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# Gut Feelings: A Literature Review on The Gut-Brain Axis and its Potential Influence on Mood

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# Gut Feelings: A Literature Review on The Gut-Brain Axis and its Potential Influence on Mood

by

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**Abstract**

In recent decades, research on the gut-brain axis has evolved due to an increasing interest in the connection between gut health and mental health. The gut-brain axis presents a new frontier of health for both medical professionals and psychologists as there is expanding evidence illustrating the comorbidity of gut disorders and mood disorders. Due to the complex nature of studying the gut-brain axis and the myriad of influences on mood disorders such as depression, research has yet to find significant results definitively tying the two together. Nonetheless, the current body of literature on the topic provides a promising outlook on mitigating depressive symptoms through psychobiotic intervention and dietary changes. This literature review seeks to illuminate the connection between gut health and mental health through an analysis of current murine model research and randomized clinical trials that illustrate the potential psychobiotic strategies for reducing depressive behaviors, emphasizing them within the context of the gut-brain axis. Additionally, applying a public health lens in this review will further elucidate the intersection between gut health and population-level health strategies.

***Keywords:*** *gut-brain axis, gut health, mental health, depression, psychobiotics, public health*

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## Introduction

In recent decades, the gut-brain connection has become a focal point in comprehensive human health and understanding how human bodies function and communicate internally. This connection, also known as the gut-brain axis, has gained popularity in both the medical and psychological fields as more research is revealing how the axis influences physical and mental health. The gut-brain axis is a bidirectional communication network, spanning across a pathway in the enteric nervous system and central nervous system. Scientists and researchers are finding that this network extends beyond basic bodily functions such as digestion and immune response, and a new understanding of mental health is being established through a greater comprehension of this pathway in the body.

In this literature review, I will be discussing the burgeoning research on the gut-brain axis and the potential links to Major Depressive Disorder (MDD). There will be discussions on the structure of the gut microbiome, why it is called the "second brain", and the role of diet and potential intervention for depression via psychobiotic treatment. Additionally, I will be expanding on the gut-brain axis analysis through a public health lens, and how the communities we live in may influence the composition of our gut microbiomes.

It has been established that some types of imbalances in the gastrointestinal tract can result in inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn's disease, irritable bowel syndrome (IBS), and other gastrointestinal illnesses (Bull & Plummer, 2014). With continued research on the gut-brain axis, we are beginning to understand that these gut illnesses may also have psychosomatic causes and that the gut impacts our mental wellbeing in a more profound way than traditional Western medical science initially thought. The intricate

systems within the gut-brain axis provide a look into how gut health influences mood, cognition, and overall mental health.

Conversely, the brain influences the gastrointestinal tract, from digestion to immune system functioning. New research continues to unravel the intricate mechanisms of the gut-brain connection within our bodies, however conclusive studies measuring the direct impact are limited due to the heterogeneous nature of mood disorders and the myriad of external influences on patients experiencing them. Regardless, the gut-brain axis has become a new concept within the scope of both physical and mental health, propelled by a fast-growing body of literature on treating mood disorders through the lens of gut microbiome mechanisms.

While examining these mechanisms, it is helpful to understand the historical perspectives of medical studies and treatment approaches. In traditional Western medicine, the "machine model" of the human body rules how doctors treat patients. This model views the body as a machine with a fixed number of independent parts. Oftentimes this way of treatment does not investigate the etiological cause of a disease but rather focuses on mitigating pain in the area with centralized treatment. An example of this is when a doctor prescribes medications for IBS symptoms, rather than working collaboratively and holistically with the patient to find the root of the disorder. This method of treatment disregards the interconnectedness of the body's various systems, such as how the nervous, immune, and endocrine systems all interact with each other. Viewing the body as a mechanical machine is a disservice to patients suffering from disorders that may have a variety of influences and centralized temporary fixes limit patients from fully healing.

An alternative approach to the machine model is outlined by Dr. Emeran Mayer, a world-renowned gastroenterologist and neuroscientist, and the author of *The Mind-Gut Connection:*

*How the Hidden Conversation Within Our Bodies Impacts Your Mood, Our Choices, and Our Overall Health.* In his book, Mayer advocates for a paradigm shift within the treatment of gastroenterology disorders. Mayer argues for the machine model to be discarded by health professionals in favor of the more nuanced "supercomputer" model. According to Mayer, the mechanisms within our bodies are not independent from each other, rather they collectively regulate vital processes such as digestion, metabolism, immune system, and neurotransmitter modulation. Embracing Mayer's proposed supercomputer model allows medical practices to foster a holistic approach to patient care and garner a deeper understanding of the underlying etiological factors contributing to various disorders and diseases. The bidirectional communication between the gut and brain plays into the supercomputer model as each part works together to influence the overall functioning and health of the body.

