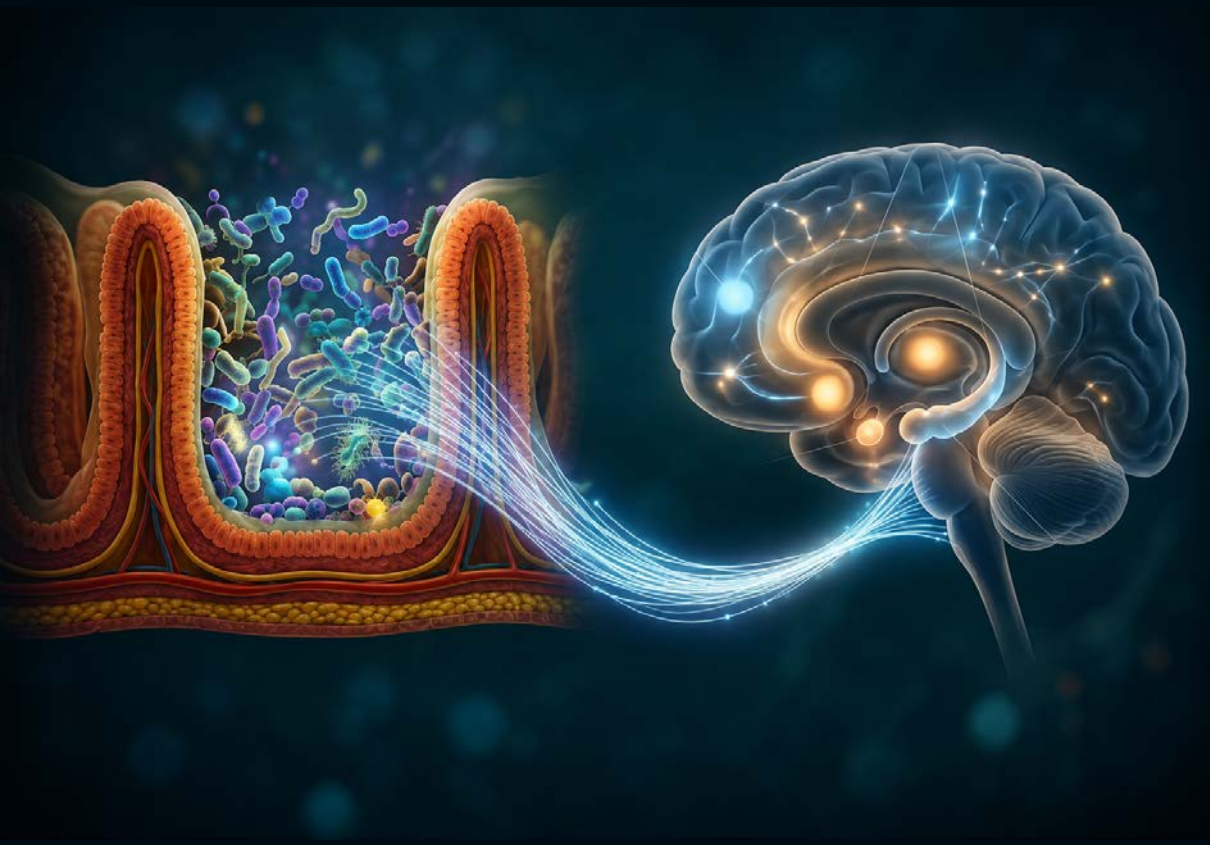
AUTISM SPECTRUM DISORDER AND GUT DYSBIOSIS

Cause, Consequence, or a Vicious Cycle?



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AUTISM SPECTRUM DISORDER AND GUT DYSBIOSIS:

Cause, Consequence, or a Vicious Cycle?

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CONTENTS

1. INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and interaction, along with restricted, repetitive patterns of behavior, interests, or activities (Hodges, Fealko, & Soares, 2020). Diagnosis rates have increased substantially over recent decades, making ASD one of the most commonly recognized neurodevelopmental disorders worldwide (Salari et al., 2022). Although increased awareness and broader clinical definitions have contributed to this rise, current evidence suggests that ASD involves complex interactions among genetic susceptibility, environmental factors, immune alterations, and metabolic disturbances (Kamijo, Miwa, & Ikeda, 2026). Despite major advances in neuroscience and genetics, the underlying biology of autism remains only partially understood (Gullapalli et al., 2025).

Recently, the gut–brain axis has emerged as an important focus in neurodevelopmental research. This bidirectional communication network connects the gastrointestinal tract and the central nervous system through neural, endocrine, immune, and metabolic pathways. The gut and brain do not function

independently; rather, they continuously exchange signals that contribute to systemic homeostasis and influence physiological and behavioral processes (Jiang et al., 2026; Zhang et al., 2025).

The gut microbiota plays a central role in this interaction. This complex microbial ecosystem contributes to nutrient metabolism, immune system maturation, maintenance of intestinal barrier integrity, and prevention of pathogen overgrowth (Khan et al., 2024). Beyond its role in gastrointestinal health, the microbiota produces bioactive metabolites that can influence brain function. These microbial-derived molecules affect neural development through modulation of neurotransmitter metabolism, short-chain fatty acid (SCFA) production, immune signaling, vagus nerve activity, and the hypothalamic–pituitary–adrenal (HPA) axis (Mhanna et al., 2024).

Interest in this field increased following observations that gastrointestinal symptoms are frequently reported in individuals with ASD. Chronic constipation, diarrhea, abdominal pain, and bloating occur more commonly in these individuals than in neurotypical populations, negatively affecting quality of life and

increasing challenges for affected individuals and their families (Młynarska et al., 2025). These findings have encouraged researchers to investigate whether gut dysbiosis contributes to ASD-related biological mechanisms or influences behavioral manifestations associated with the condition (Wang et al., 2026). Although numerous studies have identified differences in microbial composition and metabolic profiles between individuals with ASD and neurotypical controls, the evidence remains heterogeneous. These inconsistencies may result from variations in sample size, dietary patterns, medication exposure, age distribution, geographical factors, and microbiome analysis methodologies (Bezawada et al., 2020).

Animal models have provided important mechanistic insights into these interactions. Experimental studies demonstrate that alterations in the gut microbiota can influence social behaviors, modulate neuroinflammatory responses, affect intestinal permeability, and alter neurotransmitter-related pathways (Jiang et al., 2026; Xu & Lu, 2025). In clinical research, early pilot studies investigating microbiota-targeted interventions have demonstrated potential benefits for gastrointestinal symptoms and, in some cases, behavioral

outcomes (Alkuwaiti et al., 2025). These findings raise an important question: does gut dysbiosis contribute to autism-related pathophysiology, or does it primarily emerge as a consequence of behavioral and physiological characteristics associated with ASD? (Młynarska et al., 2025; Zhang et al., 2025).

Available evidence indicates that a simple unidirectional cause–effect model may not adequately explain the relationship between ASD and gut dysbiosis (Li et al., 2023). Instead, selective eating behaviors, gastrointestinal dysfunction, immune alterations, impaired intestinal barrier function, low-grade inflammation, and microbial changes may interact reciprocally. This dynamic interaction may create a self-reinforcing cycle in which gut microbial alterations influence brain-related processes, while ASD-associated behaviors and physiological changes further modify the intestinal ecosystem (Chen et al., 2026). Understanding this complex relationship is essential for clarifying ASD mechanisms and developing targeted microbiota-based therapeutic strategies (D'Angelo et al., 2025).

This chapter critically examines the current evidence regarding the relationship between autism and gut

dysbiosis, addressing whether this association represents a cause, a consequence, or a self-perpetuating cycle. The biological mechanisms underlying the gut–brain axis, findings from animal models and human studies, potential therapeutic approaches, and current research limitations will be discussed, followed by future research priorities in this rapidly evolving field.

