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Patho physiology of autism spectrum disorders and the gut micro biome: A systematic review

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Abstract Investigating any possible connections between the two and comprehending any potential processes underlying these connections is the main objective of research on the interaction among autism spectrum disorders (ASD) and guts micro biota. In the world, 1 in 160 persons suffers from ASD, a neuro improvement provision. It is increasingly recognized that environmental variables can contribute to the beginning of ASD, even though it has a substantial genetic component. The essential part of the gut micro biota in ASD is extensively researched because GI symptoms are 4 times more general in ASD patients. ASD patients' abnormal synthesis of bacterial metabolites has been shown to go hand in hand with disordered microbiota composition. The physiological processes that gut microbiota may perturb and so contribute to the path physiology of ASD are now being investigated in clinical research as well as preclinical investigations carried out in rats. The early findings point to the immune system, stomach tryptophan metabolism, and the central nervous system (CNS) as potential contributors. Several clinical studies include the use of antibiotics and probiotic among greater counts of studies involving a transplantation of fecal microbiota, showed behavioral improvements. This study's findings highlight the importance of considering the involvement of the physiological course of ASD is influenced by the gut microbiome, even if our understanding of this relationship is still in its infancy.

Keywords: ASD, gastrointestinal, metabolism of tryptophan, animal prototypes of ASD, immune system, microbiota-gut-brain axis

1. Introduction

The major common neurological improvement disorder, autism spectrum disorder (ASD), is distinguished by difficulty with social interaction, social behavior, and repeated and stereotyped behaviors. Cognitive dysfunction and anxiety problems may also occur (Gorzelańczyk et al., 2020). Despite recent advancements in the behavioral diagnosis of ASD, particularly in high-functioning individuals, it is still very difficult to diagnose. Furthermore, the analysis cannot be performed until the child is at least 18 months old, and confirmation cannot occur until then, making preventive actions ineffective (Roussin et al., 2020). ASD has been linked to several environmental and genetic factors, including nutritional shortages or excesses, viral exposure, abnormalities during the closure of the neural tube in the developing fetus, immune system dysfunction, and allergies. Complicated genes participating in the growth of the CNS are part of the genetic background of ASD. Over 100 genes and genomic areas have been linked to the etiology of ASD, and between 350 and 400 genes may be responsible for autism susceptibility. Environmental factors have been highlighted by accumulating research, and it is now believed that they are significantly more important than previously believed growth in individuals with ASD (Fattorusso et al., 2019). An assortment of neuron developmental illnesses with early childhood diagnoses is known as autism spectrum disorders. The diagnosis depends on behavioral traits such as shortcomings in communication and social interaction. Although the increasing incidence of ASD over the past few years has been undeniable, epidemiological research on the prevalence of ASD has produced widely inconsistent findings.

The estimated ASD incidence ranges from 1.76 per 1000 people to 7.17 per 1000 people worldwide. For those with autism, there is no standard course of treatment. Various treatments, including educational adjustments and medications, are used for children with ASD to improve their quality of life by easing disease-associated conditions such as hopelessness, restlessness, and difficulty. Both lifetime therapy and the condition itself place financial and physical burdens on people and

their families. Additionally, the difficulty in integrating people with ASD into society is exacerbated by the absence of particular therapies (Feng et al., 2023). The two-way interactions among the gut microbiome and the brain involve the neuronal, neuroendocrine, immunologic, and humoral pathways. The mother's contribution to early gut colonization in the child is significant, and environmental variables that significantly alter the mother's microbiome throughout pregnancy and postpartum usually have an impact on the microbial makeup of the offspring. Possible routes of ectopic transmission and dispersion of harmful oral bacteria include the blood, perivascular space, and circumventricular organs to the central nervous system and the digestive system. These pathways are likely to cause metabolic dysregulation and neuroinflammation in the brain. GI issues, such as stomach aches, diarrhea, and constipation, are among the common complaint signs and affect 9 to >70% of children with ASD. Due to their frequent resistance to conventional therapy, certain GI illnesses can be challenging to treat. These gastrointestinal problems could be due to bacteria in the gut.

