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The Gut–Brain Axis in Autism: Pediatric Perspectives

El eje intestino-cerebro en el autismo: perspectivas pediátricas

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ABSTRACT

Introduction: autism spectrum disorder (ASD) is a neurodevelopmental condition frequently associated with gastrointestinal comorbidities such as constipation, diarrhea, abdominal pain, and feeding difficulties. Emerging evidence implicates the gut–brain axis and gut microbiota dysregulation in ASD pathophysiology.

Objective: to summarize current evidence on gut microbiota alterations in pediatric ASD, highlighting mechanistic insights, clinical correlations, and potential microbiota-targeted therapies.

Method: a narrative review was conducted of studies published between 2019 and 2025 in PubMed, Scopus, and Web of Science. Included studies focused on pediatric populations (0–18 years) reporting gut microbiota composition, metabolite profiles, or interventions targeting the microbiota in ASD. Non-original research, animal studies, and studies without relevant outcomes were excluded.

Results: children with ASD exhibit gut dysbiosis, characterized by increased Firmicutes and Pseudomonadota (formerly Proteobacteria), decreased Bacteroidetes, and a reduced Bacteroidetes-to-Firmicutes ratio. These microbial shifts correlate with gastrointestinal and behavioral manifestations and are associated with intestinal barrier dysfunction, immune activation, and altered short-chain fatty acid (SCFA) profiles—specifically elevated propionate and reduced butyrate—potentially contributing to neuroinflammation, neurotransmitter imbalance, and synaptic dysfunction. Microbiota-targeted interventions, including probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation, show potential benefits in improving gastrointestinal symptoms and, in some studies, behavioral outcomes. However, methodological heterogeneity, small sample sizes, and interindividual variability limit the generalizability of findings.

Conclusions: gut dysbiosis appears to play a significant role in the pathogenesis and clinical heterogeneity of pediatric ASD. Future research with standardized methodologies, validated biomarkers, and precision medicine approaches is essential to develop individualized therapeutic strategies and optimize long-term outcomes.

Keywords: Autism Spectrum Disorder; Gut–Brain Axis; Pediatrics; Microbiota; Gastrointestinal Manifestations.

RESUMEN

Introducción: el trastorno del espectro autista (TEA) es una afección del desarrollo neurológico que se asocia con frecuencia a comorbilidades gastrointestinales como estreñimiento, diarrea, dolor abdominal y dificultades para alimentarse. Las pruebas más recientes apuntan a la implicación del eje intestino-cerebro y la desregulación de la microbiota intestinal en la fisiopatología del TEA.

Objetivo: resumir las pruebas actuales sobre las alteraciones de la microbiota intestinal en el TEA pediátrico, destacando los conocimientos mecánicos, las correlaciones clínicas y las posibles terapias dirigidas a la microbiota.

Método: se realizó una revisión narrativa de los estudios publicados entre 2019 y 2025 en PubMed, Scopus y Web of Science. Los estudios incluidos se centraron en poblaciones pediátricas (0-18 años) que informaban sobre la composición de la microbiota intestinal, los perfiles metabólicos o las intervenciones dirigidas a la microbiota en el TEA. Se excluyeron las investigaciones no originales, los estudios con animales y los estudios sin resultados relevantes.

Resultados: los niños con TEA presentan disbiosis intestinal, caracterizada por un aumento de Firmicutes y Pseudomonadota (antes Proteobacteria), una disminución de Bacteroidetes y una reducción de la proporción de Bacteroidetes con respecto a Firmicutes. Estos cambios microbianos se correlacionan con manifestaciones gastrointestinales y conductuales y se asocian con la disfunción de la barrera intestinal, la activación inmunitaria y la alteración de los perfiles de ácidos grasos de cadena corta (AGCC), concretamente el aumento del propionato y la reducción del butirato, lo que podría contribuir a la neuroinflamación, el desequilibrio de los neurotransmisores y la disfunción sináptica. Las intervenciones dirigidas a la microbiota, como los probióticos, los prebióticos, las modificaciones dietéticas y el trasplante de microbiota fecal, muestran beneficios potenciales en la mejora de los síntomas gastrointestinales y, en algunos estudios, en los resultados conductuales. Sin embargo, la heterogeneidad metodológica, el pequeño tamaño de las muestras y la variabilidad interindividual limitan la generalización de los resultados.

