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REVIEW

Possible links between gut–microbiota and attention-deficit/hyperactivity disorders in children and adolescents

Nonglak Boonchooduang[1] · Orawan Louthrenoo[1] · Nipon Chattipakorn[2,3] · Siriporn C. Chattipakorn[2,3,4]

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Abstract

An association between gut–microbiota and several neuropsychiatric conditions including autism, depression, anxiety, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD) has been observed. Despite being the most prevalent neurodevelopmental disorders in children and adolescents worldwide, the etiology and curative approaches to treatment of ADHD remain unclear. There is a probability that gut–microbiota may contribute to ADHD via bidirectional communication between the gut and brain, a system known as the "gut–brain axis". Although a mechanistic link in the gut–brain axis in ADHD has been proposed, there is still a lack of information about the correlation of the microbiome profile with the mechanisms involved. The objective of this review was to summarize the diversity of the gut–microbiota and taxonomic profiles in children and adolescents with ADHD. In this review, we have provided an overview of the association between ADHD and gut–microbiota. The evidence pertinent to potentially distinctive gut–microbiota in children and adolescents with ADHD is also discussed and compared to that of their non-ADHD peers. Finally, the implications and future directions for investigation into the gut microbiome in ADHD patients are proposed.

Keywords ADHD · Microbiome · Dysbiosis · Gut–brain axis · Gut–microbiota

Introduction

Gut–microbiota, the microbiotic organisms existing in large numbers in the human intestine, have a metagenome harboring millions of genes, a number in excess of the genes of the host [1]. In a dynamic process of maturation, the adult-associated gut–microbiota is established at the age of 2–3 years [2]. To date, most of gut–microbiota research has been carried out via next-generation sequencing of 16S rRNA and analyzed for taxonomy and diversity. Gut–microbiota consists of six major phyla, including Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, Verrucobacteria, and Fusobacteria. The microbiota is known to affect both the physiology and psychology of human health [3]. Not only are there a large amount of gut–microbiota in the human intestine, it is also extensively diverse with more than 1000 phylotypes [1]. A more diverse gut–microbiota is believed to be more beneficial to human health [4].

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder in children and adolescents. The estimated prevalence of ADHD is between 3.4 and 7.2% in children and adolescents worldwide [5–7]. Diagnosis of ADHD is primarily reliant on subjective clinical interview and diagnostic criteria. The American Psychiatric Association's Diagnostic and Statistical Manual of mental disorders, fifth edition (DSM-5) divides ADHD into three types based on the predominant symptoms, including predominantly inattention, predominantly hyperactivity/impulsivity, and combined presentations [8]. With an increasing number of cases and chronicity, the disorder is continuing from childhood into adulthood resulting in low academic achievement, and interpersonal and family

✉ Siriporn C. Chattipakorn
scchattipakorn@gmail.com; siriporn.c@cmu.ac.th

1 Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

2 Neurophysiology Unit, Cardiac Electrophysiology Research and Training Center, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand

3 Center of Excellence in Cardiac Electrophysiology Research, Chiang Mai University, Chiang Mai 50200, Thailand

4 Department of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai 50200, Thailand

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difficulties [9]. Although many potential biomarkers have been proposed, there is currently not enough evidence for their use clinically [10, 11]. Despite intensive research into ADHD, the precise underlying pathology remains unknown.

Genetics plays an important role in the pathophysiology of ADHD. Common genetic variants explain ~ 40% of ADHD heritability based on genome-wide association studies (GWAS); however, the specific significance at genome-wide level has not identified. The strongest possible association between genetic variants and ADHD are the variants in the genes encoding for the D4 and D1B dopamine receptors (*DRD4*, *DRD1B*). Other genes which have been shown to have a possible association with ADHD include the dopamine transporter genes (*SLC6A3*, *ALC6A4*), the serotonin transporter gene (*5HTT*), the serotonin 1 B receptor gene (*HTR1B*), and a gene coding for a synaptic vesicle regulation protein (*SNAP25*) [12, 13]. Furthermore, rare genomic insertions and deletions known as copy number variants (CNVs) also play a role in ADHD. These studies implicated genes at the 16p13.11 and 15q11-15q13 region [12, 13].

There is some evidence, suggesting that maternal stress and acetaminophen used during pregnancy increased the risk of ADHD occurring in offspring [14, 15]. These environmental factors might trigger alterations in the maternal gut–microbiota and affect fetal brain development. In addition, a previous study in an animal model reported that prenatal stress changed the vaginal microbiome, and was associated with gut–microbiota and metabolome alteration in the offspring [16].

