⚕ Thieme

Exercise Changes Gut Microbiota: A New Idea to Explain that Exercise Improves Autism

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ABSTRACT

The effect of exercise interventions on autism spectrum disorder (ASD) has been demonstrated in many studies, and the discovery of a bidirectional relationship between the gut microbiome (GM) and the central nervous system (CNS) has led to the concept of the microbial gut-brain axis (MGBA) and has linked the abnormal GM to a variety of neuropsychiatric disorders, autism being one of them. Research on improving the GM through exercise is also starting to come into focus. However, there are currently few studies on exercise intervention in the GM of autism. The purpose of this review was to find evidence to explore the possible potential effects of exercise to improve the behavior of individuals with autism in the MGBA in this treatment, as well as the potential of GM as an exercise treatment for autism. We will explore (1) changes in GM components of ASD and their relationship to the pathophysiology of ASD; (2) the relationship between exercise and changes in GM components, and (3) the effect of exercise on GM in CNS disorders. Ultimately, we concluded that *Streptococcus*, *Bifidobacterium*, *Clostridium*, *Bacteroides*, and *Blautia* may be potential effectors through the MGBA network during exercise to ameliorate ASD targeting microbiotas. They deserve high attention in the follow-up studies.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that primarily includes social impairment and repetitive stereotypic behaviors that typically develop by age 3 and persist into adulthood [1]. These are the core abnormal symptoms in individuals with ASD. In addition, there are several abnormal behaviors, including sensory-motor abnormalities, speech delay, and gastrointestinal (GI) symptoms [2, 3]. According to the results of the Center for Disease Control and Prevention (CDC) Autism Developmental Disabilities Surveillance Survey, the prevalence of ASD is 1/54, which is higher than 1/59 [4]. In addition, the prevalence in males is 3–4 times higher than in females [5]. The disease may be associated with multiple factors, including genetic factors as well as some non-

genetic factors [6–8]. Genetic factors are mainly caused by chromosomal abnormalities. Environmental factors were mainly related to pregnancy stress, diet, and perinatal exposure to drugs or heavy metals [9–13]. In addition, individuals with autism are not only susceptible to illness, but also have difficulty obtaining the same level of education and full-time employment as their peers, or even living independently [14]. There is no doubt that the burden on families, schools, health care systems, and individuals is substantial and ongoing [15]. Therefore, addressing autism is of great importance to schools, families, and society.

The intersection of microbiology and neuroscience has given rise to the new concept of the gut-brain axis. Subsequently, gut-brain axis is a bidirectional communication system between the

brain and the nerves of the gut [16]. It controls the bidirectional communication between the gut and the brain, which in turn affects brain function. Neural signals can influence gut function and alter the composition of the gut microbiome (GM), while the GM can signal the brain through different pathways, including immune and vagal activation, microbial metabolite, peptide and neurotransmitter production [17]. GM affects various neurological disorders by affecting the vagus, neuroendocrine and immune connections with the brain [18, 19]. Dysfunction of this axis can lead to many neuropsychiatric disorders such as Alzheimer's disease; Parkinson's disease; and autism [20, 21]. Previous studies have shown that the relative abundance of GM in patients with ASD changes with the development of gastrointestinal disorders, such as diarrhea, constipation and exchange diarrhea/constipation, compared to normal subjects [22, 23]. Transplantation of gut microbes from ASD patients into germ-free mice was found to exhibit autistic-like behavior [24]. Similarly, social impairment in mouse models of ASD was well ameliorated by supplementation with *Lactobacillus Reuteri* [25]. These findings strongly suggest a close relationship between GM and ASD. At the same time, recent research findings also provide favorable evidence for the treatment of ASD by improving the GM [26].

Exercise induces physiological and biochemical reactions in all tissues and organs of the body through energy expenditure in skeletal muscle, resulting in a combination of effects, including improved metabolism, neuromuscular and contractile function, and rebalancing of electrolytes [27]. In recent years, the effects of exercise on the microbiota have become a focus of interest and have been extensively studied. The positive effects of exercise are mainly associated with changed GM diversity and a balanced relationship between beneficial and pathogenic bacterial communities [28]. For example, increasing the diversity of *Lactobacillus*, *Bifidobacterium*, *Blautia*, and reducing the diversity of *Clostridium* and *Enterococus* through exercise will help maintain a healthier intestinal environment [29]. *Lactobacillus* plays an important role in the production of bacteriocin, bile hydrolase, and phosphoketolase pathway, and is closely related to the urogenital system of healthy women [30, 31]. Metabolites of *Bifidobacterium* can regulate the system, restore intestinal mucosal barrier and regulate oxidative stress reaction [32, 33]. *Clostridium* plays an indispensable role in the body, but it can produce toxins and propionate. Excessive *Clostridium* is related to disease [34, 35]. An experimental animal study found that exercise played a causal role in regulating GM benefits for health by colonizing microbiota from exercising mice along with microbiota from sedentary mouse controls in germ-free mice [36]. Not only in animals, but also in humans. Exercise can regulate GM in a beneficial way [37, 38]. This can be found in the GM study of athletes [39]. Exercise as an intervention leads to changes in their GM [29, 40]. This change may be due to the close relationship between exercise and oxidative stress leading to alterations in GM [41]. GM plays an important role in regulating body metabolism and immune system development [42].

