

Review

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## Review

# Perturbations of Gut Microbiota Compositions in Autism Spectrum Disorder: A Review and Meta-analysis

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**Abstract:** Autism spectrum disorder (ASD) is a neurodevelopmental disorder with high heterogeneity and has a prevalence of 0.7% to 3.2% in children. Gut microbiota are a collection of microorganisms that inhabit in human guts, which can produce various metabolites that affect the homeostasis and functions of nervous and endocrine systems. There are many studies on the relationship between various gut microbiota and ASD, but the alteration pattern of microbial profiles in ASD children is not conclusive. In order to more robustly describe the deregulations of gut microbiota compositions in ASD, a meta-analysis was performed. The related investigations from PubMed, Embase and Web of Science were collected and manually reviewed. By procedure, 26 eligible studies until 2023, with a total of 1021 ASD and 951 typically developed children and adolescents, were included for the meta-analysis. RevMan5.4 was used to assess the overall effect of 8 microbes at the phylum level and 19 microbes at the genus level. Results demonstrated relatively up-regulated abundance of Bacteroidetes, Verrucomicrobia, *Bacteroides*, *Clostridium*, *Dorea* and *Sutterella*, and down-regulated abundance of Proteobacteria, *Bifidobacterium*, *Coprococcus*, and *Akkermansia* in ASD children, indicating partly agreement in the ASD-associated microbes, albeit the heterogeneity of ASD.

**Keywords:** Autism spectrum disorder; microbiota; meta-analysis

## 1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication and interaction deficits, as well as restricted and repetitive behaviors, interests, or activities, which has high clinical and etiologic heterogeneity<sup>[1]</sup>. In recent years, the prevalence of ASD has significantly increased worldwide, possibly due to the joint effects of environmental, genetic and epigenetic factors, as well as improvements in diagnostic criteria, better detection methods and increased awareness<sup>[2]</sup>. According to the latest data from the Centers for Disease Control and Prevention in 2023, the prevalence of ASD among 8-year-old children in the United States is as high as 1 in 36, about four times that in 2000, and the male-to-female ratio is about 4:1<sup>[3]</sup>. Studies reports a prevalence of ASD ranging from 0.7% to 3.2%, indicating a public health issue<sup>[4–7]</sup>. In terms of GI dysfunction, including constipation, diarrhea, abdominal pain, bloating, gastroesophageal reflux, and intestinal inflammation, the comorbidity rate reaches 46.8% (4.2%-96.8%), which is about 3 times higher than that of typically developed (TD) children<sup>[8,9]</sup>. Research has reported that children with frequent diarrhea and constipation scored higher on the Autism Behavior Checklist (ABC), representing a greater likelihood of irritable, socially withdrawn, and stereotypical, and hyperactive behaviors<sup>[9]</sup>.

The gut microbiome is the collection of microorganisms inhabiting the intestine, numbering ~10<sup>14</sup> or more, which is approximately 10 times the total number of cells in the body<sup>[10]</sup>. It has been found

that children with ASD have widespread gut microbiota dysbiosis and that metabolites associated with energy metabolism, gut microbiota metabolism and oxidative stress differ significantly from TD<sup>[11–13]</sup>. Studies have also found a positive correlation between gastrointestinal symptoms and the repetitive/stereotyped behaviors and behavioral problems in children with ASD, indicating that gastrointestinal problems may be related to the nervous system in some way<sup>[14]</sup>.

As the microbiome-gut-brain axis theory develops, many studies have shown that the gut microbiota might play an important role in the bidirectional regulation of the brain-gut axis through the nervous, immune, and endocrine systems<sup>[15–17]</sup>. Animal research has discovered that the provision of *Lactobacillus farciminois* and *Lactobacillus salivarius*, two types of probiotic bacteria, resulted in regulation of their disrupted gut microbiota in ASD model mice. Additionally, disrupted cortisol hormone secretion and neural development as well as abnormal stress behavior were significantly restored, suggesting the association between the microbiota and ASD<sup>[18]</sup>. Some clinical trials have also demonstrated that ASD patients have alterations in both the structure and the abundance of gut microbiota compared to TD subjects<sup>[19–21]</sup>. However, the reported patterns of microbial alterations vary greatly among different studies and the data from meta-analyses are outdated. To better understand the role of microbiota in the development of ASD, we conducted a review and meta-analysis to identify differences in gut microbiota profiles between ASD and TD as well as to provide a theoretical basis for targeted interventions and treatments for ASD through gut microbiota.

## 2. Methods

### 2.1. Search Strategy and Selection Criteria

The review and meta-analysis were carried out following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines<sup>[22]</sup>. We performed a systematic study search of PubMed, Embase and Web of Science as far as April 2023. The search strategy for the PubMed was as follows:

- #1 "autism spectrum disorder"[MeSH Terms] OR "autistic disorder"[MeSH Terms]
- #2 "ASD"[Title/Abstract] OR "Autism"[Title/Abstract] OR "Autistic"[Title/Abstract] OR "PDD"[Title/Abstract] OR "Asperger Syndrome" [Title/Abstract]
- #3 #1 OR #2
- #4 "microbiota"[MeSH Terms] OR "Microbiome"[Title/Abstract] OR "Microflora"[Title/Abstract] OR "Fecal microbiota"[Title/Abstract] OR "Gastrointestinal"[Title/Abstract] OR "Intestinal flora"[Title/Abstract] OR "Mycobiome"[Title/Abstract]
- #5 #3 AND #4

No restrictions were applied in terms of language or year of publication. Moreover, the reference lists of original records and relevant reviews were also checked for additional studies. The titles and abstracts of records were screened to filter irrelevant papers and full text were checked to identify studies met the eligibility criteria.