The deviations from the optimal assembly of the gut–microbiota in early life may also have an important role in ADHD. It is possible that the microbiota in ADHD is altered during critical neurodevelopmental windows with the damage being done before assessment for ADHD is carried out. Several pieces of evidence have demonstrated that the obstetric mode of delivery, gestation age, maternal health, early life stressors, as well as diet in early life such as breastfeeding, ingestion of short-chain fatty acids (SCFA), polyunsaturated fatty acids (PUFA), antibiotic exposure, and probiotic supplementation play roles in the alteration of gut–microbiota during critical neurodevelopmental ADHD [17, 18].

With the lack of curative treatment, the current mainstay treatments of ADHD are behavioral and pharmacological therapies. Methylphenidate, one of the psychostimulants used, is a central nervous system stimulant drug of choice in treating children with ADHD [19]. The common adverse effects of methylphenidate are insomnia, anorexia, abdominal pain, and headache [20]. The incidence of the withdrawal from methylphenidate is 6.2–16.2% of patients, and the most common reason for withdrawal is adverse effects of the drug [21]. The concern about safety of psychostimulants and non-adherence to treatment has led to increasing research into the possibility of non-pharmacological treatment of ADHD [22, 23].

Previous studies into dietary therapies as a treatment for ADHD showed the adverse effects of excessive ingestion of sugar, preservatives, and food coloring agents [24, 25], whereas protective effects of zinc [26], iron [27], and polyunsaturated fatty acids on the disease have been demonstrated [28, 29]. A previous study evaluated the effect of diet interventions on ADHD and found that the few food diet (FFD) had a level of efficacy as an intervention in cases of ADHD [30]. Diet patterns may modulate gut–microbiota via alterations in nutrient availability. A recent systematic review and meta-analysis of dietary patterns and ADHD demonstrated that a diet high in refined sugar and saturated fat can increase the risk of ADHD, while a healthy diet characterized by the high consumption of fruits and vegetables could protect against ADHD or hyperactivity [31]. The gut–microbiota involved with the gut–brain axis may play a significant role in the mechanistic insight of this dietary intervention in ADHD.

In this review, we summarize the evidence for an association between ADHD and gut–microbiota. We also discuss the potentially distinctive gut–microbiota in children and adolescents with ADHD, in comparison to their non-ADHD peers. Finally, we describe the implications and the possibility for future investigations concerning the gut–microbiota in ADHD patients.

The gut–brain axis acts as the link between ADHD and gut–microbiota

The possible putative mechanisms involved in microbiotic impact on ADHD symptoms are the metabolic pathway, vagus nerve pathway, and immune pathways. They are shown in Fig. 1 and discussed in the following paragraphs [18, 32, 33].

Metabolic pathway

Gut dysbiosis could be linked to ADHD via the dysregulation of the metabolic pathway which is the interaction between the microbiome, the epigenome, and metabolome of the host through the synthesis of neurotransmitters and metabolites. There is evidence that neurotransmitters involved in ADHD symptoms can be produced by the microbiota. For example: (1) *Bifidobacterium spp.* can produce dopamine, (2) *Lactobacillus spp*., *Streptococcus spp*., *Escherichia spp*., *Morganella spp*., *Klebsiella spp*., *Hafnia spp*., and enterochromaffin cells in the gut can produce serotonin. (3) *Bifidobacterium spp*., *Lactobacillus spp*., and *Escherichia spp*. can produce gamma-aminobutyric acid (GABA) [34–36].