The effectiveness of exercise in improving autism has been widely demonstrated [43]. So, are changes in GM in patients with ASD an important mediator between exercise to improve GM and exercise to improve behavior? It is worth exploring. However, the effect of exercise on the autism microbiome has been little studied. In this review, we will collate GM changes in individuals with autism, exercise-induced GM changes, and the possible relationships between these changes. Furthermore, the effect of exercise intervention on autism was analyzed from the perspective of GM changes.

Autism gut microbiota abnormalities

The relationship between microorganisms and autism is becoming increasingly apparent. Various intestinal problems in ASD have become co-morbid, including: abdominal pain, diarrhea, and constipation, the incidence of which has been confirmed by retrospective and prospective studies ranging from 9% to 84% [44]. Bolte first suggested in 1998 that GM may have an association with the onset of autism [45]. Currently, many studies have confirmed that people with ASD have different GM compared to normal people [46, 47]. This includes not only human but also mouse ASD models such as knockout models, Sodium Valproate (VPA) models, etc. [48, 49]. An interesting study found that mice exhibited ASD-like behavior after feces from ASD patients and normal humans were colonized into a germ-free (GF) mouse model [24]. Research has identified that GM can access pathways that control neuronal differentiation and survival through neurotrophins and their receptors, it can influence the fate of neurons in different regions of the brain, which in turn affects neurodevelopment and health [50]. Thus, there may be a strong relationship between GM and ASD. The gut bacteria mainly include six major phyla of *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinomycetes*, *Verrucomicrobia* and *Fusobacteria*, with *Bacteroidetes* and *Firmicutes* as the dominant ones [51]. We organized and classified the collected studies on ASD and GM. We use the keywords ASD, autism, intestinal flora, and gut microbiota etc. to search in PubMed, web of science, and google school databases. The studies included in the table are human studies, excluding animal experiments and review articles.

Proteobacteria phyla

In *Proteobacteria* phyla, *Sutterella* is a gram-negative non-phage that grows in a microaerobic environment or under anaerobic conditions; it is resistant to bile acids, and regulates mucosal metabolism and intestinal epithelial integrity [52, 53]. The relationship between *Sutterella* and gastrointestinal symptoms in ASD has been explored in studies [54]. Several studies have demonstrated that the relative abundance of *Sutterella* is significantly elevated in patients with ASD [23, 52, 54, 55]. However, the opposite result was also found [56, 57].

Coprococcus, is a Gram-positive anaerobic bacterium. In the current study, *Coprococcus* is equally controversial, but there is a trend towards a decrease in the relative abundance of *Coprococcus* relative to normal human ASD patients [58–60]. Development of the present *Clostridium perfringens* with a role in regulating host 5-hydroxytryptamine(5-HT) biosynthesis and release [61]. And by regulating the changes in 5-HT, it led to the rescue of social impairment in the mouse model of autism [62]. Whether this is related to the abnormality of this flora makes it worthwhile to continue to think deeply about the study.

Bacteroidetes phyla

Bacteroides, *Corynebacterium* and *Prevotella* belong to *Bacteroidetes* phyla. The trend in the relative abundance of *Bacteroides* in ASD pa-

tients in the current study was elevated [56, 63–66]. *Bacteroides* are polymorphic, non-spore producing Gram-negative anaerobic bacteria with the ability to digest dietary fiber and polysaccharides. In the genus *Bacteroides*, *Bacteroides uniformis* has effects on brain reward responses, amelioration of binge eating, and reduction of anxiety-like behavior. These effects were mediated, at least in part, by changes in voxel nucleus dopamine, 5-HT and norepinephrine levels and changes in prefrontal cortex and intestinal dopamine D1 and D2 receptor expression [67]. In contrast, the reduced relative abundance of *Prevotella* in ASD patients showed a decreasing trend [58, 59, 63, 68]. *Prevotella* is a beneficial bacterium and determines the distribution of the intestinal microbiota in a key genus with physiological importance. It may also be associated with intestinal inflammation [69, 70]. In one study, it was found that women with high *Prevotella* caused their negatively valences images to be higher [71]. *Corynebacterium* is a serious pathogen in humans or animals, a gram-positive bacterium with an irregular shape and varying thickness [72]. It has been found that its relative abundance showed an increasing trend in ASD patients [65].