2. AUTISM SPECTRUM DISORDER: CURRENT OVERVIEW

2.1. Definition and Diagnostic Criteria

ASD is a heterogeneous neurodevelopmental condition characterized by persistent difficulties in social communication and interaction, accompanied by restricted or repetitive behaviors and highly focused interests (Hodges et al., 2020). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR), these characteristics emerge during early childhood but may become fully apparent only when social demands exceed the individual's developmental capacities (Hodis et al., 2025). The spectrum encompasses individuals with diverse levels of functioning, ranging from those who achieve independent living to those requiring substantial lifelong

support due to significant cognitive and functional limitations (Lord et al., 2018).

The clinical classification of autism has undergone substantial changes over time. Earlier diagnostic systems categorized autism-related conditions separately, including autistic disorder, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS) (Hodis et al., 2025; McPartland & Volkmar, 2012). However, accumulating genetic and clinical evidence demonstrated considerable overlap among these conditions, leading the DSM-5 to consolidate them into a single diagnostic category (Rosen et al., 2021). This transition reflects the current understanding of autism as a continuous spectrum of neurodevelopmental variation rather than a collection of completely distinct disorders (Waizbard-Bartov et al., 2023).

Clinical heterogeneity represents one of the defining characteristics of autism. Individuals differ considerably in cognitive abilities, language development, adaptive functioning, sensory processing, and the presence of co-occurring medical conditions (Hodges et al., 2020; Lord et al., 2018). While some develop functional language and

independent living skills, others remain minimally verbal or experience intellectual disability (Waizbard-Bartov et al., 2023). This variability suggests that autism does not result from a single biological abnormality but rather reflects multiple, partially overlapping developmental pathways (Gullapalli et al., 2025; Kamijo et al., 2026).

2.2. Epidemiology

Autism is among the most commonly diagnosed neurodevelopmental conditions worldwide (Lord et al., 2018). Recent surveillance data indicate that approximately 1 in 31 8-year-old children across monitored sites in the United States are identified with ASD; however, prevalence estimates vary globally due to differences in screening practices, healthcare accessibility, diagnostic criteria, and awareness levels (Shaw et al., 2025; Salari et al., 2022). Although improved detection and broader diagnostic definitions have contributed substantially to increasing prevalence estimates, these factors may not fully account for observed trends, suggesting that biological and environmental influences may also contribute (Kamijo et al., 2026).

ASD occurs across all racial, ethnic, geographic, and socioeconomic populations. It is diagnosed more

frequently in males than females, with reported male-to-female ratios generally ranging from approximately 3:1 to 4:1; however, recent evidence suggests that females may be underdiagnosed (Salehi et al., 2025). Females may present with different behavioral patterns, subtler social difficulties, and increased use of compensatory strategies, which can contribute to delayed recognition and diagnosis. Understanding sex-related differences in autism presentation has therefore become an important area of current research (Napolitano et al., 2022). Although symptoms typically emerge in early childhood, ASD represents a lifelong neurodevelopmental condition, and early identification is associated with improved access to support and developmental outcomes (Okoye et al., 2023).

2.3. Etiology and Risk Factors

The etiology of autism is considered multifactorial, involving complex interactions between genetic susceptibility and environmental influences during critical periods of brain development (Kamijo et al., 2026; Lord et al., 2018). Hundreds of genetic variants have been associated with ASD, including genes involved in synaptic development, neuronal connectivity, chromatin remodeling, immune regulation, and intracellular

signaling pathways (Gullapalli et al., 2025; Kamijo et al., 2026). Rather than being explained by a single genetic alteration, most cases are thought to result from the combined effects of multiple genetic factors (Hodges et al., 2020; Kamijo et al., 2026).

Environmental factors may interact with genetic susceptibility and influence neurodevelopmental trajectories. Advanced parental age, maternal metabolic conditions, prenatal exposure to air pollution, maternal infections, certain medication exposures, preterm birth, and obstetric complications have been associated with increased ASD risk (Kamijo et al., 2026; Okoye et al., 2023). However, these factors are not considered direct causes of autism; instead, they may influence fetal brain development through mechanisms involving oxidative stress, immune activation, and alterations in gene regulation (Gullapalli et al., 2025; Kamijo et al., 2026). Consequently, autism is increasingly viewed as a complex, multisystem neurodevelopmental condition rather than an isolated disorder of the brain (Leisman et al., 2026). In recent years, interactions between immune pathways and the gut microbiome have emerged as an important component of this broader biological framework (Wang et al., 2026).

2.4. Clinical Manifestations and Common Comorbidities

Autism encompasses a broad range of clinical features beyond the core characteristics of social communication difficulties and restricted or repetitive behaviors (Waizbard-Bartov et al., 2023). Individuals may experience varying degrees of language impairment, difficulties with reciprocal communication, preference for routines, and highly focused interests (Hodges et al., 2020). Sensory processing differences are also frequently reported, including increased or reduced sensitivity to auditory, visual, tactile, or olfactory stimuli. These sensory characteristics may affect daily functioning and contribute to selective eating behaviors commonly observed in individuals with ASD (Balasco et al., 2020).

Autism is frequently accompanied by medical and psychiatric comorbidities, including anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), sleep disturbances, epilepsy, and intellectual disability (Salehi et al., 2025). Among these conditions, gastrointestinal (GI) disturbances have received considerable attention due to their high prevalence and potential effects on physical health and behavioral outcomes (Młynarska et al., 2025;

Zhang et al., 2025). Constipation, diarrhea, abdominal discomfort, bloating, and gastroesophageal reflux symptoms are reported more frequently among individuals with ASD compared with neurotypical populations (Alkuwaiti et al., 2025; Wang et al., 2026). These gastrointestinal symptoms may be influenced by factors such as restricted dietary patterns and food selectivity, which can subsequently affect gut microbial composition and function (Jiang et al., 2026; Młynarska et al., 2025).

The frequent observation of gastrointestinal abnormalities in ASD has strengthened interest in the bidirectional relationship between the intestine and the brain. Recent findings indicate that intestinal barrier function, immune regulation, microbial metabolites, and neuroendocrine signaling may influence ASD-related biological processes, providing a framework for investigating the gut–brain interaction in autism (Gullapalli et al., 2025; Kamijo et al., 2026; Leisman et al., 2026; Jiang et al., 2026; Xu & Lu, 2025).

3. GUT MICROBIOTA AND THE GUT–BRAIN AXIS

3.1. The Human Gut Microbiota

The human gastrointestinal tract harbors a highly complex microbial community known as the gut microbiota (Hou et al., 2022). This ecosystem consists of bacteria, viruses, fungi, and archaea that coexist with the host and contribute to numerous physiological processes (Afzaal et al., 2022). The majority of these microorganisms reside in the colon, where they perform functions essential for host metabolism and immune regulation (Al Bander et al., 2020).

The development of the gut microbiota begins at birth and undergoes substantial changes throughout infancy and childhood before reaching a relatively stable adult composition (Hou et al., 2022; Khan et al., 2024). Although each individual possesses a unique microbial profile, the human gut microbiota is largely dominated by four major bacterial phyla: Firmicutes, Bacteroidota, Actinobacteriota, and Proteobacteria (Afzaal et al., 2022; Al Bander et al., 2020). This microbial composition is continuously influenced by genetic background, mode of delivery, early-life feeding practices, dietary patterns,

antibiotic exposure, aging, and environmental factors (Chen et al., 2026; Jiang et al., 2026).

Rather than functioning as passive inhabitants, gut microorganisms actively contribute to host physiology. They participate in the degradation of indigestible dietary fibers, synthesis of essential vitamins, regulation of bile acid metabolism, protection against pathogenic microorganisms, and maturation of immune responses (Jiang et al., 2026; Xu & Lu, 2025; Zhang et al., 2025). Through these functions, the gut microbiota represents an important regulator of systemic homeostasis (Alkuwaiti et al., 2025; Młynarska et al., 2025; Wang et al., 2026).