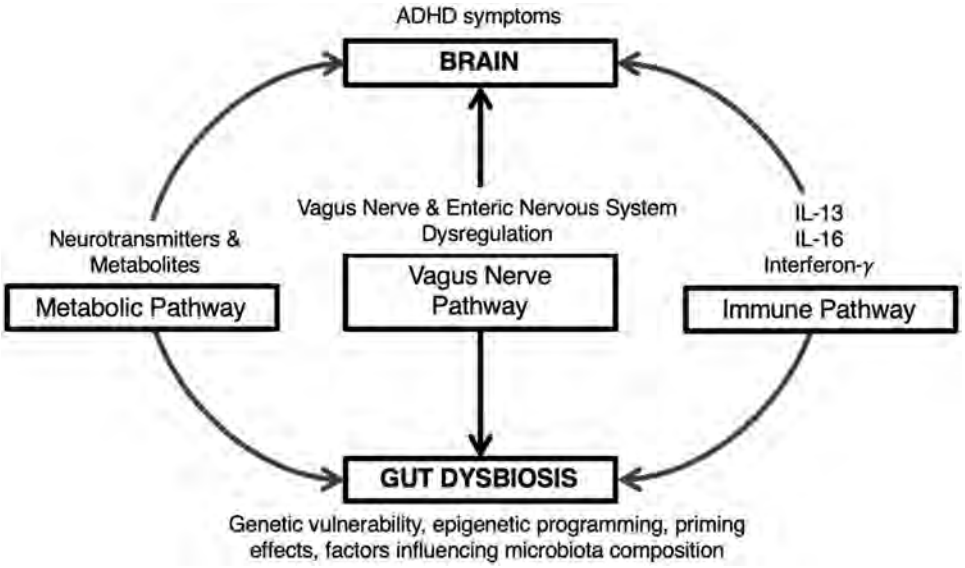

Fig. 1 Proposed mechanistic links between gut–microbiota and ADHD gut–brain axis. Three possible of mechanistic links between ADHD and gut–microbiota. From left to right: communication via the metabolic pathway, the vagus nerve pathway, and the immune pathway. *ADHD* attention-deficit/hyperactivity disorder, *IL* interleukins

Although the intestinal neurotransmitters have not been shown to directly cross the BBB or been precisely linked to brain function in ADHD, gut–microbiota increased the circulating availability of tryptophan (a precursor of serotonin), which has been produced by *Lactobacilli* spp., *Bifidobacterium* spp., *Clostridium sporogenes,* and *Clostridium bartettii* [37]. The circulating tryptophan can subsequently cross the BBB, affecting serotonin synthesis in the brain [38]. With regard to this possibility, a previous animal study also showed that germ-free mice had low levels of circulating serotonin, a finding similar to an observation in ADHD patients [32]. Furthermore, a recent study showed that many gut microbial-derived molecules, such as imidazole propionate, are able to cross the BBB either in their detected form or in precursor molecules for further processing by the host neurotransmitters in the brain [39].

In addition, bacterial metabolic factors, which pre-dispose for ADHD such as vitamin B6 and short-chain fatty acids (SCFAs), were also produced by gut–microbiota [40, 41]. Pyridoxal phosphate (PLP), an active form of vitamin B6, is an important coenzyme for the metabolism of norepinephrine, tryptophan, serotonin, dopamine, and GABA. When the tryptophan metabolism was investigated, impaired activity of PLP-dependent enzymes was found in ADHD children. The authors considered vitamin B6 disorders as the core biochemical disturbances in ADHD [42].

Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, are the main metabolites produced by gut–microbiota through the anaerobic fermentation of dietary fiber and resistant starch [43]. *Bacteroides* spp. and *Clostridiae* spp. are two of the most important microbiota for the production of SCFAs [17]. SCFAs might influence gut–brain communication and brain function either directly or indirectly. A previous study showed the effect of high dose propionate administration on increased levels of locomotor activity [44].

Vagus nerve pathway

The vagus nerve, which is the main component of the parasympathetic nervous system and is the 10th cranial nerve, is involved in mood regulation, immune response, digestion, and heart rate. The vagus nerve consists of afferent and efferent fibers that connect the gastrointestinal tract and the central nervous system. The stimulation of the vagal afferent fibers in the gut influences the monoaminergic systems in the brainstem; monoamines are involved in treatment of mood and anxiety disorders [45]. Several studies have reported a relationship between altered vagal tone and reactivity of the parasympathetic nervous system in cases of ADHD [33, 46–48].

Vagus nerve stimulation (VNS), the electrical stimulation of vagus nerve via a surgically implanted electrode, was found to increase noradrenaline levels via the activation of locus coeruleus [49], a region in the brain stem involved in selective attention [50]. VNS had positive effects on post-error slowing [51], and response to inhibition [52], both of which behaviors are deficient in ADHD patients [53, 54]. However, no study has directly assessed the effects of VNS on patients with ADHD. Trigeminal Nerve Stimulation (TNS), which works in a similar way to VNS, conveys sensory input from the skin, muscles, and skull via the trigeminal nerve to the locus coeruleus [55]. Recent studies showed that ADHD symptoms improved in children administered with TNS for 4 [56], and 8-weeks [57]. These pieces of evidence support the potential role of under-arousal of the parasympathetic pathway as a pathophysiology in ADHD patients.