The inclusion criteria were: (1) design: case-control studies or observed studies; (2) subjects: the case group consisted of individuals diagnosed with ASD based on ICD, DSM, or clinical physician assessment, and the control group consisted of healthy individuals without psychiatric disorders and with normal cognitive function, both groups were under the age of 18; (3) content: the composition of the gut microbiota of the study population, including the mean and standard deviation (SD) of microbial relative abundance. The exclusion criteria were: (1) meta-analyses, reviews, conferences, case reports, research protocols, or animal studies; (2) subjects with other neurological disorders or taking other medications; (3) inconsistent with study content or small sample size ( $n < 5$ ); (4) unavailable full text or missing data; (5) duplicate studies.

### 2.2. Data Extraction and Study Quality Assessment

The following information was extracted from the eligible studies: (1) general items: title, first author, year of publication and country; (2) subjects: sample size, age, sex, gastrointestinal symptoms and diet, and diagnostic criteria for the ASD group; (3) microbiota: detection methods, and relative abundance (mean and SD) at phylum and genus level.

The Newcastle–Ottawa Scale (NOS) was used for study quality assessment, and articles were classified into high (7–9), medium (4–6), and low (0–3) quality, based on the total score of three dimensions: study-participant selection (0–4), the comparability of study participants (0–2) and the exposure or outcome of studies (0–3).

### 2.3. Statistical Analysis

For each bacteria phylum and genus, the random-effects model and the inverse-variance method were used to calculate the overall effect size and 95% confidence interval (95% CI) through mean  $\pm$  SD of children and adolescents with and without ASD, using Review Manager 5.4 software. The standard mean difference (SMD) measure of effect was accessed to compare the differences in microbiota between two groups of children. SMD  $> 0$  indicated that the relative abundance of the bacteria was significantly higher in ASD group compared to TD group, while SMD  $< 0$  indicated that ASD group had a lower bacterial relative abundance. Heterogeneity was measured using both Cochran's Q test and the  $I^2$  statistic, whereby  $I^2$  represented the proportion of heterogeneity present, with  $I^2 \geq 50\%$  indicative of a more pronounced level of heterogeneity. In order to test the reliability of the findings, sensitivity analyses were performed by excluding one individual study at a time. All statistical analyses were considered significant at  $p < 0.05$ .

## 3. Results

### 3.1. Characteristics of the Included Studies

Figure 1 shows the PRISMA flow diagram of the identification of the included studies. A total of 1922 records were retrieved through three databases: 620 records in PubMed, 873 records in Embase, and 429 records in Web of Science. The title and abstract of 1135 articles were screened after discarding the duplicated studies. Among these publications, 74 studies were selected for a further review of the full texts while 1061 publications were excluded for the following reasons: not access the association of the study, reviews and case reports, studies on animals, age of participants exceeding 18 years old, meta-analysis and others. Finally, 26 eligible records of a total of 2152 participants were included in this meta-analysis.

The summary characteristics of the eligible studies were shown in Table 1. In total, this meta-analysis integrated gut microbiota results from 26 studies of 1021 ASD and 951 age-matched TD children and adolescents aged 2–17 years old. Generally, these articles were published between 2010 and 2023 with the sample size ranging from 6 to 143. The majority of the investigations were conducted in China<sup>[21,23–31]</sup>, the United States<sup>[32–37]</sup>, Australia<sup>[38–40]</sup> and Italy<sup>[20,41,42]</sup>, with one article each from India<sup>[43]</sup>, Japan<sup>[44]</sup> and Spain<sup>[45]</sup>. About half of the literatures reported the gastrointestinal condition of the subjects, and the results showed that the frequency and severity of gastrointestinal dysfunction in children and adolescents with ASD were higher than those of TD to varying degrees. In terms of microbial detection, all the studies provided microbial variation data at the phylum or genus level, while only a small portion of the studies reported microbial variation at the family or species level<sup>[29,31,41]</sup>, therefore, the meta-analysis was performed at the levels of phylum and genus. In regard to the quality assessment of the studies, only 4 records were of moderate quality<sup>[26,35,37,38]</sup>, and the rest 22 were of high quality according to NOS.

