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REVIEW



Exercise influence on the microbiome–gut–brain axis

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ABSTRACT

The microbiome in the gut is a diverse environment, housing the majority of our bacterial microbes. This microecosystem has a symbiotic relationship with the surrounding multicellular organism, and a balance and diversity of specific phyla of bacteria support general health. When gut bacteria diversity diminishes, there are systemic consequences, such as gastrointestinal and psychological distress. This pathway of communication is known as the microbiome–gut–brain axis. Interventions such as probiotic supplementation that influence microbiome also improve both gut and brain disorders. Recent evidence suggests that aerobic exercise improves the diversity and abundance of genera from the *Firmicutes* phylum, which may be the link between the positive effects of exercise on the gut and brain. The purpose of this review is to explain the complex communication pathway of the microbiome–gut–brain axis and further examine the role of exercise on influencing this communication highway.

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Introduction

The microbiome in the gut is a diverse environment, housing the majority of our bacterial microbes. Consisting of over 1,100 genera among different phyla, the gut epithelium harbors nearly 39 trillion microbes which is a 1:1 ratio of microbes to eukaryotic cells in the human body.^{1,2} The gut microbiome promotes digestion and food absorption for energy production, performs a fundamental role in the function of the immune system,^{3–5} produces and communicates with hormonal products as an endocrine-like organ,⁶ and appears to have an impact on brain function.^{7–12} The diverse roles of the microbiome are mediated through production and release of various molecules. For example, microbes are capable of producing short-chain fatty acids (SCFAs) which are used as nutrients for colonocytes and brain microglia cells, support cholesterol metabolism, and regulate various hormones involved in appetite.^{13,14} Gut bacteria are also capable of producing enzymes that regulate inflammatory pathways and amino acids that have both free radical generating and scavenging properties.^{15,16} The gut microbiome is not only comprised of bacteria, but houses other prokaryotes (i.e., Archaea) along with viruses

and fungi. The current review will specifically emphasize the bacterial component of the gut.

In human adults, approximately 90% of the gut bacteria belong to the *Bacteroidetes* and *Firmicutes* phyla, whereas the minority bacteria belongs to *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* phyla.^{17,18} The *Firmicutes* phylum contains over 250 genera of bacteria, including *Lactobacillus* and *Clostridium*, while *Bacteroidetes* phylum includes around 20 genera, the most abundant being *Bacteroides*.¹⁸ The gut bacterial community is maintained through the symbiotic relationship between both pathogenic and non-pathogenic bacteria and can be demonstrated by balanced ratio of the *Bacteroidetes* or *Firmicutes* phyla and other nondominant phyla.^{19,20} Substantial shifts to the microbial communities in response to dietary changes, antibiotics, or invasions of pathogens may cause a shift to a nonequilibrium, or inflammatory state, and has important health implications.²¹ Gut microbiome disruption is thought to play a key role in the development of several diseases including type 2 diabetes,^{8,22,23} irritable bowel syndrome (IBS),²⁴ cardiovascular diseases,²³ allergies, mood disorders,^{7,9,11} and many others via intestinal inflammation.^{3,6}

The gut has long been overlooked when it comes to human health and disease prevention. Emerging research has proved that an imbalanced diet of highly saturated fats, high sugar, and low fiber intake has a large influence on the composition of the microbiome.⁸ The alterations induced by poor dietary habits contribute to gastrointestinal (GI) dysfunction that may further lead to the development of inflammatory diseases.²⁵ Interestingly, a prebiotic intervention that promoted changes in the microbiota of diabetic rats lowered inflammation while improving glucose intolerance.^{26,27} Moreover, individuals diagnosed with inflammatory conditions such as IBS and obesity have been found to have a comorbidity of lower cognitive function^{28,29} and higher instances of stress-related psychiatric symptoms, such as anxiety.³⁰⁻³² In accordance, interventions that specifically treat neural disorders such as selective serotonin uptake inhibitors (SSRIs) have been shown to improve GI function.³³ These data have sparked curiosity among investigators, which has led to a growth of research into understanding the connection between the GI tract and the brain.^{7,9,11,30,34} Further interest has grown in discovering the role of the microbiome in mediating the connection between the gut and brain. Altering the gut microbiome through probiotic supplementation has improved symptoms of both psychological disorders (e.g., depression and anxiety) and cognition and positively supports GI function.³⁵⁻³⁹ This demonstrates the complexity of the relationship between the gut microbiome and the brain.