Immune pathway

There is evidence to show an increase in incidence of atopic disease including atopic dermatitis, allergic rhinitis, eczema and autoimmune disease in ADHD patients. Individuals with these atopic diseases also have a 30–50% greater chance of developing ADHD in later life, when compared with non-atopic children [58, 59]. Furthermore, several studies have reported that heightened levels of circulating proinflammatory cytokines such as interleukin-13 (IL-13), IL-16, and TNF-α were found to be related to ADHD symptoms [60–62]. This evidence suggests a common pathophysiological mechanism underlying both atopic diseases and ADHD via the link of the immune system.

Previous studies showed that the gut–microbiota is also involved in immunoregulation. For example: (1) there was disproportionate concentration of proinflammatory microbiota in gut dysbiosis, leading to an increased intestinal permeability and inflammation. All of those events resulted in low-grade systemic inflammation and immune dysregulation [63, 64]. (2) Low-grade systemic inflammation might lead to gradual destruction of the blood brain barrier and neuroinflammation as observed in cases of ADHD [18, 65].

Gut metabolites, especially SCFAs, might influence gut–brain communication and brain function directly or indirectly via the immune pathway. SCFAs, which interact locally with intestinal epithelial cells and immune cells such as neutrophils and monocytes, can influence epithelial barrier function and immune tolerance to promote gut homeostasis [66]. They influence systemic inflammation by regulating the secretion of interleukins. SCFAs might also reach the brain directly and act on antigen-presenting cells to decrease the inflammatory responses that are associated with neuroinflammation [67].

All of these findings suggest a mechanistic link of the microbiota–gut–brain axis in ADHD patients. However, there is still a lack of information about how the gut–microbiota and specific ADHD microbiome profiles are associated with this axis.

The diversity of gut–microbiota in children and adolescents with ADHD

As the true extent of the diversity is unknown, many statistical approaches have been used to assess the diversity of gut–microbiota. Beta diversity is a term used to describe the differences in microbial composition between individuals, members of a population exhibiting similar organisms. Alpha diversity is a measure of the quantification and evenness of microbial composition in individuals which can be measured using the Shannon or Chao Indexes, Abundance-based Coverage Estimators (ACE), and Simpson index [68].

It has been hypothesized that gut dysbiosis, involving both the diversity and taxonomy of gut–microbiota, is associated with many neuropsychiatric conditions including autism, depression, anxiety, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD) [69–71].

Several studies have demonstrated the diversity of gut–microbiota in children and adolescents with ADHD, suggesting that those differences in components of the gut–microbiota might result in the development of ADHD [72–75]. Findings regarding the diversity of gut–microbiota in children and adolescents with ADHD have been presented in the outcomes of various studies. Some studies found no significant difference in alpha and beta diversities between ADHD patients and normal controls [72, 74]. However, one study has reported the reduction of alpha diversity in a gut microbiome [73], while another study demonstrated an increase in alpha diversity of ADHD children when compared to that of non-ADHD controls [75].

The study by Prehn-Kristensen et al. [73] reported a reduction in alpha diversity, and also described a significant negative correlation between the alpha diversity and hyperactivity score ($r = -0.35$, $p = 0.03$). However, there was no correlation between the alpha diversity and level of attention problems ($r = -0.15$, $p = 0.28$), impulsivity ($r = -0.22$, $p = 0.13$), and clinical symptoms ($r > 0.2$, $p > 0.2$). In an animal study, germ-free mice had an increase in level of *m*otor activity, when compared with that of mice with normal gut–microbiota. These findings imply that gut–microbiota also plays an important role in motor activity [76]. All of these findings suggested that lower diversity in gut–microbiota might be associated with a greater degree of ADHD. These findings are summarized in Table 1.

The alterations in genera and taxa of gut–microbiota in children and adolescents with ADHD

Several studies investigated whether specific gut–microbiota have been associated with ADHD [72–75]. *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* have been shown to constitute the four dominant phyla in children and adolescents with ADHD. There were no significant differences in the phyla levels in the fecal microbiota between the ADHD and control groups in several studies [73–75]. Only one study found an increase in the *Actinobacteria* phylum, and a decrease in the *Firmicutes* phylum in the ADHD group when compared to a non-ADHD control group [72].

