Association Between Gut Microbiota and Autism Spectrum Disorder: A Systematic Review and Meta-Analysis

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Autism spectrum disorder (ASD) is characterized by stereotyped behavior and deficits in communication and social interactions. Gastrointestinal (GI) dysfunction is an ASD-associated comorbidity, implying a potential role of the gut microbiota in ASD GI pathophysiology. Several recent studies found that autistic individuals harbor an altered bacterial gut microbiota. In some cases, remodeling the gut microbiota by antibiotic administration and microbiota transfer therapy reportedly alleviated the symptoms of ASD. However, there is little consensus on specific bacterial species that are similarly altered across individual studies. The aim of this study is to summarize previously published data and analyze the alteration of the relative abundance of bacterial genera in the gut microbiota in controls and individuals with ASD using meta-analysis. We analyzed nine studies, including 254 patients with ASD, and found that children with ASD had lower percentages of Akkermansia, Bacteroides, Bifidobacterium, and Parabacteroides and a higher percentage of Faecalibacterium in the total detected microflora compared to controls. In contrast, children with ASD had lower abundance of Enterococcus, Escherichia coli, Bacteroides, and Bifidobacterium and higher abundance of Lactobacillus. This meta-analysis suggests an association between ASD and alteration of microbiota composition and warrants additional prospective cohort studies to evaluate the association of bacterial changes with ASD symptoms, which would provide further evidence for the precise microbiological treatment of ASD.

Keywords: autism spectrum disorder, children, GI problems, gut microbiota, microflora, meta-analysis

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by stereotyped behavior and deficits in communication and social interactions. ASD is highly heterogeneous and its etiology is unclear. Previous studies have revealed several potential causes of this disease, such as genetic abnormalities, dysregulation of the immune system, inflammation, and environmental factors (1–5). Gastrointestinal (GI) problems, including constipation, abdominal pain, gaseousness,
The criteria for study inclusion were as follows: 1) observational studies; 2) investigating gut bacteria in children diagnosed with autism or ASD; 3) including information about sample size and prevalence of the specific bacteria assessed; and 4) written in English. Studies about non-human subjects as well as reviews, case reports, and duplicate publications were excluded. All articles providing sufficient information about the relationship between the gut microbiota and ASD were included.

The outcome of interest was the association between ASD and the gut microbiota. The definition of ASD was based on a physician’s diagnosis according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision or a history of ASD reported by the parents of the children. Assessments of the biodiversity and composition of microbiota were based on stool sample testing using culture-dependent methods (32, 33), real-time polymerase chain reaction (PCR) (34), fluorescence in situ hybridization (FISH) (35), and pyrosequencing for bacterial 16S ribosomal ribonucleic acid (rRNA) genes (23, 29, 30, 36, 37). To conduct the meta-analyses, at least three studies were used to assess the bacteria. To maintain consistency within the present meta-analysis, all bacterial information were reviewed and selected before the final analyses, including bacterial taxonomy, percentage, and relative abundance. In general, gut bacteria were classified at different taxonomic levels from phylum (high taxonomic level) to genus (low taxonomic level). For consistency, the included studies were analyzed at the genus level. We contacted the investigators of the eligible studies if we were unable to extract data on bacterial abundance from the published articles.

Quality Assessment
Four investigators independently carried out data extraction of the following items: author(s), publication year, study design, country, study population age, diagnosis of ASD, and effect size. Two reviewers completed the quality assessment independently. A set of structured criteria modified from previous studies was used to complete the quality assessment of publications. The total score ranged from 5 to 9 (with 9 as the highest), with a higher score indicating higher quality. In case of disagreement regarding the extracted data, discrepancies were resolved by consensus discussion.

Statistical Analysis
A fixed-effects model and a random-effects model were used to report the most conservative result. Statistical heterogeneity was assessed using the I² value, which represents the percentage of total variation across different studies, owing to heterogeneity rather than chance. I² values of 25%, 50%, and 75% were related to low, moderate, and high heterogeneity (38). A random-effects model was applied when there was notable heterogeneity (I² index > 50%); otherwise, a fixed-effects model was used. The standardized mean difference (SMD) measure of effect was used for the continuous variables (39). SMD > 0 indicates that participants with ASD have a higher bacterial abundance than controls, and SMD < 0 indicates participants with ASD have a lower bacterial abundance than controls. We also planned to analyze the influence of bias control in subgroup analyses as well as the evidence of publication bias and other small study effects using funnel plots and regression analyses. However, because of the limited number of studies,
we only conducted subgroup analyses of studies that included participants with ASD or typically developing children. In our primary analysis, we included all published studies. The ratio of the bacterial percentage between children with ASD and controls was calculated to assess the relative abundance of bacteria in children with ASD compared to controls. All statistical analyses were carried out using Stata version 12.0 (Stata Corp, College Station, TX, USA).