Regular aerobic exercise has been shown to prevent age-related global brain atrophy and increases brain volume in the frontal lobes and left superior temporal lobe, which are important for cognition and control of attention and memory.⁴⁰ Moderate-intensity aerobic exercise training has also promoted improvement (in older adults aged 60–79 years) in functional activation in the brain which allows for increased efficiency when completing tasks, as well as regulating behavior and mood.⁴¹ More recently, aerobic exercise has been shown to impact the gut by increasing microbiome diversity and functional metabolism in both humans and mice. Altering the bacterial profiles and influencing the by-products produced from gut bacteria through

exercise may have the potential to reverse the conditions associated with obesity, metabolic diseases, poor diet, along with neural and behavioral disorders.⁴²⁻⁴⁵ To date, the impact of exercise on the relationship between the gut and the brain is unknown. Therefore, the purposes of this review are to briefly introduce the complex interaction between the microbiome, gut, and brain and to further explain how exercise impacts these relationships. For this review, we have chosen to state this relationship as the microbiome-gut-brain axis where the composition of the gut microbiota influences both the GI and central nervous systems (CNSs).^{34,46} More specifically, alterations to the microbiome may impact (both positively and negatively) GI (e.g., secretion, motility, and integrity) and higher brain function (e.g., neurotransmission, neurogenesis, and behavior), and these influences may be bidirectional.³⁴

Microbiome-gut-brain axis pathways of communication

The relationship between the gut and the brain begins *in utero* as the CNS and the enteric nervous system (ENS) are derived from the same tissues during fetal development.⁷ The communication between the gut and the brain is a bidirectional pathway that is mediated through the autonomic nervous system (ANS) efferent and afferent signals via the vagus nerve; neuroendocrine signaling through the hypothalamic-pituitary-adrenal axis (HPA axis), and serotonin (5-HT) regulation.⁴⁷⁻⁵⁰ It has now been established that alterations of gut microbiome enact some influence on the communication between the gut and brain through these pathways.

The vagus nerve serves a critical role in communication between the gut microbes and the brain, as it connects the CNS to the ENS.^{51,52} The vagus nerve is able to communicate with gut microbiota in the ENS and transfer vital information to the CNS where it is deciphered, to then generate a response based on the information received. For example, if the information received via the vagus nerve from the gut indicates an imbalance in gut microbiome bacteria, the CNS will then decipher if an inflammatory response is necessary. Decreased vagus nerve activity has been associated with conditions such as IBD,⁵³ IBS,⁵⁴ and depression⁵⁵⁻⁵⁷ and is attributed to dysfunction of

gastric motility and gastric emptying.⁵⁸ Specifically targeted probiotic supplements that alter the microbiome have also been shown to improve brain function, and this positive neural benefit is abolished when a vagotomy procedure is performed among rodents.⁵⁹ More specifically, mice induced with colitis demonstrated lower anxiety-like behavior after 21 days of being fed a probiotic supplement containing *Bifidobacterium longum*. The anxiolytic effect of *Bifidobacterium longum* was lost when vagotomized mice were fed the supplement. The authors concluded that the behavior benefits of the *Bifidobacterium longum* is vagally mediated.⁵⁹ This provides evidence that vagal communication between the gut and brain is influenced by the release of molecules from the gut microbiota.