Regarding the genus and family levels of gut–microbiota in ADHD, the findings were inconsistent across those previous studies. In adolescents with ADHD, the researchers found an increase in the genus *Bifidobacterium*, and *Bacteroidacea* and *Neisseriaceae* families [72, 73]. A study in a middle-to-late adolescent group with ADHD found a significant increase in the genus *Bifidobacterium*

Table 1 The diversity of gut–microbiota in children/adolescents with ADHD

Participants (number/mean age)	Psychostimulants	Stool sample method	Nucleic acid extraction	Computational pipelines	Major findings						
					Beta diversity	Alpha diversity				Interpretations	References
						Shannon	Chao-1	ACE	Simpson		
ADHD (19/19.5) Control (77/27.1)	Yes[a]	16S rRNA V3–V4 region	DNeasy blood and tissue kit	QIIME (version1.2)	NS	↔	↔	N/A	N/A	No significant difference in beta and alpha diversity	Aarts [72]
ADHD (14/11.9) Control (17/13.1)	Yes[b]	16S rDNA V1–V2 region	FastDNA™ SOIN KIT FOR SOIL	MOTHUR	S	↓	↓	N/A	N/A	Reduced microbiome alpha diversity	Preh-Kristensen [73]
ADHD (51/8.47) Control (32/8.5)	No	16S rRNA V3–V4 region	QIAamp DNA stool miniKit	QIIME (version1.7)	NS	↔	↔	↔	↔	No significant difference in beta and alpha diversity	Jiang [74]
ADHD (30/8.4) Control (30/9.3)	No	16S rRNA V3–V4 region with pretreat lytic enzyme	QIAamp DNA stool miniKit	MOTHUR QUIIME LEfSe	NS	↑	↑	↔	↓	Significantly increased alpha diversity without significant difference in beta a diversity	Wang [75]

MPH withheld 9/10 for 48 h before study

ADHD attention-deficit/hyperactivity disorder, *MPH* methylphenidate, *NS* non-significant, *S* significant, *N/A* not available

[a]MPH withheld for 48 h before study

[b]10 participants on MPH for more than 1 year and MPH withheld 9/10 for 48 h before study

[72]. In addition to fecal microbiota studied, the researchers investigated the functional brain of adolescents with ADHD using MRI [72]. They found a significant increase in the enzyme cyclohexadienyl dehydratase (CDT) which showed a correlation with an increasing abundance of the genus *Bifidobacterium* in the ADHD cases. The enzyme CDT, a monoamine precursor, is involved in the synthesis of phenylalanine. Phenylalanine, an essential amino acid, is the precursor of dopamine and noradrenaline. These neurotransmitters are important hormones associated with the brain reward response in patients with ADHD [77]. This is the first evidence to show a correlation between microbiota-derived phenylalanine and brain function in adolescents with ADHD.

Prehn-Kristensen et al. [73] has proposed that *Neisseria* spp. and *Bacteroides* spp. were promising ADHD-associated candidates in their study. They found significantly increased levels of the family *Neisseriaceae*, in particular the *Proteobacteria* phylum, in ADHD adolescent cases. This was consistent with a previous study which found an association between the abnormal expansion of *Proteobacteria* and several diseases including metabolic disorder, intestinal inflammation, and cancer [78]. Furthermore, the authors [73] also found a significant positive correlation between *Bacteroides* spp. and levels of hyperactivity and impulsivity in the ADHD group. A recent publication [75] found an increase in *B. uniformis,* and *B. ovatus,* and a decrease in *B. coprocola* species in ADHD children. The authors proposed that these three bacterial species may play a role in the pathophysiology of ADHD.

In children, the results pertaining to specific taxonomic microbiota were also not consistent. One study found a decrease in the genus *Faecalibacterium* [74]. Another study [75] found an increase in *Sutterella stercoricanis,* in ADHD subjects. This bacterium is a non-spore-forming, Gram-negative, and rod-shaped species, firstly isolated from canine feces [79]. The finding, which was concordant with a previous study revealed that *S. stercoricanis* was a major component of the gut–microbiota in autistic children with gastrointestinal dysfunction [80]. This brings into question the possibility that Sutterella may play a role in the pathogenesis of neurodevelopmental disorders.

Results concerning the correlation between ADHD symptoms and specific gut–microbiota are unclear. One study found a negative correlation between *Faecalibacterium* and parental reports of ADHD symptoms in young children (Conner's parent rating scales (CPRS): $R = -0.294$ ($p = 0.037$), hyperactivity: $R = -0.564$ ($p < 0.001$) [74]. Another study found that the level of *Bacteroides* spp. showed a correlation with levels of hyperactivity and impulsivity [73]. The relative abundance of *B. ovatus* and *S. stercoricanis* had a positive correlation with ADHD symptoms [75].