Peralta-Marzal et al. (2021) examined the main objective of research on the connection between ASD and the gut microbiota to determine whether there are any possible connections between the two and to determine any potential processes underlying these connections (Figure 1). According to previous studies, people with ASD frequently have altered gut microbiota compositions and gastrointestinal symptoms compared to neurotypical people. These results suggest that there may be two-way communication between ASD and the gut microbiome, with ASD possibly affecting the gut microbiome and causing variations to potentially contribute to onset. A further part of the study included Phase II, which indicates related works; Phase III, which indicates the role of the gut microbiota in ASD: Clinical and Preclinical Proof; Phase IV, which indicates the Interventions in Medicine and Biology aimed at the gut microbiota; and Phase V, which indicates the conclusion.

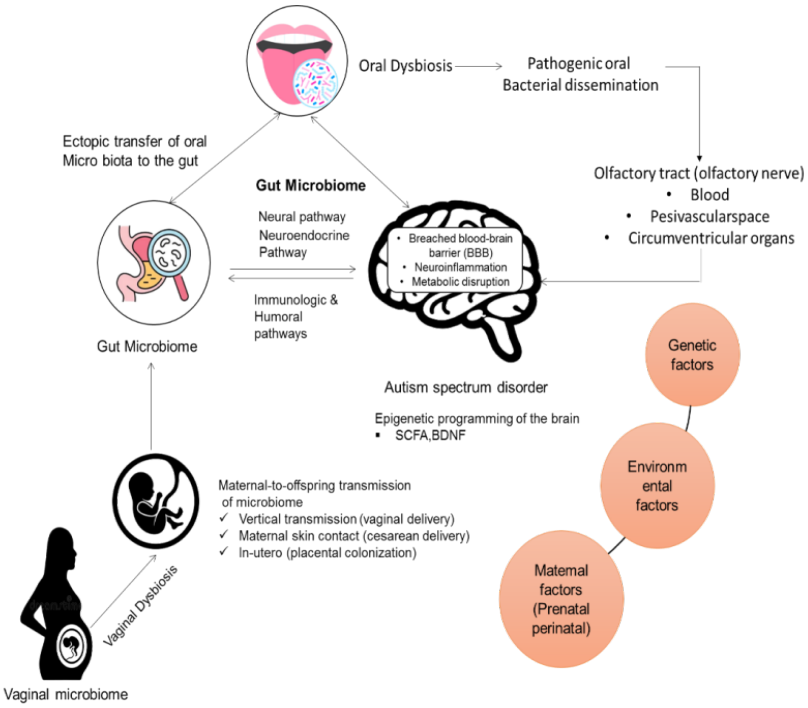

Figure 1 Relationships between the microbiota and ASD.
Source: https://www.mdpi.com/behavsci/behavsci-13-00548/article_deploy/html/images/behavsci-13-00548-g001.png

Wang et al. (2019) investigated the metabolite and gut microbial composition of young people affected by ASD. The two-stage research included ninety-two children with ASD and forty-two age-identified kids who were developing normally (TD). Hughes et al. (2018) investigated the pathophysiology of ASD through both clinical research and preclinical rodent investigations. The initial evidence is in favor of tryptophan metabolism and immune system participation, both in the stomach and the central brain systems. The modification of the microbiota by the administration of antibiotics and probiotics, as well as by fecal microbiota transplantation, has also been linked to behavioral improvements in a small number of clinical trials as well as a larger number of preclinical investigations. The information acquired in this review shows that although knowledge of the physiopathology of ASD is still developing, it must be considered.