3.2. The Gut–Brain Axis: A Bidirectional Communication Network

The bidirectional communication system connecting the gastrointestinal tract and the central nervous system is referred to as the gut–brain axis (Carabotti et al., 2015). This complex network involves neural, endocrine, immune, and metabolic pathways that enable continuous communication between intestinal and cerebral systems (Li et al., 2026).

The vagus nerve represents one of the major neural pathways involved in gut–brain communication. Signals

originating from intestinal microorganisms, epithelial cells, and enteroendocrine cells can influence vagal activity, thereby affecting processes related to mood regulation, cognition, stress responses, and gastrointestinal function (Hou et al., 2022; Jiang et al., 2026). In turn, central nervous system signals can modify gastrointestinal motility, secretion, intestinal barrier function, and microbial composition through autonomic nervous system regulation (Afzaal et al., 2022; Carabotti et al., 2015).

Endocrine pathways also contribute significantly to this interaction. Activation of the hypothalamic–pituitary–adrenal (HPA) axis during stress can increase glucocorticoid secretion, potentially affecting intestinal barrier integrity and microbial composition (Al Bander et al., 2020). At the same time, the gut microbiota can influence HPA axis activity, demonstrating the reciprocal nature of this communication system (Afzaal et al., 2022; Li et al., 2026).

3.3. Immune Regulation and Microbial Metabolites

The immune system represents a major mediator of gut–brain communication. The gastrointestinal tract contains a substantial proportion of the body's immune

components and maintains continuous interactions with resident microorganisms (Balakrishnan et al., 2024). Under physiological conditions, these interactions promote immune tolerance while maintaining effective defense mechanisms against pathogens (Cortés et al., 2025). Disruption of microbial homeostasis may alter immune signaling, increase production of pro-inflammatory cytokines, and affect mucosal immune responses (Zeng et al., 2025). These inflammatory processes may influence both intestinal function and neurological pathways, providing a potential biological link between gastrointestinal alterations and brain function (Balakrishnan et al., 2024; Zeng et al., 2025).

Gut microorganisms produce a wide range of biologically active metabolites (Hou et al., 2022; Zeng et al., 2025). Among these, short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate, are among the most extensively studied microbial metabolites generated through bacterial fermentation of dietary fibers (Afzaal et al., 2022; Li et al., 2026). SCFAs contribute to intestinal barrier maintenance, immune regulation, energy metabolism, and modulation of signaling pathways involved in gut–brain communication (Al Bander et al., 2020; Chen et al., 2026; Li et al., 2026).

Furthermore, gut microorganisms participate in amino acid metabolism and the production or regulation of neuroactive compounds, including serotonin, gamma-aminobutyric acid (GABA), dopamine-related metabolites, and tryptophan-derived molecules (Carabotti et al., 2015; Mhanna et al., 2024; Xu & Lu, 2025). Although many of these compounds do not directly cross the blood–brain barrier, they may influence neural function indirectly through immune signaling, endocrine pathways, and vagal mechanisms (Młynarska et al., 2025; Wang et al., 2026; Zhang et al., 2025).

3.4. Gut Homeostasis and Dysbiosis

A healthy gut ecosystem is characterized not by the dominance of a single beneficial microorganism but by a dynamic equilibrium among microbial diversity, metabolic activity, and host physiological processes (Balakrishnan et al., 2024; Li et al., 2026). This balance contributes to intestinal barrier integrity, immune regulation, pathogen control, and metabolic stability (Chen et al., 2026; Cortés et al., 2025; Khan et al., 2024).

Disruption of this equilibrium is referred to as gut dysbiosis (Hou et al., 2022). Dysbiosis generally involves reduced microbial diversity, alterations in the abundance

of beneficial and potentially harmful microorganisms, and changes in microbial metabolic profiles (Afzaal et al., 2022; Li et al., 2026). Such alterations have been associated with impaired intestinal barrier function, chronic low-grade inflammation, immune dysregulation, and abnormal metabolite production (Al Bander et al., 2020; Balakrishnan et al., 2024). Importantly, dysbiosis is not considered an independent disease entity but rather a dynamic microbial state that may interact with various chronic conditions and influence host physiology, including neurodevelopmental processes (Zeng et al., 2025; Młynarska et al., 2025; Wang et al., 2026; Zhang et al., 2025).

3.5. Relevance of the Gut–Brain Axis to Autism Spectrum Disorder

Research on the gut–brain axis has expanded current perspectives on autism by emphasizing interactions beyond the central nervous system alone (Młynarska et al., 2025). Rather than viewing ASD exclusively as a brain-centered condition, current approaches consider the contribution of interconnected systems involving neural pathways, immune regulation, gastrointestinal function, and microbial activity (Wang et al., 2026; Zhang et al., 2025).

This systemic perspective does not suggest that gut microorganisms independently cause autism. Instead, it proposes that microbial composition, immune activity, intestinal physiology, and brain function are interconnected components of an integrated biological system (Jiang et al., 2026; Xu & Lu, 2025). This framework offers a conceptual basis for interpreting microbial and metabolic alterations observed in clinical and experimental studies of ASD (Alkuwaiti et al., 2025; Zhang et al., 2025).

4. GUT DYSBIOSIS IN AUTISM SPECTRUM DISORDER

4.1. Evidence of Microbial Alterations in ASD

Research investigating the gut microbiota of individuals with Autism Spectrum Disorder (ASD) has expanded considerably over the past decade. Numerous clinical studies have reported differences in microbial diversity, community composition, and metabolic profiles compared with neurotypical controls (Młynarska et al., 2025; Zhang et al., 2025). Although specific microbial alterations vary among studies, the overall evidence suggests that individuals with ASD may exhibit differences

in both the structural and functional characteristics of the gut microbiota (Wang et al., 2026).

Reduced microbial diversity is among the commonly reported findings and may indicate decreased ecosystem stability and resilience (Cortés et al., 2025). Lower diversity has been associated with impaired metabolic capacity, altered immune regulation, and reduced resistance to microbial disturbances (Hou et al., 2022; Afzaal et al., 2022). However, this finding is not consistently observed across all studies, emphasizing the heterogeneity of ASD populations and differences in microbiome assessment approaches (Zhang et al., 2025).

Beyond overall diversity, alterations in specific microbial taxa have also been reported. Several studies have described reductions in potentially beneficial microorganisms, including Bifidobacterium and Prevotella, alongside increases in certain potentially pro-inflammatory or opportunistic bacterial groups, such as some Clostridium species and Desulfovibrio (Młynarska et al., 2025; Wang et al., 2026). Nevertheless, these reported microbial differences are not consistently reproduced across different cohorts, and a universal microbial

signature specific to ASD has not yet been established (Finegold et al., 2017; Kang et al., 2013; Strati et al., 2017).

4.2. Gastrointestinal Manifestations and Their Relationship with Dysbiosis

Gastrointestinal (GI) symptoms represent some of the most frequently reported medical comorbidities in individuals with ASD and occur more commonly compared with neurotypical populations (Lord et al., 2018). Constipation is among the most prevalent complaints, followed by diarrhea, abdominal discomfort, bloating, gastroesophageal reflux, and altered bowel habits (Hodges et al., 2020). These symptoms may persist over time and negatively affect nutrition, sleep quality, daily functioning, and overall quality of life (Młynarska et al., 2025).

Increasing evidence suggests an association between gastrointestinal symptom severity and alterations in microbial composition and function (Strati et al., 2017). Individuals experiencing more severe gastrointestinal disturbances may exhibit greater changes in microbial profiles, intestinal permeability, and metabolite production. However, these associations do not establish whether gastrointestinal dysfunction contributes to

behavioral characteristics or develops as a consequence of ASD-related factors (Kang et al., 2013; Zhang et al., 2025).

Importantly, gastrointestinal discomfort may influence behavioral presentation in individuals with ASD. Chronic pain, constipation, or gastrointestinal distress may contribute to irritability, sleep disturbances, anxiety symptoms, and increased repetitive behaviors, particularly among individuals with limited ability to communicate discomfort verbally (Kang et al., 2013). This interaction may complicate the clinical distinction between core ASD characteristics and behavioral responses secondary to physical discomfort (Finegold et al., 2017; Strati et al., 2017).