## Structure of the Gut

An imbalance of gut microbiota often correlates with an imbalance of neurotransmitters in the brain, and vice versa (Mitrea, et al., 2022). The trillions of microorganisms residing in the gastrointestinal tract, collectively known as the microbiome, transmit signals to the brain and influence our emotional state more than we may think (Mayer, 2016). Examining the structure of the gut microbiome and its extensive components gives insight into how bidirectional communication works and allows for more understanding of its role in behavior and mood.

According to The Human Microbiome Project, "The microbiome is defined as the collective genomes of the microbes (composed of bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body" (Yang, 2012). The terms "microbiome" and "microbiota" are sometimes used interchangeably, however, there are subtle differences between

the two. The *microbiome* refers to the collection of microorganisms in the environment, whereas *microbiota* refers to the specific microorganisms (or microbiota) that are found in an environment. (Ursell et al., 2012). This paper will focus on the general microbiome, as defined by The Human Microbiome Project.

In a cohort study conducted by the Human Microbiome Project with a sample size of 300 individuals, it was determined that the human gut microbiome comprises more than 8 million unique genes. According to Ursell et. al., the diversity among the microbiome of individuals is immense compared to genomic variation. About 99.9 percent of human genetic makeup is identical to one another in terms of the host genome, however, the bacterial species can be 80-90% different from one another in the microbiome of the hand or gut (Ursell et al., 2012). This biodiversity indicates that the collective human microbiome could potentially impart genetic influence on each individual several hundred times greater than their entire genome. The research indicates that the various bacteria, viruses, and other microbes living in and on humans can have a significant impact on genetic traits and how bodies function, possibly several hundred times more than inherited genetic information (Mayer, 2016).

Every person possesses a distinct microbiome in their gastrointestinal tract, demonstrating the immense diversity among individuals. Distinct microbial populations have been discovered on the human body with the help of new technologies. Scientists now know that there are microbial communities present on various parts of our body, including the skin, face, eyelids, nostrils, mouth, lips, teeth, extending to the tips of our fingers. The largest concentration of microbes in the human body is found in the large intestine. In fact, the 100 trillion microbes residing in the human gut is about the same number of human cells in the body and it is

estimated that the totality of all the microbes in the gastrointestinal tract weighs between two and six pounds (Mayer, 2016).

This ecosystem within the human body plays a crucial role in maintaining health and influences various physiological processes such as immune system regulation and modulating the endocrine system. The largest number of immune cells in the human body are found in the gut, outnumbering immune cells found in blood and bone marrow (Mayer, 2016). These immune cells are primarily found in small groupings around the small intestine and are known as Peyer's Patches. These pockets of immune cells constantly monitor the gut environment for potentially harmful pathogens that could contribute to inflammation or imbalance of the microbiome, which can lead to diseases or disorders that affect the rest of the body.

Gut-based immune cells are shielded by a minuscule layer of cells, forming a protective barrier between them and the interior of the gut. Among them are cells called dendritic cells, which inform the immune system of invasive pathogens by performing a kind of immune surveillance. They do this by extending through the gut layer and interacting with gut microbes to discern potential harmful pathogens and promote tolerance to harmless environmental antigens (Liu, 2016). This happens via signaling molecules called cytokines, which are small proteins that coordinate immune responses and regulate inflammation of the gut microbiome. As cytokines are released from dendritic cells and cross the gut lining, they enter the systemic circulation where they are messengers and eventually reach the brain (Mayer, 2016).

The lining of the gut is also coated in endocrine cells, which contribute to the regulation of hormonal responses throughout the body. Additionally, endocrine cells in the gut play crucial roles in signaling our nervous system. The hormones released in the gut act as powerful modulators for the digestive and metabolic processes which, in turn, impact our stress response.

This interconnectedness highlights the importance of considering the endocrine system's impact on the gut-brain axis. According to Mayer, the endocrine system establishes a close relationship with the gastrointestinal system through enteroendocrine cells. Enteroendocrine cells are specialized cells that produce most of the body's serotonin and gut hormones which impart appetite level signaling to the brain.