Liu et al. (2019) examined the gut microbiome and fecal SCFAs in autistic and neurotypical people and, consequently, the bacterial 16S rRNA gene; additionally, they found fecal SCFAs and evaluated GI indices to determine the associations among the two. The findings demonstrated that individuals with ASD have different gut microbiota and SCFA compositions. (Oh and Cheon 2020) investigated the microbial composition of ASD patients. However, the outcomes could have been more consistent. Despite the evident differences in gut microbiota composition between persons with ASD and typically developing people,

animal studies have shown repeatedly that the gut microbiota plays a crucial role in the pathophysiology of ASD. Nitschke et al. (2020) aimed to integrate research performed in the last six years to determine the connection between the gut microbiota and ASD, especially about the explanation of the ASD microbiota and potential treatment methods. Zhang et al. (2018) investigated differences in the fecal microbiome of 35 ASD and 6 TD kids. Sutterella, Odoribacter and Butyricimonas were substantially more common in the ASD collection than in the control group at the genus level, whereas Veillonella and Streptococcus were considerably less common. Dargenio et al. (2023) explained that the development of metabolomics has also been extremely beneficial in this area. Based on these findings, several therapeutic approaches, most notably the use of probiotics, are being researched as a means of reducing the symptoms of ASD by modifying the microbiome. The variety of the studies prevents definitive evidence, although the results are encouraging. Mehra et al. (2023) studied the connections among the gut microbiota and microbial metabolites and the symptoms of autism by focusing on the gut microflora and thereby on autism through the use of prebiotics, probiotics, and herbal treatments.

2. The Role of the Gut Microbiota in ASD: Clinical and Preclinical Proofs

2.1. Modifications of Bacterial Metabolites and Dysbiosis in ASD

Proof of preclinical: Numerous mouse studies have been created due to the complex nature of ASD. Some of these include genetic designs and the BTBR mouse strain, which can be defined as a sporadic ASD method depending on its cognitive phenotype, or the NL3R451C, PCDH9 KO or Shank3 KO, which depend on the genes predicted to be involved in ASD loss or mutation in specific cases. Numerous ecological approaches, such as cow's milk allergy (CMA), are also based on the conditions that develop. All of those ASD frameworks can be categorized according to the changes in behaviors associated with ASD symptoms. However, an increasing number of studies show that some of these approaches result in GI symptoms resembling those observed in ASD patients. Improved intestinal permeability was discovered in mice lacking the Shank3 gene, BTBR mice, and MIA mice. The ileum of VPA-treated mice was shown to express myeloperoxidase (MPO), a hallmark of inflammation. More often, aberrant cytokine outlines in the stomachs of BTBR, MIA, and MHFD animals were found to contain these substances. Finally, faster transit was detected in NL3R451C animals, which was accompanied by an increase in inhibitory signals in the GI epithelium, whereas the opposite trend was observed in BTBR mice. In male VPA rats, BTBR and MIA mice, the phylum Bacteroidetes was shown to be more prevalent than the phylum Firmicutes. According to the aforementioned meta-analyses, ASD individuals have a high Bacteroidetes/Firmicutes ratio, which is consistent with this finding. However, prior studies revealed that the abundance of Firmicutes increased while that of Bacteroidetes decreased in Shank3 KO, VPA, and MHFD-fed mice. Research using ASD mice failed to detect an increase in Proteobacteria abundance in humans with ASD, except for Shank3 KO mice.

Overall, there is much variance in the bacterial mutations found among ASD patients according to the methods used by researchers and methodologies, and these differences do not necessarily match the changes found in people with ASD. It has been suggested that germ-free (GF) mice, which lack microbiota and exhibit modified behaviors associated with ASD, including decreased social interactions and enhanced stereotypical behaviors, can serve as an environmental framework for ASD. This finding is consistent with the theory. It is important to note that similar alterations in bacterial metabolite levels have also been reported for various ASD treatment regimens. Several serum metabolites have been shown to change in response to MIA, but “4-ethyl phenyl sulfate (4-EPS)”, which is produced from the bacterial metabolite 4-EPS, was shown to be present at significantly greater levels. Tyrosine is the source of 4-EPS, which is related to p-cresol.