The HPA axis regulates an organism's response to a multitude of stressors (e.g., physical or mental).^{60,61} The HPA is influenced by the GI system through a complex neural-immunoregulatory mechanism. Afferent feedback from the gut via the vagus nerve acts on the hypothalamus and hippocampus regions of the brain, resulting in activation of the HPA.⁶² It also appears that disruption to the gut mucosal layer via lipopolysaccharide (LPS) insult promotes the release of pro-inflammatory cytokines, which are capable of exaggerating HPA activation.^{47,63} HPA axis hyperresponsiveness and disturbances in the gut microbiome are found in those suffering from both IBS and psychological disorders.⁶¹ This demonstrates potential roles for the neuroendocrine system and the gut microbiome in the regulation of both the gut and brain. Rodents raised in a germ-free environment (no-microorganism exposure and no potential for gut microbiota colonization) from birth are found to have an inflated release of adrenocorticotrophic hormone (ACTH) and corticosterone levels in response to physical restraint stress exposure when compared to free-living control rodents.^{6,34,48,64-66} The germ-free rodents also displayed lower expression of brain-derived neurotrophic factor (BDNF) in the hippocampal and cortex regions of the brain. BDNF promotes neurogenesis and is vital for CNS growth and health.⁶⁷ BDNF has also been shown to be an important regulator of GI tight junction protein expression and regulation.⁶⁸ Treatment with *Bifidobacterium* ameliorated the exaggerated HPA response in the germ-free rodents and restored BDNF levels in the brain.⁶⁴ It has become clear that

the gut microbiome is important in the adequate development of both the HPA axis and the CNS during early life.^{64,69} While extremely complex, when a diverse and healthy microbiome communicates with the CNS, tighter HPA control occurs, which may further promote both neural and GI growth through BDNF regulation.^{70,71}

Serotonin (5-HT) is a crucial neurotransmitter and hormone and is often known as one of the primary mood and cognition regulators.⁷² Lower platelet serotonin receptor function is associated with higher levels of anxiety and depression, while higher platelet serotonin is associated with improved mood.⁷³ It is also a major contributor to the modulation of intestinal secretion and motility,^{74,75} as well as a key signaling molecule within the microbiome-gut-brain axis.^{30,65} Recently, it has been demonstrated that indigenous bacteria in the gut regulate serotonin synthesis and release.⁷⁶ In addition, germ-free animals have demonstrated higher levels of serotonin in the hippocampal region of the brain while showing lower expression in the colon.^{76,77} This demonstrates that the microbiome plays a role in the regulation of serotonin and may influence both brain and gut function. It appears that various gut microbe strains synthesize serotonin and may be the reason why germ-free rodents have lower expression of 5-HT in the gut. Other strains control tryptophan metabolism, the precursor to 5-HT synthesis, and have been shown to influence both tryptophan and serotonin levels.^{78,79} For example, the *Bacteroides fragilis* bacterium is a known consumer of tryptophan, and supplementation has been linked to improving intestinal wall stability, and also protection against CNS demyelinating disease.^{65,80,81} Autism spectrum disorder is a developmental disorder that affects behavior and is commonly associated with GI symptoms. Autistic like mice demonstrated improved GI function and also began to resemble normal behaving animals after supplementation with *Bacteroides fragilis*.⁸¹

In summary, the microbiome is capable of influencing both brain and gut function by modulating vagus nerve afferent feedback; influencing the hyperresponsiveness of the HPA axis; and altering the regulation of the tryptophan and serotonin synthesis pathways. However, it is important to understand that other communication channels in the gut-brain axis such as GABA-glutamate and catecholamines have been shown to be influenced by specific microbiota.^{82,83}