Conclusiones: la disbiosis intestinal parece desempeñar un papel importante en la patogénesis y la heterogeneidad clínica del TEA pediátrico. Es esencial realizar investigaciones futuras con metodologías estandarizadas, biomarcadores validados y enfoques de medicina de precisión para desarrollar estrategias terapéuticas individualizadas y optimizar los resultados a largo plazo.

Palabras clave: Trastorno del Espectro Autista; Eje Intestino-Cerebro; Pediatría; Microbiota; Manifestaciones Gastrointestinales.

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INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social communication and the presence of restricted interests and repetitive behaviors. Its prevalence has risen considerably in recent decades, with current estimates indicating that approximately 1 in 36 children are affected, rendering it a significant pediatric public health concern. Despite considerable research efforts, the precise etiological mechanisms underlying ASD remain incompletely elucidated, and targeted therapeutic options are limited.[1]

Increasingly, the gut–brain axis has emerged as a salient area of investigation in ASD pathophysiology. This bidirectional communication network integrates neural, immune, endocrine, and metabolic signaling pathways between the gastrointestinal tract and the central nervous system. Disruptions along this axis may account for the high prevalence of gastrointestinal disturbances—such as constipation, diarrhea, abdominal pain, and feeding difficulties—observed in children with ASD compared to neurotypical populations.[2] (figure 1) illustrates the bidirectional interactions between gut microbiota and the Central Nervous System (CNS), highlighting mechanisms that may influence neurodevelopment in pediatric ASD.

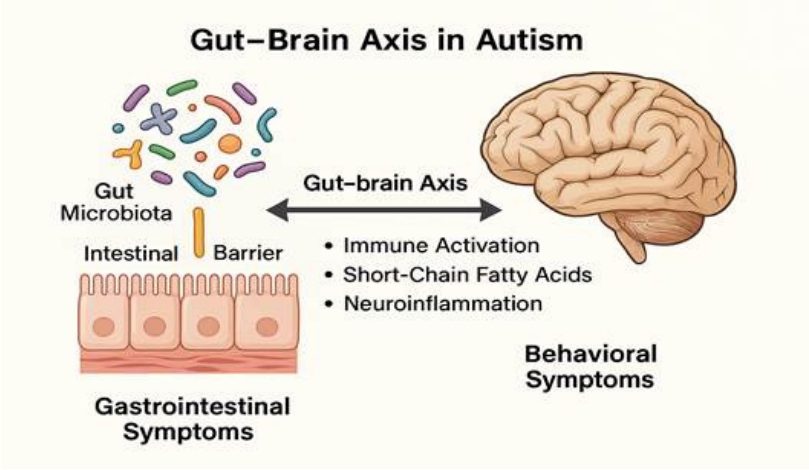

Figure 1. Schematic representation of the gut–brain axis in autism spectrum disorder

The illustration shows bidirectional communication between gut microbiota and the central nervous system via neural (vagus nerve), immune, and metabolic pathways. Key mechanisms include intestinal barrier disruption, immune activation, altered short-chain fatty acids (SCFAs), and neurotransmitter imbalance, which may contribute to neurodevelopmental and behavioral manifestations in children with ASD.

Dysbiosis, characterized by compositional and functional alterations in the gut microbiota, has been associated with aberrant neurotransmitter activity, immune dysregulation, and systemic inflammation, each of which may contribute to neurodevelopmental abnormalities and behavioral manifestations. Advances in high-throughput sequencing and metabolomic technologies have begun to identify distinct microbial and metabolic profiles in individuals with ASD, providing a foundation for potential biomarker discovery and personalized treatment approaches.[3] Interventions targeting the gut microbiome - including dietary modifications, probiotics, prebiotics, and fecal microbiota transplantation - have yielded encouraging preliminary results, although current evidence is constrained by methodological heterogeneity and limited replication.[4]

Elucidating the role of the gut–brain axis in ASD is especially pertinent within pediatric populations, where early intervention may significantly influence long-term neurodevelopmental trajectories. This review synthesizes contemporary evidence on microbial dysbiosis, putative mechanistic pathways, and novel microbiota-based interventions, emphasizing their potential implications for advancing individualized medicine in autism care.