As mentioned above, consensus between studies are rare. Many of these studies are small and fail to create a coherent picture of a connection between gut–microbiota and ADHD. Several factors, however, appear to be associated with ADHD microbiota profiles. First, with regard to the age of the participants, two studies focus on children while the other two focus on an adolescent and young adult population [72–75]. In the study by Aarts et al. [72], the age of the control group was significantly older than that of ADHD group. Since *Bifidobacterium* decreased with age [81], the differences in age between the groups might be a confounding factor in this study. In addition, comparison and transference between studies are problematic as they were conducted in different parts of the world with different ethnicities and geographic habitats. For confident transference and comparability, other variables affecting the microbiota such as dietary habits, dietary supplements or medication used, and gastrointestinal symptoms need to be considered when analyzing the results.

Dietary patterns may have a significant effect on patient gut–microbiota. With regard to diet, only one study investigated the correlation between diet and the specific species of gut–microbiota. That study reported a significant correlation between *S. stercoricanis* with the intake of dairy, nuts/seeds/legumes, ferritin, and magnesium, while *B. uniformis* showed a correlation with fat and carbohydrate intake [75]. More studies in this area might provide strong grounds for specific dietary intervention for ADHD patients.

Recent studies have shown a link between medication metabolism and gut–microbiota [82, 83]. Exposure to psychostimulants was another factor which might interfere with the profile of the gut–microbiota. To date, there is still no evidence about the interaction of gut–microbiota with methylphenidate, one of the most commonly used of the psychostimulants in ADHD patients. Half of the present studies report on investigations involving medicated patients [72–75]. However, within these studies, there were different findings. One study found that the ADHD patients who were being treated with methylphenidate had a higher alpha diversity than the untreated group [73], while another study found no significant difference [72].

In addition, it is also important to note that these results might be confounded by the stool sample preparation methods, nucleic acid extraction, or bioinformatics analysis. For DNA sequencing, most studies chose to amplify the V3 and V4 regions of 16S rRNA [72, 74, 75, 84]. Only one study chose to amplify the variable regions V1 and V2 of 16s rDNA [73]. The variation in results might be due to the differences in targeting of the different regions of the gene in the stool samples. The details of the alterations in the taxonomy of gut–microbiota in children and adolescents with ADHD are listed in Table 2. All of these findings suggest that *Bifidobacterium* and *Bacteroides* genera might be

Table 2 The alterations in genera and taxa of gut–microbiota in children and adolescents with ADHD

Participants (number/mean age)	MPH	Major findings						
		Gut microbiome				Other parameters	Interpretations	References
		Actinobacteria	Bacteroidetes	Firmicutes	Proteobacteria			
ADHD (19/19.5) Control (77/27.1)	Yes[a]	↑ Genus *Bifidobacterium*		↓ Order Clostridiales		fMRI: ventral striatal responses for reward anticipation in ADHD ↑ CDT enzyme associated with ↑ *Bifidobacterium*	Increased Bifidobacterium related to decreased neural responses to reward anticipation	Aarts [72]
ADHD (14/11.9) Control (17/13.1)	Yes[b]		↑ Genus *Bacteroides*		↑ Genus *Neisseria*		Increased *Bacteroides* spp. and *Neisseria* spp. in ADHD group	Preh-Kristensen [73]
ADHD (51/8.47) Control (32/8.5)	No			↓ Genus *Faecalibacterium*$^{-}$			Decreased genus *Faecalibacterium*	Jiang [74]
ADHD (30/8.4) Control (30/9.3)	No		↓*B. coprocola* ↑*B. uniformis* ↑*B. ovatus*$^{+}$ ↑*S. stercoricanis*$^{+}$			↑ Genus Fusobacteria ADHD ∝ higher intake of refined grains and lower dairy and vitamin B2 *S. stercoricanis* ∝ dairy, nuts/seeds/legumes, ferritin, magnesium *B. uniformis* ∝ fat, carbohydrate	Increased proportion of *B. uniformis*, *B. ovatus* and *S. stercoricanis* and decreased proportion of *B. coprocola* Specific diet showed a correlation with gut–microbiota profiles	Wang [75]

ADHD attention-deficit/hyperactivity disorder, *MPH* methylphenidate, *fMRI* functional magnetic resonance imaging, *CDT* cyclohexadienyl dehydratase

[a]The participants withheld MPH for 48 h before study

[b]10 participants on MPH more than 1 year and 9/10 of them withheld for 48 h before study

+The relative abundance of microbiome had a positive correlation with ADHD symptoms

$^{-}$ The relative abundance microbiome had a negative correlation with ADHD symptoms

possible markers for children and adolescents with ADHD. More information concerning the specific species of microbiota in these genera correlated with dietary intervention and ADHD symptoms is still needed.