Clinical Proof: It was hypothesized that certain children would experience regression autism, which was the result of dysbiosis caused by antibiotic use in young children. Clinical trials of 18 kids were initiated with vancomycin to eradicate the bacteria that were suspected to be responsible for this eradication by colonizing and producing neurotoxins. Those children's behavior improved while receiving therapy, but it did not continue once it was stopped. Despite the lack of evidence linking early antibiotic usage and ASD, the changes in composition among a sample of children with ASD, the microbiomes of the gut and maternal health were connected. One genus, Desulfovibrio, was found only in irrelevant controls; it was found in fifty percent of ASD children and some of their siblings. The prevalence of Desulfovibrio and the severity of signs of ASD were also associated. Despite inconsistent findings from individual research, these investigations and meta-analyses confirm the presence of imbalances in ASD. These differences might be due to methodological differences, but they might also be a result of the reality that the various cohorts arise from various nations with various lifestyles and eating habits. The ages of the kids participating in the trials also varied greatly; children as young as two years old, when the gut microbiota is still developing, participated in certain analyses. Despite this, there appears to be a fairly steady increase in the abundance of the putatively toxic genus Clostridium and a decrease in the abundance of the beneficial genus Bifidobacterium. The fact that the control groups varied throughout several studies is interesting to note. There were three different types of discordance: those made up solely of unrelated people, those made up solely of siblings of ASD children, and those made up of both unrelated people and siblings. In studies utilizing both types of control groups, sibling groups sometimes exhibited microbiota profiles that more closely resembled the "ASD profile" than did unrelated individuals. This study also revealed a relationship between GI symptoms and the composition of the gut flora. The variation between studies may be partially explained by the difference in

the make-up of the ASD and control groups. Only additional research and improved group composition standards could be used to resolve this issue.

Several ASD children exhibit dysbiosis in their guts, which is now widely acknowledged, although its exact nature is still not well known. Research has concentrated on the bacterial metabolites that are differentially expressed in ASD children to better understand how this dysbiosis affects health. According to various research teams, young children with ASD have higher urinary levels of p-cresol, a bacterial metabolite generated from tyrosine. These teams proposed the hypothesis that this increase might be caused by an increase in p-cresol-producing bacteria, such as Clostridium difficulta. Although there have been repeated observations of an increase in urine p-cresol in early childhood with ASD, there is currently no information available to explain the mechanisms driving this increase. Interestingly, patients with propionic acidosis, a genetic illness marked by a buildup of propionate, had neurodevelopmental delay, and a recent study revealed that these patients had a high prevalence of ASD. The oxidative stress caused by propionate can affect mitochondrial function. Many people with ASD have reported mitochondrial malfunction, which is thought to contribute to the pathogenesis and physiology of this disease.

2.2. Effect of Immunologic Dysregulation and Gut Microbiota Autism Spectrum Disorder

Proof of preclinical: First, studies using a mouse model of VPA-induced ASD revealed that the expression of markers of neuroinflammation increased in the dorsal hippocampus and drastically changed the microbiota in the digestive tract. According to a study, immature microglia exhibit a muted response to LPS stimulation in mice lacking microbiota beginning at birth (GF mice). By living together with SPF mice that have diverse microbiota, this effect was reversed. Interestingly, administering a combination of SCFAs in the water also restored a normal microglial phenotype. These findings demonstrated the importance of complicated maturation of neurons, the impacts on atrocities, and the functions of metabolites and microglia both during improvement and throughout adulthood. The majority of the proofs for the role of the microbiome in the other immunological changes observed in ASD are likewise supported by animal research. Initial investigations of animals indicated the importance of microbes for immune system development and the maintenance of immunological homeostasis. In addition to the previously noted effects, immune difficulties associated with MIA during pregnancy also result in dysbiosis, poor interactions, social and repeated behaviors, and anomalies in the brain that suggest ASD. MIA children were shown to have immune changes resembling those reported in ASD patients, including an increase in the peptides IL-6 and IL-17 that promote inflammation and a greater number of Th17 cells. Notably, ASD caused by genetic or environmental factors that are not connected to immune issues may also cause immunological dysregulation. Additionally, bacterial alterations are frequently connected to these dysregulations. Curiously, this model's IL-17 levels might be reduced by L. reuteri MM4-1A therapy.

