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The role of gut microbes in autism: A meta-analysis of dysbiosis and functional implications

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Abstract

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by social communication deficits, repetitive behaviors, and restricted interests. While the exact etiology of ASD remains unclear, emerging research highlights the role of gut microbiota in its development and symptomatology. This meta-analysis synthesizes current evidence on gut microbiome dysbiosis in individuals with ASD, focusing on microbial diversity alterations, functional implications, and potential therapeutic interventions. Studies indicate that ASD is associated with an imbalance in gut microbiota, including decreased levels of beneficial bacteria such as Bifidobacterium and Prevotella and an increased abundance of potentially pathogenic species like Clostridium. Dysbiosis may contribute to ASD pathophysiology through immune system dysregulation, altered neurotransmitter production, and gut-brain axis disruptions. Furthermore, gut-derived metabolites, including short-chain fatty acids (SCFAs), have been implicated in modulating neurodevelopment and behavior. Given these findings, microbiome-targeted therapies, including dietary interventions, probiotics, and fecal microbiota transplantation (FMT), have been explored for their potential to restore microbial balance and alleviate ASD-related symptoms. However, variability in study designs, methodological inconsistencies, and the heterogeneity of ASD populations present significant challenges in establishing definitive causal links and therapeutic strategies. This review underscores the need for standardized research methodologies, large-scale longitudinal studies, and multi-omics approaches to enhance the understanding of gut microbiota's role in ASD. Future research should focus on personalized interventions tailored to individual microbiome profiles, potentially offering novel therapeutic avenues for ASD management.

Keywords: Autism Spectrum Disorder (ASD); Gut Microbiota Dysbiosis; Gut-Brain Axis; Microbiome-Targeted Therapies; Neurodevelopmental Disorders

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that is linked to repetitive behaviors, limited interests, and ongoing challenges with social communication and interactions (Mauliddiyah, 2021; Xu et al., 2019). According to Xu et al., (2019), ASD exhibits significant variability in its presentation, and its underlying causes remain elusive. Past research has implicated several potential factors in the development of ASD, such as genetic anomalies, immune system dysregulation, inflammation, and environmental influences (Almeida et al., 2020). The prevalence of gastrointestinal (GI) problems, which range from 23% to 70%, is commonly observed in people with ASD. These symptoms include constipation, stomach pain, gaseousness, diarrhea, and flatulence (Hernan Garcia-Ruiz, 2019; Xu et al., 2019). Additionally, recent estimates indicate that ASD affects 0.6% to 1.7% of children and adolescents, underscoring its significance as a pressing public health concern (Iglesias–vázquez et al., 2020). There is a significant gender gap in the diagnosis of ASD, with men up to four times more likely than women to be diagnosed. New research

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indicates that the gut may be crucial in the development of ASD, even though there is no proven direct causal connection between GI symptoms and the disorder. This emphasizes the significance of investigating the relationship between GI health and ASD symptoms, given the significant individual variation brought on by intricate genetic, environmental, and neurological factors (C. Almeida et al., 2020; Iglesias–vázquez et al., 2020; Xu et al., 2019). Almeida et al., (2020) observed that the human body contains approximately ten times more microbial cells than human cells, primarily due to the vast diversity of microorganisms in the gastrointestinal tract. The predominant microorganisms in this setting are anaerobic bacteria, especially Bacteroidetes, and Firmicutes; nevertheless, this intricate ecology also includes viruses, protozoa, archaea, and fungi. The human microbiome is a dynamic microbial community that resides in different bodily locations and is made up of these microorganisms and their genetic material. It is essential for promoting growth and development, affecting disease processes, and preserving health. Research on ASD has traditionally focused on genetic and neurological variables, but more recently, studies have looked into how the gut microbiota affects neurodevelopment (Cryan et al., 2019). This diverse microbial community, residing in the gastrointestinal tract, is integral to brain function through the gut-brain axis—a bidirectional communication system that includes neural, hormonal, and immune pathways (Dalile et al., 2018; Margolis et al., 2021). The significance of examining the potential role of gut microorganisms in the development and progression of ASD is highlighted by an understanding of these interactions. Compared to neurotypical people, research shows that children with ASD frequently have dysbiosis, or imbalances in their gut microbiota, which is characterized by changes in microbial diversity and composition (Lukianowicz, 1972; Strati et al., 2017). These disruptions have been associated with gastrointestinal (GI) issues, immune system irregularities, and metabolic disturbances, all of which are commonly reported in individuals with ASD (Coretti et al., 2018; Eltokhi & Sommer, 2022; Hsiao, 2014). Additionally, microbial metabolites including neurotransmitter precursors and short-chain fatty acids (SCFAs) affect behavior, cognition, and neural function, which lends credence to the idea that gut microorganisms contribute to the pathophysiology of ASD (Sharon et al., 2019). The exact mechanisms underlying the growing body of data connecting gut microbiota to ASD are still unknown, and variations in study designs, participant cohorts, and analysis techniques lead to inconsistent results (Zhao et al., 2021). This study aims to synthesize the existing literature on gut microbiome alterations in ASD, examine the functional consequences of dysbiosis on neurodevelopment, and assess microbiome-targeted interventions such as dietary changes, probiotics, and fecal microbiota transplantation (FMT) (Dalile et al., 2018). By consolidating current knowledge, this review provides a clearer understanding of the gut microbiome's role in ASD while identifying future research directions that may facilitate the development of novel therapeutic approaches.