The alterations in gut–microbiota following interventions for gut dysbiosis in children with ADHD

Probiotics are living microorganisms that exert health benefits on the host when ingested in adequate amounts [85]. Probiotic microorganisms affect the host in a variety of ways including improving gut barrier integrity and enzyme formation, production of organic acids and antimicrobial compounds, interaction with gut–microbiota, and modulation of immune function [86]. Prebiotics are dietary ingredients selectively utilized by gut microbes conferring host's health benefit [87]. Manipulating the gut–microbiota with probiotics and prebiotics are the novel approaches for treating diseases with gut–brain axis disorders such as depression and neurodevelopmental disorders [88–90]. Studies in rodents showed that the prebiotic, bimuno-galacto-oligosaccharides (BGOS) increased cortical *N*-methyl-D-aspartate (NMDA) receptor function and improved cognitive flexibility in an attentional set-shifting task [91]. Studies into the use of several prebiotic and/or probiotic supplementary interventions in children with autism spectrum disorder have indicated possible improvement in GI and behavioral symptoms [92, 93].

The first intervention study in the gut–microbiota of children with ADHD was conducted in 75 Finnish infants. A 13-year Randomized Control Trial (RCT) using Lactobacillus rhamnosus GG (LGG) supplementation during the first 6 months of life was conducted and the fecal microbiota was assessed using fluorescein in situ hybridization (FISH) and qPCR six times from 3 weeks to 2 years of age and again at 13 years old when ADHD was diagnosed. Six patients in the placebo group were diagnosed with ADHD or Asperger syndrome (AS), whereas none was diagnosed in the treatment group ($p = 0.008$). With FISH and qPCR techniques at that time point, the study focused on particular microbiota. A reduced abundance of *Bifidobacterium longum* at 3 months old and the genus *Bifidobacterium* at 6 months old was observed, while *Bacteroides*, *Lactobacillus-Enterococcus,* and *Clostridium histolyticum* were lower when compared to age-matched controls at 18 and 24 months of age, respectively. No significant fecal microbiome composition and structure was found in 13-year-old ADHD or AS patients compared to their control counterparts [94]. From this study, probiotic supplements in early life showed some benefit in reducing the risk of ADHD. However, the sample size was very small, and the old versions of technology could not identify specific species of gut–microbiota associated with the disease.

Another study conducted a 10-week RCT of micronutrient supplementation in 17 children with ADHD. They found that micronutrient supplements did not show any correlation with large-scale changes in the microbiome structure and composition. However, a significant decrease in the abundance of bacteria from the phyla *Actinobacteria* was observed, which was largely attributed to species from the genus *Bifidobacterium* in the treatment group. The two major species contributing towards this effect were *B. longum* and *B. adolescentis.* Although no significant correlations with ADHD symptoms were observed, the researchers found a general trend supporting the observation that higher *Bifidobacterium* was correlated with a lower ADHD-IV-RS score. However, with regard to cases in which there was post-micronutrient treatment, a low *Bifidobacterium* abundance was associated with a low ADHD-IV-RS score [84]. Even though the outcomes are unclear and appeared contradictory, this study identified *Bifidobacterium* as being of potential relevance to informing a possible link between gut–microbiota and ADHD children. These pilot data suggested that micronutrient supplementation could be safe and be used as a therapeutic method to modulate *Bifidobacterium* abundance in children with ADHD. The details regarding interventions for gut dysbiosis are listed in Table 3. All of these findings suggest that probiotics and micronutrients may modulate the gut–microbiota in cases of ADHD. More evidence from larger RCT intervention studies is required. Study into dietary management in these patients may enhance treatment in young children by families unwilling to medicate their children and adults reluctant to adhere to a perceived pharmacologic treatment.

More studies are required to investigate how gut–microbiota may influence ADHD symptoms, medical response, and side effects. To our knowledge, the effects of medication on gut–microbiota and the associations between gut–microbiota and symptoms have not been fully investigated in ADHD patients. The impact of psychostimulants on the gut–microbiota and vice versa are still unclear. Further studies into gut–microbiota involvement in the treatment response to ADHD medication may explain the reason for children unresponsive to the first-line standard treatments.