RESULTS

Characteristics of Included Studies

Literature searches revealed 431 potentially eligible records (Figure 1). Three additional records were identified through a review of reference lists. After the review of the titles and abstracts and the removal of 246 duplicates, 112 publications were selected for a further review of the full texts. After the exclusion of records that were clearly irrelevant, involved nonhuman subjects, or have incomplete data, 30 full-text records were reviewed individually. Of these 30 articles, 9 studies were included in the present meta-analysis, as the remaining studies did not provide quantitative data about bacterial abundance or percentage in the report or after our request for essential details. In total, there were 254 participants with ASD and 167 age-matched typically developing controls with an age range from 6 to 11 years (Table 1). The diagnostic methods of ASD and comorbidity disease in the included studies are shown in Table 2. Gut microbiology was assessed using quantitative PCR (QPCR) or PCR, pyrosequencing, culture methods, or FISH (Table 3). Each study provided different types of bacteria for the meta-analysis (Table 3). The percentage and relative abundance of bacterial genera in the gut microbiota were used in the present analysis to avoid potential variation caused by different detection methods of the microbiota in the included papers. The absolute number of bacterial populations reported only in three studies was insufficient to perform a meta-analysis. The standard deviation of the mean was calculated for one study that only provided the mean and range (33) using a previously published method (40).

Akkermansia

We analyzed the percentage of Akkermansia from five trials (Figure 2A). A fixed-effects meta-analysis showed that the percentage of Akkermansia in the total detected microflora was 0.1% in participants with ASD [95% confidence interval (CI): −0.005 to 0.007] compared to 0.2% in typically developing children (95% CI: −0.007 to 0.01). There was no evidence of between-study heterogeneity ($I^2 = 0$%; Figure 2A). However, its effect size ($Z = 0.44, P = 0.658$) was relatively small. The ratio of bacterial percentage between the ASD group (0.1%) and the control group (0.2%) was 0.5. The percentage of Akkermansia in patients with ASD was clearly lower compared to controls (Figure 5A).
Bacteroides

Bacteroides is a Gram-negative bacterium and is one of the earliest colonizing and most abundant constituents of the gut microbiota and may induce an anti-inflammatory milieu (41). A fixed-effects meta-analysis showed that the percentage of Bacteroides in the total detected microflora was 10.2% (95% CI: 0.041–0.163) in children with ASD but 14.3% in typically developing children (95% CI: 0.069–0.218). There was low between-study heterogeneity within the ASD group ($I^2 = 43.7$%; Figure 2B). The effect size ($Z = 4.92, P = 0.000$) was significant and large. The ratio of the bacterial percentage between the ASD group (10.2%) and the control group (14.3%) was 0.71 (Figure 5A). Furthermore, a random-effects model also showed a lower abundance of Bacteroides in participants with ASD compared to controls (SMD $−0.35, 95\%$ CI: $−1.2$ to $0.51$; Figure 3D). However, its effect size ($Z = 0.8, P = 0.427$) was relatively small.

Bifidobacterium

Bifidobacterium has long been used as a probiotic to alleviate various diseases by changing the gut microbiota composition (34, 42). A random-effects meta-analysis showed 2.2% of Bifidobacterium in the total detected microflora of children with ASD (95% CI: −0.008 to 0.052), whereas the percentage in typically developing children was 4.2% (95% CI: −0.00 to 0.084).
with moderate between-study heterogeneity \((F = 78.2\% \text{ and } 69.7\%, \text{ respectively}; \text{ Figure 2C})\). The effect size \((Z = 2.27, P = 0.023)\) was significant and moderate. The ratio of the bacterial percentage between the ASD group (2.2%) and the control group (4.2%) was 0.52 (Figure 5A). The percentage of \textit{Bifidobacterium} in patients with ASD was clearly lower compared to controls.

\textbf{Faecalibacterium}  

Five studies were used to evaluate the percentage of \textit{Faecalibacterium} (Figure 3A). A fixed-effects meta-analysis showed that the percentage of \textit{Faecalibacterium} in the total detected microflora of children with ASD was 10.2% (95% CI: 0.039–0.166), clearly higher than that of typically developing children (7.7%; 95% CI: 0.021–0.133). The effect size \((Z = 4.12, P = 0.000)\) was significant and large. The ratio of the bacterial percentage between the ASD group (10.2%) and the control group (7.7%) was 1.32 (Figure 5A).