Antibiotics were given to pregnant mice by the researchers to produce offspring with diminished microbiota. The offspring were subsequently given the intestinal microbiota of control or MHFD-fed mice of comparable age. Compared to offspring colonized with control microbiota, those colonized with MHFD microbiota had a greater percentage of ILC3s. This study demonstrated how the microbiota impacts ILC3s. Similarly, the microbiota of VPA-treated mice and rats was disrupted, and these mice produced more butyrate. Butyrate is frequently regarded as a beneficial SCFA and has been shown to improve the “blood–brain barrier (BBB)” and intestinal functions as well as boost anti-inflammatory responses.

As a result, these preclinical findings demonstrate that immunological issues experienced during pregnancy or throughout life result in behaviors similar to those of ASDs and that this impact may be microbiota dependent. These results point to a potential connection among the brain, immune system, and microbiome that may contribute to the path physiology of ASD. Numerous ASD investigations have shown immune dysregulation, which usually corresponds to alterations in multiple micro biomes and altered behavior. Additional clinical research on the gut microbiota-immune-brain nexus in ASD must continue, as the majority of the available information is still preclinical.

3. Gut microbiota impact on the dysregulation of tryptophan metabolism in ASD patients

3.1. Preclinical Evidence

Preclinical research has shown that the microbiota may have a range of effects on Trp, also referred to as catabolism. It was discovered that male and female GF mice had higher plasma Trp levels and lower plasma KYN/Trp ratios, the latter of which were remedied by colonization of the SPF gut microbiota. Notably, at approximately postnatal day 42, healthy human donors colonized GF animals, restoring 5-HT seroconversion and colonic phases and regular TPH1 and SLC6A4 gene activity. These results imply that Trp metabolism through the five-HT and KYN pathways may be influenced by certain kinds of gut microbiota bacteria and the metabolites they produce. There is inconsistent evidence connecting the gut microbiota to various neurotransmitter networks connected to ASD, notably the glutamatergic and GABAergic systems. Most of the related research points to the role of gut bacteria in the alteration of neurotransmitter processes in individuals with ASD has focused on 5-HT. Clinical research has revealed increased central or peripheral GABA or glutamate levels and modified receptor expression in the brains of ASD patients. A subsequent investigation examined the metagenomes of ASD patients and revealed that the expression of genes essential for GABA production was downregulated.

Observations of reduced GABA receptor expression in the hippocampus of Shank3 KO mice provide additional support. A curious correlation was observed between these changes and the levels of the mouse microbiota

L. reuteri and L. reuteri MM4-1A therapy partially resaved those communication stages. Although there is presently no proof that the microbiome plays a role in the changes in GABA and glutamate levels in individuals with ASD, these initial findings offer a potential direction for examination. In summary, it is now widely acknowledged that people with ASD have disrupted microbiota and altered metabolic activity. A growing corpus of studies indicates that congenital disabilities may impact the Trp alimentary and immunological responses of the brain and peripheral nerves. Consequently, the gut microbiota can affect brain function and neurodevelopment in patients with ASD. Recent discoveries have led to the examination of whether therapies targeting the gut microbiota can improve GI signs, cognitive function, and behaviors in individuals with ASD.

4. Interventions in Medicine and Biology Aiming at the Gut Microbiota

4.1. Research on the impacts of probiotics for treating ASD on symptoms

Recent publications of a few interventional clinical studies and additional interventional preclinical studies have shown that altering the gut microbiota can affect behaviors related to ASD. They also provide some details on the processes underlying this impact.

