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Exploring Gut Microbiome, Gut-Brain Axis and Relationship with Exercise; Exploring the Impact of Exercise on Metabolic and Mental Well-Being

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Abstract— *An individual's gut microbiome influences multiple mechanisms within host physiology, playing a crucial role in metabolism, immunity, and neurological function. The diversity of gut microbes evolves throughout an individual's lifetime, with disturbances and alterations linked to metabolic diseases such as obesity and type 2 diabetes. The gut comprises approximately 100 million neurons, more than the human spinal cord, and is often referred to as the "second brain." Emerging research highlights a bidirectional communication between the gut and the brain through multiple mechanisms, including neural, immune, and endocrine pathways. While scientists have extensively explored the role of nutrition and probiotics in gut health, the independent effects of exercise on the gut microbiome and gut-brain axis remain under-researched. This review aims to examine the gut microbiome, its intricate connections, and the influence of exercise in modulating gut microbial composition, thereby improving host physiology. Additionally, it investigates the impact of physical activity on the gut-brain axis, particularly in relation to mood and behavioral disorders. Given the increasing burden of chronic diseases and mental health disorders, understanding the exercise-gut interaction offers valuable insights for public health strategies focused on disease prevention, mental well-being, and holistic health promotion.*

Keywords— ***Exercise, Gut-Brain Axis, Gut Microbiome, Mental Health***

I. INTRODUCTION

The gut-brain-behavior connection has emerged as a significant area of research in recent years, revealing the critical role of the gut microbiome in physiological and neurological processes. The gut-brain-behavior connection has emerged as a new field of research in recent years. Evidence has shown that the gut microbiome plays an essential role in behavioral responses such as emotion, social interactions, and food intake (1). The gut communicates with the brain by using different channels, mainly through the immune system via inflammatory signals, through hormones produced in the gut by endocrine pathways, and the nervous system via the vagus nerve, which is a bidirectional signaling system from both ends of the nerve at the brain and the gut (2). Despite the growing body of knowledge about gut-brain communication processes, few studies on the microbiota and exercise have been conducted.

Additionally, scientists remain uncertain about exactly how the exercised gut microbiota affects the brain in depressed individuals (3). Different gut bacteria and metabolites influence the brain through different connection pathways, with the vagus nerve being the most studied (4). Research has indicated that intestinal mucosal dysfunction with an increased translocation of lipopolysaccharide (LPS) from gram-negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression (5). Inflammation is indicated by increased levels of pro-inflammatory cytokines (PICs), including IL-1, IL-6, and tumor necrosis

factor (TNF)-α (5). Furthermore, numerous studies from neuro-gastroenterology journals have established the importance of tryptophan degradation into its metabolites by gut microbial cells, particularly serotonin and kynurenine, in intestinal mucosal dysfunction mechanisms (6). Kynurenine and its metabolites have been correlated with inflammation, immune function, and psychiatric illnesses due to their effects on the central nervous system (CNS) (7). This review examines the gut microbiome, its mechanisms, and how exercise can benefit people with major depressive disorder by regulating their gut microbiome and metabolites.

Given the increasing burden of non-communicable diseases (NCDs), such as obesity, diabetes, cardiovascular disease, and mental health disorders, understanding the exercise-gut-brain connection is essential for developing novel public health interventions. Exercise is a low-cost, accessible, and non-pharmacological strategy that may have profound implications for preventing and managing chronic diseases. This review explores the gut microbiome's role in human physiology, the mechanisms underlying the gut-brain axis, and the influence of physical activity on gut microbial composition and mental health. Additionally, it discusses the public health implications of these findings, highlighting the need for exercise-based interventions to improve population health outcomes.