It is well established that a majority of enteroendocrine cells mainly regulate appetite and food intake, however, new research studies now suggest that gut hormones are closely related to other essential physiological processes such as balancing inflammation. The precise pathways in which hormones communicate with the gut microbiota are still being deciphered. However, there is growing evidence to suggest that chronic inflammation of the gut can be linked to brain disorders such as anxiety and depression (Bastiaanssen et al., 2020). By acknowledging this potential link, scientists can begin to explain the bidirectional communication between the brain and gut and how it impacts our mood (Sun, Li, & Nie, 2020).

The gut-brain axis interacts with all the organs in the gastrointestinal tract, although most research within this context focuses on the large intestine as it hosts the largest microbial population in the body and facilitates the bidirectional communication of the gut and brain. The neuroactive substances secreted by the bacteria in the large intestine, such as neurotransmitters and short-chain fatty acids or amino acids, may influence our behavior and emotions (O'Riordan et al, 2022). Such neurotransmitters as norepinephrine (NE), epinephrine (E), dopamine (DA), and serotonin can regulate not only physiological functions such as blood flow, gut motility, nutrient absorption, and immune system defense, but they can also modulate emotional response (Mittal et al., 2017). More specifically, this emphasis on research of the large intestine within the gut-brain axis framework stems from its significant role in synthesizing and degrading these

neurotransmitters that are sent to the brain via the vagus nerve pathway and enteric nervous system (ENS) and central nervous system (CNS).

The primary route of communication between the ENS and CNS is through the vagus nerve. It is an essential component of the gut-brain axis and works to convey information from our gut to our mind and vice versa (Bonaz et al., 2018). It is a cranial nerve that extends from the brainstem to the abdomen and is composed of 80% afferent (sensory) fibers and 20% efferent (motor). Afferent fibers provide sensory feedback, such as taste, and visceral and somatic sensations from the gut to the brain. Simultaneously, efferent fibers carry signals from the brain to the gut that work to regulate functions in the gastrointestinal tract such as smooth muscle contractions, secretion of digestive enzymes, and immune responses within the microbiome (Han et al., 2022). The fibers within the vagus nerve serve as a signaling bridge, facilitating communication between the CNS and various physiological systems.

The enteric nervous system within the gut is sometimes referred to as the "second brain" because it contains a complex network of neurons and neurotransmitters that can operate somewhat autonomously of the brain. The ENS works as an independent nervous system that manages digestive processes without conscious help from the brain. The bidirectional correspondence between the CNS and ENS is essential for maintaining the balance of mental health and physical wellbeing. Referring to the role of our “second brain” is critical when it comes to understanding the underlying reasons of our emotional responses and, consequently, our overall mental and physical health.

The physiological mechanisms of the microbiome have been recognized in the field of medicine for a long time. Research on how the microbiome impacts the mechanisms in the CNS and ENS has provided valuable insights into the regulating physiological processes within the

gut-brain axis. For example, these complex systems send information about satiety, immune system functioning, and digestion. The physiological interconnectedness of the CNS and ENS highlights the importance of these systems within the human body. These networks carry out functions every second without us consciously asking our bodies to do so. It is only natural to continue research on how these functions impact our mind and mood, given that current studies are limited. Studies done on animals have highlighted the influence of the gut-brain axis, however, they are simplistic in comparison to the human body and brain.

## Neurological Signaling of the Gut

In recent decades the expansion of research into neurological signaling within the gut microbiome is showcasing its potential impact on cognitive functioning and mental wellbeing. Beyond its traditional association with digestion, the gut microbiome is now recognized as a potential key player in modulating neurological signals to the brain, which may implicate the regulation of stress response and overall mental health. Major depressive disorder affects roughly 21 million adults (8.4% of the population) in the United States, making it one of the most prevalent mental illnesses to affect adults (NSDUH, 2022) and a pressing issue to address within the context of the gut-brain axis.

Perhaps the most compelling aspect of the gut-brain axis is the creation of serotonin and dopamine in the gut microbiome. In fact, it is estimated that more than 90% of serotonin and 50% of dopamine is created in the gut (Mayer, 2016). Serotonin's role in the overall functioning of the body includes supporting digestion, regulating sleep, modulating cognition and memory function, pain sensitivity, and mood stabilization (Myers, 2020). Serotonin is synthesized by endocrine cells within the gastrointestinal tract, however, the metabolization of gut-derived

serotonin remains unclear (Yano et al., 2015). Dopamine works similarly in that it aids in digestion by regulating mucosal blood flow, motility, and gastric secretion (Chen, Xu, & Chen, 2021).