2. Gut Microbiome Dysbiosis in ASD

The gut microbiota, composed of billions of bacteria residing in our gastrointestinal (GI) tract, plays a vital role in maintaining host homeostasis (Eltokhi & Sommer, 2022; Schroeder & Bäckhed, 2016). There are more than 160 types of bacteria, but the two most prevalent phyla in healthy people are Bacteroidetes and Firmicutes. Two layers of mucus and one layer of epithelial cells divide immune cells from the gut microbiota, which regulates the immune system (Chen et al., 2016; Thursby & Juge, 2017). These bacteria benefit the host by providing essential nutrients, enhancing gut integrity, preventing colonization by pathogenic species, and generating energy (Eltokhi & Sommer, 2022; Rowland et al., 2018; Scott & Dezzutti, 2016). However, the host's health may suffer as a result of dysbiosis, a disturbance in the gut microbiota's makeup that can result in anything from chronic gastrointestinal diseases to neuropsychiatric problems (Indiani et al., 2018; Schroeder & Bäckhed, 2016). Over the past decade, advancements in high-throughput, low-cost sequencing techniques have allowed researchers to explore the gut microbiota's role in human health (Thursby & Juge, 2017). Schroeder & Bäckhed, (2016) state that there is growing evidence linking the gut microbiota to several human illnesses, as illustrated in Figure 1. However, the 16S ribosomal RNA gene, which is found in all bacteria and offers nine highly variable areas for phylogenetic analysis as well as sequence conservation, can now be used to easily identify different species of bacteria (Eltokhi & Sommer, 2022).