RESULTS AND DISCUSSION

Gut microbiota alterations in children with ASD

Multiple studies have demonstrated consistent alterations in gut microbiota composition among children with autism spectrum disorder (ASD).[5] The most frequently reported pattern includes an increased abundance of Firmicutes and reduced Bacteroidetes, leading to a decreased Bacteroidetes: Firmicutes ratio, a finding that aligns with the meta-analyses by Iglesias-Vázquez et al.[5] and by Shen et al.[6] This imbalance is thought to contribute to gastrointestinal dysfunction and behavioral symptoms. Additional findings include increased representation of potentially pro-inflammatory taxa such as Klebsiella, Collinsella, Dorea, and Oscillospira, alongside a reduction of beneficial butyrate-producing genera, including Coprococcus and Akkermansia as reported by Kong et al.[7] As shown in (figure 2), children with ASD exhibit gut dysbiosis characterized by an elevated Firmicutes-to-Bacteroidetes ratio. (figure 3) summarizes compositional shifts in gut microbiota, showing reduced beneficial taxa and increased pro-inflammatory genera in ASD.

The figure highlights reductions in beneficial genera (Bifidobacterium, Akkermansia, Coprococcus) and increases in potentially pro-inflammatory taxa (Klebsiella, Collinsella, Clostridium XIVa). Colors indicate relative abundance levels.

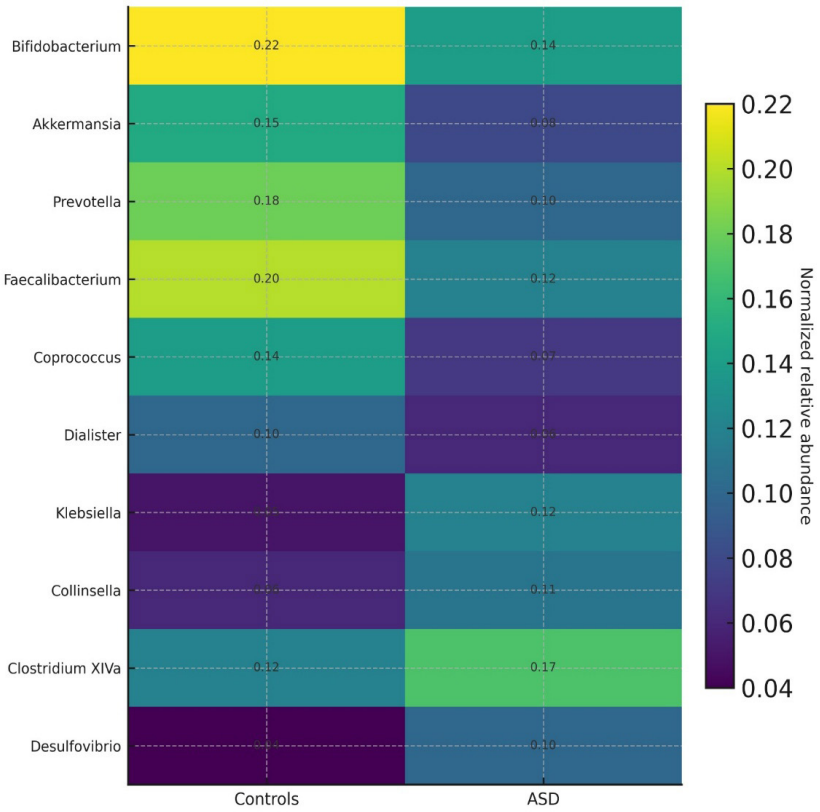

Figure 2. Heatmap of gut microbial taxa in children with ASD versus controls

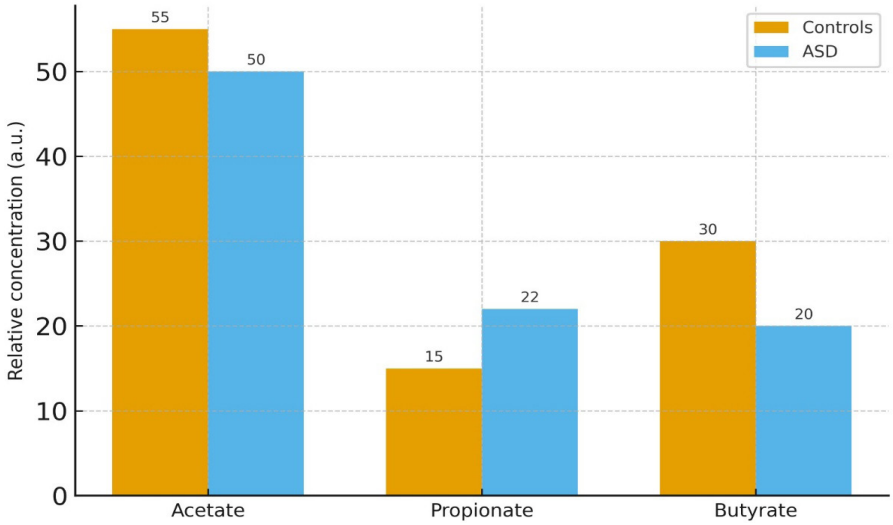

Figure 3. Altered SCFA profiles in children with ASD compared to controls. Propionate levels are elevated, while butyrate levels are reduced in children with ASD, suggesting potential impacts on neuroinflammation and neuronal signaling