Knowledge of common biomarkers of depression is also useful in understanding the gut-brain axis and its connection to depressive symptoms. Elevated levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6), interleukin-8 (IL-8), and c-reactive protein (CRP) all provide researchers with a baseline of what to look at when defining the composition of the gut microbiome in depressed patients. Additionally, biomarkers of stress and depression are lower levels of serotonin and dopamine, and elevated cortisol levels (Gururajan, Clarke, Dinan, & Cryan, 2016). These biomarkers further suggest that depression is correlated to inflammation of the gut and brain, stress, and immune dysfunction (Sandhu et al., 2017). Due to these biomarkers, depression can be thought of as an inflammatory disease in addition to a mood disorder.

Many people know serotonin as a neurotransmitter of the brain. As scientists and researchers have uncovered more understanding of the gut-brain axis, the role of serotonin within the gut microbiome has become so apparent that it is no longer only associated with just the brain. Due to the gut having large storages of serotonin that are closely located to the vagal nerve pathway, it is predicted that a constant stream of low-level serotonin-related gut signals are sent to the brain's emotional centers. Even if we are not consciously aware of these signals, they may have a profound impact on the background of our emotional state (Mayer, pg. 64, 2016). Serotonin levels help with the regulation of mood, meaning that suboptimal levels in the gut may not be enough to properly regulate the brain's emotional response, leading to a higher risk of

depression. Additionally, suboptimal levels of dopamine in the gut can lead to constipation and increased risk of bowel dysbiosis.

Due to the bidirectional pathway of the brain and gut and the creation of serotonin within this pathway, scientists have delved into research that expands on the neurological component of the gut-brain axis. Conclusive evidence in human studies is yet to be found on the direct impact of gut microbes and our mind due to the myriad of influences on mental health. However, compelling studies on mice have shown promising evidence that microbiota can influence mood and behavior. A 2011 study done on mice by Premysl Bercik and his group at McMaster University found that the subjects with diverse intestinal microbiota exhibited stability in mood and stress response, whereas those with anxious and/or depressive behaviors had less diversity and their microbiomes became unstable over time. This study further corroborates the proposed idea that alterations in the gut microbiome may contribute to depressive behaviors.

Murine model studies about the gut-brain axis have proved to be advantageous to researchers as they can be highly controlled. In using rodents as study subjects, the environment (humidity, air flow, temperature), diet, and genetics can all be controlled, unlike human studies. Additionally, the lifespan of mice being 2-3 years long allows researchers to study subjects from the beginning to the end of their lives, giving crucial information about how the gut microbiome evolves (Bastiaanssen et al., 2020). Germ-free mice are born in sterile environments via cesarean section and are essential for microbiome research. Due to the germ-free environment, the mice can be inoculated with specifically chosen microorganisms to distinguish between the effects of varying genomes in the gut microbiome and how they interact with the vagus nerve. Researchers can also see how mice act behaviorally if they are deficient in immune or inflammation-related

genes within the microbiome (Wu, 2011). This is helpful for researchers as the sterility of germ-free mice can give insight into isolated microorganisms that contribute to gut imbalances.

However, there are limitations to animal studies. One of the most prominent limitations is the different anatomical structures in mice compared to humans. Despite the advanced knowledge of murine genetics, and the similarities of their anatomy and physiology to humans, they cannot be completely translated over. This is due in part to the fact that mice do not have as extensive gastrointestinal tracts and are restricted in the distribution of microorganisms in their gut microbiomes. Moreover, it can be argued that the highly controlled environments of germ-free mice can be construed as a disadvantage to research on the gut microbiome as these conditions cannot be translated into human conditions (Bastiaanssen et al., 2020). These differences are enough to inhibit conclusive evidence that human microbiomes are affected just the same as murine microbiomes (Nguyen et al., 2015). Despite that, the research is still a gateway to understanding certain gut microorganisms and their impact on neurotransmitter modulation of a host microbiome.