Phylum Firmicutes

Faecalibacterium [73], *Lactobacillus* [23, 65, 74], *Runminococcus* [56], *Clostridium* [56, 75], *Roseburia* [76] belong to *Firmicutes* phylum shows an increased trends in the gut of ASD patients. The relative abundance of *Streptococcus* and *Blautia* was reversed [64, 73, 76]. After four weeks of administration of *Faecalibacterium prausnitzii* to rats, behavior, growth status, SCFA produced, plasma cytokines, endocrinology, and bone density were assessed. *Faecalibacterium prausnitzii* was found to reverse the effects of chronic unpredictable mild stress in rats [77]. For the genus *Lactobacillus*, *Lactobacillus reuteri* could improve social impairment in autism model rats, while cutting the vagus nerve revealed that social impairment could not be improved. So it was found that *Lactobacillus reuteri* affected dopaminergic (DA) neurons through the vagus nerve to release oxytocin and thus improve autism social impairment [25]. The abnormalities of *Ruminococcus* may be related to respiratory or skin allergies [75]. *Clostridium* is one of the largest genera of prokaryotes, consisting of about 200 different species of bacteria, which are associated with intestinal diseases, such as severe diarrhea [78, 79]. *Roseburia* consists of specific Gram-positive anaerobic bacteria that produces short-chain fatty acids that affect colonic activity and may be associated with obesity, neurological disorders, etc. [80]. Even its relative abundance has been explored as a biomarker for ASD [76]. In the genus *Roseburia*, *Roseburia* intestinalis treatment reduced depression-like behavior in rats, and experiments on neuronal cells showed that *Roseburia* intestinalis treatment reduced the expression of interleukin- 6 (IL-6), interleukin- 7(IL-7) and 5-HT in serum and brain tissue [81].

Actinobacteria phyla

In *Actinobacteria* phyla, *Bifidobacterium* is a genus of Gram-positive anaerobic bacteria that promotes health by fermenting complex polysaccharides to regulate host function [82, 83]. It has good anti-inflammatory and immunomodulatory effects and even reported that *Bifidobacterium bifidum* is associated with the production of Gamma-aminobutyric acid (GABA) [84, 85]. This further links *Bi-*

fidobacterium to ASD, where most of the existing studies found reduced abundance of *Bifidobacterium* in patients with ASD [23, 63, 64, 86–89], Zhou found the opposite trend [57]. *Bifidobacterium longum* in the genus *Bifidobacterium* is anxiolytic by means of the vagus nerve but does not involve intestinal immune regulation or nerve cell production of brain-derived neurotrophic factor (BDNF). There is a close relationship between BDNF and ASD, and it was even once used as a biomarker for ASD patients [90]. Whether abnormalities of *Bifidobacterium* in ASD patients are associated with abnormalities of their BDNF deserves to be studied further. Since *Bifidobacterium longum* reduces the excitability of intestinal neurons, it may send signals to the central nervous system by activating the vagal pathway at the level of the enteric nervous system [91]. However, many studies have elaborated changes in ASD *Bifidobacteria*, and the mechanisms between its effects on brain mechanisms and ASD deserve further exploration.

Phylum Verrucomicrobia

Finally, there is the phylum *Verrucomicrobia Akkermansia*, an oval Gram-negative anaerobic bacterium whose function is mainly to improve the metabolic function and immune response of the host. In patients with ASD the same was found to produce changes in its relative abundance compared to the normal group [92]. Zurita found that the relative abundance of *Akkermansia* was increased in patients with ASD compared to normal subjects, but the opposite was true in Maria [60, 93]. It was found that *Akkermansia muciniphila* in the genus *Akkermansia* affects the 5-HT system in the colon and hippocampus of mice, causing them to produce more 5-HT [94]. There may be a relationship between this and the development of autism, pending subsequent studies to be conducted.