Metabolomic analyses further highlight unique microbial signatures in ASD, such as elevated levels of propionate and reduced butyrate. These short-chain fatty acids (SCFAs) have direct effects on neuronal signaling and synaptic plasticity, providing a mechanistic link between microbiota shifts and neurodevelopmental outcomes; which agrees with the findings reported by Plaza-Díaz et al.[3] Although alpha diversity is not consistently different between ASD and controls, beta diversity is frequently altered, suggesting that microbial community structure may be more relevant to ASD pathophysiology, as also proposed by Ho et al.[2]

Pathophysiological mechanisms of the gut–brain axis in ASD

The gut–brain axis operates through neural, immune, endocrine, and metabolic pathways. In ASD, several mechanisms have been proposed:

- Disruption of the intestinal barrier may permit microbial products to enter systemic circulation, triggering inflammatory responses.[1]

- Immune activation and low-grade inflammation have been documented, with increased pro-inflammatory cytokines reported in both gastrointestinal and systemic compartments.[7]
- Altered microbial metabolites are strongly implicated, with SCFA imbalances affecting neuronal signaling and gut epithelial health.[8]
- Neurotransmitter modulation is another key mechanism, as microbial dysbiosis has been linked to altered synthesis of serotonin, dopamine, and GABA, thereby influencing synaptic function and neuroplasticity.[6]

These findings are in agreement with those of Lord et al.[1], Kong et al.[7], Tao et al.[8] and Iglesias-Vázquez et al.[6] Furthermore, these findings underscore a biological basis for gut–brain communication in ASD, although causality remains unproven.

A range of interventions aimed at modifying the microbiota are under investigation:

- Dietary interventions have shown variable outcomes, with evidence remaining inconsistent according to meta-analyses by Yang et al.[4] Gluten-free and casein-free diets, as well as ketogenic regimens, have been trialed with variable outcomes. While some children exhibit improvements in gastrointestinal or behavioral symptoms, evidence remains inconsistent, and adherence challenges are significant.
- Probiotics and prebiotics have demonstrated some benefits, as seen in studies such as that of Yang et al.[4] Several randomized controlled trials (RCTs) in pediatric ASD populations have evaluated strains such as Bifidobacterium and Lactobacillus. Some studies report reductions in constipation, irritability, and social withdrawal, but sample sizes are small and results heterogeneous.
- Fecal microbiota transplantation has shown promising results, with Kang et al.[9] demonstrating long-term beneficial changes in both gut symptoms and core autism behaviors. Pilot studies in children with ASD and gastrointestinal comorbidities have shown promising results, with improvements in both gut symptoms and behavior. However, concerns about long-term safety, donor variability, and standardization limit widespread clinical use.

Therapeutic interventions targeting the gut–brain axis

Overall, while these interventions show potential, they should currently be regarded as experimental, pending confirmation in large, well-designed clinical trials, a conclusion consistently reached by all cited authors.

The findings of this review underscore the pivotal role of the gut–brain axis in pediatric autism spectrum disorder (ASD), highlighting consistent alterations in gut microbiota composition, metabolite profiles, and immune signaling. Children with ASD exhibit dysbiosis characterized by an increased Firmicutes-to-Bacteroidetes ratio, reductions in beneficial genera such as Bifidobacterium and Akkermansia, and elevated levels of pro-inflammatory taxa. These compositional shifts are associated with gastrointestinal manifestations, including constipation, diarrhea, abdominal discomfort, and feeding difficulties, and may contribute to behavioral symptoms through complex interactions along neural, immune, endocrine, and metabolic pathways.