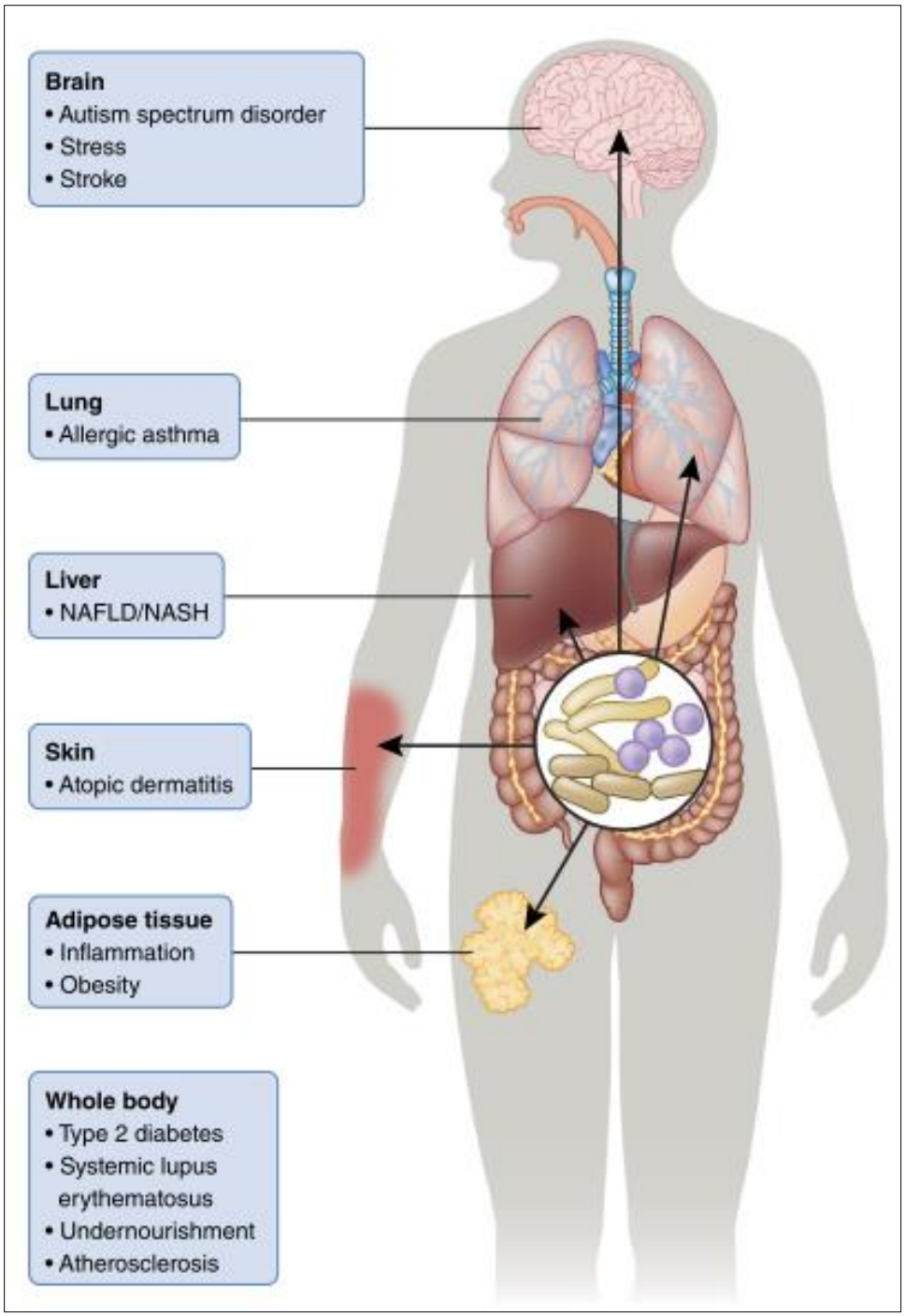

Figure 1 Human diseases linked to the gut microbiota (Schroeder & Bäckhed, 2016)

In addition, the Human Microbiome Project (HMP), which was carried out in two stages over a ten-year period, aimed to describe the human microbiota and expand on our knowledge of how it affects health and illness (Proctor et al., 2019). In order to improve our understanding of human nutritional needs, the HMP also sought to discover new diagnostic health biomarkers. Age is one of the recognized factors that affect the composition of the gut microbiota (Figure 3) (Aleman & Valenzano, 2019), similarly, host genetics (Elderman et al., 2018; Kim et al., 2016), medications (Enin et al., 2021 & 2023; Maier et al., 2018; Vich Vila et al., 2020), body mass index (BMI) (Bai et al., 2019; Gao et al., 2018; Stanislawski et al., 2018), diet, delivery method (Akagawa et al., 2019; Reyman et al., 2019), and environmental factors (Osadchiy et al., 2019), as illustrated in Figure 2. These elements contribute to the complex and dynamic nature of the human gut microbiota.