II. THE GUT MISCROBIOME

Gut microbiota comprises approximately 100 trillion microbial cells, including viruses, fungi, protozoa, archaea, and more than 1,000 different bacterial species that collectively form the commensal microbiome, which varies between individuals (8). Research statistics have shown that our bodies contain ten times more microbial cells than human eukaryotic cells (8). These trillions of species in the gut reflect over 3.3 million unique genes, which are estimated to be 150 times more than the human genome (9). Within the gut, these microbes play essential roles in host physiology and health by producing metabolites, enzymes, and hormones, detoxifying toxins, stimulating the immune system, metabolizing dietary fibers, and aiding in nutrient absorption. They also synthesize vitamins B and K, and produce short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate, which enhance nutrient availability and protect the human gut barrier from harmful pathogens (10).

Because of the complex roles these microbes play, researchers are now recognizing the microbiome as a significant contributor to diseases that were previously overlooked. Multiple non-communicable diseases and lifestyle disorders, such as obesity, cancer, diabetes, inflammatory bowel disease (IBD), asthma, cardiovascular disease (CVD), kidney disease, and neurological conditions including Alzheimer's, Parkinson's, schizophrenia, ADHD, and autism, have all been linked to gut dysbiosis (11,12,13,14,15,16). Additionally, behavioral disorders including depression, anxiety, and bipolar affective disorder have shown associations with disruptions in gut microbiota (17). As a result, there is an increasing need to investigate gut microbes and their interactions with host physiology to better understand disease etiology and pathophysiology.

The Gut-Brain Connection

Growing research has unfolded the importance of gut microbiota in brain function and plays a significant role in communicating to the brain(18,19). The neuroimmune and neuroendocrine systems, the central nervous system, sympathetic and parasympathetic limbs of the autonomic nervous system, and the enteric nervous system include microbial metabolites such as short-chain fatty acids, essential amino acids, and branched-chain amino acids, are all engaged in this bidirectional communication. These pathways allow for constant communication between the gut and the brain(18,19). This connection becomes evident when we link gastrointestinal (GI) disorders (11,20) like IBD, Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS), and gastroesophageal reflux disease (GERD) to emotional problems like depression and anxiety (21). Food allergies and sensitivities have also been attributed to mental health (22). Additionally, chronic psychological conditions, including major depressive disorder, and post-traumatic stress disorder (PTSD), have also been reported to affect the gastrointestinal system (22).

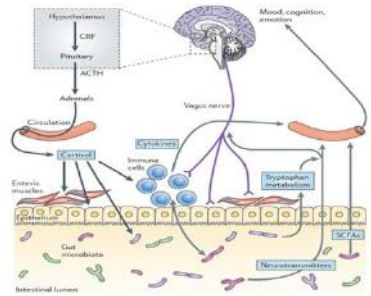

Image Source: PMID: 24266656
This figure explores bidirectional communication between the gut microbiota and the brain via multiple pathways

Fig. 1

Gut Microbiome and Immune Inflammation

Gut microbes build and maintain the gut wall, protecting the body from outside invaders. Gut microbiota also plays

a role in immune system functioning and regulates the production of chemical messengers called cytokines (**23)**. An imbalance of pro- inflammatory cytokines can result in chronic inflammation and autoimmune conditions that often co-occur with depression (**23)**. In the study by Schirmer *et.al*. monocyte [IL-6, TNFα, IL-1β] and lymphocyte-derived cytokines [IFNγ, IL-17, IL-22] were measured in connection with three bacteria (LPS, B. fragilis, and S. aureus), showing a link between the gut and inflammatory response by the immune system (**23)**. Inflammation is indicated by increased levels of pro-inflammatory cytokines (PICs), including IL-1, IL- 6, and tumor necrosis factor (TNFα) (**24).** Therefore, gut microbes can modulate your immune response by stimulating circulating cytokines, affecting brain function (24).