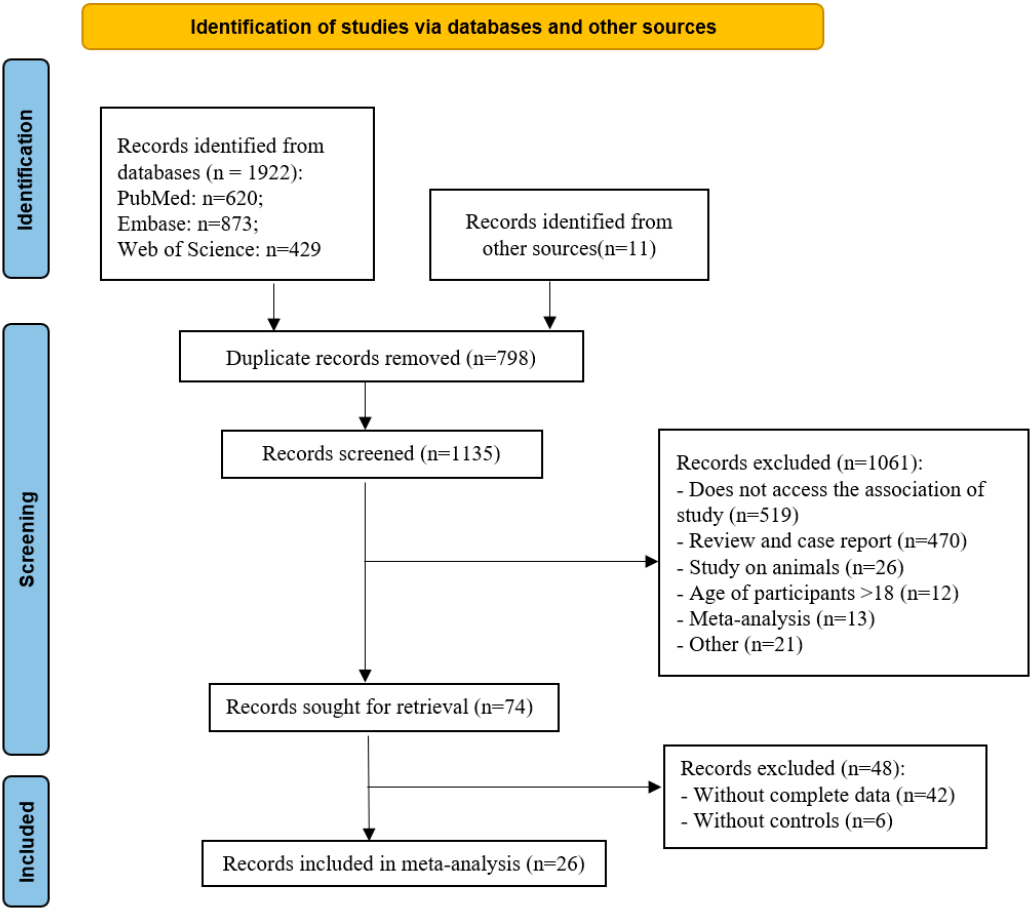


Figure 1. PRISMA flow diagram of the identification of the included studies.

**Table 1.** Summary characteristics of the studies included in the meta-analysis.

Study	Country	ASD			TD			Bacteria Detected
		n	Age(y)	male: female	n	age(y)	male: female	
Li et al. (2023) <sup>[23]</sup>	China	107	3.34 ± 0.75	79: 28	30	3.61 ± 0.48	21: 9	<b>Phylum:</b> Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria, Verrucomicrobia <b>Phylum:</b> Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteriota, Proteobacteria, Verrucomicrobia <b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Bilophila</i> , <i>Blautia</i> , <i>Collinsella</i> , <i>Dorea</i> , <i>Fusobacterium</i> , <i>Parabacteroides</i> , <i>Phascolarctobacterium</i> , <i>Sutterella</i>
Wong et al. (2022) <sup>[24]</sup>	China	92	8.43 ± 1.54	92: 0	112	8.12 ± 1.99	112: 0	<b>Phylum:</b> Actinobacteria, Firmicutes <b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Blautia</i> , <i>Clostridium</i> , <i>Streptococcus</i> , <i>Sutterella</i>
Zhang et al. (2022) <sup>[25]</sup>	China	25	6.72 ± 2.56	18: 7	24	7.68 ± 2.93	14: 10	<b>Genus:</b> <i>Bacteroides</i> , <i>Collinsella</i> , <i>Coprococcus</i> , <i>Faecalibacterium</i> , <i>Prevotella</i> , <i>Megamonas</i> , <i>Sutterella</i>
Chen et al. 2021 <sup>[26]</sup>	China	138	6.11 ± 2.00	117: 21	60	6.65 ± 2.22	27: 33	<b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Clostridium</i>
Cheng et al. (2021) <sup>[27]</sup>	China	36	7.44 ± 1.53	21: 15	50	7.33 ± 1.49	27: 23	

Table 1. Summary characteristics of the studies included in the meta-analysis (Cont.)

Study	Country	ASD			TD			Bacteria Detected
		n	age(y)	male: female	n	age(y)	male: female	
Dan et al. (2020) <sup>[28]</sup>	China	143	4.94 ± 0.16	130:13	143	5.19 ± 0.17	127:16	<b>Phylum:</b> Bacteroidetes, Cyanobacteria, Fusobacteria <b>Genus:</b> <i>Blautia</i> , <i>Fusobacterium</i> , <i>Parabacteroides</i> , <i>Paraprevotella</i> , <i>Prevotella</i>
Ding et al. (2020) <sup>[29]</sup>	China	77	38.50±11.70m	59: 18	50	42.9±14.5m	39: 11	<b>Phylum:</b> Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobia



Zeng et al. (2020) <sup>[30]</sup>	China	90	3.50 ± 1.20	70: 20	50	3.00 ± 1.50	39: 11	<b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Blautia</i> , <i>Collinsella</i> , <i>Dorea</i> , <i>Faecalibacterium</i> , <i>Paraprevotella</i> , <i>Streptococcus</i> <b>Phylum:</b> Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Fusobacteria, Tenericutes, Verrucomicrobia
Zou et al. (2020) <sup>[31]</sup>	China	48	5 (2–7)	38: 10	48	4	24: 24	<b>Genus:</b> <i>Akkermansia</i> , <i>Bacteroides</i> , <i>Megamonas</i> , <i>Prevotella</i> <b>Phylum:</b> Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Fusobacteria, Proteobacteria, Tenericutes, Verrucomicrobia
Ma et al. (2019) <sup>[21]</sup>	China	45	7.27 ± 1.07	39: 6	45	7.04 ± 1.19	39: 6	

Table 1. Summary characteristics of the studies included in the meta-analysis. (Cont.)