This shows a controversial trend in many of the current studies on the GM of patients with ASD. However, these studies all indicated significant differences in GM in ASD patients compared to normal subjects. (insert ▸ **Table 1**)

Exercise changes gut microbiota

Exercise: An effective tool

The World Health Organization (WHO) recommends physical activity at certain doses to improve physical fitness and quality of life [95]. This shows that exercise is a tool to be active and stay healthy. Research has identified a potential external effect of exercise on the ability to alter gut biodiversity by promoting GM diversity [96]. The change of microbiotas by exercise should first be reflected in athletes, who are groups that have undergone regular exercise training, and the change of their GMs is important evidence to reflect the effect of exercise on GM. For example, analysis of the GM of professional cyclists, rugby players, marathon runners, and skiers revealed significant changes in their GM [97–99]. The relative abundance of *Prevotella* in marathon runners, skiers and competitive cyclists produced a significant upward trend [37, 97, 99]. The relative abundance of *Bacteroides*, *Ruminococcus* and *Akkermansia* also changed significantly among the athletes. These changes may be the result of the athlete's long-term athletic training, and the changes do not just respond to the athlete. The relative abundance of GM can also be altered by active regular physical activity, as has been demonstrated in experiments with animals and in humans [29, 40, 100]. However, because the changes caused by exercise

▶ **Table 1** ASD abnormal gut microbiota.

Author	Sample	methods	groups	Outcomes (Genus) Rising relative abundance	Outcomes (Genus) Decrease in relative abundance
Kang [58]	Feces	16 S rDNA	ASD:20		Prevotella, Coprococcus, Unclassified Veillonellaceae
			HC:20		
Zhang [55]	Feces	16 S rRNA	ASD:35	Sutterella	Streptococcus, Veillonella
			HC:6		
Luna [56]	Rectal biopsy	16 S rDNA	ASD-FGID:14	Clostridia, Clostridium, Lachnoclostridium, Runminococcus	Flavonifracto, Sutterella, Dorea, Blautia
			NT-FGID:15		
			NT:6		
Zhou [57]	Feces	16 S rDNA	ASD:143		Sutterella, Prevotella, Bacteroides
			HC:143		
Finegold [64]	Feces	16 S rDNA	ASD:33	Desulfovibrio, Bacteroides	Bfidobacterium,
			NS:7		
			NT:8		
Kang [59]	Feces	16 S rRNA	ASD:21		Feacalibacterium, Prausnitzii, Haemophilus Parainfluenzae
			HC:23		
Pulikkan [68]	Feces	16 S rRNA	ASD:20 HC:20	Lactobacillus, Megasphaera, Mitsuokella	
Strati [65]	Feces	16 S rRNA	ASD:40	Alistipes, Bilophila, Dialister, Parabacteroides, Veillonella	Collinsella, Corynebacterium, Dorea, Lactobacillus,
			HC:40		
Tomova [74]	Feces	16 S rRNA	ASD:10	Lactobacillus, Desulfovibrio	
			NS:9		
			HC:10		
Julio [66]	Feces	16 S rRNA	ASD:52	Bacillus, Butyrivibrio, Enterococcus, Hespellia, Prevotella	
			(ANMR:32		
			AMR:20)		
			HC:57		
María [93]	Feces	16 S rRNA	ASD:25	Bacteroides, Akkermansia, Coprococcus, Ruminococcus	
			HC:35		
Inoue [73]	Feces	16 S rRNA	ASD:6	Faecalibacterium	Blautia
			HC:6		
Maria [60]	Feace	16 S rRNA	PDD-NOS:10	Dorea, Clostridia, Desulfovibrio, Sutterella, Bacteroides	Faecalibacterium, Coprococcus, Akkermansia, Streptococcus
		16 S rDNA	ASD:10		
			HC:10		

ASD: autism spectrum disorder; HC: healthy contral; ASD-FGID: autism spectrum disorder-children with functional gastrointestinal disorders; NT-FGID: neurotypical-children with functional gastrointestinal disorders; NT: neurotypical; AMNR:ASD by no mental regression; AMR: ASD by mental regression; PDD-NOS: Pervasive Developmental Disorder Not Otherwise Specified; NS: non-autistic siblings.

are affected by individual metabolic status, this factor must be considered in future research.

Exercise changes the relative abundance of gut microbiota

The effect of exercise on the improvement of GM is significant, and according to the length of the exercise cycle can be simply divided into short-term and long-term exercise. Both short-term and long-term exercise can improve the composition of the GM. Immediate post-half marathon (21.1 km) testing of 20 runners revealed significant alterations in the *Actinobacteria* phylum of the athletic participants [101]. Changes in the relative abundance of GM were also reflected after a single cycling session [102]. The test results 72 hours after exercise showed more significant changes compared

to 48 hours. Moreover, regular physical activity in the medium to long term can also have an impact on the GM, which we will summarize below from a genus perspective (▶ **Table 2**) .