Mechanistic evidence suggests that intestinal barrier disruption, immune activation, and imbalances in short-chain fatty acids (SCFAs), such as propionate and butyrate, mediate the effects of dysbiosis on neurodevelopment. Elevated propionate levels have been implicated in neuroinflammation and synaptic dysfunction, whereas reduced butyrate may impair neuronal signaling and intestinal epithelial integrity. Dysregulated neurotransmitter synthesis, including alterations in serotonin, dopamine, and GABA, further supports the notion that microbial imbalances can influence neurobehavioral outcomes in children with ASD. Collectively, these findings provide a biologically plausible explanation for the frequent comorbidity of gastrointestinal and neurodevelopmental symptoms in pediatric populations.

Interventions targeting the gut microbiome—including dietary modifications, probiotics, prebiotics, and fecal microbiota transplantation (FMT)—have shown promising preliminary results. Some studies report improvements in gastrointestinal symptoms, social behaviors, and cognitive functioning. However, the evidence is limited by methodological heterogeneity, small sample sizes, and short follow-up periods. Dietary interventions, such as gluten-free/casein-free or ketogenic diets, have yielded inconsistent outcomes, often influenced by adherence challenges. Probiotic and prebiotic strategies demonstrate potential in modulating gut microbiota composition and alleviating gastrointestinal distress, yet strain-specific effects and interindividual variability remain critical factors. FMT has emerged as a particularly compelling approach, producing durable changes in gut microbiota and behavioral improvements in small pediatric cohorts, although safety, standardization, and long-term efficacy require further investigation.

Despite these advances, several challenges limit the clinical translation of microbiota-targeted therapies. Methodological heterogeneity across studies—including differences in diagnostic criteria, sequencing technologies, and outcome measures—complicates direct comparisons and meta-analytic synthesis. The lack of validated biomarkers for dysbiosis or treatment response hampers personalized intervention strategies, and small cohort sizes reduce statistical power and generalizability. Addressing these limitations through large, multicenter, longitudinal studies with standardized protocols is essential. Integrating microbiome data with clinical, genetic, and neurobiological information could enable precision medicine approaches tailored to the heterogeneity of pediatric ASD.

In conclusion, current evidence supports a mechanistic and clinical link between gut microbiota alterations and neurodevelopmental outcomes in children with ASD. The gut–brain axis represents a promising therapeutic target, but interventions must be rigorously evaluated in well-designed clinical trials before they can be recommended for routine

clinical practice. Continued multidisciplinary research will be critical to translate mechanistic insights into safe, effective, and individualized strategies that improve both gastrointestinal and behavioral outcomes, ultimately enhancing quality of life for pediatric patients with autism.

Challenges, Limitations, and Future Directions

Research on the gut-brain axis in autism spectrum disorder (ASD) faces several important limitations:

- Methodological heterogeneity: Variations in participant selection, diagnostic criteria, sequencing technologies, and outcome measures complicate cross-study comparisons and meta-analyses.
- Limited sample sizes: Many investigations are underpowered due to small cohort sizes (typically fewer than 100 participants), reducing statistical power and generalizability.
- Lack of validated biomarkers: There are currently no standardized microbial or metabolomic signatures for identifying ASD subtypes or predicting treatment response.
- Need for personalized approaches: High interindividual variability in microbiome composition necessitates precision medicine strategies that integrate multimodal data.

Future research should prioritize large, multicenter pediatric cohorts, standardized protocols, and longitudinal designs to establish causality and treatment efficacy. Incorporating microbiome science into clinical practice may ultimately offer novel approaches for improving both gastrointestinal and behavioral outcomes in children with ASD.

CONCLUSION

Current evidence supports the significant involvement of the gut-brain axis in autism spectrum disorder pathophysiology, particularly in pediatric populations. Children with ASD demonstrate distinctive alterations in gut microbiota composition, metabolic output, and immune signaling, which may contribute to both gastrointestinal and neurobehavioral symptoms. These findings provide a mechanistic basis for the frequent comorbidity of gastrointestinal and neurodevelopmental manifestations in clinical practice.

While microbiota-targeted interventions - including dietary modifications, probiotics, prebiotics, and fecal microbiota transplantations - show therapeutic potential, they remain investigational due to methodological variability, limited sample sizes, and absence of validated biomarkers. Existing evidence highlights the necessity for large, rigorously controlled pediatric trials and the integration of microbiome research with clinical, genetic, and neurobiological data.

In conclusion, the gut-brain axis represents a promising yet underexplored target for personalized interventions in ASD. Continued multidisciplinary research is essential to translate mechanistic insights into effective, safe, and individualized therapies that improve gastrointestinal health, behavioral outcomes, and quality of life for children with autism.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of Interest.

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