Study	Country	ASD			TD			Bacteria Detected
		n	age(y)	male: female	n	age(y)	male: female	
Ma et al. (2019) <sup>[21]</sup>	China	45	7.27 ± 1.07	39: 6	45	7.04 ± 1.19	39: 6	<b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Bilophila</i> , <i>Faecalibacterium</i> , <i>Fusobacterium</i> , <i>Lactobacillus</i> , <i>Megamonas</i> , <i>Parabacteroides</i> <b>Phylum:</b> Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobia
Plaza et al. (2019) <sup>[45]</sup>	Spain	30	44.19 ± 1.60m	-	57	51±2.59 m	-	<b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Blautia</i> , <i>Coprococcus</i> , <i>Streptococcus</i> <b>Genus:</b> <i>Akkermansia</i> , <i>Bacteroides</i> , <i>Coprococcus</i> , <i>Faecalibacterium</i> , <i>Prevotella</i>
Coretti et al. (2018) <sup>[41]</sup>	Italy	11	35 ± 5.7m	9: 2	14	35 ± 8.40m	8: 6	<b>Phylum:</b> Bacteroidetes, Firmicutes
Kang et al. (2018) <sup>[33]</sup>	USA	23	10.1 ± 4.1	22:1	21	8.4 ± 3.4	15:6	
Pulikkan et al. (2018) <sup>[43]</sup>	Indian	30	9.5 (3–16)	28: 2	24	9.5 (3.5–16)	15: 9	
Zhang et al. (2018) <sup>[46]</sup>	China	35	4.9±1.5	29: 6	6	4.6±1.1	5: 1	<b>Phylum:</b> Bacteroidetes, Firmicutes

Kang et al. (2017) <sup>[32]</sup>	USA	18	7-16	-	20	7-16	-	<b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Clostridium</i> , <i>Coprococcus</i> , <i>Parabacteroides</i> , <i>Phascolarctobacterium</i>
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Table 1. Summary characteristics of the studies included in the meta-analysis. (Cont.)

Study	Country	ASD			TD			Bacteria Detected
		n	age(y)	male: female	n	age(y)	male: female	
Strati et al. (2017) <sup>[20]</sup>	Italy	40	10 (5–17)	31: 9	40	7 (3.6–12)	28: 12	<b>Genus:</b> <i>Akkermansia</i> , <i>Bifidobacterium</i> , <i>Blautia</i> , <i>Collinsella</i> , <i>Coprococcus</i> , <i>Dorea</i> , <i>Faecalibacterium</i> , <i>Lactobacillus</i> , <i>Paraprevotella</i> , <i>Prevotella</i> , <i>Streptococcus</i>
Inoue et al. (2016) <sup>[44]</sup>	Japan	6	3-5	-	6	3-5	-	<b>Genus:</b> <i>Akkermansia</i> , <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Bilophila</i> , <i>Blautia</i> , <i>Clostridium</i> , <i>Collinsella</i> , <i>Coprococcus</i> , <i>Dorea</i> , <i>Faecalibacterium</i>
Son et al. (2015) <sup>[36]</sup>	USA	34	7–14	-	31	7–14	-	<b>Phylum:</b> Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Proteobacteria, Tenericutes, Verrucomicrobia
Angelis et al. (2013) <sup>[42]</sup>	Italy	10	4-10	-	10	4-10	-	<b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Clostridium</i> , <i>Faecalibacterium</i> , <i>Parabacteroides</i>
Kang et al. (2013) <sup>[34]</sup>	USA	20	6.70 ± 2.70	18: 2	20	8.30 ± 4.40	17: 3	<b>Phylum:</b> Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobia
Wang et al. (2013) <sup>[38]</sup>	Australia	23	10.25 ± 0.75	21: 2	9	9.50 ± 1.25	4: 5	<b>Phylum:</b> Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria <b>Genus:</b> <i>Sutterella</i>

Table 1. Summary characteristics of the studies included in the meta-analysis. (Cont.)