Regular exercise as an effective means of improving GM has been well validated in experiments using exercise as an intervention. This is reflected not only in human studies, but also in animal studies. In *Proteobacteria* phyla, Karl Found that the relative abundance of *Sutterella* after military training was lower than that before training [103]. This is a microbiota associated with intestinal verification by inhibiting the secretion of immunoglobulin A [104]. For *Prevotella*, exercise increased the relative abundance of *Prevotella* compared to resting controls with lower BMI, which was also reflected in the animal model [28, 37]. Lower levels of *Bacteroides/Prevotella* were also found in the mouse model of diabetic exercise compared to the sed-

▶ Table 2 Exercise improves gut microbiota.

Author	Sample	Groups	Method	Plan	Outcomes (Genus) Rising relative abundance	Outcomes (Genus) Decrease in relative abundance
Morita [106]	Feace	AE:17	16SrRNA	AE: 1 h of brisk walking; intensity ≥ 3MET	AE: Bacteroides	AE:Clostridium subcluster XIVa
		TM:12 pre-post test		TM: weekly 1 h for 12 weeks		
Zhao [101]	Feace	HG:20 pre-post test	16SrRNA	half marathon	Ezakiella, Romboutsia	Coprococcus, Ruminococcus
Motiani [108]	Feace	SIT:13	16SrRNA	2 weeks 6 times	Veillonella, Lachnospira	Blautia, Clostridium
		MICT:13 Pre-post test		SIT: Wingate protocol		
				MICT:40–60 min 60%VO2peak		
Mariangela [109]	Feace	HG:40 pre-post test	16srRNA	running 1 km at maximum speed	Romboutsia, Blautia	Ruminiclostridium, Clostridium
Rocío [110]	Feace	OE:25	16srRNA	Oe:12 weeks 24 times strength and endurance training	OE VS OC:Blautia, Dialister, Roseburia, Flavobacteriia	OE VS OC : Bacteroides Gammaproteobacteria,
		OC:14 pre-post test				
						Flavobacterium
						Faecalibacterium
						Clostridium
Allen [40]	Feace	LG:18	16SrRNA	6 weeks exercise 60%–75% of HR 30 to 60 min	Faecalibacterium	Bacteroides
		OG:14 pre-post test			Roseburia	
					Faecalibacterium	
					Lachnospira	
Eveliina [112]	Feace	HG:19 pre-post test	16SrRNA	6 weeks 3 times/week	Streptococcus	Odoribacter
				1–2 week 40 min	Bifidobacteriaceae	
				3–4 week 50 min	Akkermansia	
				5–6 week 60 min		

AE: aerobic exercise training; TM: trunk muscle training; HG: healthy group; SIT: sprint interval; MICI: moderate-intensity continuous training; OE: obesity exercise group; OC: obesity control; LG: lean group; OG: obesity group.

entary mice [100]. Apparently, exercise is associated with an increase in the metabolic pathways associated with *Prevotella* in the GM, and exercise leads to a higher relative abundance of *Prevotella* in the gut [105]. In contrast, the relative abundance of bacteriophages did not vary as consistently [40, 106].

Regarding *Firmicutes* phyla, studies have shown that movement can independently reduce the relative abundance of *Lactobacillus*, *Clostridium* and *Actinobacteria* [100, 107–109]. While the relative abundance of *Ruminococcus*, *Roseburia* and *Streptococcus* was increased by exercise [37, 39, 40, 101, 103, 109–111]. These findings are relatively consistent.

In *Actinobacteria* phyla, Eveliina found that the relative abundance of *Bifidobacteria* was elevated after exercise by using exercise as an intervention [112]. This was also found in animals [100]. *Roseburia* is a genus of *Actinobacteria* whose relative abundance can be increased by motor intervention [110].

Finally, in *Verrucomicrobia*, *Akkermansia* as a typical colony was found to have elevated its relative abundance after an exercise intervention [112]. This was achieved through six weeks of aerobic exercise.

Potential mechanism by which exercise influences gut microbiota

GM of athletes showed a relative increase in amino acid synthesis and carbohydrate utilization. There is a relative increase in fecal metabolites such as: short-chain fatty acid (SCFA), acetate, propionate and butyrate produced by microorganisms [98]. However, athletes show a more diverse gut microbiome, but not all of these changes are necessarily beneficial. Exercise may affect the integrity of the gut mucus layer, which plays an important role in preventing microbial adhesion to the gut epithelium and is an important substrate for certain mucosa-associated bacteria [39]. The effects of exercise on the gut can also reduce intestinal blood flow by more than 50%, with significant intestinal ischemia occurring within 10 minutes of high-intensity exercise [113]. Exercise can reduce blood flow to the gut by more than 50%, especially within 10 minutes of high-intensity exercise when significant intestinal ischemia can occur [113]. Heat stress and ischemia induced by exercise may temporarily cause more direct contact between the microbes in the intestinal lumen and mucosa, thereby potentially affecting the GM. Of course, these changes may also be the enterohepatic circulation of bile acids. Compared with sedentary hypercholester-

olemia mice, hypercholesterolemia mice showed increased bile acid secretion and increased fecal bile acid output after 12 weeks of roller exercise [113]. Bile acids are effective regulators of the structure of the gut microbial community, and the absence of these molecules is related to the significant changes in the gut microbial community [114].

