disorders, auto-immune diseases, allergic diseases, and asthma.

Summary

The human intestine harbors a vast number of microorganisms that are essential to host physiology. Although invisible to the naked eye, bacteria, viruses, and fungi form a complex community known as the microbiota, which is integral to the maintenance of health. Their functions extend beyond digestion; the microbiota modulates immunity, metabolism, and even mood and brain development. Bacterial colonization of the newborn begins at birth. Infants delivered vaginally are typically colonized by microbial communities resembling the maternal vaginal and intestinal microbiota, which may support early immune development. In the case of cesarean section, this transmission is disrupted; early colonization is more strongly influenced by skin – associated and hospital – derived bacteria. As a result, infants delivered by cesarean section may be at increased risk of allergies, infections, or metabolic diseases. Although a cesarean section is sometimes unavoidable, interventions can be implemented, for example, through probiotic administration or breastfeeding, which plays a crucial role in shaping the infant gut microbiota. The composition of the microbiota is also influenced by various environmental factors, such as place of residence, the presence of siblings, and contact with animals. Children raised in rural areas or living in households with pets tend to exhibit a more diverse gut microbiota, which may protect them against allergies or autoimmune diseases. In contrast, urban children more often exhibit microbial profiles associated with inflammatory conditions. However, microbial homeostasis can easily be disrupted, for instance, by antibiotics. Although often indispensable, these medications may also reduce the abundance of beneficial bacterial taxa. The consequences may be long lasting and include an increased risk of obesity, asthma, and even mental disorders. Excessive antibiotic therapy in children is particularly concerning while the microbiota is still developing. Moreover, bacteria can transfer resistance genes among themselves, which may complicate the treatment of infections in the future.

Increasing evidence also indicates that the microbiota plays an important role in brain development, especially during early life. Studies show that children with autism spectrum disorders or ADHD often have disturbed intestinal flora. Alterations have been reported in bacterial taxa involved in the production of neuroactive compounds influencing the nervous system, such as serotonin or GABA. Interestingly, these differences are visible already in early childhood, before symptoms appear. These observations suggest potential future applications of diet or microbiota – targeted interventions. In the future, appropriately designed dietary or probiotic interventions may support not only gut health but also neurodevelopmental outcomes. However, it should be noted that the microbiota is extremely variable. Each individual harbors a distinct microbial profile, and what is beneficial for one individual may not confer the same benefit to another. Nevertheless, substantial evidence suggests that maintaining of a healthy gut microbiota, beginning at birth, may represent a key determinant of long – term health outcomes.

Statement of conflict of interest.

The authors declare no conflict of interest.

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