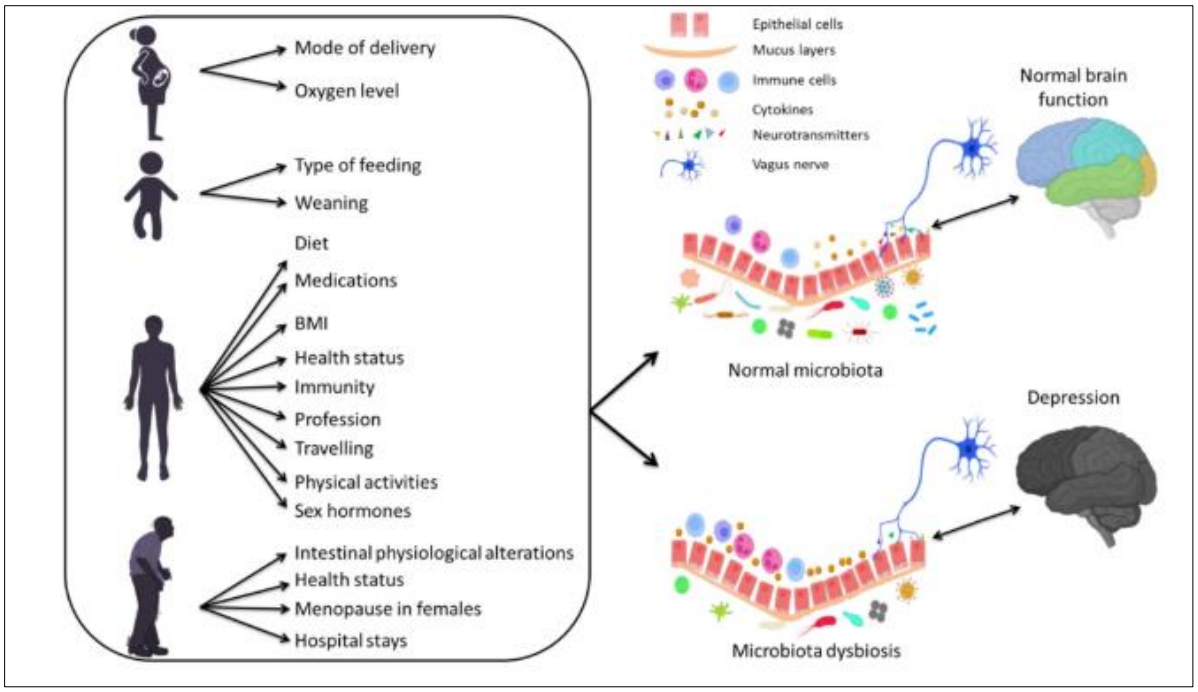

Figure 2 The effects of different factors at different periods of life on the composition of the gut microbiota and how these factors relate to depression by altering inflammatory responses (Eltokhi & Sommer, 2022)

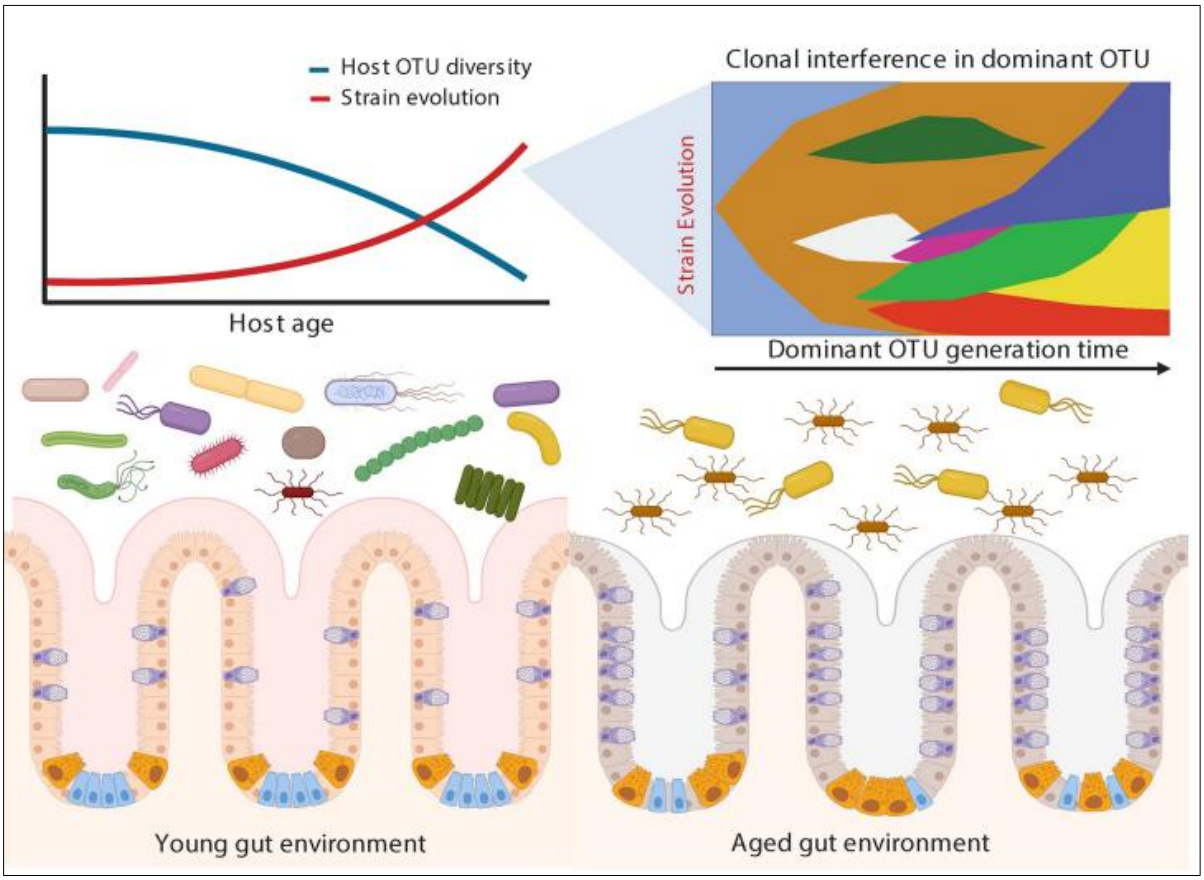

Figure 3 Aging alters gut microbiota, reducing diversity and enabling certain species to expand, increasing the risk of pathogenic strain evolution (Aleman & Valenzano, 2019)