In summary, it has been found that exercise has the effect of improving GM through exercise intervention, which has been well demonstrated in both animal and human experiments. However, due to the instability of external factors such as environment, diet, stress and other conditions, it is difficult to make the human experiments more precise. Also, there is no clear reference for the intensity, frequency, and duration of exercise to improve GM through exercise intervention, and we expect that subsequent studies can explore the indexes of exercise to improve GM more systematically.

Effect of diet on exercise mediated intestinal intervention

Diet is an important factor influencing and shaping GM [115]. A study confirmed that exercise and diet orthogonal changes GM [116]. Furthermore, some also discussed the effects of dietary intake and supplements on the GM of athletes [96, 117]. The influence of diet and exercise is also closely related to people's health [118]. As the result, diet also plays an important role in the process of changing GM through exercise. A study was carried out on the changes of GM of elite race walkers who had undergone intensive training under different dietary patterns. The diet of high fat and low carbohydrate increased the relative abundance of athletes' intestinal *Bacteroides* and *Dorea* and the relative abundance of *Faecalibacterium*. In the baseline group, the GM was dominated by *Prevotella* or *Bacteroides* [119]. Protein supplementation will also affect the GM of endurance athletes. For cross-country runners, high protein supplement increases the abundance of their *Bacteroidetes* phylum, and reduces the existence of health-related groups, including the relative abundance of *Roseburia*, *Blautia*, and *Bifidobacterium longum* [120]. These changes have a negative impact on the GM. The study of beneficial effects of nominal exercise on GM diversity under the intervention of extreme diet of football players provides evidence, but also shows that this relationship is complex and related to the accompanying extreme diet [37]. Some researchers even think that some differences or changes in GM seem to be related to exercise, but it may be mainly due to differences or changes in dietary intake, especially plants and carbohydrates, rather than exercise itself [117]. However, the relationship between diet and exercise on GM is very close. Therefore, it is necessary to study the relationship between GM and exercise to control and regulate the dietary intake of participants.

Potential mechanism of exercise on ASD gut microbiota

Gut-brain axis is a two-way communication system between brain and enteric nerve [16]. Nerve signals can affect intestinal function and change the composition of GM, while GM can send signals to the brain through different ways, including immune and vagus nerve activation, production of microbial metabolites, peptides, and neurotransmitters [17]. Intestinal microorganisms contact the brain by affecting vagus nerve, intestinal nerve, etc., thus affecting

various neurological diseases [18]. The dysfunction of this axis can lead to many neuropsychiatric diseases, such as autism and Parkinson's disease. This provides a new perspective for the pathogenesis and treatment of autism, has good guiding value, and may become a potential new target for clinical treatment of autism.