Exercise effect on the microbiota–gut–brain axis

The bulk of previous exercise research on GI physiology has shown a negative effect. For example, in several studies from our group and others, intense exercise leads to an increase in intestinal permeability, GI damage, and mild endotoxemia.^{84–86} However, targeted exercise therapies have been developed to treat those suffering from IBS with reported improvements in symptoms of the disorder.⁸⁷ Exercise also promotes cognition and improved symptoms of both mood and psychological disorders among humans. Cognitive improvements have been observed among stroke patients, while symptoms of depression and schizophrenia have also been improved after aerobic exercise training.^{88–90} Interestingly, the improvements observed among IBS patients after exercise were linked to changes in mental health and emotion.⁸⁷ Evidence suggests that the bacterial diversity of the gut contributes to the disordered state of GI disorders by negatively impacting GI function and the psychological state.^{91,92} Altering the microbiome through probiotic supplements improves both GI integrity and mood among IBS patients.^{92,93} Probiotic supplements also reduced stress-induced GI symptoms (abdominal pain and nausea) among participants with a history of elevated stress.⁹⁴ Exciting research within the last 5 years has demonstrated that exercise promotes a diverse community

of microbes that contribute to the biodiversity of the bacteria in the gut.^{42–44,66} Exercise appears to be a potential external influence on the capacity to alter the gut biodiversity in both quantitative and qualitative ways.⁶ Exercise alterations to the gut microbiome may provide a link to the exercise-related benefits on GI function, mood, and higher brain centers. Figure 1 highlights the impact of exercise on the microbiome, and how alterations may mediate improvements in both the gut and brain.

Research conducted among volunteers from the American Gut Project⁹⁵ concluded that those who exercised at a higher frequency demonstrated diversity in the *Firmicutes* phylum (specifically, *Faecalibacterium prausnitzii* and species from the genus *Oscillospira*, *Lachnospira*, and *Coprococcus*). Athletes have been shown to exhibit higher diversity of gut microorganisms compared to nonathletes. More specifically, in a group of professional rugby players, 22 phyla were detected, while only 11 phyla were identified in age-matched low BMI control and 9 phyla in an age-matched high BMI control. The distinct phyla among the athletes correlated with both dietary protein intake and creatine kinase, suggesting that diet and exercise facilitate diversity in the gut. The researchers identified higher proportions of the *Firmicutes* phyla and lower *Bacteroidetes* phyla in the athlete group compared to the high BMI control.⁴² While the athlete group had greater diversity than the low

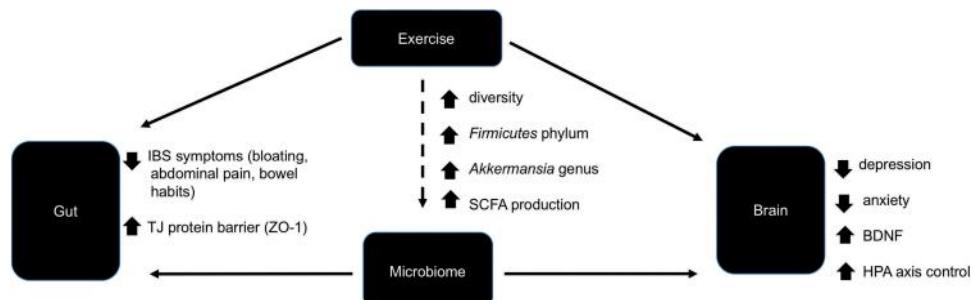


Figure 1. The role of exercise in the microbiome–gut–brain axis. Exercise and the gut microbiome have been independently shown to improve symptoms of IBS and stabilize the TJ barrier and have also been linked to decrease psychological disorders (e.g. depression, anxiety), promote neurogenesis (through BDNF), and improve HPA axis control. It has been demonstrated that aerobic exercise caused greater diversity in the microbiome along with increasing genera of the *Firmicutes* phylum, which produce short-chain fatty acids. In addition, athletes have demonstrated higher levels of the *Akkermansia* genus, which has been linked to metabolic and neural diseases. The extent to which the effect of exercise on the gut and brain is mediated through alterations in the microbiome is unknown. The dotted line represents a proposed mechanism. Solid lines represent known mechanisms. BDNF – brain-derived neurotropic factor, SCFA – short-chain fatty acids, ZO-1 – zona occludens-1 protein, HPA axis – hypothalamic–pituitary–adrenal axis, TJ – tight junction.