Study	Country	ASD			TD			Bacteria Detected
		n	age(y)	male: female	n	age(y)	male: female	



Gondalia et al (2012) <sup>[40]</sup>	Australia	28	2-12	-	25	2-12	-	<b>Genus:</b> <i>Bacteroides</i> , <i>Bifidobacterium</i> , <i>Coprococcus</i> , <i>Faecalibacterium</i> , <i>Parabacteroides</i> , <i>Phascolarctobacterium</i>
Adams et al. (2011) <sup>[35]</sup>	USA	58	6.91 ± 3.40	50: 8	39	7.70 ± 4.40	18: 21	<b>Genus:</b> <i>Bifidobacterium</i> , <i>Lactobacillus</i>
Wang et al. (2011) <sup>[39]</sup>	Austrilia	23	10.25 ± 0.75	21: 2	9	9.50 ± 1.25	4: 5	<b>Genus:</b> <i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Prevotella</i>
Finegold et al. (2010) <sup>[37]</sup>	USA	11	-	-	8	-	-	<b>Phylum:</b> Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Fusobacteria, Proteobacteria, Tenericutes

### 3.2. Decreased alpha diversity in ASD

The Shannon index and Chao 1 index are alpha diversity indicators used to measure diversity and richness of species, respectively. In the meta-analysis of Shannon index, 5 studies were included, but there was no significant difference between ASD and TD ( $p = 0.82$ ). While 4 studies were included in the meta-analysis of Chao 1 index, leading to a significant reduction in ASD, indicating a decreased richness of species in ASD.

In Shannon's meta-analysis, 5 articles were included, but there was no difference between two groups of children. However, in Chao 1's meta-analysis, 4 articles were included, and the results showed a significant reduction in Chao 1 in ASD (SMD = -0.51; 95% CI: -0.76, -0.27;  $p < 0.001$ ) with a low heterogeneity ( $I^2 = 27\%$ ), indicating a decrease in species abundance in ASD.

### 3.3. Microbes Upregulated in ASD

Table 2 shows the results of meta-analysis of the microbiota compositions in children and adolescents with and without ASD at the phylum and genus levels. The genera, belonging to their respective phyla, were grouped together and displayed in italics, while the phyla were displayed in boldface. Totally, we compared the differences of 8 phyla and 19 genera between two groups of subjects.

The results demonstrated that Bacteroidetes, Verrucomicrobia, *Bacteroides*, *Clostridium*, *Dorea* and *Sutterella* were upregulated in ASD. Twelve articles were included in the meta-analysis of Bacteroidetes, and 7 articles were included in the meta-analysis of Verrucomicrobia at the phylum level, arriving at the following results: ASD had 0.42% higher relative abundance of Bacteroidetes (95% CI: 0.02, 0.82;  $p = 0.04$ ) (Figure 2) and 0.25% higher relative abundance of Verrucomicrobia (95% CI: 0.01, 0.49) (Figure 3) than those in TD, which were similar to results of the previous meta-analysis<sup>[47]</sup>.

**Table 2.** Results of meta-analysis at phylum and genus level in ASD and TD.

Phylum/Genus	Studies included	SMD	95% CI	$I^2$	Overall effect(Z)	$p$ value
<b>Actinobacteria</b>	11	-0.1	(-0.46, 0.26)	87	0.53	0.60
<i>Bifidobacterium</i>	13	-0.85	(-1.35, -0.34)	91	3.27	<b>0.001</b>
<i>Collinsella</i>	5	0.23	(-0.14, 0.60)	76	1.21	0.23
<b>Bacteroidetes</b>	12	0.42	(0.02, 0.82)	89	2.05	<b>0.04</b>
<i>Bacteroides</i>	13	0.47	(0.01, 0.93)	91	2.01	<b>0.04</b>
<i>Parabacteroides</i>	6	-0.05	(-0.40, 0.31)	76	0.26	0.79
<i>Prevotella</i>	6	-0.01	(-0.44, 0.42)	85	0.04	0.97
<i>Paraprevotella</i>	3	-0.12	(-0.46, 0.21)	66	0.72	0.47
<b>Cyanobacteria</b>	5	-0.09	(-0.59, 0.40)	86	0.38	0.71
<b>Firmicutes</b>	13	-0.24	(-0.81, 0.33)	94	0.83	0.41
<i>Blautia</i>	7	-0.13	(-0.54, 0.28)	84	0.61	0.54
<i>Clostridium</i>	5	1.01	(0.15, 1.87)	85	2.31	<b>0.02</b>
<i>Coprococcus</i>	7	-0.43	(-0.80, -0.06)	65	2.25	<b>0.02</b>
<i>Dorea</i>	4	0.5	(0.31, 0.70)	0	5.03	<b>&lt;0.001</b>
<i>Faecalibacterium</i>	8	-0.02	(-0.43, 0.40)	81	0.07	0.94
<i>Lactobacillus</i>	4	0.27	(-0.36, 0.89)	85	0.84	0.40
<i>Megamonas</i>	3	0.04	(-0.40, 0.48)	76	0.19	0.85
<i>Phascolarctobacterium</i>	4	-0.21	(-0.62, 0.21)	71	0.99	0.32
<i>Streptococcus</i>	4	-0.47	(-1.04, 0.10)	79	1.63	0.10
<b>Fusobacteria</b>	6	-0.1	(-0.49, 0.28)	71	0.99	0.32
<i>Fusobacterium</i>	3	0.05	(-0.26, 0.36)	69	0.32	0.75
<b>Proteobacteria</b>	9	-0.31	(-0.59, -0.04)	67	2.24	<b>0.03</b>

<i>Bilophila</i>	3	-0.36	(-0.87, 0.15)	68	1.37	0.17
<i>Sutterella</i>	4	1.04	(0.04, 2.05)	95	2.03	<b>0.04</b>
<i>Tenericutes</i>	4	-0.47	(-1.08, 0.15)	84	1.48	0.14
<i>Verrucomicrobia</i>	7	0.25	(0.01, 0.49)	55	2.05	<b>0.04</b>
<i>Akkermansia</i>	4	-0.41	(-0.77, -0.05)	38	2.26	<b>0.02</b>