Gut Microbiome Communication via the Endocrine and Nervous Systems

The autonomic nervous system (ANS) regulates organ and gland activity, being divided into the sympathetic (fight-or-flight) and parasympathetic (rest-and-digest) systems (25). The enteric nervous system (ENS), located within the walls of the gastrointestinal tract, is often considered the "second brain" (26). The hippocampus transmits signals to the ANS, which then relays messages to the gut through the vagus nerve, the primary neural conduit connecting the gut and the brain. Several bacterial species, including Lactobacillus, Bifidobacterium, Escherichia, Enterococcus, and Trichuris, have been shown to produce neurotransmitters and neuropeptides such as gamma-aminobutyric acid (GABA), serotonin, brain-derived neurotrophic factor (BDNF), dopamine, and acetylcholine (27). These neurotransmitters influence mood, cognition, and gut motility (28). The gut microbiota produces approximately 95% of the body's serotonin, which plays a critical role in mood regulation and gastrointestinal activity (28). It was noted that the shortage of serotonin in the gut slowed the motion of contents in the GI tract and demonstrated a deterioration in the gut lining followed by symptoms of constipation (29). Gut microbes regulate body's serotonin (5-hydroxytryptamine(5-HT)) in the colon and blood (28). Spore-forming bacteria modulate metabolites that promote colon 5-HT biosynthesis. It has been seen that altering the microbiota could improve 5-HTP- related disease symptoms (28). Serotonin has the capacity to influence the immune system and may communicate with enterochromaffin cells and the microbiota (30). Tryptophan, an essential amino acid, is the first step in the synthesis of serotonin (5-HTP), which further breaks down into melatonin (31).

gut microbiome and Tryptophan metabolism

The ingested tryptophan (TRP) gets degraded by two metabolic pathways – kynurenine (KYN) and serotonin. 95% of tryptophan catabolizes via the kynurenine pathway (KP), 1- 2% is used for serotonin synthesis, and 1-2% is used for protein synthesis (32). TRP metabolism through the KP in the gut is mediated by the rate-limiting enzyme IDO1 (indoleamine 2,3 dioxygenase) in the presence of stress and immune-cytokines (33). It leads to the production of kynurenine and its downstream products such as neurotoxin quinolinic acid (QA) and neuroprotective kynurenic acid (KA). This process can reduce the production of serotonin and may increase the probability of developing psychiatric conditions, including major depressive disorder (34).

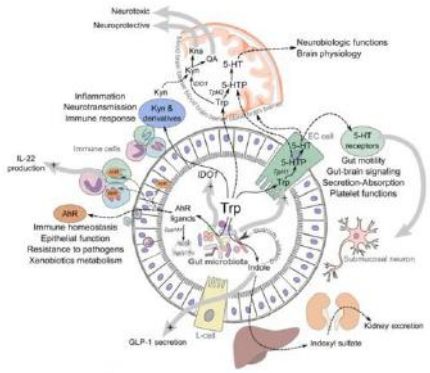

Image source (Kenedy et al)[34]: Integration of TRP Metabolism under the Control of the Gut physiology in Host Physiology

Fig. 2

Major Depressive Disorder

Depression affects all areas of an individual's well-being including, sleep, diet, mental and physical health, self-esteem, social interaction, and academic interaction. Previously, the focus of depression was particularly on brain health, and it has been shown that it can affect the gut-microbiome (35). Also, recent evidence has shown that brain and gut interactions are bidirectional. Hence, an alteration in the gut microbiome can affect the function of the intestinal barrier (35). The inflammation caused by harmful microbiota can activate the vagal system, impacting neuropsychological functions. In the study done by Naseribafrouei et al. (2014) (36), it was noted that taxonomic units associated with depression were found more in the fecal samples of depressed patients (36).

Desbonnet et al. (37) reported that probiotic 'bifidobacterium infantis' can affect the tryptophan metabolism. On ingestion of bacteria B. infantis in animal models, the inflammatory response was decreased, and serotonergic precursor was increased, followed by a reduction in GI inflammation, and depression was treated

(37). Kynurenine which is a tryptophan metabolite has been associated with major depressive disorder Kynurenine can further degrade into a neurotoxin, quinolinic acid. Both aerobic and endurance exercises are beneficial to maintaining normal kynurenine levels because skeletal muscle breaks down kynurenine to form kynurenic acid (KA), which acts as a neuroprotector and not allowing to the blood-brain barrier (38).