Furthermore, the gut microbiome of individuals with ASD is clearly aberrant, often displaying altered composition and lower microbial diversity when compared to neurotypical controls. Notable differences include an increase in Bacteroides and Clostridium species and a decline in beneficial taxa like Bifidobacterium and Prevotella (Strati et al., 2017; Vernocchi et al., 2022). An increased Firmicutes-to-Bacteroidetes ratio, altered short-chain fatty acid (SCFA) production and an abundance of potentially pathogenic bacteria like Clostridium bolteae are characteristics of dysbiosis, an imbalance in gut microbiota that has been linked to gastrointestinal (GI) distress and inflammatory responses in ASD (Houtman et al., 2022; Kapoor et al., 2023).

Notably, a decrease in Prevotella—a genus associated with fiber metabolism and anti-inflammatory properties—has been frequently reported in ASD, suggesting a disrupted gut environment (Jiang et al., 2022; Kovatcheva-Datchary et al., 2015).These dysbiotic patterns have a major effect on the host's metabolomic profile, affecting gut-brain axis communication, immunological regulation, and neurotransmitter production. The pathophysiology of ASD is linked to increased intestinal permeability, systemic inflammation, and impaired brain function, all of which are correlated with lower levels of SCFAs like butyrate, which are produced by helpful bacteria like Faecali bacterium (Fukui, 2016; Venegas et al., 2019). Furthermore, by interfering with neurotransmission and mitochondrial function, elevated levels of toxic metabolites, such as propionic acid, a byproduct of Clostridium species, have been demonstrated to exacerbate symptoms similar to ASD. Microbiome-targeted therapies such as probiotics, prebiotics, and fecal microbiota transplantation (FMT) may have therapeutic potential in lowering symptoms of ASD by improving metabolic function and reestablishing microbial balance. This is due to the gut-brain axis, which is a reciprocal link between the central nervous system and gut microbiota. More research on the gut microbiota's alterations in ASD could result in personalized treatment regimens and innovative microbiome-based diagnostics that improve the lives of those who have the disorder (Borrego-Ruiz & Borrego, 2024).

2.1. Functional Implications of Gut Dysbiosis in ASD

The establishment of the human gut microbiome commences during the prenatal period, with its maturation occurring within the initial 2-3 years of life (Borrego-Ruiz & Borrego, 2024). The gut microbiota composition of children with ASD is frequently altered, according to study findings on neurodevelopmental diseases associated with gut microbiome dysbiosis. Reduced microbial diversity and an increase in the prevalence of particular bacterial species, including Clostridium, Desulfovibrio, and Bacteroides, are characteristics of this change (Ho et al., 2020; Rendon-Rosales et al., 2024). However, human studies have revealed that children exposed to maternal inflammation during gestation face a higher risk of developing ASD, though the underlying mechanisms remain unclear (Ho et al., 2020). Interest in the possible links between ASD and the gut microbiota has been rekindled by recent groundbreaking animal research that offer fresh perspectives on the ways in which inflammation and gut bacteria affect neurobehavioral outcomes (Ho et al., 2020; Xu et al., 2019). For instance, mice born to mothers with immune-activating intestinal bacteria exhibited impaired sociability and repetitive behaviors, suggesting a link between gut microbiota and neurodevelopmental disorders (Elderman et al., 2018; Sharon et al., 2019). Microbial imbalance may contribute to the gastrointestinal (GI) disturbances commonly reported in ASD, including constipation, diarrhea, and increased intestinal permeability or "leaky gut" (Navarro et al., 2015; Tetz & Tetz, 2016). Systemic and neuroinflammation are brought on by increased gut permeability, which permits endotoxins such as lipopolysaccharides (LPS) and bacterial metabolites to enter the bloodstream. Short-chain fatty acids (SCFAs), immunological mediators, and neurotransmitter precursors are examples of microbial metabolites that are part of the gut-brain axis, a network of bidirectional communication between the gut microbiota and the brain (Candelli et al., 2021; Ho et al., 2020). Propionate exposure has been linked in animal studies to symptoms resembling ASD, demonstrating how SCFAs such as butyrate and propionate can change neurodevelopment and behavior. Abnormalities in neurotransmitter synthesis, including gamma-aminobutyric acid (GABA) and serotonin, caused by dysbiosis, may be a factor in the social and anxiety problems linked to ASD. Therapies such as fecal microbiota transplantation (FMT), probiotics, and prebiotics have demonstrated potential in reestablishing gut microbial balance and alleviating symptoms of ASD. Nonetheless, as Table 1 shows, a number of investigations on the functional consequences of gut dysbiosis in ASD have been carried out. New therapeutic avenues and a better understanding of this complex disorder could result from more research on the gut-brain axis and its role in the development of ASD (O'Riordan et al., 2022; Parker et al., 2020; Zhong et al., 2023).