4.3. Microbial Metabolites and Functional Changes

Alterations in microbial composition are accompanied by changes in microbial metabolic activity. Accumulating evidence indicates that functional characteristics of the microbiota, including metabolite production, may provide important insights beyond taxonomic differences because these metabolites interact with host physiological systems through the gut–brain axis (Hou et al., 2022; Xu & Lu, 2025; Zhang et al., 2025).

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, represent some of the most

extensively studied microbial metabolites (Al Bander et al., 2020). These compounds contribute to intestinal barrier maintenance, immune regulation, metabolic homeostasis, and signaling processes involved in gut–brain communication. Several studies have reported alterations in SCFA concentrations or ratios in individuals with ASD; however, the direction and magnitude of these changes differ among study populations (Carabotti et al., 2015; Młynarska et al., 2025).

Alterations in microbial tryptophan metabolism have also received increasing attention. Because tryptophan serves as a precursor for serotonin and other neuroactive molecules, changes in microbial regulation of this pathway may influence neuroimmune signaling, mood-related processes, and gastrointestinal function (Mhanna et al., 2024; Xu & Lu, 2025). In addition, alterations in bile acid metabolism and other microbial-derived metabolites suggest that functional changes in ASD-associated microbiota extend beyond differences in bacterial composition alone (Chen et al., 2026; Wang et al., 2026).

These findings have shifted the research focus from identifying individual bacterial species toward

understanding microbial community interactions and their collective effects on host physiology (Cortés et al., 2025; Zeng et al., 2025).

4.4. Factors Contributing to Variability Among Studies

Despite the rapid expansion of microbiome research in ASD, findings remain highly heterogeneous (Alkuwaiti et al., 2025). Differences in microbial profiles are frequently observed among studies, and a consistent microbiome-based pattern capable of reliably distinguishing individuals with ASD from neurotypical individuals has not yet been identified (Jiang et al., 2026).

Several factors contribute to this variability. Study populations differ in age, geographic location, genetic background, dietary habits, medication exposure, gastrointestinal symptoms, and ASD severity (Afzaal et al., 2022). In addition, methodological differences, including sample storage conditions, DNA extraction procedures, sequencing platforms, and bioinformatic analyses, may influence reported microbial outcomes (Gullapalli et al., 2025). Small sample sizes in many studies further limit statistical power and generalizability (Khan et al., 2024).

These methodological limitations should be considered when interpreting current findings. Rather than representing direct contradictions, variations among studies likely reflect the complexity of both human microbial ecosystems and ASD heterogeneity (Jiang et al., 2026; Leisman et al., 2026).

4.5. Current Interpretation of the Evidence

Overall, current evidence indicates that gut microbial composition and metabolic activity are altered in a substantial proportion of individuals with ASD (Kamijo et al., 2026). However, available findings do not support the existence of a single microbial profile that can consistently distinguish ASD from neurotypical development (Gullapalli et al., 2025).

Instead, gut dysbiosis should be considered a dynamic biological state influenced by genetic, environmental, dietary, and behavioral factors (Salehi et al., 2025). This perspective is consistent with the clinical heterogeneity of ASD and highlights the importance of integrating microbiome data with individual dietary patterns, gastrointestinal characteristics, immune profiles, genetic background, and lifestyle factors when searching

for clinically meaningful biomarkers (Gullapalli et al., 2025; Salehi et al., 2025; Wang et al., 2026).

Although research supporting the presence of gut dysbiosis in ASD continues to accumulate, a fundamental question remains unresolved: does microbial alteration contribute to ASD-related pathophysiology, or does it primarily reflect consequences of the condition? The following section examines experimental and clinical evidence regarding the potential causal contribution of dysbiosis.

5. IS DYSBIOSIS A CAUSE OF ASD?

5.1. Experimental Evidence Supporting a Causal Role

Whether gut dysbiosis contributes directly to Autism Spectrum Disorder (ASD) development remains one of the most debated questions in contemporary autism research (Zhang et al., 2025). Although observational studies consistently demonstrate associations between altered gut microbiota and ASD, they cannot determine whether these microbial changes precede ASD-related features or emerge as a consequence of the condition. Therefore, much of the evidence supporting a potential

causal contribution has been derived from experimental animal models (Xu & Lu, 2025).

Among these models, germ-free (GF) mice have provided valuable insights into the role of intestinal microbiota during neurodevelopment (Carabotti et al., 2015). Raised under sterile conditions without microbial colonization, these animals exhibit alterations in social interaction, repetitive behaviors, anxiety-like responses, stress regulation, and cognitive functions. They also demonstrate differences in synaptic plasticity, microglial maturation, and blood–brain barrier integrity compared with conventionally colonized animals (Jiang et al., 2026). Interestingly, some of these abnormalities can be partially reversed following microbial colonization during early developmental periods, suggesting that the gut microbiota contributes to normal brain maturation processes (Alkuwaiti et al., 2025).

Another widely used experimental approach is the maternal immune activation (MIA) model. In this model, activation of the maternal immune system during pregnancy produces offspring displaying behavioral and neurological characteristics resembling aspects of ASD (Leisman et al., 2026; Zeng et al., 2025). These offspring

frequently exhibit gut dysbiosis, increased intestinal permeability, systemic inflammation, and altered microbial metabolite profiles. Restoration of microbial balance through selected probiotic strains or microbial metabolites has been reported to improve gastrointestinal abnormalities and some behavioral outcomes in experimental studies (Jiang et al., 2026; Wang et al., 2026).

Additional experimental support has been provided by fecal microbiota transplantation (FMT) studies. Transfer of intestinal microbiota from individuals with ASD into germ-free or antibiotic-treated mice has been shown to induce alterations in social behavior, anxiety-like behavior, and repetitive behaviors in recipient animals (Młynarska et al., 2025; Zhang et al., 2025). Although these findings cannot be directly extrapolated to humans, they indicate that gut microbial communities have the capacity to influence neurodevelopmental and behavioral processes under experimental conditions (Alkuwaiti et al., 2025; Xu & Lu, 2025).

5.2. Early-Life Microbiota and Neurodevelopment

Early life represents a critical developmental period during which the intestinal microbiota, immune system, and central nervous system mature simultaneously

(Carabotti et al., 2015). Microbial colonization begins at birth and continues throughout infancy, coinciding with periods of rapid synapse formation, neuronal maturation, immune development, and establishment of intestinal barrier function (Hou et al., 2022).

Several factors influence early microbial development, including delivery mode, breastfeeding, antibiotic exposure, maternal health, and environmental microbial exposure. Vaginal delivery promotes colonization by maternal microorganisms, whereas cesarean delivery has been associated with differences in early microbial maturation patterns (Afzaal et al., 2022; Khan et al., 2024). Similarly, breastfeeding supports the growth of beneficial bacterial groups, particularly Bifidobacterium, through human milk oligosaccharides (Alkuwaiti et al., 2025; Hou et al., 2022). Conversely, repeated antibiotic exposure during infancy may reduce microbial diversity and interfere with normal microbial development (Afzaal et al., 2022; Zeng et al., 2025).

Experimental studies suggest that disruptions occurring during these early developmental windows may have long-term effects on immune regulation, stress responses, and social behavior. However, the extent to

which these findings translate to human ASD remains an active area of investigation (Alkuwaiti et al., 2025; Kamijo et al., 2026).

5.3. Potential Biological Mechanisms

Several biological mechanisms have been proposed to explain how gut dysbiosis may contribute to ASD-related pathophysiology (Zhang et al., 2025). Rather than acting through a single pathway, microbial alterations appear to affect multiple interconnected biological processes (Zeng et al., 2025; Balakrishnan et al., 2024).