III. THE GUT MICROBIOTA, EXERCISE, AND DISEASE

Regular physical activity has shown multifactorial benefits in improving human physiology and disease conditions. Exercise is an inexpensive modality that can be incorporate to remain healthy. Scientists are exploring the effects of exercise on various GI diseases and have noted that exercise offers protective effects on the gastrointestinal lining, reducing the risk of colon cancer, colitis, Crohn's disease, inflammatory bowel disease, and may also help in constipation (39). One of the first studies done by Matsumato et al. to explore exercise and the gut microbiome relationship on animals in 2008 discovered that five weeks of exercise induce an increase in butyrate-producing gut microbes in comparison to the sedentary group (40). The species of Eubacterium, Roseburia, Faecalibacterium, Bifidobacterium, Lactobacillus, and Enterobacter, are associated with producing primary metabolites of gut bacteria, SCFAs, (acetate, butyrate, isobutyrate, hexonate, and propionate) (Nicholson et al., 2012) manufactured from the bacterial fermentation of dietary fiber and have been associated in promoting gut barrier integrity, increase colon-lining cell proliferation, and regulate host immune system and gene expression (41). Campbell et al (42). showed that exercise could be used as a medium to prevent diet-induced obesity (with high-fat diets). It produces a unique microbial composition independent of the dietary protocol in lean mice (42).

Moreover, they also noted that exercised mice revealed Faecalibacterium prausnitzii, which is associated with producing butyrate and may protect the digestive tract. Furthermore, a cross-sectional study performed by Clarke et al. (43) noted that gut microbes of professional rugby players had a greater alpha diversity; additionally, a higher relative abundance of forty different bacterial taxa than their sedentary controls was observed. Recently, Motiani et al. (2019) (44) conducted a randomized controlled trial on twenty-six sedentary middle-age insulin-resistant participants. They observed that exercise training for two weeks (3times per week) modulated gut-microbiota profile of the insulin-resistant participants with a reduction in endotoxemia by the decrement in intestinal inflammatory marker was noted; additionally, there was also a reduction in the bacteria associated with obesity(Bacteroidetes), immune response (Clostridium genus), inflammation (Blautia genus) and an increment in the bacteria associated with protection from obesity (Bacteroidetes) was detected (44). Furthermore, Woods et al. (45) discovered forced treadmill exercise training in mice model of colitis exacerbated the condition in contrast to voluntary wheel training, suggesting the stress from involuntary exercise training might reduce the benefits. Collectively these findings propose that low, moderate, and voluntary exercise has positive effects on microbiota, but longer duration or forced higher intensity training may be subjected to inflammatory changes in the gut microbiome (45).

Mounting research establishes the connection between the gut microbiome and brain and how gut microbes and gut microbiome-derived metabolites are responsible for behavioral symptoms1-20. Exercise is associated with increasing butyrate formation in the gut, which supports the development of new neurons and synapses, boosts brain serotonin levels, and regulates the activation of specialized immune microglial cells in the brain (41). In mice models, Kang et al. 46 observed that an hour of daily wheel running increased the production butyrate production by gut microbe Lachnospiraceae, which reduces anxiety- like behavior in mice (46).

Furthermore, Skeletal muscle PGC-1α1 initiated by exercise training has been associated with easing depressive symptoms via the kynurenine pathway, activated in the gut (47). A sedentary lifestyle can lead to chronic low-grade inflammation leading to the activation of the immune system in the skeletal muscle region47. Schittlar et al. (48) concluded from a mouse model study that endurance exercise increased skeletal muscle kynurenine aminotransferase (KAT) expression, which shifts KYN metabolism away from the neurotoxic kynurenine to the production of neuroprotective, kynurenic acid (KYNA) (48).