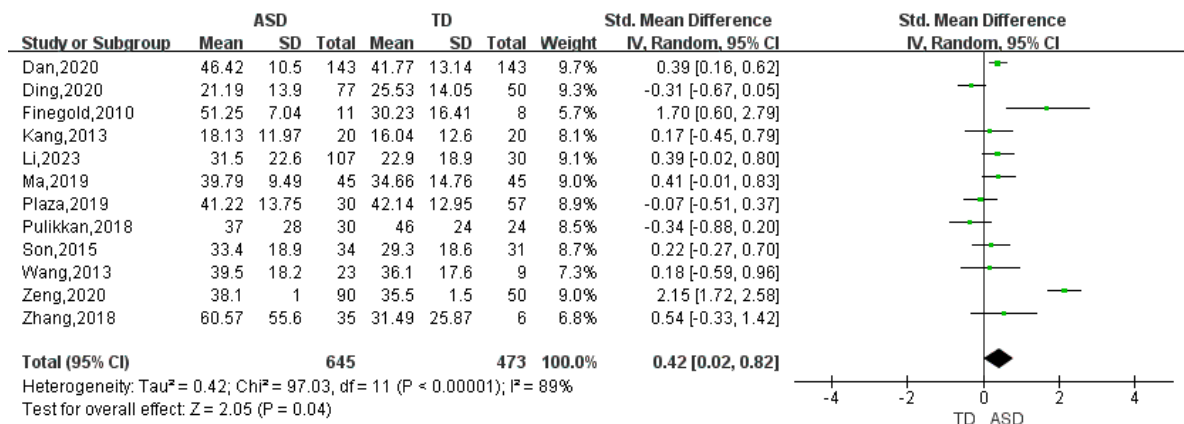


Figure 2. Forest plot of relative abundance of Bacteroidetes in ASD and TD.

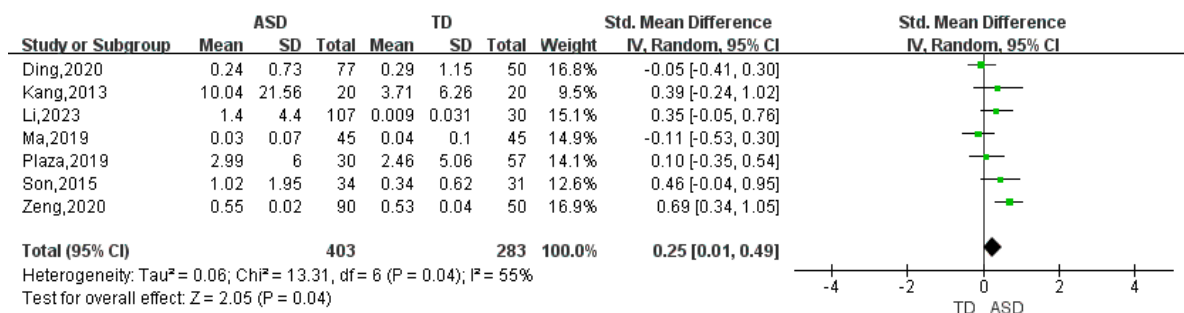
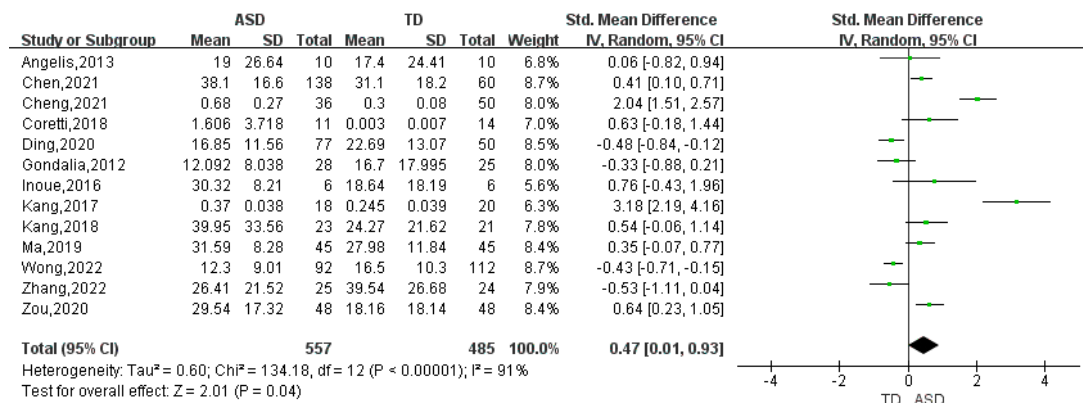


Figure 3. Forest plot of relative abundance of Verrucomicrobia in ASD and TD

At the genus level, the relative abundance of *Bacteroides* was evaluated on the basis of 13 clinical trials and was confirmed upregulated in children and adolescents with ASD (SMD = 0.47; 95% CI: 0.01, 0.93). The effect size was moderate and significant ( $Z = 2.01$ ,  $p = 0.04$ ) (Figure 4). Similarly, the increased relative abundance of *Clostridium* (SMD = 1.01; 95% CI: 0.15, 1.87;  $p = 0.02$ ), *Dorea* (SMD = 0.5; 95% CI: 0.31, 0.70;  $p < 0.001$ ) and *Sutterella* (SMD = 1.04; 95% CI: 0.04, 2.05;  $p = 0.04$ ) were also observed in ASD. However, the heterogeneity among studies was very high in the meta-analysis of *Bacteroides*, *Clostridium* and *Sutterella* (91%, 85% and 95%).