Table 1 Research on the Functional Implications of Gut Dysbiosis in Autism Spectrum Disorder (ASD)

Objectives	Implications	Outcomes	References
Roles of gut microbiome in ASD using fecal metagenomics and metabolomics.	The metabolic analysis of children with autism spectrum disorder (ASD) reveals 18 dysregulated pathways and 29 differential species, along with elevated serum TNFα levels. Neuroinflammation is exacerbated by microbial dysbiosis, highlighting the part TNFα plays in the pathophysiology of ASD.	The study suggests that gut microbiome-based treatments for children with ASD may be improved by examining the axis of TNFα-sphingolipids-steroid hormones.	(Shao et al., 2024)
The study explores the influence of gut microbes and their metabolites on blood-brain barrier integrity, brain function, and communication networks between the gastrointestinal tract and brain.	Although precise processes are not well understood, dietary and microbial manipulation are intriguing approaches to treating neurological and neurodegenerative illnesses.	Understanding gut microbial ecology, metabolism, and signaling networks could lead to new microbiome-targeted strategies for disease treatment and prevention.	(Parker et al., 2020)
Research indicates gut microbiome impact on early brain development and its correlation with neurological disorders like autism, Tourette syndrome, cerebral palsy, fetal alcohol spectrum disorders, and genetic disorders.	NDDs affect not just the people who are diagnosed but also their families and communities, which has a big social impact.	The study suggests that understanding the changes in the gut microbiome in non-diabetic individuals could offer new opportunities for future treatment.	(Borrego-Ruiz & Borrego, 2024)
The study explores the brain-gut-microbiome system and examines findings from recent research conducted on both animals and humans.	The development of treatments that target microbiota, which can have a substantial impact on the molecular, structural, and functional networks of the brain, depends heavily on the brain-gut-microbiome system.	Gaining deeper insights into the gut microbiome's role in ASD requires examining its interactions with both host and environmental factors.	(Chernikova et al., 2021)
The study aims to identify specific microorganisms involved in various processes and clarify metabolic pathways, particularly those linked to dietary component metabolism and host-derived substances.	Through specific routes, the gut microbiota is essential to the metabolism of phytochemicals, particularly polyphenols. Variations in gut microbiota makeup are a major factor in individual variances in polyphenol metabolism, which in turn affects the health implications of these compounds. This demonstrates how the microbiota affects the digestion of dietary polyphenols and the possible consequences for general health.	Gut microbiota-derived compounds can be absorbed and integrated into host metabolic pathways, both endogenous and exogenous, shaping the host's overall metabolic profile.	(Rowland et al., 2018)
The study examines the gut microbiome's ecological and functional traits in ASD, considering GI symptoms, diet, fecal biomarkers, and age as key factors.	Using metagenomics and biomarkers, fecal samples from 35 neurotypical and 41 ASD children (ages 3–15) were examined. Proteobacteria, Bacteroidetes, and Klebsiella were found to be more prevalent in ASD individuals, but zonulin and lysozyme levels were	In the patient cohort, despite evaluating multiple factors influencing the gut microbiome, GI hallmarks and age were	(Vernocchi et al., 2022)

	lower in those with GI symptoms. Eighty percent of ASD cases were categorized by machine learning using microbial differences.	the primary determinants.	
The study examines microbiota and metabolites in ASD, exploring potential mechanisms through which microbes influence brain function and behavior.	Human research on the microbiota-gut-brain axis is still scarce and contradictory, despite extensive research on animals that demonstrates how microbiome changes impact behavior. ASD is associated with dysbiosis, though results vary. The potential significance of microbiota in neurological and behavioral outcomes is highlighted by promising therapies such as fecal microbiota transplants, which suggest microbiome involvement in ASD.	Microbiota likely influences ASD, but more studies on mechanisms and interventions are needed.	(Hughes et al., 2018)