One proposed mechanism involves immune activation (Balakrishnan et al., 2024). Dysbiosis may impair intestinal barrier integrity, potentially allowing bacterial components such as lipopolysaccharide (LPS) to enter circulation (Al Bander et al., 2020). This process may stimulate the production of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α). Persistent immune activation may subsequently affect neurodevelopment through alterations in microglial activity, synaptic maturation, and neuronal connectivity (Leisman et al., 2026; Balakrishnan et al., 2024).

Microbial metabolites represent another important link between the gut and the brain. Altered production of short-chain fatty acids (SCFAs), particularly butyrate and propionate, has been associated with changes in intestinal barrier function, mitochondrial activity, oxidative stress responses, and neurotransmitter regulation (Chen et al., 2026; Li et al., 2026). Similarly, disturbances in microbial tryptophan metabolism may influence serotonin pathways and broader neuroimmune signaling mechanisms (Mhanna et al., 2024; Xu & Lu, 2025).

Neural communication through the vagus nerve and modulation of the hypothalamic–pituitary–adrenal (HPA) axis provide additional mechanisms through which intestinal microorganisms may affect brain function and behavior (Carabotti et al., 2015; Jiang et al., 2026). Together, these mechanisms highlight the complex biological interactions connecting gut microbial communities with the central nervous system (Alkuwaiti et al., 2025; Hou et al., 2022).

5.4. How Strong Is the Current Evidence?

Despite increasing experimental evidence, several limitations should be considered before concluding that gut

dysbiosis represents a primary cause of ASD (Alkuwaiti et al., 2025; Zhang et al., 2025).

Much of the mechanistic evidence originates from animal models. Although these studies provide valuable biological insights, they cannot fully represent the genetic diversity, environmental exposures, and clinical heterogeneity observed in humans (Gullapalli et al., 2025; Kamijo et al., 2026). Furthermore, most human studies remain cross-sectional, limiting the ability to establish temporal relationships between microbial alterations and ASD development (Korteniemi et al., 2023; Xu & Lu, 2025). Differences in diet, medication exposure, gastrointestinal symptoms, geographical background, and sequencing methodologies also contribute substantially to variability among microbiome studies (Afzaal et al., 2022; Cortés et al., 2025; Hou et al., 2022).

These limitations do not diminish the importance of gut microbiota research in ASD; rather, they emphasize the difficulty of distinguishing causation from association. Taken together, current findings suggest that gut dysbiosis may influence neurodevelopment through multiple biological pathways, but whether these alterations

represent an initiating factor in ASD remains uncertain (Alkuwaiti et al., 2025; Jiang et al., 2026).

5.5. Current Perspective

Findings from experimental models provide supportive evidence that gut microbiota can influence brain development, immune regulation, and behavior (Carabotti et al., 2015; Jiang et al., 2026). However, translation of these findings to human ASD requires careful interpretation. Current clinical evidence supports an association between gut dysbiosis and ASD, whereas definitive evidence that dysbiosis independently initiates the disorder remains unavailable (Korteniemi et al., 2023).

Experimental and clinical findings supporting the dysbiosis–ASD hypothesis are summarized in Table 1 (Hsiao et al., 2013; Kang et al., 2013; Kang et al., 2019; Sharon et al., 2019; Strati et al., 2017), while proposed biological mechanisms linking gut dysbiosis to ASD are illustrated in Figure 1 (Cryan et al., 2019; Sharon et al., 2019; Wang et al., 2026).

Table 1. Experimental Evidence Supporting the Dysbiosis–ASD Hypothesis

Evidence	Main Findings	Biological Significance
Germ-free mice	Impaired social behavior, altered anxiety-like behavior, and repetitive behaviors	Demonstrates the importance of gut microbiota in normal neurodevelopment
Maternal immune activation (MIA)	Dysbiosis, neuroinflammation, ASD-like phenotype	Highlights the interaction between immunity and microbiota
Fecal microbiota transplantation (FMT)	ASD microbiota induces behavioral changes in mice	Suggests microbial communities can influence behavior
SCFA administration	Propionate induces ASD-like behaviors; butyrate shows neuroprotective effects	Supports metabolite-mediated gut–brain communication
Probiotic intervention in animal models	Partial improvement of social behavior and GI function	Indicates that microbiota modulation may reverse some abnormalities

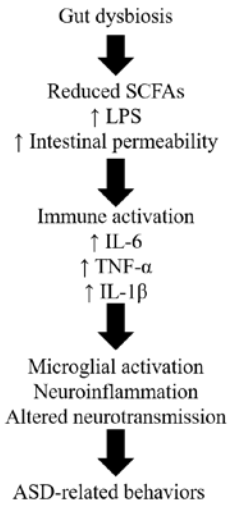

Figure 1. Proposed mechanisms by which gut dysbiosis may contribute to ASD development

Rather than considering gut dysbiosis as a universal cause of ASD, it is more appropriate to interpret it as one component within a complex network involving genetic susceptibility, environmental exposures, immune regulation, and metabolic factors (Kamijo et al., 2026; Leisman et al., 2026). This perspective is consistent with the heterogeneous nature of ASD and provides a balanced interpretation of current evidence (Gullapalli et al., 2025; Rosen et al., 2021).

At the same time, an alternative explanation requires consideration. Several ASD-associated characteristics, including selective eating behaviors, gastrointestinal dysfunction, medication exposure, and lifestyle-related factors, may themselves influence intestinal microbial composition (Afzaal et al., 2022; Hodges et al., 2020). Therefore, an important complementary question remains: could gut dysbiosis represent a consequence of ASD-related factors rather than an initiating cause? The following section examines evidence supporting this alternative hypothesis (Alkuwaiti et al., 2025).

6. IS DYSBIOSIS A CONSEQUENCE OF ASD? AN ALTERNATIVE PERSPECTIVE

6.1. The Shift in Focus

Although numerous studies have investigated whether gut dysbiosis contributes to Autism Spectrum Disorder (ASD) development, another important possibility has received increasing attention: whether microbial alterations observed in ASD may arise as secondary consequences of the condition itself (Li et al., 2022; Zhang et al., 2025). This perspective is supported by the fact that many ASD-associated characteristics, including selective eating behaviors, gastrointestinal dysfunction, medication exposure, altered lifestyle patterns, and chronic stress, are recognized factors that can influence intestinal microbial composition and function (Afzaal et al., 2022; Yap et al., 2021; Hofer, 2022).

Unlike experimental animal models, individuals with ASD are exposed throughout life to complex interactions among biological, behavioral, and environmental factors (Gullapalli et al., 2025; Kamijo et al., 2026). These factors may independently influence the gut microbiota and contribute to alterations in microbial composition and metabolic activity (Yap et al., 2021).

Therefore, gut dysbiosis may reflect, at least partially, ASD-related characteristics rather than represent an initiating factor of the condition (Hofer, 2022; Li et al., 2022).

6.2. Selective Eating and Dietary Habits

Selective eating is one of the most frequently observed behavioral characteristics in individuals with ASD, particularly during childhood. Many individuals demonstrate strong preferences or aversions related to food texture, color, taste, smell, or temperature, which may result in restricted dietary patterns (Hodges et al., 2020; Rosen et al., 2021). These dietary limitations may reduce the intake of fruits, vegetables, whole grains, and other fiber-rich foods while increasing consumption of processed or energy-dense foods (Hofer, 2022; Yap et al., 2021).

Dietary intake represents one of the major factors influencing gut microbial composition. Reduced consumption of dietary fiber decreases the availability of fermentable substrates for beneficial microorganisms and may reduce the production of short-chain fatty acids (SCFAs), particularly butyrate (Afzaal et al., 2022; Li et al., 2026). Furthermore, long-term dietary restriction may contribute to reduced microbial diversity and alterations in

microbial community structure (Hou et al., 2022; Yap et al., 2021).

These findings suggest that some microbial differences reported in ASD may be influenced by dietary patterns rather than reflecting ASD-related biological mechanisms alone. Therefore, nutritional factors should be carefully considered when interpreting microbiome findings in ASD populations (Alkuwaiti et al., 2025; Zhang et al., 2025).