BMI control, it was difficult for the researchers to identify specific bacteria that help to understand the role of extreme exercise on the microbiome in this study. Interestingly, both the athletes and low BMI group demonstrated a higher proportion of the *Akkermansia* genus (*Verrucomicrobia* phylum), which has been negatively associated with metabolic dysfunction in humans and rodents.⁴² The administration of *Akkermansia* has been shown to reverse diet-induced metabolic disorders in obese mice.⁹⁶ The *Akkermansia* genus has also been linked to cognitive impairment as a result of poor dietary habits.⁹⁷ Mice demonstrated a 5.4-fold reduction in *Akkermansia* and associated behavioral decline in response to the Western diet (high fat and sugar intake).⁹⁸ While the link between exercise changes to the gut microbiome and resulting changes in brain function is unknown, the alterations among athletes appear to be a result of exercise and dietary behaviors, which may provide protection against both metabolic and cognitive decline.

In a follow-up study, the same group of researchers confirmed the microbial diversity among elite rugby athletes compared to nonactive, age-matched control and again demonstrated higher levels of *Akkermansia*.⁹⁹ The researchers also performed metabolomic phenotyping of the microbiome to further understand the differences between athletes and controls at the functional metabolic level. The athletes reported higher activity of several pathways, including amino acid synthesis, and carbohydrate metabolism. As a result, athletes demonstrated an enriched profile of SCFAs, indicating greater production and host absorption rates. Identified SFCA s in the athletes were acetate, propionate, and butyrate, which are produced by gut microbes from protein, fibers, and nondigestible starches.¹⁰⁰ The researchers attributed the differences between athletes and controls to heavy physical activity and the associated diet. They highlighted the impact of the high protein and fiber diet among the athletic group and the resulting metabolism by gut microbes. In support of these findings, Estaki et al.¹⁰¹ distinctly identified an association between cardiorespiratory fitness and microbiome function rather than diversity of specific bacterial taxa. A strong relationship was observed between

aerobic fitness ($\text{VO}_{2\text{max}}$) and fecal SCFAs, indicating that more aerobically fit humans produce higher rates of SFCA s.¹⁰¹ Total dietary protein intake was also a significant contributor to the diversity and functional changes (SFCA production) in the gut, further highlighting the role of diet. Higher SFCA production is attributed to many health benefits, including protection against inflammation and atherosclerosis.¹⁰² SFCA s produced from the microbiome also appear to provide nutrients to brain microglia to support healthy maturation and function.¹⁰³ In summary, a link has been established between the functional by-products (i.e., SFCA) of the gut microbiome and healthy behaviors (exercise and diet).⁹⁹

The bulk of research examining the role of exercise interventions on changes in the gut microbiome has been performed in rodent models. Kang et al.¹⁰⁴ analyzed changes in the gut bacteria among mice after a 16-week exercise program (forced wheel running 5 days/week) compared to a high-fat diet group.¹⁰⁴ Exercise appeared to increase the bacteria of phylum *Firmicutes* and lower *Bacteroidetes*, which was surprisingly similar to the changes observed in the high-fat diet group. Conversely, Evans et al.¹⁰⁵ reported opposite findings with lower *Firmicutes* and higher *Bacteroidetes* after 12 weeks of voluntary wheel running. The group also demonstrated exercise prevention of high-fat diet-induced obesity and suggested a microbial altering mechanism of exercise on averting high-fat diet-related obesity.¹⁰⁵ The differential results between the Kang and Evans groups may be attributed to the forced vs. voluntary wheel running protocols utilized in the studies, respectively (discussed in next section). A link has been made between low gut *Bacteroidetes* and obesity and further supported by increased *Bacteroidetes* in response to weight loss among obese individuals.¹⁰⁶ The richness and diversity of the gut microbiome has been correlated with various metabolic markers where low richness corresponds with higher adiposity, insulin resistance, and dyslipidemia.¹⁰⁷ Exercise is an established treatment for metabolic disorders, and these results may indicate that exercise-related changes in the gut microbiome may support metabolic health.