Clinical research: Because such effects vanish following treatment, a lengthy antibiotic course is not realistic. The potential value of probiotic therapies for ASD has been the subject of several studies. Probiotic treatments for kids with ASD have been shown to improve GI symptoms as well as microbiota composition, according to many studies. Although many of these studies either did not examine children's conduct or did not observe any improvements following probiotic delivery, some research has shown improved behavior. Thirty ASD kids received daily, 3-month therapy comprising a patented probiotic mixture that improved their cognition, sociability, and interactions, as evidenced by a reduction in “ATEC (autism treatment evaluation checklist) scores. These statistics are ultimately adequate to prove that probiotic therapies have a positive impact on behaviors in individuals with ASD, given the variability in probiotic choices, group sizes, treatment durations, and behavioral methods. However, several preclinical studies demonstrating the impact of probiotics on behaviors associated with ASD, which will be discussed later, indicate that using probiotics may be a fascinating avenue for treatment or preventive measures.

Preclinical research: As already mentioned, a large number of mouse representations of ASD, whether genetic or environmental, exhibit changes in behaviors that are indicative of ASD. Numerous research teams have questioned whether altering the gut microbiota through probiotic treatment might worsen the modified behaviors of those methods or whether several of these techniques also impair GI function and the gut microbiota. Improved communication, cognitive function, stereotyped behavior, and anxiety-like conduct were noted. On the other hand, social conduct was unaffected by probiotic treatment. Importantly, probiotic treatment lowered the high serum levels of 4-EPS, a metabolite, in MIA mice, returning them to normal levels. In addition, when naive mice received sustained systemic dosages of 4-EPS, they exhibited anxiety-like behaviors. Probiotics have since been explored in additional mouse models of ASD in various studies. This research also provided an extremely thorough molecular characterization of the antibiotic effect, revealing that oxytocin requires receptors to be present in the dorsal segmental zone that are connected to the neuroplasticity induced by social interaction and showing that the impact of probiotics is based on this region. The way in which the gut microbiota, gut, and brain interact together in ASD patients is supported by these most recent findings, as are the possible behavioral benefits of certain probiotic therapies in ASD patients. These findings in rodents are just the beginning; investigations involving people with ASD will need to corroborate them.

4.2 Fecal microbiota transplantation (FMT)

4.2.1. Clinical analysis

As far as researchers are aware, there are many clinical studies examining how FMT affects patients' ASD symptoms. FMT is most effective at treating difficult C. cruzi infections, where it is most frequently utilized. Furthermore, some research has indicated which FMT might be therapeutically advantageous for those with irritable bowel syndrome and may show promise for those with metabolic syndrome in terms of insulin resistance and metabolic factors; however, these outcomes still need further investigation. The effects of FMT on different neurological illnesses have also been examined in several studies. Even though those outcomes seem encouraging, it is important to keep in mind that additional extensive longitudinal studies are required because this process is still being perfected. These findings suggest the efficacy of FMT for treating behavioral and gastrointestinal problems in individuals with ASD, but additional research in controlled trials with larger cohorts is needed.

Preclinical Studies: Autism spectrum disorder (ASD) mouse models must be used in preclinical research to develop a more comprehensive understanding of how FMT impacts microbiomes, gastrointestinal tract (GI) signs, other ASD-based indicators, and autism spectrum disorder (ASD)-like actions. According to a preclinical investigation, FMT may be utilized therapeutically to treat a range of neurological diseases, including ASD. In contrast to the findings concerning colonization, the sociability and anxiety-related actions of GF mice were affected by the microbiomes of the MHFD-fed mice, which were

corrected after weaning by colonization with microbiota from normal mice. The mouse-fed MIA microbiota performed worse on the item recognition tests than did the mouse-fed control microbiota. Overall, our findings demonstrated that while FMT from ASD animals can impair behavior in healthy mice, in ASD models, FMT from healthy mice can improve behavior. Compared to TD mice, ASD animals had less social contact and more stereotypical behavior. Researchers subsequently discovered a link between these behavioral changes and the presence or absence of specific bacteria in the micro biomes of ASD animals.