6.3. Gastrointestinal Dysfunction

Gastrointestinal symptoms are common among individuals with ASD and may themselves influence intestinal microbial composition (Hodges et al., 2020; Młynarska et al., 2025). Chronic constipation, diarrhea, abdominal pain, gastroesophageal reflux, and altered intestinal transit time can modify the intestinal environment and affect microbial community structure (Hou et al., 2022; Strati et al., 2017).

For example, prolonged intestinal transit associated with constipation may promote changes in bacterial growth patterns, whereas diarrhea may influence microbial stability by altering nutrient availability and transit dynamics. Additional factors, including mucus production,

luminal pH, bile acid metabolism, and oxygen gradients, may further shape microbial habitats (Afzaal et al., 2022; Li et al., 2026).

Importantly, gastrointestinal dysfunction and gut dysbiosis may influence one another bidirectionally. Alterations in microbial composition may contribute to gastrointestinal symptoms, while persistent gastrointestinal disturbances may further disrupt microbial homeostasis. This reciprocal relationship makes it challenging to determine the temporal sequence of these changes (Alkuwaiti et al., 2025; Zhang et al., 2025).

6.4. Medication Exposure and Antibiotic Use

Medication exposure represents another factor that may influence intestinal microbial communities. Individuals with ASD may receive pharmacological treatments for associated conditions, including anxiety, epilepsy, sleep disturbances, or attention-deficit/hyperactivity disorder (ADHD) (Gullapalli et al., 2025; Hodis et al., 2025). Although these medications primarily target neurological or behavioral symptoms, some may affect microbial diversity and metabolic activity (Hou et al., 2022; Khan et al., 2024).

Antibiotic exposure is of particular interest because of its substantial impact on microbial ecosystems. Repeated or prolonged antibiotic use may reduce microbial diversity, impair colonization resistance, and delay restoration of beneficial microbial populations (Afzaal et al., 2022; Hou et al., 2022). Since some children with ASD may experience recurrent infections or repeated antibiotic exposure during early life, antibiotic history represents an important potential confounding factor in microbiome studies (Alkuwaiti et al., 2025; Zhang et al., 2025). Therefore, medication exposure should be carefully considered when interpreting microbial differences reported in ASD populations (Yap et al., 2021; Zhang et al., 2025).

6.5. Host-Related Biological Factors

The intestinal microbiota is shaped not only by external influences but also by host physiological characteristics. Immune function, intestinal barrier integrity, gastrointestinal motility, hormonal regulation, and genetic background all contribute to microbial homeostasis (Hou et al., 2022; Khan et al., 2024).

Altered immune responses observed in ASD may influence the intestinal environment through changes in cytokine production, mucosal immunity, and epithelial

barrier function (Balakrishnan et al., 2024; Zeng et al., 2025). Similarly, alterations in autonomic nervous system activity and stress-related endocrine pathways may affect gastrointestinal motility and secretion, indirectly modifying microbial communities (Carabotti et al., 2015; Jiang et al., 2026).

These mechanisms highlight that the gut microbiota continuously responds to changes in the host physiological environment. Consequently, microbial alterations observed in ASD may partly reflect broader biological characteristics associated with the condition rather than acting exclusively as independent disease triggers (Leisman et al., 2026; Zhang et al., 2025).

6.6. Current Interpretation of the Evidence

Current evidence indicates that several factors commonly associated with ASD, including dietary selectivity, gastrointestinal dysfunction, medication exposure, and host physiological changes, may contribute to alterations in gut microbial composition. These factors may help explain the substantial variability observed among microbiome studies and the absence of a consistent ASD-specific microbial profile (Al Bander et al., 2020; Hou et al., 2022; Yap et al., 2021).

At present, the available literature does not support the interpretation that gut dysbiosis is solely a consequence of ASD. Similarly, existing data are insufficient to conclude that dysbiosis consistently precedes ASD development. Instead, both experimental and clinical findings suggest that these processes may occur simultaneously and influence each other over time (Młynarska et al., 2025; Zhang et al., 2025).

This perspective supports a broader conceptual model in which ASD and gut dysbiosis interact through reciprocal biological mechanisms. Rather than representing mutually exclusive explanations, cause and consequence may constitute interconnected components of a dynamic and self-reinforcing process (Jiang et al., 2026; Xu & Lu, 2025).

7. A VICIOUS CYCLE: BIDIRECTIONAL INTERACTIONS BETWEEN GUT DYSBIOSIS AND ASD

7.1. Beyond Cause or Consequence

The relationship between Autism Spectrum Disorder (ASD) and gut dysbiosis is increasingly considered a dynamic and reciprocal interaction rather

than a simple linear cause-and-effect relationship (Al Bander et al., 2020). Although experimental studies indicate that alterations in the gut microbiota may influence neurodevelopmental processes, clinical evidence also demonstrates that ASD-associated characteristics—including selective eating behaviors, gastrointestinal dysfunction, medication exposure, and altered lifestyle patterns—can substantially affect intestinal microbial composition (Zhang et al., 2025). Therefore, neither a purely causal nor a purely consequential explanation fully accounts for the available evidence (Hou et al., 2022; Yap et al., 2021).

Current conceptual models suggest that ASD and gut dysbiosis may interact through multiple interconnected biological pathways. Changes in one system may influence responses in the other, potentially creating a self-reinforcing cycle that develops over time (Alkuwaiti et al., 2025; Jiang et al., 2026). This bidirectional framework has become an important model for interpreting the complex relationship between the gut microbiota and ASD (Młynarska et al., 2025; Wang et al., 2026).

7.2. Biological Mechanisms Underlying the Vicious Cycle

Several interconnected mechanisms may contribute to this reciprocal relationship. Alterations in the gut microbiota may impair intestinal barrier integrity, increase microbial product translocation, and promote inflammatory signaling (Al Bander et al., 2020; Hou et al., 2022). These processes may influence central nervous system function through effects on immune regulation, microglial activity, neurotransmitter metabolism, and neuroendocrine pathways (Xu & Lu, 2025; Zeng et al., 2025).

In turn, ASD-related physiological and behavioral characteristics may further modify the intestinal environment. Restricted dietary patterns can reduce microbial diversity, gastrointestinal dysmotility can alter microbial habitats, and chronic stress may influence intestinal permeability and microbial composition through HPA axis activation (Carabotti et al., 2015; Hofer, 2022; Yap et al., 2021; Zhang et al., 2025). These changes may contribute to further disturbances in microbial balance, inflammation, and metabolic regulation (Al Bander et al., 2020; Chen et al., 2026).

Thus, immune regulation, microbial metabolites, intestinal barrier function, neural signaling, and gastrointestinal symptoms should be considered as interconnected components of a broader gut–brain network (Carabotti et al., 2015; Młynarska et al., 2025; Wang et al., 2026).

7.3. The Role of Inflammation and Intestinal Barrier Dysfunction

Among the mechanisms proposed to connect gut dysbiosis and ASD, chronic low-grade inflammation and altered intestinal barrier function have received considerable attention. Increased intestinal permeability, commonly described as "leaky gut," may facilitate the movement of microbial components such as lipopolysaccharide (LPS) into the circulation, potentially promoting immune activation and inflammatory cytokine production (Al Bander et al., 2020; Zeng et al., 2025).

Persistent immune activation may influence brain function through effects on neuronal development, synaptic plasticity, and microglial responses (Balakrishnan et al., 2024; Xu & Lu, 2025). At the same time, inflammatory processes may further affect intestinal barrier integrity and microbial composition, contributing to a possible feedback

mechanism within the gut–brain axis (Cortés et al., 2025; Zeng et al., 2025).

Although the clinical relevance of increased intestinal permeability in ASD remains under investigation, current evidence suggests that barrier dysfunction may represent an important interface linking microbial alterations, immune responses, and neurodevelopmental processes (Młynarska et al., 2025; Wang et al., 2026).