In a study conducted by Itoh et al. (49) on human subjects who exercised and those who did not, blood levels of KYN rose in physically active participants after more than one hour of aerobic training. They could run long distances in a shorter time and showed vigor (behavior levels). KYN levels in serum either lowered or did not change in the sedentary participants who could not run fast and did not exhibit lower vigor. Serotonin is a primary hormone involved in mood control, and lower levels have been linked to depressive symptoms (49). Several interventions have demonstrated that enhanced serotonin levels have been attributed to yoga and yogic techniques such as breathwork and meditation (50). Breathing and meditation

activities were found to suppress the dangerous protein complex arsonist (NF-kB), responsible for causing inflammation in the immune system and the GI tract, as per a nine-week study at Massachusetts General Hospital (51).

IV. FUTURE RESEARCH ASPECTS: SPORTS PERFORMANCE AND GUT MICROBIOME

With the increasing research in gut-microbiome and its connections. Recently gut microbes are being studied to enhance athletic health. For athletes, lactate acidosis is the final byproduct of energy use in muscle cells, increasing muscle acidity and interfering with muscle function (52). The lactate then moves out of the muscle cells into the blood and travels to multiple organs, including the liver, where it can turn back into glycogen to support further muscle energy demand and make ATP (52). The latest research study using both mice and human models led by Scheiman et al. (53) presents compelling data suggesting that the gut microbes may modulate lactate homeostasis in high-intensity endurance athletic performance. When compared to sedentary controls, bacterial species (Veillonela) that specialize in breaking down lactate were found to be overrepresented in the gut microbiomes of Boston marathon runners pre- and post-race (53). The researchers showed that these gut microbes convert lactate into propionate, a short-chain fatty acid (SCFA). Propionate is consumed in the colon and aids in glucose production in the liver. While the circulating lactate in the blood can cross into the gut lumen (the passage space through the gut), the researchers observed that its levels did not decrease with Veillonella colonization (53). This study is promising; however, such inferences are still in their infancy as the data presented in the study does not support the theory that probiotic treatment consisting of Veillonella enhances athletic performance; this combination probiotic treatment was tested relative to a probiotic containing Lactobacillus bulgaricus, which is not associated in degradation of lactate (54).

Additionally, lactate in the gut can affect performance, mainly when it gets transported into the systemic circulation; in contrast, lactate clearance can be beneficial (54). This study exhibits promising results for improving athletic performance. However, certain unresolved conjectures increase the need for future multiple longitudinal training studies, using several variables such as volume, intensity, and frequency of the exercise program. The association between exercise, gut bacteria, and mood disorders is still in its early stages. To better understand the correlation between the gut and mental illnesses, future studies with longitudinal randomized controlled human trials is needed.

V. PUBLIC HEALTH IMPLICATIONS

The increasing recognition of the gut microbiome's role in human health has profound implications for public health and epidemiology, particularly in the prevention and management of chronic diseases. The research presented in this paper, highlights the critical link between the gut microbiome, physical activity, and overall health, positioning exercise as a key factor in public health interventions. The gut microbiota, composed of trillions of microbial cells, plays a fundamental role in immune function, metabolism, and neurological processes (55). Disruptions in microbial composition, known as gut dysbiosis, have been strongly correlated with non-communicable diseases (NCDs) such as obesity, type 2 diabetes, cardiovascular disease, inflammatory bowel disease (IBD), and neurodegenerative conditions like Alzheimer's and Parkinson's (56, 57). Given that these diseases account for most of the global morbidity and mortality, public health efforts must increasingly focus on microbiome-centered strategies, particularly lifestyle modifications, to prevent disease onset and progression.

The gut-brain axis, a bidirectional communication network linking the gastrointestinal tract and the central nervous system, further underscores the relevance of gut health in epidemiology, particularly in mental health disorders (58). Depression and anxiety, which contribute significantly to the global burden of disease, have been linked to alterations in gut microbiota composition and immune-inflammatory responses (59). The paper highlights the role of microbial metabolites, such as short-chain fatty acids (SCFAs) and neurotransmitter precursors, in regulating mood and behavior (60). Disruptions in gut microbial balance can lead to increased inflammation, immune activation, and changes in neurochemical signaling, all of which are implicated in mental health disorders (61). These insights emphasize the need for epidemiological research that examines the gut microbiome as a key determinant of mental health outcomes. Traditional psychiatric approaches focusing solely on brain-centered interventions may benefit from incorporating gut microbiome research, leading to more holistic mental health strategies (62).