## Psychobiotic Interventions

As stated previously, the gut contains the largest number of neurons in the body, closely following the brain. Due to the large number of neurotransmitters in the gut, medical researchers theorize that an imbalanced microbiome from bowel diseases or disorders may have psychosomatic symptoms like Major Depressive Disorder (MDD). The role of the microbiota in the gut was reviewed within the context of MDD in an article by Thomas F.S. Bastiaanssen and his group at Harvard Psychiatry. In the review, the authors introduce the potential of developing

therapeutic strategies for treating MDD through microbiome alteration and consider the alterations of the gut microbiome as a potential factor in patients experiencing MDD.

A study done by Zheng et al. in 2016 at the National Basic Research Program of China, involved both mice and rats who received fecal microbiota transplantation from depressed humans. The studies found that the rodents exhibited higher levels of inflammation and increased anxious behaviors. However, in a swim test, the mice displayed lower levels of immobility (associated with depressive behaviors) whereas the rat study found no significant difference. While murine model research continues, it is important to note that despite the knowledge that the depressed microbiome differs from the general population, it is not enough to establish a causative relationship between alterations in the microbiome and the development of MDD.

Alterations in the microbiome may affect the onset of MDD through differing amounts of bacteria produced in the gut. Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al., 2014, p. 506). An example of this alteration is a decrease of Bifidobacterium and Lactobacillus genera. Both Bifidobacterium and Lactobacillus are considered probiotic bacteria and are commonly referred to in discussions regarding a healthy, diverse gut microbiome. Bifidobacterium produces short-chain fatty acids and lactobacillus ferment refined sugars which ultimately generate lactic acids (Vlasova et al., 2016).

It is not uncommon for doctors to prescribe patients with increased probiotic intake for gut-related disorders, however as knowledge about the gut-brain axis unfolds, they are now being seen as a potential strategy for treatment of mood disorders due to their influence on the CNS, ENS, cognition and behavior (Diana, Stanton & Cryan, 2013). Using these two strains of probiotic bacteria has led to a new classification of probiotics referred to as "psychobiotics."

Alleviation of MDD through an increased intake of psychobiotics may be attributed to the probiotics anti-inflammatory actions within the gut and their ability to produce and deliver neuroactive substances such as serotonin (Dinan, Stanton & Cryan, 2013).

Researchers emphasize that the anti-inflammatory properties of psychobiotics are worth looking into despite the uncertainty regarding the origin of chronic low-grade inflammation of the gut (Mörkl, et al., 2020). Using probiotics to modify the gut-brain axis remains a novel strategy, and a review done by Sabrina Mörkl and her group at APC Microbiome Ireland and University College Cork Ireland discusses this potential. Patients with depression show significant differences in microbiome composition, with depleted levels of Bifidobacterium and Lactobacillus genera. The Mörkl review points to a study done by Kazemi et al. (2019) which included 110 participants, with 36 receiving a probiotic supplement, 38 receiving a placebo, and 35 receiving a prebiotic. Participants partook in a questionnaire by the Beck Depression Inventory (BDI) to quantify their depressive symptoms. At the end of the eight-week study, the probiotic group showed a significant reduction of BDI depressive symptoms when compared to the placebo and prebiotic groups.

Interestingly, patients who also experienced anxiety symptoms had no significant change, pointing to evidence that anxious behaviors do not respond in the same way as MDD behaviors to psychobiotic mitigation. Elevated levels of stress cortisol may be altered by several probiotics, however, studies remain inconsistent and not sufficient enough to draw conclusions (Mörkl, et al, 2020). Similar to the Kazemi study, a randomized controlled trial (RCT) done by Eskandarzadeh et al. (2019) studied the effect of psychobiotics on anxiety disorders. For eight weeks, 24 participants were given multi-strain probiotics containing Bifidobacterium and Lactobacillus and 24 participants were given placebos. Both groups were given the probiotic and placebo capsules

as an add-on therapy to their selective serotonin reuptake inhibitor (SSRI) therapy with sertraline. The study used the Beck Anxiety Inventory (BAI), State Trait Anxiety Inventory (STAI), and Hamilton Rating Scale for Anxiety (HAM-A) to quantify anxiety symptoms and record quality of life before and after the probiotic intervention.