Conclusion and future perspectives

The current studies show an altered gut–microbiota in children and adolescents with ADHD. Various microbes which might be possible biomarkers of ADHD are summarized in Fig. 2. *Bifidobacterium* and *Bacteroides* genus were found to be of note in many studies.

Table 3 The alterations in gut–microbiota following interventions pertinent to gut dysbiosis in children with ADHD

Model	Subjects	Method	Major findings	Interpretations	References
Longitudinal study for13-years	77 infants LGG 3ADHD 2ADHD + AS 82 controls	FISH qPCR	ADHD patients gut–microbiota profiles ↓ *Bifidobacterium longum* at 3 months old ↓ The genus *Bifidobacterium* at 6 months old ↓ *Bacteroides* and *Lactobacillus-Enterococcus* group at 18 months old ↓ *Clostidium histolyticum* group at 24 years old	No significance difference in taxa at 13 years old compared with controls Administration of LGG during first 6 months of life might reduce the risk of ADHD	Partty [94]
RCT within 10 weeks	17 ADHD 10 (10.3) micronutrient group 7 (9.3) control group	NucleoSPIN DNA stool isolation V3-V4 region 16S rRNA QUIIME2	Significant increases observed OTUs in the treatment group ADHD at based line: ↑ *Bifidobacterium* ∝ ↓ ADHD symptoms ADHD post-micronutrient: ↑observed OTUs ↓ *Bifidobacterium* ∝ ↓ ADHD symptoms	Significant decrease in the abundance of the genus *Bifidobacterium* in the micronutrient group	Stevens [84]

ADHD attention-deficit/hyperactivity disorder, *LGG Lactobacillus rhamnosus GG*, *RCT* randomized-controlled trial

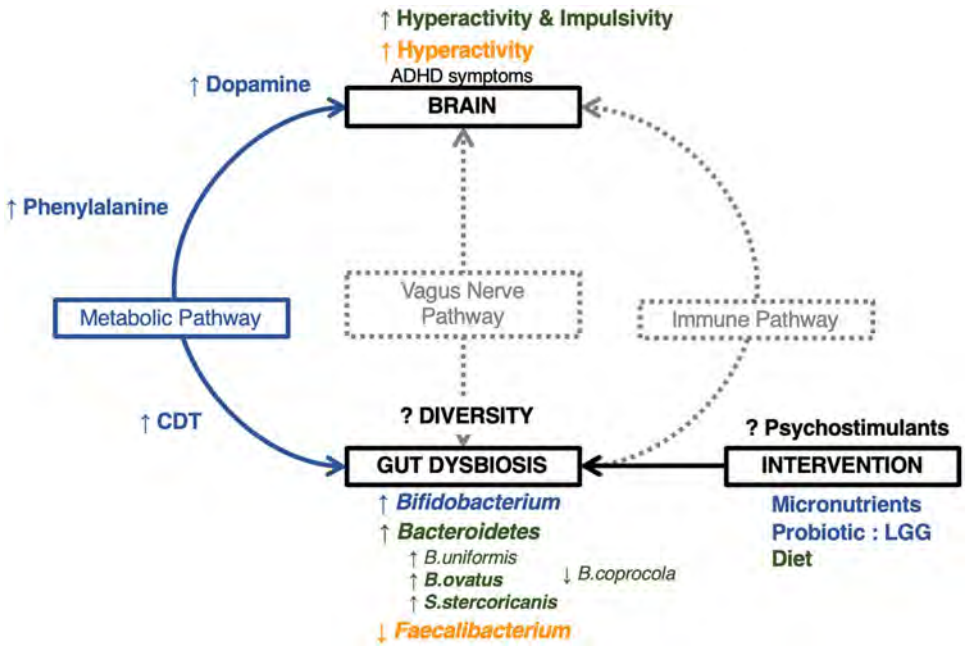

Fig. 2 Gut–microbiota in children and adolescents with ADHD. Existing evidence of specific gut–microbiota associated with mechanistic links between ADHD and gut–microbiota. The metabolic pathway mechanistic link between the gut–brain axis and ADHD symptoms. *ADHD* attention-deficit/hyperactivity disorder, *IL* interleukins, *CDT* cyclohexadienyl dehydratase, *LGG Lactobacillus rhamnosus GG*

There is increasing evidence to support the improvement in ADHD symptoms following diet supplements indicating that gut–microbiota might underlie these results. Understanding the role of gut–microbiota, both in the etiology and treatment in this disorder, will be crucial in establishing microbiota-targeted treatment and the clinical utilization of microbial modulation which may improve the management of ADHD.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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