2.2. Diet, Probiotics, and Microbiome Modulation in ASD

According to Ersöz Alan et al., (2019), a number of recent evaluations highlight how important food composition is in controlling or reducing symptoms of ASD. Utilizing probiotics has been demonstrated to enhance gut flora, which has positive health effects. Children with ASD have been demonstrated to benefit from probiotic therapy, establishing them as a potential supplementary therapeutic approach. Additionally, Momen et al., (2024) pointed out that new research has shown how microbial metabolites and gut-brain communication play a part in several illnesses, such as type 2 diabetes and Alzheimer's disease (AD). The most prevalent type of dementia, AD, is mostly sporadic and has no known cause, though several factors influence it. These factors fall into one of two categories: changeable (like type-2 diabetes and dietary habits) or non-modifiable (like hereditary predisposition). The significance of food and probiotics in controlling the gut microbiota, which might affect symptoms of ASD, was also emphasized by Azad et al., (2018). A surplus of pathogenic bacteria and a reduction in microbial diversity are two common changes in the gut microbiota of children with ASD. Probiotics and dietary modifications are being researched as potential means of reducing ASD symptoms and reestablishing microbial balance (Shao et al., 2024). Furthermore, it has been demonstrated that the gut microbiota influences a number of bodily systems, including the brain, metabolism, cardiovascular system, and immune system. Among the numerous ailments that alter their composition are cardiovascular diseases, cancer, type-2 diabetes, obesity, colitis, asthma, mental illnesses, and inflammatory diseases. Changing the gut microbiota has shown therapeutic potential since probiotic supplementation in high-fat diets has been linked to changes in microbial composition, namely a decrease in Firmicutes and Actinobacteria in rats. Diet has a major impact on the gut flora, and as Figure 4 illustrates, GFCF diets are the subject of many studies in relation to ASD. Gluten and casein peptides are hypothesized to be the cause of increased gut permeability and inflammatory responses (Navarro et al., 2015). Although results are still mixed, studies suggest that GFCF diets may help certain ASD patients with their behavioral issues and GI symptoms (Ehrlich et al., 2021). Additionally, high-fiber, prebiotic-rich diets that include fructooligosaccharides and inulin encourage the development of beneficial bacteria and boost the production of short-chain fatty acids (SCFAs), which are critical for gut-brain communication (Bai et al., 2019; De Almeida et al., 2019; Elderman et al., 2018). Probiotics, particularly Lactobacillus and Bifidobacterium strains, have been shown to have the ability to change ASD symptoms. Clinical research have demonstrated the potential of probiotics to improve GI health, reduce inflammation, restore microbial balance, and positively influence behavior. Additionally, some studies suggest that probiotics may boost the production of neurotransmitters that are crucial for mood regulation and social behavior, such as serotonin and gamma-aminobutyric acid (GABA). All things considered, probiotic supplements and dietary modifications that modify the microbiome have promise as an ASD therapy strategy (C. V. De Almeida et al., 2019; Huang & Wu, 2021; Zhong et al., 2023).