Figure 4. Forest plot of relative abundance of *Bacteroides* in ASD and TD.

3.4. Microbes Downregulated in ASD

The random effect meta-analysis of Proteobacteria was conducted on the basis of 9 studies supporting the down-regulation of Proteobacteria in ASD (SMD = -0.31; 95% CI: -0.59, -0.04;  $p = 0.03$ ) (Figure 5).

From the 13 eligible records, we found that relative abundance of *Bifidobacterium* was significantly decreased in ASD compared to TD children and adolescents (SMD = -0.85; 95% CI: 0.01, 0.93). The effect size was moderate and significant ( $Z = 3.27$ ,  $p = 0.001$ ) (Figure 6) In the meta-analysis of *Coprococcus* involving 7 studies (SMD = -0.43; 95% CI: 0.01, 0.93;  $p = 0.02$ ) and *Akkermansia* involving 4 articles (SMD = -0.41; 95% CI: -0.77, -0.05;  $p = 0.02$ ), the results demonstrated that the level of both bacteria significantly decreased in ASD compared to TD.

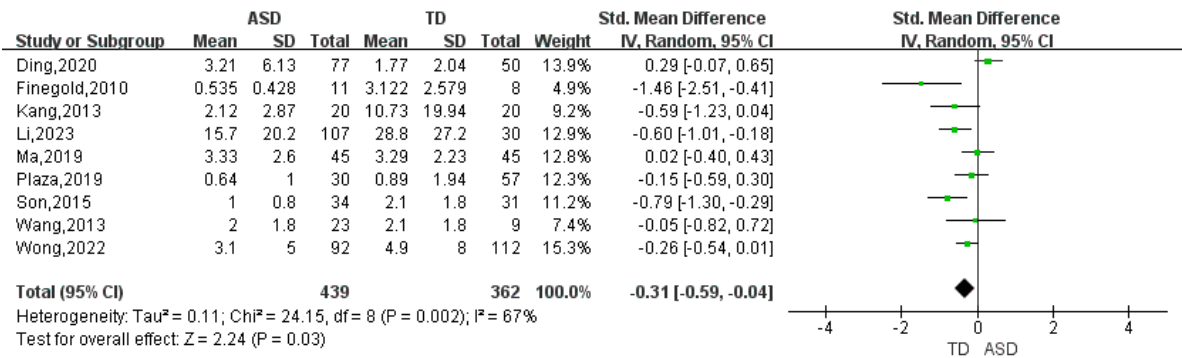


Figure 5. Forest plot of relative abundance of Proteobacteria in ASD and TD.

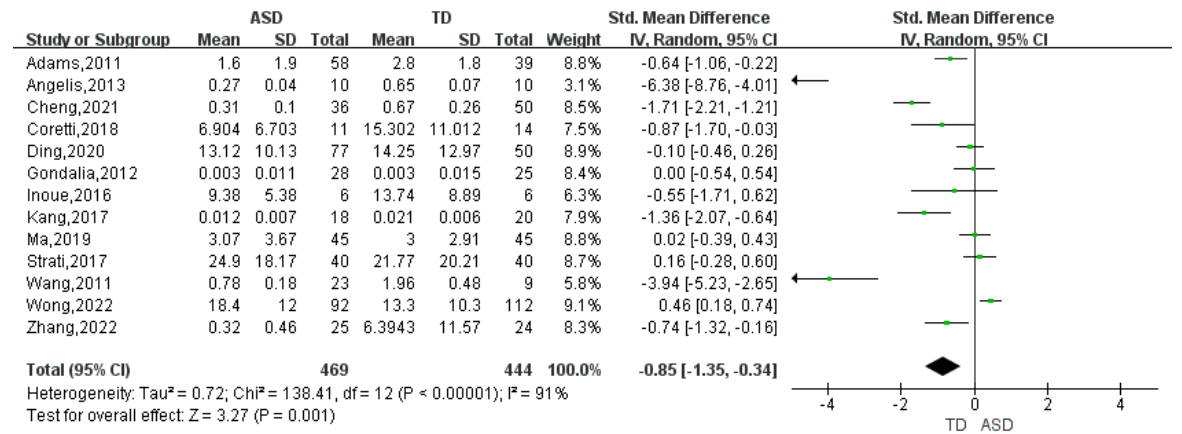


Figure 6. Forest plot of relative abundance of Bifidobacterium in ASD and TD.

3.5. Microbes with No Difference between ASD and TD

The random-effect meta-analysis of Actinobacteria, Cyanobacteria, Firmicutes, Fusobacteria and Tenericutes at the phylum level showed no significantly difference between ASD and TD. The overall effect ranged from 0.38 in Cyanobacteria to 1.48 Tenericutes, and the heterogeneity amongthe studies ranged between 71% to 94%. Although the evidence was insufficient to observe a statistically significant difference between children and adolescents with and without ASD, the disparity in microbe relative abundance suggested that ASD had a lower level of Tenericutes compared to TD.