At the end of the eight weeks, participants who took a multi-probiotic along with an SSRI (PS) had decreased anxiety levels according to their HAM-A rating in comparison to those who took sertraline only (S). Although levels of anxiety were lower in the PS group, it was not significantly different from that of the S group. Furthermore, despite the lower HAM-A score of the PS group, there was no statistically significant difference in comparison to the S group in regard to the BAI score or STAI score. As for QOL, there was no significant difference between the two groups, with minimal change to the initial reported QOL. Eskandarzadeh et al. (2019) concluded that the probiotics and sertraline combination was superior to treatment of sertraline alone, but the minimal difference in QOL leaves more to be considered in treating patients with anxiety.

Drawing from the study done by Kazemi, there is some potential for treating MDD via novel psychobiotic treatments. This may have to do with the fact that the gut microbiome in depressed patients shows a lack of diverse microorganisms (specifically Bifidobacterium and Lactobacillus genera). Conversely, the treatment of generalized anxiety disorder with psychobiotic intervention requires more research as results from the Eskandarzadeh study showed. Probiotic supplementation in patients may help rebalance the gut microbiome and help with the severity of mood disorders, however, current research on anxiety shows that this supplementation works best when supplemented with an SSRI. Moreover, the knowledge garnered from animal studies (ie Zheng et al., 2016 study) provides a promising model for future

research to further understand the influence of microorganisms on hosts and the potential impacts of alterations on the gut-brain axis.

In The Mind-Gut Connection, Mayer asserts that inflammation of the gut can lead to inflammation of the brain. He recalls the stories of patients he has treated who have come in for gastrointestinal disorders and upsets. Oftentimes, these patients also disclosed that they experienced bouts of anxiety or depression when their gut felt most imbalanced. Mayer proposes treatments for his patients through wellbeing practices, stress reduction techniques, and diet changes in addition to medications formulated to aid in gastrointestinal upset. This type of treatment illustrates that interventions for disorders of the gut-brain axis must consider a myriad of factors. A holistic view of the patient (i.e. supercomputer model) and treatment for them cannot come from one medication or change in their lifestyle. Medical specialists who treat patients suffering from inflammatory bowel disorders who have psychosomatic comorbidities must consider all the factors that contribute to disease.

## The Influence of Diet on the Gut

Diet represents a compelling facet of the gut-brain connection and the potential impacts of food on our microbiome composition, thus in turn impacting our mood. Recent literature shows “a strong influence of both diet and gut microbiota on emotional behavior and neurological processes, and because the gut microbiota is strongly affected by diet, these 2 factors are also intertwined” (Bear et al., 2020). Emerging studies that focus on the impact of dietary supplementation with foods rich in prebiotic fibers, such as fruits and vegetables show promising results in modulating the microbiome and gut-brain axis (Han & Xiao, 2020). While this knowledge does encourage more understanding of how specific foods impact gut health, the

isolated nature of it does not give much insight into the effects of the combined food groups humans consume. A whole dietary approach, in addition to adjunctive therapies, probiotic supplements, and quality of life improvements is needed in regard to the development of interventions for healing an imbalanced gut (Berding et al., 2021).

Gut microbes aid in digestion, metabolism, and absorption and transformation of undigested macronutrients. They work to extract the bioactive compounds in the food humans eat, meaning they are the drivers of effects on the microbiome composition (Bear et al., 2020). A diet containing a variety of anti-inflammatory foods rich in vitamins and minerals contributes to a balanced and thriving gut microbiome composition. Thus, the interaction between diet and mood is notable within the context of the gut-brain axis. Keeping in mind that depression is thought of as an inflammatory disease with psychosomatic causes (Sandhu et al., 2017), dieticians/nutritionists and psychologists recommend that patients experiencing depression consider improving their diet as a component of their treatment.

The etiology of depression is not yet fully established, however, its potential link to diet gives insight into how it behaves within the context of the gut-brain pathways and gut microbiome imbalances. Few studies have been conducted with conclusive results concerning the direct causality between depressed mood and gut imbalances, due to the many influences that coincide with the disorder. A 2018 systemic review sought to unravel the connection between diet and depression and identified that a high-quality diet regardless of type (ie Mediterranean or Paleo) with a higher intake of fish and vegetables was associated with a lower risk of depressive symptoms. Conversely, it was found that those following a lower-quality diet did not have a higher risk of depression incidence (Molendijk et al., 2018). This signifies that while a nutritious diet appears to be a promising intervention for MDD, more comprehensive research that

considers the multiple facets of MDD is crucial for a significant understanding and interventions of the disorder.