In a short voluntary wheel running exercise protocol (6 days), Queipo-Ortuno et al.¹⁰⁸ reported an increase in genera *Lactobacillus* and *Blautia coccoides-Eubacterium rectale* from the *Firmicutes* phylum,

along with genus *Bifidobacterium* from the *Actinobacteria* phylum. All three genera are capable of producing SCFAs,¹⁰⁹ which may be considered a functional change in the gut microbiome as a result of exercise. Queipo-Ortuno et al.¹⁰⁸ also posted a positive association between *Lactobacillus* and *Bifidobacterium* and serum leptin levels in the animals. Leptin is a hormone secreted from adipose tissue and helps to control appetite and eating behavior.¹¹⁰ These results demonstrate that exercise alterations to the gut microbiome are related to dietary food intake and may indicate a connection between exercise, the gut, and behavioral change.

Several recent exercise intervention studies have been conducted among human subjects. While the primary aim of this review is to assess the impact of exercise training on the gut microbiome. Zhao et al.¹¹¹ analyzed fecal samples before and after a half-marathon event among human participants. An increase in the richness of the *Actinobacteria* phylum was reported with a notable correlation between the *Coriobacteriaceae* family and several metabolites. *Coriobacteriaceae* has been associated with higher levels of high-density lipoprotein (HDL) and metabolic improvements, and the researchers identified the change in bacteria as a potential mechanism for exercise-induced health benefits.^{112,113} These results indicate that an acute bout of exercise, while extreme (i.e., half-marathon) has a profound impact on the gut microbiome.

In the first known human exercise study, Allen et al.¹¹⁴ compared microbiota changes between lean and obese humans before and after a 6-week aerobic exercise program and further evaluated changes after a period of de-training. Exercise caused changes in gut microbiome diversity and microbial production of SCFAs among both the lean and obese subjects. The authors aimed to identify groups of bacteria that responded to exercise training and identified the *Faecalibacterium*, *Lachnospira*, *Clostridia*, and *Roseburia* genera, which are all part of the *Firmicutes* phylum. These genera increased in abundance in response to exercise training and returned to baseline upon cessation. A notable finding was that changes in the gut were associated with changes in lean mass and reduction in fat mass, meaning that shifts in microbial content were more substantial among those subjects that demonstrate these changes.

These findings suggest that aerobic exercise affects the content and diversity of the gut microbiome in humans and may additionally raise the question about how gut microbes influence adaptations to exercise.

The identified “exercise” genera by Allen et al.¹¹⁴ were all producers of SCFAs and more specifically butyrate. Butyrate and other SFCAs are known energy substrates for colonocytes, with butyrate being the primary energy source.^{115,116} This may explain why exercise improves symptoms and reduces the risk for IBS and colon cancer.¹¹⁷ Further, butyrate has been shown to stimulate neural proliferation in the dentate gyrus brain regions of mice and has also been used to induce neurogenesis after ischemic brain insult in adult rodents.^{118,119} These results may provide a link between exercise-induced microbial SCFA production and improvements in both brain and GI function. However, it is unknown if the positive benefits of exercise on gut and brain are mediated through adjustments to the microbiome (see Figure 1).