Additionally, many genes with alternate splicing in the prefrontal cortex were noted, which includes a few genes that are known to play a role in some human cases of ASD. Another recent study performed FMT in MIA mice utilizing pooled fecal samples from 3 healthy human donors. Mice either obtained their microbiota immediately after the donor samples were taken or during an in vitro cultivation phase. Both FMT processes diminished the number of repeated actions in the marble burial tests and the self-grooming study. The three-chamber social communication examination FMT using donor-derived microbiota was the only FMT to impact anxiety-like behavior. No FMT method had a discernable effect on social conduct. FMT is a potential strategy for helping ASD individuals maintain their behavior and experience GI problems. To support this idea, additional clinical research is needed. Additionally, additional preclinical research is needed to determine whether FMT may cause systemic and neuronal variations that enhance behaviors.

Figure 2 shows the prevalence of ASD among young individuals and teenagers aged 1 to 17 years, broken down by age group and sex, and Table 1 shows the percentage of ASDs. Approximately one in fifty (or 2.0%) kids and teenagers aged one with seventeen had an ASD diagnosis.

- ASD was identified in approximately 1 in 50 kids and teenagers, or 2.0% [95% confidence interval: 1.8, 2.2] (Figure 2).
- Those aged 5 to 11 years had the highest frequency of ASD, accompanied by those aged 12 to 17 years and infants and young children. Patients aged 1 to 4 years had a significantly lower incidence of ASD than did those in the two older age groups.
- One in 32 males and one in 125 girls were diagnosed with ASD, which is approximately four times more common in males than in females. This variation was statistically important.
- Overall, across all age categories, males exhibited a significantly greater incidence of ASD than females did, with the highest relative variance occurring in children between the ages of 5 and 11.
- The small sample size precluded reporting on sex diversity in this community.

Figure 3 shows the ASD market by treatment method, and Table 2 shows the results for ASD by treatment method. The Global Autism Spectrum Disorders Market has been divided into Behavioral Approaches, Early Intervention, Medication, and others based on the Treatment Approach. In 2022, behavioral strategies held the largest market share. Children with ASD benefit from behavior and communication strategies because they can give the child framework, focus, and order in addition to involving the family. Parents, siblings, and other family members may participate in these programs, which are typically quite structured and intensive. Numerous behavioral treatments address the variety of social, linguistic, and behavioral challenges linked to ASD.

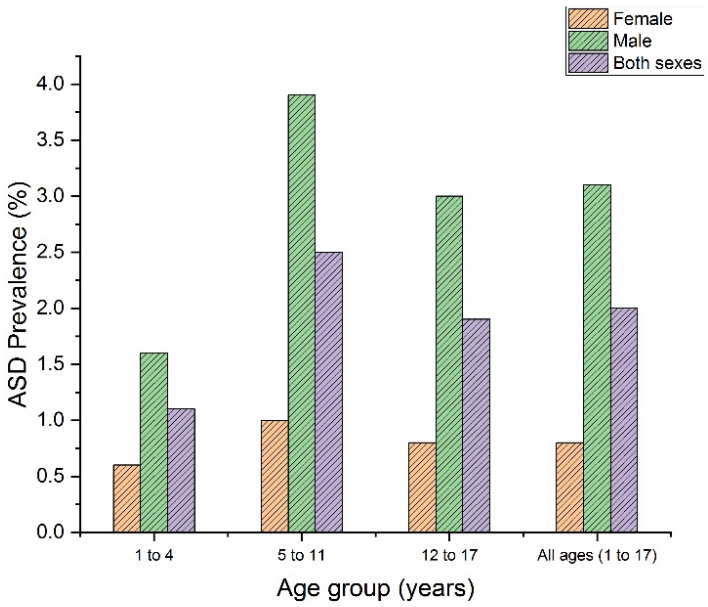

Figure 2 ASD incidence among young individuals and teenagers aged 1 to 17 years, broken down by age group and sex.
Source: https://www.canada.ca/content/dam/phac-aspc/images/services/publications/diseases-conditions/autism-spectrum-disorder-canadian-health-survey-children-youth-2019/Fig-01-EN-01.png

Table 1 Percentage of ASD incidence.