Meanwhile, there was not enough sufficient evidence to indicate significant differences in 12 microbes at the genus level between ASD and healthy controls. The overall effect ranged from 0.04 in *Prevotella* to 1.37 *Bilophila*, and the heterogeneity between studies ranged between 66% to 85%. Regardless, the relative abundance of *Collinsella* (SMD = 0.23; 95% CI: 0.14, 0.60) and *Lactobacillus* (SMD = 0.27; 95% CI: -0.36, 0.89) was higher in ASD, and relative abundance of *Streptococcus* (SMD =

-0.47; 95% CI: -1.04, 0.10) and *Bilophila* (SMD = -0.36; 95% CI: -0.87, 0.15) was lower in ASD, respectively.

#### 4. Discussion

This study updated the other published meta-analysis of gut microbiome composition in ASD<sup>[47,48]</sup> with substantially increased number of eligible studies. A total of 26 articles were included, of which 9 literatures were performed in the past three years. As far as we know, this has been the meta-analysis with the most records included of ASD gut microbiota. In fact, our study consisted of 2152 subjects, including 1201 ASD and 951 TD children and adolescents, and analyzed 8 microbes at the phylum level and 19 microbes at the genus level.

In accordance with our results, there was a disruption of various gut microbes in individuals with ASD. Specifically, in the 8 microbes at the phylum level analyzed in the meta-analysis, Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria had the highest relative abundance in both ASD and TD. Among them, the relative abundance of Firmicutes was mostly reported to be over 40%, and in most studies, the relative abundance of Bacteroidetes was over 30%. In contrast, Cyanobacteria, Fusobacteria, Verrucomicrobia, and Tenericutes had relatively low levels, especially Tenericutes, whose relative abundance was less than 0.55%. For Bacteroidetes, the overall effect and most studies showed its upregulation in ASD, while 3 studies found its downregulation in ASD. The same situation could also be observed for Verrucomicrobia. For Proteobacteria, the overall effect and most studies indicated a higher level in ASD, while the records of Ding et al.<sup>[29]</sup> and Ma et al.<sup>[21]</sup> reported its upregulation in ASD. As for Firmicutes, which had the highest relative abundance, we did not find significant differences between the two groups. At the genus level, increased relative abundance of *Bacteroides*, *Clostridium*, *Dorea* and *Sutterella*, and decreased relative abundance of *Bifidobacterium*, *Coprococcus* and *Akkermansia* were observed in ASD children and adolescents.

It is noteworthy that harmful bacteria, such as *Clostridium* and *Sutterella*, were significantly upregulated in ASD, while beneficial bacteria, such as *Bifidobacterium* and *Akkermansia*, were significantly downregulated. *Clostridium* can produce neurotoxic substances such as cresol and propionic acid<sup>[27]</sup>, which may block the transmission of neurotransmitters and damage neuron activities after entering the brain through the blood-brain barrier, thereby increasing abnormal behavior in ASD<sup>[49]</sup>. Propionic acid could also be produced by *Sutterella* and studies have reported a positive correlation between *Sutterella* and gut inflammation and diarrhea<sup>[50]</sup>. Moreover, IgA protease would be over-secreted with increased *Sutterella*, leading to a decrease of IgA in the mucosa and disruption of the intestinal antibacterial immune response function<sup>[51]</sup>.

*Bifidobacterium* plays an important role in inhibiting the growth of harmful bacteria and promoting the release of anti-inflammatory cytokines, thereby promoting intestinal homeostasis and improving gastrointestinal function<sup>[10]</sup>. Additionally, *Bifidobacterium* can also improve the host's memory function by promoting the expression of brain-derived neurotrophic factors and N-methyl-D-aspartate receptors<sup>[10]</sup>. A study has found that *Bifidobacterium longum* intervention could reduce abnormal behavior and gastrointestinal symptoms in children with ASD<sup>[52]</sup>. *Akkermansia* has anti-inflammatory effects<sup>[53]</sup>. Accompanied by the downregulated of *Akkermansia*, toxins in the intestines are more easily able to invade the human body, with thinning of the mucosal layer and weakening intestinal barrier function<sup>[54]</sup>. Additionally, *Akkermansia* produces more than 60 enzymes that can degrade oligosaccharides, providing energy for beneficial bacteria<sup>[54]</sup>.

Currently, characteristics and alterations of gut microbiota in ASD individuals is gradually being discovered, revealing the potential correlation between ASD pathogenesis and the dysbiosis of gut microbiota. Nonetheless, it is unneglectable that inconsistency among conclusions still remains across studies. This may due to genetic and environmental confounders such as ethnics, habitual diet, daily lifestyle, etc. One study has found significant similarities in gut microbiome compositions of genetically unrelated healthy individuals who share a household, indicating that there has been a tight correlation between gut microbiome composition and habitual diet, whereas the host genetics play a minor role<sup>[55]</sup>. Furthermore, another study has found that individuals with greater healthy food intake have higher abundance of beneficial gut microbiota<sup>[56]</sup>. This also suggests that the disrupted

microbiome of ASD individuals may be reformed not only through supplementing probiotics or fecal microbiota transplantation but also by altering the dietary structure. Further research is needed to investigate personalized intervention strategies, and by facilitating gut microbial-related treatments may ultimately improve the quality of life of ASD individuals.

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