Exercise has emerged as a potent, cost-effective, and non-pharmacological intervention capable of modifying the gut microbiome, thereby influencing both physical and mental health (63). The research presented in the paper demonstrates that regular physical activity increases beneficial gut bacteria associated with improved metabolic

function, reduced inflammation, and enhanced neuroprotection (64). The findings suggest that individuals who engage in moderate, voluntary exercise have a more diverse and resilient gut microbiome, which in turn supports immune function and reduces the risk of chronic disease (65). Epidemiological studies have shown that populations with higher levels of physical activity have lower prevalence rates of metabolic disorders, gastrointestinal diseases, and mood disorders, further reinforcing the role of exercise in disease prevention (66). Given the high burden of lifestyle-associated diseases, public health policies should prioritize exercise promotion as a microbiome-centered intervention.

Furthermore, the connection between gut health and immune regulation is of critical importance in epidemiology, particularly in the context of inflammation-related diseases and autoimmune conditions. The research emphasizes that gut microbes regulate immune responses by influencing the production of cytokines, which are key mediators of inflammation (67). Chronic low-grade inflammation is a common pathway linking gut dysbiosis to conditions such as obesity, cardiovascular disease, and depression (68). Public health initiatives must recognize the gut microbiome's role in modulating inflammation and explore interventions that promote microbial balance through lifestyle modifications, including diet, exercise, and stress reduction (69). Surveillance of gut microbial markers in population studies could provide new insights into disease risk prediction and early intervention strategies.

Epidemiological trends also reveal a growing prevalence of conditions associated with poor gut health, exacerbated by modern sedentary lifestyles and processed food consumption (70). This paper discusses how exercise not only modulates gut microbiota but also enhances intestinal barrier function, reducing the risk of metabolic endotoxemia and systemic inflammation (71). This finding is particularly relevant to public health efforts aimed at reducing the impact of lifestyle-related diseases. Future research should focus on longitudinal epidemiological studies examining how variations in gut microbiota contribute to disease progression and how exercise-based interventions can be effectively implemented at a population level. Additionally, the emerging field of microbiome research in sports performance highlights another potential avenue for public health applications. This paper also references studies showing that certain gut bacteria may enhance athletic endurance by metabolizing lactate, a byproduct of exercise, into beneficial metabolites (72). While this area requires further research, the implications for athletic training, rehabilitation, and general health promotion are significant. If specific microbial strains can be linked to enhanced exercise performance and recovery, they could be incorporated into public health recommendations for maintaining an active lifestyle across different age groups and populations (73).

VI. CONCLUSION

Over the past two decades, research has increasingly highlighted the profound connection between exercise, gut microbiome composition, and overall health. Accumulating evidence supports the notion that regular physical activity independently modulates gut microbiota, offering significant mental and physical health benefits. A well-balanced microbiome can reduce the risks of gastrointestinal disorders, cardiovascular diseases, obesity-related comorbidities, and neurological conditions by regulating inflammation and enhancing metabolic function. The gut-brain axis serves as a crucial pathway in these interactions, underscoring the broader implications of gut health in mental well-being and disease prevention.

Despite mounting data on the gut-exercise relationship, further research is needed to establish stronger causal inferences and optimize exercise interventions for public health. From an epidemiological perspective, understanding how exercise influences microbial diversity, immune responses, and disease progression is vital for developing preventive health strategies. Public health policies should integrate microbiome research into exercise promotion programs, mental health initiatives, and chronic disease prevention efforts. Given the rising prevalence of lifestyle-associated diseases, large-scale epidemiological studies on the gut microbiota's role in health outcomes are essential. By shifting toward microbiome-informed public health strategies, we can develop more effective, holistic interventions that address the root causes of many modern diseases.

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