7.4. A Systems Biology Perspective

Advances in microbiome research have encouraged a transition from single-factor explanations toward a systems biology perspective. Current evidence does not support attributing ASD to a single microorganism or isolated metabolic pathway; instead, multiple biological systems appear to interact throughout development (Gullapalli et al., 2025; Jiang et al., 2026).

Genetic susceptibility, environmental exposures, immune regulation, microbial metabolism, gastrointestinal physiology, nutrition, and neurodevelopment should therefore be considered interacting components of an integrated biological system (Jiang et al., 2026; Kamijo et al., 2026; Wang et al., 2026). Within this framework, gut

dysbiosis is unlikely to represent either the sole cause or merely a passive consequence of ASD. Rather, it may function as one component of a dynamic system that influences disease-related processes in susceptible individuals (Młynarska et al., 2025; Zhang et al., 2025).

This systems-based perspective may also explain the variability observed among microbiome studies. Differences in genetics, diet, age, medication exposure, environmental factors, and gastrointestinal status can substantially influence microbial profiles and contribute to clinical heterogeneity in ASD (Wang et al., 2026; Zhang et al., 2025).

7.5. Current Conceptual Understanding

Current evidence supports a bidirectional model in which ASD-related factors and gut microbial alterations may influence each other throughout development (Gullapalli et al., 2025; Jiang et al., 2026). Rather than representing mutually exclusive explanations, causation and consequence may coexist within a dynamic feedback network. In some individuals, microbial alterations may contribute to immune or neurodevelopmental changes, whereas in others they may primarily reflect ASD-

associated behavioral and physiological factors (Yap et al., 2021; Zhang et al., 2025).

Recognizing this reciprocal relationship has important clinical implications (Alkuwaiti et al., 2025). Microbiota-targeted interventions should not currently be considered treatments for ASD itself; instead, they may represent supportive strategies aimed at improving gastrointestinal function, modulating selected biological pathways, and addressing specific symptoms in appropriately selected individuals (Alkuwaiti et al., 2025; Jiang et al., 2026).

8. MICROBIOTA-BASED THERAPEUTIC STRATEGIES

8.1. Rationale for Microbiota-Targeted Interventions

Growing recognition of the relationship between gut dysbiosis and Autism Spectrum Disorder (ASD) has led to increasing interest in therapeutic strategies aimed at modulating the intestinal microbiota (Wang et al., 2026; Zhang et al., 2025). Since the gut microbiome contributes to immune regulation, intestinal barrier function, microbial metabolism, and gut–brain communication, modulation of

microbial composition and function has been proposed as a potential influence to improve gastrointestinal health and possibly influence selected ASD-associated symptoms (Jiang et al., 2026; Xu & Lu, 2025).

It is important to recognize, however, that current microbiota-based interventions are considered supportive or adjunctive approaches rather than disease-modifying therapies (Alkuwaiti et al., 2025; Wang et al., 2026). Their primary objective is not to alter the underlying neurodevelopmental condition itself, but rather to improve intestinal function and potentially reduce biological disturbances that may contribute to symptom burden in some individuals with ASD (Młynarska et al., 2025).

8.2. Probiotics, Prebiotics, Synbiotics, and Postbiotics

Among microbiota-targeted interventions, probiotics have received considerable attention (Alkuwaiti et al., 2025; Zhang et al., 2025). Probiotics are live microorganisms that, when administered in adequate amounts, provide health benefits to the host (Jiang et al., 2026). Several clinical studies have evaluated probiotic supplementation in individuals with ASD, most commonly

using strains belonging to the genera Lactobacillus and Bifidobacterium (Młynarska et al., 2025; Wang et al., 2026).

Some studies have reported improvements in gastrointestinal outcomes, including constipation, abdominal discomfort, and stool consistency, as well as changes in selected behavioral measures. However, the magnitude and consistency of these effects vary considerably across studies (Alkuwaiti et al., 2025; Zhang et al., 2025; Wang et al., 2026).

Prebiotics, which are nondigestible dietary substrates that selectively stimulate beneficial microorganisms, have also been investigated (Jiang et al., 2026; Li et al., 2026). By promoting the growth of commensal bacteria and increasing the production of short-chain fatty acids (SCFAs), prebiotics may contribute to improved intestinal function (Li et al., 2026; Xu & Lu, 2025). Although preliminary findings are encouraging, clinical evidence supporting their effectiveness in ASD remains limited (Alkuwaiti et al., 2025; Zhang et al., 2025).

The combination of probiotics and prebiotics, referred to as synbiotics, has attracted increasing interest because of its potential to enhance microbial stability compared with either approach alone (Jiang et al., 2026; Li

et al., 2026). Similarly, postbiotics, including inactivated microorganisms and their bioactive metabolites, represent an emerging area of microbiome research (Chen et al., 2026; Xu & Lu, 2025). These approaches may offer potential advantages regarding stability and safety; however, clinical evidence in ASD remains insufficient (Alkuwaiti et al., 2025; Wang et al., 2026).

Overall, current evidence suggests that these interventions are generally well tolerated, but larger and methodologically standardized randomized controlled trials are required before definitive clinical recommendations can be established (Alkuwaiti et al., 2025; Wang et al., 2026; Zhang et al., 2025).

8.3. Dietary Interventions

Diet represents one of the major modulators of gut microbial composition and therefore constitutes an important component of microbiota-targeted management strategies (Afzaal et al., 2022; Hou et al., 2022). Increasing dietary diversity, improving fiber intake, and promoting balanced nutritional patterns may support microbial diversity and metabolic activity (Khan et al., 2024; Li et al., 2026).

Various dietary approaches have been investigated in ASD, including gluten-free and casein-free diets, ketogenic diets, elimination diets, and Mediterranean-style dietary patterns (Hofer, 2022; Yap et al., 2021). Although some individuals report symptomatic improvements, particularly regarding gastrointestinal complaints, overall evidence remains inconsistent (Alkuwaiti et al., 2025; Młynarska et al., 2025). Differences in study design, participant characteristics, dietary adherence, and outcome assessment limit direct comparisons between studies (Zhang et al., 2025).

Because many individuals with ASD already experience selective eating behaviors, dietary interventions should be implemented carefully to minimize the risk of nutritional deficiencies. When possible, dietary modifications should be supervised by healthcare professionals with expertise in nutrition and ASD (Alkuwaiti et al., 2025; Hodges et al., 2020).

8.4. Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) has emerged as one of the most discussed microbiota-based therapeutic approaches. The procedure involves transferring processed fecal material from a carefully screened donor to a recipient

in order to modify microbial composition and restore aspects of microbial function (Khoruts & Sadowsky, 2016).

Preliminary studies in individuals with ASD have reported improvements in gastrointestinal symptoms accompanied by alterations in microbial composition and, in some cases, modest behavioral changes (Kang et al., 2017). However, these findings should be interpreted cautiously because most available studies include small sample sizes, limited follow-up periods, and heterogeneous treatment protocols (Alkuwaiti et al., 2025; Zhang et al., 2025).

Although FMT has established clinical efficacy for recurrent Clostridioides difficile infection, evidence from this indication cannot be directly extrapolated to ASD. The long-term efficacy, optimal donor characteristics, treatment protocols, and safety profile of FMT in ASD require further investigation before routine clinical application can be considered (Cammarota et al., 2017; Alkuwaiti et al., 2025; Kang et al., 2017).

8.5. Emerging Therapeutic Approaches

Advances in microbiome science have expanded therapeutic concepts beyond conventional microbial supplementation (Zhang et al., 2025). Emerging approaches

include psychobiotics, precision probiotics, engineered microbial strains, bacteriophage-based strategies, microbial metabolite supplementation, and personalized nutrition approaches based on individual microbiome characteristics (Alkuwaiti et al., 2025; Wang et al., 2026).

The integration of multi-omics approaches may improve understanding of host–microbiome interactions and facilitate identification of patient subgroups who may benefit from targeted interventions (Jiang et al., 2026; Wang et al., 2026). Although many of these approaches remain experimental, they highlight the rapidly developing potential of microbiome-based medicine (Alkuwaiti et al., 2025; Zhang et al., 2025).