Currently, there are few studies examining the effects of exercise on the improvement of GM and its core symptoms in autism. However, by the above summary we also found that the relative abundance of GM in ASD patients does differ from normal individuals and that exercise does have an improving effect on the relative abundance of GM (▶ **Fig. 1**).
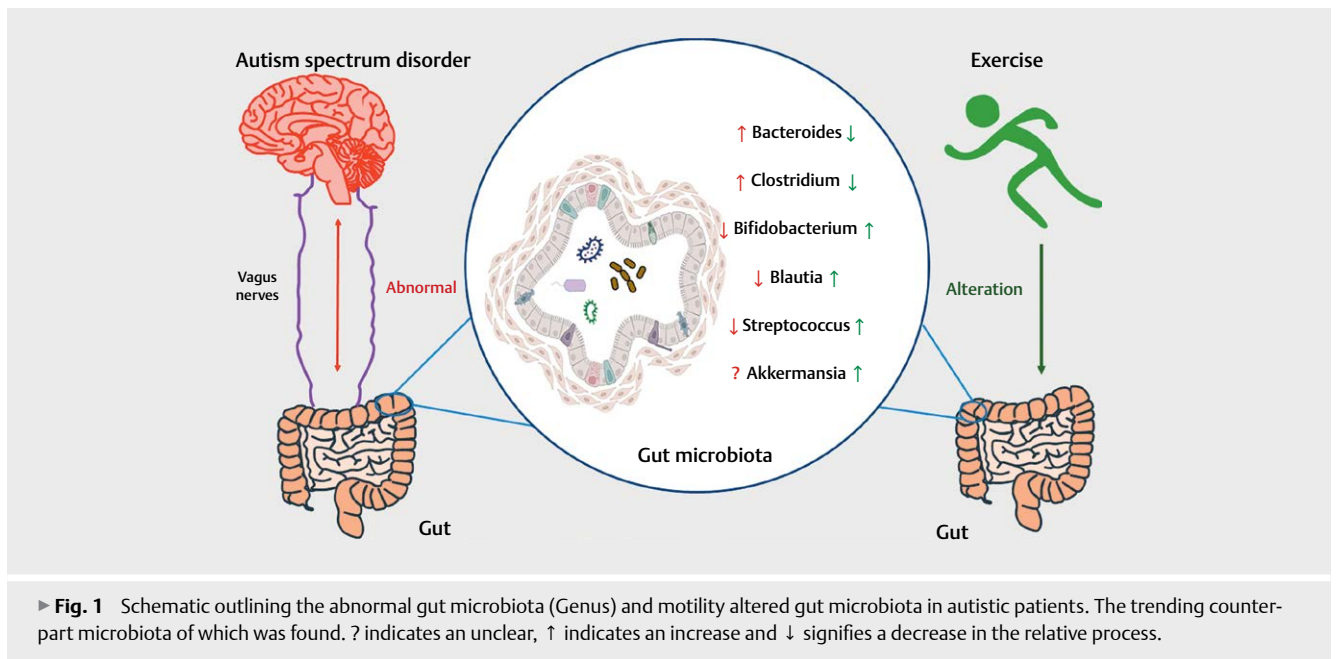
Bacteroides genus

Here, we have identified some abnormal flora in autistic patients through a review. These microbiotas can be altered by movement. Firstly, we found that the relative abundance of *Bacteroides* was significantly elevated in many patients with ASD and many studies have found that exercise as an intervention can reduce its relative abundance [37, 40, 57, 93]. Studies have shown that high levels of *Bacteroides* affect infants' cognitive and language skills, and it is also related to the production of GABA [121–123]. The higher levels of *Bacteroides* in children with ASD may be related to the underlying mechanisms of certain behaviors, which are worthy of further study. Reduced relative abundance of *Bacteroides* can prevent pathogen invasion, reduce immune function, and promote immunity [103].

Bifidobacterium genus

While *Bifidobacterium* has also been proven to be related to the production of GABA [85]. The relative abundance of *Bifidobacterium* in patients with ASD was found to be reduced in many studies, while some experiments using exercise as an intervention confirmed that exercise increased the relative abundance of *Bifidobacterium* [64, 100]. GABA is an amino acid neurotransmitter that is an important heterogeneous neurotransmitter in the central system. There are scholars who now believe that ASD results from an imbalance of excitatory and heterogeneous neurotransmitters during development [124]. Glutamatergic and GABAergic dysfunction and its impact on excitatory to inhibitory cortices is one current hypothesis to explain the social and cognitive impairments in autism and schizophrenia [125]. It was found significantly higher GABA content in the Dorsolateral Prefrontal Cortex (DLPFC) of ASD compared to the normality by hydrogen proton magnetic resonance spectroscopy (1H-MRS) [126]. And is the close relationship between *Bifidobacterium* and *Bacteroides* and GABA related to these? Could the improved relative abundance of *Bifidobacterium* and *Bacteroides* through exercise be a pathway for exercise to alleviate symptoms in ASD patients? These can all be discussed further in subsequent studies. Not only GABA, but *Bifidobacterium* may also be associated with 5-Hydroxyindole-3-acetic acid(5-HIAA), 3,4-dihydroxyphenylacetic acid(DOPAC), and tryptophan [127]. Changes in all of these substances may be associated with neurological disorders.

Clostridium genus

Clostridium perfringens was significantly increased in most of the studied patients with ASD compared to the normal group [56, 60, 75]. The intervention with exercise as the means of inter-

▶ Fig. 1 Schematic outlining the abnormal gut microbiota (Genus) and motility altered gut microbiota in autistic patients. The trending counterpart microbiota of which was found. ? indicates an unclear, ↑ indicates an increase and ↓ signifies a decrease in the relative process.

vention led to a decrease in their relative abundance [109, 110]. *Clostridium perfringens* is a Gram-positive bacterium that has also been extensively studied in ASD because of its production of exotoxins and propionates [34, 35]. A proportion of children with degenerative ASD develop neurobehavioral symptoms and chronic diarrhea due to repeated antibiotic administration, so it has been suggested that toxin-producing Clostridium may be involved [109]. While Sandler treated children with degenerative autism by administering oral vancomycin, an antibiotic known to have anti-clostridial activity, for six weeks. Eight of the 10 children studied showed significant improvement in neurobehavioral symptoms (some even scored in the neurotypical range), as well as improvement in gastrointestinal symptoms [128]. This also illustrates the close relationship between ASD and *Clostridium*.