\textbf{Ruminococcus}  

\textit{Ruminococcus} is an anaerobic Gram-positive coccus that can be found in the GI tract (43, 44). The percentages of \textit{Ruminococcus} in the total detected microflora were assessed. A fixed-effects meta-analysis showed 3.4% and 3.2% for children with ASD and typically developing controls, respectively (95% CI: −0.004 to 0.072 and −0.006 to 0.069, respectively). There was no evidence of between-study heterogeneity \((F > 50\%); \text{ Figure 2C})\) with respect to \textit{Ruminococcus} percentages. The effect size \((Z = 2.42, P = 0.016)\) was significant and moderate. The ratio of the bacterial percentage between the ASD group (3.4%) and the control group (3.2%) was 1.06 (Figure 5A). The percentage of \textit{Ruminococcus} in patients with ASD was slightly higher compared to controls.
Clostridium, Parabacteroides, Escherichia coli, Enterococcus, and Lactobacillus
A fixed-effects meta-analysis showed that the percentage of Clostridium in the total detected microflora of children with ASD was 6.4% (95% CI: 0.006–0.122), similar to that of typically developing children (6.3%; 95% CI: 0.004–0.122; Figure 2D). Additionally, the fixed-effects meta-analysis also showed that the percentage of Parabacteroides in the total detected microflora of children with ASD was 0.3% (95% CI: –0.008 to 0.014) compared to 0.5% in typically developing children (95% CI: –0.01 to 0.02; Figure 3B). The ratio of the bacterial percentage between the ASD group (0.3%) and the control group (0.5%) was 0.6, indicating a decreased percentage in children with ASD (Figure 5A).

The random-effects and fixed-effects models showed a lower relative abundance of E. coli and Enterococcus in children with ASD compared to controls (SMD −0.33, 95% CI: −1.18 to 0.52 and SMD −0.14, 95% CI: −0.47 to 0.20, respectively; Figure 4B and 4C). A random-effects meta-analysis showed a higher relative abundance of Lactobacillus in children with ASD (SMD 0.53, 95% CI: −0.001 to 1.1; Figure 4D). The pooled relative abundance of Lactobacillus, Enterococcus, E. coli, Bacteroides, and Bifidobacterium in children with ASD are shown in Figure 5B.

**DISCUSSION**
Alterations of the Gut Microbiota in Patients With ASD
The gut microbiota plays a major role in human physiology and pathology (45–47). Both experimental and clinical cross-sectional studies showed that patients with ASD had alterations of the gut microbiota (48). These alterations were potentially
relevant to behavioral and GI symptoms that are correlated with the severity of ASD (7, 43, 49–52), suggesting that the gut-brain axis participates in the pathogenesis of ASD (18, 53, 54).

Although several reviews suggested a microbiota alteration in patients with ASD (28, 30, 55–60), this is the first meta-analysis that systematically reviewed published data and examined microbiota alterations in patients with ASD. Standardized data collection, strict inclusion criteria, and multiple statistical tools were used to ensure the most accurate assessment. The present meta-analysis found that neither there were significant changes in the intestinal microbial diversity nor single microbial species may be perceived as “ASD-promoting microbes.” Our analyses showed that participants with ASD had a lower abundance of Akkermansia, Bacteroides, Bifidobacterium, E. coli, and Enterococcus, a higher abundance of Faecalibacterium and Lactobacillus, and a slightly increased abundance of Ruminococcus and Clostridium. It is possible that the reduced levels of beneficial bacteria combined with the increased levels of harmful bacteria contribute together to ASD symptoms. Our analysis is consistent with previous reviews (61), with one exception of Clostridium. Several studies showed there was a higher level of Clostridium in individuals with ASD compared to controls and hypothesized that Clostridium can produce neurotoxins and contribute to ASD (62, 63). The current analysis showed slightly increased levels of Clostridium and Ruminococcus, indicating that further studies should be performed to confirm these trends. In contrast, there is potentially a decrease in “beneficial” bacteria in patients with ASD (34, 64). This notion is further supported by a recent study showing that the supplementation of Bifidobacterium species-containing probiotics improves specific ASD symptoms (65).