8.6. Current Clinical Perspective

Current evidence supports the potential of microbiota-targeted interventions to improve gastrointestinal health and influence selected biological pathways associated with ASD. However, existing clinical data do not support their use as stand-alone treatments for the core symptoms of ASD (Młynarska et al., 2025). Current microbiota-based therapeutic approaches, together with their proposed mechanisms, supporting evidence, and limitations, are summarized in Table 2 (Alkuwaiti et al.,

2025; Młynarska et al., 2025; Wang et al., 2026; Zhang et al., 2025).

Table 2. Microbiota-Based Therapeutic Strategies for ASD

Intervention	Proposed Mechanism	Current Evidence	Current Limitation
Probiotics	Modulate microbiota, reduce inflammation, increase SCFAs	Moderate evidence for GI symptom improvement; limited behavioral benefits	Strain-specific effects; heterogeneous studies
Prebiotics	Stimulate beneficial bacteria	Preliminary evidence	Limited clinical trials
Synbiotics	Combined probiotic + prebiotic effects	Promising early results	Insufficient large RCTs
Postbiotics	Deliver beneficial microbial metabolites	Emerging evidence	Few ASD-specific studies
Psychobiotics	Modulate gut–brain signaling	Experimental	Lack of standardized protocols
FMT	Restore microbial diversity	Encouraging pilot studies	Safety, regulation, long-term efficacy
Dietary interventions	Modify microbial ecology	Mixed evidence	Difficult adherence; nutritional concerns

Clinical decision-making should therefore remain individualized, considering gastrointestinal symptoms, nutritional status, coexisting medical conditions, age, medication exposure, and family preferences (Alkuwaiti et al., 2025). Importantly, microbiota-based approaches should be considered complementary to established

multidisciplinary interventions rather than replacements for evidence-based behavioral, educational, and medical management strategies (Hodges et al., 2020; Młynarska et al., 2025).

Future studies should prioritize standardized methodologies, larger randomized controlled trials, and mechanistic investigations to determine which individuals may benefit most from microbiota-based interventions and how these approaches can be appropriately integrated into clinical practice (Wang et al., 2026; Zhang et al., 2025).

9. FUTURE PERSPECTIVES

9.1. The Shift to Mechanistic Understanding

The expanding body of evidence linking the gut microbiota with Autism Spectrum Disorder (ASD) has shifted research interest from descriptive associations toward a more mechanistic investigation of host–microbiome interactions (Cryan et al., 2019; Hsiao et al., 2013). Despite considerable progress, important uncertainties remain regarding the biological significance of microbial alterations observed in ASD (Sharon et al., 2019). Determining whether gut dysbiosis represents a contributing factor, a consequence, or part of a bidirectional process will require rigorous

experimental approaches, standardized methodologies, and long-term clinical investigations (Kang et al., 2019; Yap et al., 2021).

9.2. Longitudinal Studies and Developmental Windows

One of the major priorities for future research is the establishment of large-scale longitudinal studies (Krajmalnik-Brown et al., 2015). Most available human studies are cross-sectional and therefore cannot clarify whether microbial alterations precede ASD-related features or emerge as consequences of behavioral, dietary, and physiological changes. Following individuals from early infancy through childhood may help define the temporal relationship between microbiota development and ASD-associated processes (Matsuyama et al., 2022; Yap et al., 2021). Such studies may also help identify developmental periods during which microbiota-targeted interventions could have the greatest potential impact (Borre et al., 2014; Cryan et al., 2019).

9.3. Multi-Omics Integration

Technological advances will continue to expand the ability to investigate the functional interplay between the host and the gut microbiome. Integration of multi-omics

approaches, including metagenomics, metatranscriptomics, metabolomics, proteomics, and transcriptomics, may provide deeper insight into microbial function beyond taxonomic composition alone (Gullapalli et al., 2025; Jiang et al., 2026). Combining these functional datasets with host genetics, immune profiling, neuroimaging, and detailed clinical characteristics may reveal biological networks that remain difficult to identify using isolated approaches (Wang et al., 2026).

9.4. Personalized Microbiome-Based Medicine

A major future direction is the development of personalized microbiome-based strategies. The substantial heterogeneity observed in both ASD and gut microbial profiles suggests that a universal intervention is unlikely to be effective for all individuals. Future approaches may therefore be tailored according to microbial composition, metabolic characteristics, gastrointestinal symptoms, dietary patterns, genetic background, and immune status (Alkuwaiti et al., 2025; Li et al., 2026).

Advanced computational models and bioinformatic approaches may support this precision medicine framework by identifying clinically relevant microbial

patterns and patient subgroups that are more likely to respond to specific interventions (Wang et al., 2026).

9.5. Methodological Standardization

Improved methodological standardization remains essential for advancing the field. Differences in participant characteristics, dietary assessment, sequencing platforms, analytical pipelines, and outcome measurements continue to limit comparisons between studies (Bezawada et al., 2020). International collaboration and harmonized research protocols will be important for improving reproducibility and strengthening evidence quality.

Further research should move beyond the identification of individual bacterial taxa and focus on understanding the gut microbiota as part of an integrated biological system. Investigating interactions among microbial communities, immune regulation, metabolism, and neural pathways may provide a more comprehensive framework for understanding ASD and support the development of targeted and evidence-based therapeutic approaches (Balakrishnan et al., 2024; Leisman et al., 2026).

10. CONCLUSION

Autism Spectrum Disorder (ASD) is a highly heterogeneous neurodevelopmental condition whose biological mechanisms extend beyond the central nervous system. Growing interest in the gut–brain axis has expanded current perspectives on ASD by highlighting the potential contribution of the intestinal microbiota to neurodevelopment, immune regulation, metabolism, and gastrointestinal function (Cryan et al., 2019; Lord et al., 2018).

This chapter examined a central question: whether gut dysbiosis represents a cause of ASD, a consequence of the disorder, or part of a self-reinforcing biological cycle. Accumulating evidence suggests that none of these explanations alone fully accounts for the complexity of the relationship. Experimental studies demonstrate that microbial alterations can influence immune responses, neurodevelopmental processes, and behavior, supporting a potential contributory role of the gut microbiota (Hsiao et al., 2013; Sharon et al., 2019). In parallel, ASD-associated characteristics such as selective eating, gastrointestinal dysfunction, medication exposure, and lifestyle factors can

also shape microbial composition and function (Hofer, 2022; Yap et al., 2021).

Therefore, ASD and gut dysbiosis are best understood as components of a dynamic and reciprocal interaction rather than separate biological processes. Genetic susceptibility, environmental influences, immune regulation, microbial metabolism, intestinal barrier function, and neuroendocrine signaling interact within a complex host–microbiome network that may contribute to symptom variability among individuals.

These findings also have important clinical implications. Although microbiota-based interventions, including probiotics, prebiotics, dietary modification, synbiotics, and fecal microbiota transplantation, have shown encouraging findings in selected studies, current evidence does not support their use as treatments for the core symptoms of ASD (Cammarota et al., 2017; Kang et al., 2019). Instead, these approaches should be considered complementary strategies that may support gastrointestinal health and selected aspects of well-being while established behavioral, educational, and medical interventions remain central to ASD management.

Future advances will depend on well-designed longitudinal studies, standardized methodologies, and integration of multi-omics data with clinical, immunological, and neurobiological information (Gullapalli et al., 2025; Wang et al., 2026). A more detailed understanding of host–microbiome interplay may ultimately facilitate the development of individualized approaches based on the biological characteristics of different patient groups.

In conclusion, the relationship between ASD and gut dysbiosis is not adequately explained by a simple linear model. Instead, it represents a complex and evolving biological interaction in which microbial, immune, metabolic, and neurodevelopmental processes influence one another. Although many questions remain unresolved, the gut microbiota remains a promising area of investigation that may contribute to improved understanding of ASD biology and future personalized approaches to care.

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Cause, Consequence, or a Vicious Cycle?

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