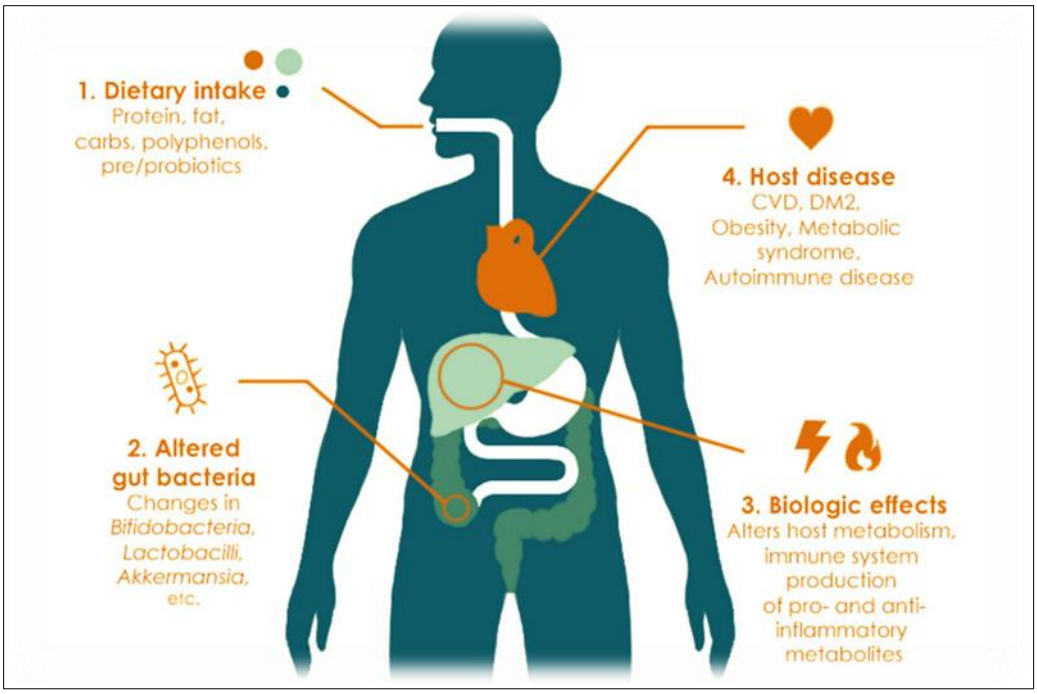

Figure 4 Dietary influences on human health and gut microbiota (Singh et al., 2017)

3. Challenges, Limitations, and Future Directions

Despite significant advancements in our understanding of the role of gut microbiota in autism spectrum disorder (ASD), numerous barriers and limitations remain. One of the major challenges is the variability of study methods, including differences in participant selection, microbiome collecting, and data analysis techniques. It is difficult to establish a shared knowledge of gut dysbiosis in ASD because of these disparities, which produce inconsistent findings. Additionally, most studies employed cross-sectional designs, which precludes concluding whether changes in gut microbiota are a cause of ASD or a causal link between the two conditions. The lack of comprehensive, long-term studies that track changes in the microbiome over time, particularly in the early stages of development, is another disadvantage. Such studies are necessary to determine whether specific microbial patterns can serve as biomarkers for the diagnosis or development of ASD. Probiotic treatments and fecal microbiota transplantation (FMT) have also demonstrated potential in altering the gut microbiota and reducing ASD symptoms, although their long-term efficacy and safety are still unknown. The variability of ASD makes microbiome-targeted therapy more difficult because individual responses to FMT, probiotics, and dietary changes vary. To provide a more thorough understanding of how microbial metabolites affect neurodevelopment, future research should concentrate on combining multi-omics approaches, such as transcriptomics, metabolomics, and metagenomics. Personalized microbiome-based interventions may result from improved data analysis brought about by developments in artificial intelligence and machine learning. Further investigation into microbial signaling networks and gut-brain axis interactions may also help identify new therapeutic targets. To increase the clinical applicability and repeatability of microbiome research and interventional studies, standardized procedures are needed. In order to effectively translate microbiome-based discoveries into treatments for ASD, an interdisciplinary strategy integrating clinical research, microbiology, and neurology will be essential.

4. Conclusion

The mounting evidence linking gut microbiota to ASD highlights the significance of the gut-brain axis in neurodevelopmental disorders. Decreased microbial diversity and an imbalance of key bacterial populations are hallmarks of dysbiosis, which appears to contribute to the symptomatology of ASD by influencing intestinal permeability, immunological responses, and neurotransmitter metabolism. Probiotics, dietary modifications, and fecal microbiota transplantation (FMT) are a few microbiome-targeted treatments that have shown promise in lowering ASD symptoms; nevertheless, there are still concerns over their long-term efficacy and safety. The heterogeneity of ASD complicates therapeutic possibilities since individual responses to microbiome alteration vary. Limited sample sizes, varied research methodologies, and cross-sectional designs further complicate the evidence of a causal connection between gut dysbiosis and ASD. To learn more about microbial interactions and their effects on neurodevelopment,

future research should concentrate on the integration of multi-omics technologies, such as transcriptomics, metabolomics, and metagenomics. Personalized microbiome-based interventions could also benefit from developments in machine learning and artificial intelligence. Standardized procedures are essential for improving clinical applicability and reproducibility in microbiome research and intervention studies. Transforming microbiome-based findings into efficient, focused treatments for people with ASD will ultimately require a multidisciplinary strategy involving neurology, microbiology, immunology, and clinical research.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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