The limited amount of research explaining how exercise influences the microbiome has indicated that genera from the *Firmicutes* phylum appear to be the most responsive to exercise-induced changes. Given that the *Firmicutes* phylum consists of over 250 genera, it is difficult to understand which genera lead to systemic inflammation and which lead to a healthy gut environment. The work from Allen et al.¹¹⁴ has implied that genera that produce SCFA appear to respond to exercise; however, this is the only known study among humans to evaluate changes after an aerobic exercise intervention, and then upon cessation of exercise. In the only other human exercise study, Cronin et al.¹²⁰ reported minimal change in gut bacterial diversity among healthy male and females who participated in an 8-week combined aerobic and resistance exercise program. The conflicting results may be due to the exercise regimen where the aerobic training program in the Allen et al.¹¹⁴ study appeared to be more vigorous, and 100% compliance was reported. Importantly, Cronin et al.¹²⁰ implemented a nonexercise control to accurately assess and compare sedentary and exercise behavior. They concluded that while the gut microbiome is adaptable, 8 weeks of exercise may not be enough stimulus to enact change. These

studies have advanced the field and future work is needed to fully characterize how the microbiome adapts to exercise, and other various forms of physical activity.

Exercise influences the microbiome-gut-brain axis pathways of communication

As mentioned previously, the vagus nerve is at the interface of the microbiome-gut-brain axis. Altered vagus nerve activation is commonly found in patients with both GI (IBS, IBD) and psychological disorders (depression).^{121,122} Various forms of exercise, including yoga and aerobic exercise training, have been shown to improve parasympathetic tone.¹²³ Meta-analytical studies have identified yoga as a proven mode of exercise to improve symptoms of IBS and depression,^{124,125} which may be partially mediated by autonomic influences. As previously discussed, alterations in the gut microbiome affect vagal communication between the gut and brain.¹²⁶ An intact vagus nerve is critical for the benefits of probiotics supplements containing strains of *Bifidobacterium* and *Lactobacillus* to be effective.⁵⁵ Further, any mediating effect of probiotics on the HPA axis and depression-related symptoms are abolished through the vagotomy procedure.¹²⁷ Therefore, it is logical to suggest that any alterations that exercise may have on the diversity and expression of gut flora would potentially be manifested through influence on vagal communication between the gut and brain. Unfortunately, empirical evidence currently does not exist to verify this conclusion.

Improvements in brain structure and function have been documented as an adaptation to repetitive aerobic exercise.^{40,128,129} Regular moderate-intensity aerobic exercise prevents age-related brain volume loss and increased brain volume in areas responsible for cognition and control of attention and memory.⁴⁰ The positive benefits of exercise on neural function appear to be mediated through regulation of BDNF. BDNF is central in the growth and the survival of striatal neurons in the brain, and it also plays a critical role in regulating mood disorders, along with learning and memory.^{34,130,131} According to Linnarsson et al.,¹³² BDNF is known for its protective role in the adult brain, because the genetic deletion of this protein

results in apoptosis (death of cells) in mice. Decreased levels of BDNF in the hippocampus have also been associated with anxiety and depression and is often comorbid with gut inflammatory diseases, such as IBS, and or inflammatory-bowel disease (IBD).^{8,133} Oral supplementation with *Bifidobacterium* has been shown to increase BDNF expression in the brains of rodents, while aerobic exercise in piglets has also been shown to increase *Bifidobacterium* in the gut.^{64,134} Antibiotic treatments that killed gut bacteria also delayed the growth of brain cells in the hippocampus regions of mice.¹³⁵ Both probiotics and aerobic exercise individually rescued the decline in neurogenesis and cognitive function among mice treated with the antibiotic.¹³⁵ However, it is unknown if the exercise effects on brain neurogenesis and cognition are mediated through *Bifidobacterium*.¹³⁶