Blautia genus

Blautia, an anaerobic genus with probiotic properties, is widespread in the feces and gut of mammals. It is significantly associated with host physiological dysfunction. For example, obesity, diabetes, cancer, and various inflammatory diseases [129]. We found that the relative abundance of *Blautia* was decreased in many of the ASD patients studied [64, 76], and that the relative abundance could be enhanced by some research exercises as an intervention [109, 110]. This genus has also been found to play a role in biotransformation and interactions with other intestinal microorganisms [130]. However, the specific relationship between ASD patients and the genus *Blautia* has not been clearly explained.

Akkermansia genus

Akkermansia muciniphila is a strictly anaerobic bacterium isolated from human feces that uses mucin as its sole source of carbon and nitrogen [131]. It is an oval-shaped bacterium, strictly anaerobic, non-motile and Gram-negative. In patients with ASD, the relative abundance of *Akkermansia* is controversial [60, 93], while its rela-

tive abundance is elevated by exercise interventions [112]. *Akkermansia muciniphila* maintains host gut microbial homeostasis by converting mucins into beneficial by-products [132]. The decrease in the relative abundance of *Akkermansia muciniphila* is thought to be associated with certain diseases. Most of them are metabolic disorders and inflammatory diseases, including obesity, type 2 diabetes, inflammatory bowel disease (IBD), autism, and atopic diseases [92]. In the future, it may be an important target for some diseases.

Streptococcus genus

Streptococcus, another large group of common gram-positive cocci in pyogenes, is widely distributed in the nasopharynx, gastrointestinal tract, and so on in nature and the human body, and is mostly a normal microbiota. *Streptococcus* showed a decreasing trend in relative abundance in autistic patients [55, 60], and exercise was an effective means of elevating its relative abundance [112]. It has been reported that it can cause life-threatening diseases such as meningitis and sepsis [133, 134]. There are many species of *Streptococcus*, mainly associated with various inflammatory conditions, but current research has found little study of the relationship with ASD.

Conclusion

This review comprehensively summarized the abnormal GM in ASD patients and its potential impact mechanism, as well as the types of GM in exercise change and their potential role. The literature reviewed supports the hypothesis that exercise may affect the behavior of autistic patients by changing the GM. The review also supports the assumption that the overall health performance of ASD can be improved by changing the GM. If *Clostridium* is found in the colon of children, it indicates that ASD may develop [26]. It produces exotoxins and propionate, which are closely related to autism. The same is true of *Bacteroides*. In most studies, abnormali-

ties of *Bifidobacterium*, *Brucella* and *Streptococcus* in ASD were also found. These GM abnormalities are closely related to inflammation and neurotransmitter production leading to ASD. Exercise, as an effective way to change GM, can reverse the abnormal GM. Therefore, the improvement of GM by exercise may be a new interpretation of the improvement of ASD patients by exercise.

Limitation

Exercise as a comprehensive effect affects all aspects of the body. Does its impact on autism include the impact of exercise on the GM? At present, there are few articles that study exercise to improve the GM of autistic patients. This may be because the GM is heterogeneous and is related to various aspects of the living environment, diet, etc., so it is difficult to determine the alteration of GM. Also, the results of GM testing in autistic patients in different regions are not completely uniform. Exercise intervention research is more selective for specific populations, and it is uncertain whether exercise will cause changes in the GM due to specific conditions of specific populations, or whether such conditions will occur in all types of individuals. In animal experiments, it is easier to control diet and exercise. Therefore, the study of human GM by exercise should strictly control diet and environment. Since the effects of different GMs on the brain are still being explored, and the effects of GM changes on the brain are slowly being confirmed. The impact of gender is also unclear. In the future, will it be possible to explain how exercise affects the symptoms of ASD by improving the GM of people with ASD? Which exercise pattern and exercise parameters are more appropriate? Which patterns and parameters, including sustained intensity, duration, and duration frequency, are worthy of continued exploration?

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Conflict of Interest

All authors participated in pre-survey, data collection, and manuscript review. ZP designed the structure of the article. YQ and SA wrote the manuscript. WN, WH and LM participated in data collection. All authors read and approved the final manuscript. The authors declare no conflict of interests.

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