Age group (years)	ASD Prevalence (%)		
	Female	Male	Both sexed
1 to 4	0.6	1.6	1.1
5 to 11	1	3.9	2.5
12 to 17	0.8	3	1.9
All ages (1 to 17)	0.8	3.1	2

Source: https://www.canada.ca/content/dam/phac-aspc/images/services/publications/diseases-conditions/autism-spectrum-disorder-canadian-health-survey-children-youth-2019/Fig-01-EN-01.png

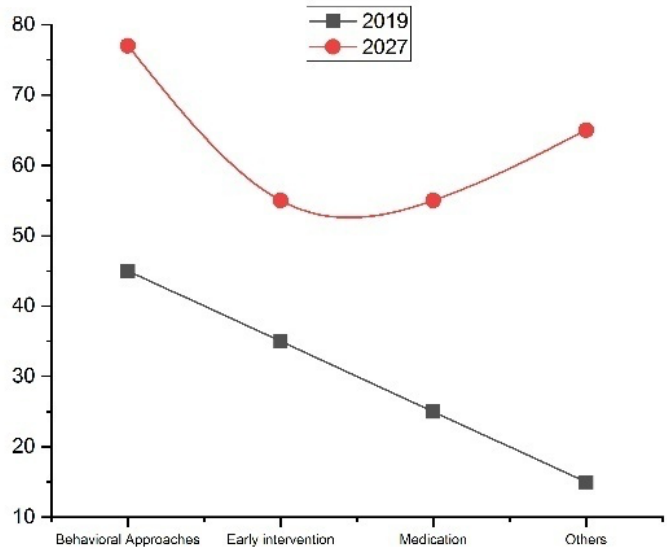

Figure 3 Autism spectrum disorder market by treatment method.
Source: https://www.verifiedmarketresearch.com/wp-content/uploads/2020/09/Autism-Spectrum-Disorders-Market-by-Treatment-Approach.png

Table 2 Results for ASD according to treatment method.

	2019	2027
Behavioral Approaches	45	77
Early intervention	35	55
Medication	25	55
Others	15	65

Source: https://www.verifiedmarketresearch.com/wp-content/uploads/2020/09/Autism-Spectrum-Disorders-Market-by-Treatment-Approach.png

5. Final considerations

Despite the differences in the study, the data presented in this summary converge to identify ASD patients who have aberrant microbiomes and altered behaviors. An increasing body of evidence indicates that these changes may exacerbate behavioral signs and biochemical indications of ASD, regardless of whether they contribute to the disease's genesis or appear throughout its growth. This prompted the adoption of animal studies for ASD treatment in a struggle to clarify the processes underlying the role of the gut microbiota in this population. These preclinical animal studies have shown that these agents have considerable effects on the immune system and metabolism of THRPs. Alterations in other neurological and physiological traits of ASD patients, including the development of neurotransmitters and glutamatergic brain cells or pulmonary activity of mitochondria, may also be caused by the gut microbiota, according to recent studies. The gut microbiome could impact additional ASD factors that are under investigation.

Like low vitamin B levels are related to ASD, symbiosis may also be a factor in vitamin production due to the influence of gut bacteria. According to findings from preclinical research, current clinical interventional research utilizing FMT or probiotic therapies has revealed some encouraging results. It is hoped that by continuing to alternate among clinical and preclinical research, additional proofs of the role of the intestinal microbiota in ASD may be discovered, as well as novel systems underpinning the function of the gut microbiota. Determining when the microbiota enters images and whether it can be employed as an early biomarker requires longitudinal studies because it is still unknown whether microbiota alterations are induced by ASD. For instance, the European GEMMA research will carry out this kind of study in the upcoming years.

Ethical Considerations

Not Applicable.

Conflict of Interest

The authors declare no conflict of interest.

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