**Potential Mechanisms of the Gut Microbiota in ASD**

The role of the gut microbiota in development and disease is not yet well understood. Potential mechanisms by which microbiota...
Bacteroides and Parabacteroides were decreased in abundance in individuals with ASD across the analyzed studies. Bifidobacteria are major producers of SCFAs, which suppress the growth of pathogens such as E. coli across the epithelium, reduce inflammation in the gut, and cooperate with the immune system (67, 68). In the present study, lower levels of Bifidobacterium and higher levels of Lactobacillus suggested an imbalance in beneficial bacteria. Decreased levels of Bifidobacterium and metabolites of free amino acids and short-chain fatty acids (SCFA) in the feces may also contribute to the development of ASD (23). A low level of SCFA was possibly related to probiotic usage, lower saccharolytic fermentation by beneficial bacteria, or increased gut permeability, subsequently exacerbating autistic symptoms (32). Akkermansia is a mucin-degrading bacterium present in the gut of typically developing adults. A lower abundance of Akkermansia in children with ASD could indicate a thinner GI mucus barrier in children with ASD compared to controls; the result might reflect an indirect evidence of impaired gut permeability in children with ASD (34). Second, animal studies have shown effects of the gut microbiota on neurodevelopment, suggesting that intestinally derived lipopolysaccharides can increase anxiety-like behavior in mice (69–71). Furthermore, gut microbial populations in ASD may produce toxic products, including neurotoxins that influence distal sites such as the brain, and exert systemic effects (35). Third, microbiota and their metabolites are essential in maintaining both white matter and epithelial barrier integrity, which is important for normal brain development and function (72). The development of the blood-brain barrier is now well established to be contingent upon the presence of commensal gut flora (10, 11). Additionally, diet-specific gut microbiota populations potentially influence white matter integrity in rats (59). These studies reveal a potential mechanism for the gut microbiota in influencing the brain-gut-enteric microbiota axis and contribute to the understanding of the role of the brain-gut axis in the pathogenesis of ASD.

Children with ASD also have a high rate of GI symptoms, which correlate with ASD severity (32, 73) and are associated with ASD-relevant emotional and behavioral problems (74, 75). More than 50% of GI symptoms may be due to dysbiotic gut microbiota, including increased Ruminococcaceae (76, 77). In our meta-analysis, only two studies enrolled children with ASD who had no GI symptoms (23, 37), and one study did not provide details about GI symptoms (33). Collectively, the studies included in the current analysis, however, indicate a high incidence of GI symptoms in children with ASD. The GI symptoms might be related to the ubiquity of food selectivity in this population, as the dietary patterns often associated with ASD involve a high intake of processed food and lack fiber-containing fruits and vegetables. Gastroesophageal reflux, gastroenteritis, food allergies, and inflammatory bowel disease are also more common in children with ASD, probably contributing to the development of GI symptoms (78).

**Limitations of the Study**

The meta-analysis is inherently limited by the included studies. First, the study design, specificity, and sensitivity of the detection methods used in the included studies varied. The studies included in our analysis mainly used culture-based methods, PCR and pyrosequencing, to analyze the changes of particular bacterial groups, which might underestimate the complexity of the gut microbiota. Indeed, we found that suitable analytical and statistical methods are critical to detect the alterations of the abundance of some gut microbiota in patients with ASD. Second, many reports had relatively small sample sizes with only two of the nine studies recruiting more than 50 participants with ASD. Significant heterogeneity was found between studies.
when the data were pooled. Finally, our study only analyzed bacterial percentages and abundance at the genus level due to the insufficiency of data for various bacterial taxonomies. Further broad-based, longitudinal, unbiased studies of fecal microbial populations in patients with ASD and age-matched controls using next-generation sequencing will be more informative for clarifying ASD-associated dysbiosis.

**CONCLUSION**

Our review summarized the association between ASD and gut microbiota composition. Participants with ASD had a lower abundance of *Akkermansia, Bacteroides, Bifidobacterium, E. coli,* and *Enterococcus,* a higher abundance of *Faecalibacterium* and *Lactobacillus,* and a slightly increased abundance of *Ruminococcus* and *Clostridium.* There were important differences, such as the abundance of *Akkermansia, Bifidobacterium, Bacteroides, E. coli,* and *Lactobacillus* between the microbiota of children with ASD and typically developing children. Our analysis warrants additional prospective cohort studies to evaluate the influence of the microbiota in the pathogenesis of ASD and associated GI symptoms. A future impact of such studies could potentially guide the implementation of dietary/probiotic interventions impacting the gut microbiota in patients with ASD.

**AUTHOR CONTRIBUTIONS**

FL and JL designed and supervised the study. MX and XX performed the data analysis and interpretation and wrote the manuscript. All authors read and approved the final version to be published and agreed to be accountable for all aspects of the work.

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