Elevated HPA axis activation and gut-microbiome disruption is seen when an exercising individual exceeds 60% of maximum oxygen uptake ($\text{VO}_{2\text{max}}$) or during prolonged exercise (>90 min). Psychological stress, such as the kind experienced by athletes pre-competition, has also led to an increased HPA axis activation and greater gut disruption.¹⁰ Likewise, research in mice has found that moderate forced treadmill running (8–12 m/min at a 5% grade for 40 min, 5 times per week) exacerbated colitis symptoms when compared to voluntary exercise, which attenuated symptoms.¹³⁷ The researchers concluded that the forced exercise may have been perceived as a psychological stressor by the mice, whereas the voluntary wheel running is a conscious decision. Hyperresponsive HPA axis appears to be influenced by the diversity of the gut microbiome where the lack of, or absence of bacteria, caused robust HPA activation in response to psychological stress.⁶⁴ Supplementation with *Bifidobacterium* species reversed HPA overactivation and alleviated symptoms of anxiety and distress among rodents and humans, respectively.³⁵ While previously noted, the *Bifidobacterium* strains are influenced by aerobic exercise, where animals with free access to wheel running showed increased numbers of *Bifidobacterium*.¹⁰⁸ Furthermore, force wheel running resulted in reduced levels of *Lactobacillus*, which is important for protection against disease-causing microorganisms.¹³⁸ It is important to mention that microbiome-altering effect of voluntary wheel

running has only been shown in male mice, whereas null findings were reported in a combined cohort of male and female mice.^{138,139} However, both voluntary and forced exercise appear to influence the average operational taxonomic units (OTUs) of several microbial species. For example, force running increased *Ruminococcus*, *Butyrivibrio*, and *Oscillospira*, which are all within *Firmicutes* phylum. Of note, many of these various species are being considered as probiotics due to their role in neuropsychiatric disorders.¹⁴⁰ In summary, it appears that the psychological state of exercise influences the microbiome, and these changes may further impact the HPA axis regulation and mood disorder symptoms.

Aerobic exercise has been shown to also influence serotonin regulation. In rats, 5-HT synthesis and metabolism increased in both the brain stem and the hippocampus in response to exercise,¹⁴¹ and this increase in 5-HT resulted in the reduction of depressive and anxiety symptoms.¹⁴² Wipfli et. al.¹⁴² described the effects of exercise as similar to the those of SSRIs used to treat depression and anxiety. The following bacteria in the gut microbiome have been found to produce serotonin: *Lactococcus lactis*, *Lactobacillus plantarum*, *Streptococcus thermophile*,¹⁴³ *Morganella morganii*, and *Klebsiella pneumoniae*.¹⁴⁴ Unfortunately, there are no previous studies that thoroughly examined if exercise has any influence on these specific strains. Because some of these serotonin-producing strains stem from the *lactobacilis* genera (which is a component of *Firmicutes* phyla), exercise may support the increased presence of these strains through the natural diversification of gut microbiota that occurs as a result of exercise. Therefore, the production of serotonin through an exercise-adapted gut microbiome might possibly be an explanation as to why subjects exhibit lower stress-related symptoms, such as anxiety and depression, after participating in physical activity. These statements, however, are purely assumptions and more research is needed to confirm this suggestion.

Conclusion

Although the exact causal relationship is unknown, current evidence allows for the assumption that exercise may mediate a bidirectional relationship between the gut and brain through alterations in the microbiome. This relationship may explain why

exercise can be a therapeutic factor and strategy for both psychological and GI disorders. The main identified phyla that respond to exercise are *Firmicutes* and *Actinobacteria*, which contain the *Lactobacillus* and *Bifidobacterium* genera, respectively. In addition, the SCFA-producing genera from the *Firmicutes* phylum also appear to increase in response to exercise. Future work should target underlying mechanisms of how specifically exercise influences the microbiome, and the mediators involved in the gut–brain axis. This may lead to the development of various treatment combinations (exercise + probiotics) to ameliorate (or improve) specific disease states.

Author contributions

AD, CM, and MZ all participated in manuscript development, design, and drafting.

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