The mixed results and difficulties of honing in on a study model do not mean that there is not a clinically meaningful relationship between diet and depression. The Bear review notes that depression is primarily understood as a psychological illness, thus the influence of a diet-depression relation varies depending on an individual's psychological traits. This may include their coping strategies, personality traits, and thought patterns/mindset. Psychological variables such as these are difficult to quantify and adequately control in studies regarding nutrition. As a result, challenges in precisely quantifying psychological variables are compounded by the need to understand the bidirectional communication of the gut-brain axis. Overall, the research on the topic of how diet can specifically alter the gut microbiome and in turn, alter emotional state is still in the beginning stages. Many different dietary patterns have been shown to have a beneficial effect on mental wellbeing, however, it does show that individual components of diet may not have as large of an impact on mood in comparison to overall nutritional practices that include whole foods rather than ultra-processed foods.The microbiome is protected within the intestine by multilayered mucus structures that coat the intestinal surface. This allows for the majority of gut bacteria to be separated from the epithelial cells lining the intestine, and allows the intestine to maintain a balance between hosting a diverse microbiota and protecting its own cells against inflammatory microorganisms and disruptions that can be found in ultra-processed foods. (Yoo, et al., 2020).

A study done on mice illustrated that common emulsifiers (carboxymethylcellulose and polysorbate-80) used in processed foods contributed to alterations in the composition of the gut microbiome. It was observed that an increased intake of carboxymethylcellulose and

polysorbate-80 in mice caused low-grade inflammation of the intestinal surface in addition to metabolic syndrome and a higher risk of colitis. Additionally, this was associated with microbiota encroachment, altered microorganism species composition of the gut, and increased pro-inflammatory levels in subjects (Chassaing et al., 2015).

The Chassaing study exemplifies the detriments of a highly processed diet on the balance of the gut microbiome. Unfortunately, the standard American diet is marked by a high intake of processed fats, refined sugars, and a low intake of fiber-rich whole foods, particularly fruits and vegetables. Additionally, processed foods contain large amounts of emulsifiers that alter the diversity of healthy bacteria in the gut microbiome. It can be hypothesized that a standard American-style diet can lead to upsets and imbalances of the gut microbiome due to its lack of nutritious foods that promote the development of diverse microbiota within the gut.

## A Public Health Perspective

Understanding the gut microbiome at the population level presents an interesting lens to the conversation surrounding the gut-brain axis and its impact on mental health. As of 2024, there is not much literature on the connection between the microbiome and public health disparities. That being said, through a review of articles on the proportion of those affected by gastrointestinal disorders in conjunction with their quality of life (i.e. their environment, socioeconomic status, ease of access to healthcare, etc.), imbalances of the gut-brain axis can be considered a public health issue.

The microbiome should be an area of concern in the public health field as there is a "potentially shared nature of the human microbiome across communities and vertical and horizontal mechanisms for transferring microbiomes among humans." (O'Doherty, Virani, &

Wilcox, 2016). The human gut microbiome does not exist in isolation, it responds to the environment and is thus impacted by imbalances surrounding it. O'Doherty, Virani, & Wilcox consider this in their article titled, *The Human Microbiome and Public Health: Social and Ethical Considerations.* They elaborate on the communal ecosystem aspect of the gut microbiome and comment on how much the individual's microbiome is influenced by "environmental factors such as antibiotic use, diet, and the microbiomes of family and other community members." Additionally, they argue that "damage" to the human microbiome and the increasing amount of adverse health outcomes due to this may be attributed to standard societal practices. This reiterates why it is important to consider the standard American diet within the context of the gut-brain axis as it has become a societal dietary norm.

There is also a growing amount of literature suggesting that the composition of an individual's microbiome is affected by the individuals they come in contact with often. People of the same household have been shown to have similar microbiome composition. A study by Dill-McFarland et al. was done in 2019 that demonstrated similar microbiome composition of people who played on the same sports team. Ethical considerations of the microbiome should be discussed within the public health sphere, as most often a majority of research is done on individual subjects. In doing microbiome transplant studies such as the one done by Zheng et al. in 2016, it may be worth considering the possible influence of the host's surrounding community before and after the transplant.

A new horizon of public health intervention is being presented to us through the communal aspect of microbiome compositions and the influence individuals have on each other just by existing in the same space. The likely shared nature of the microbiome presents a potential new avenue for disease intervention via community strategies such as healthier diet

initiatives or encouragement of prebiotic and probiotic supplements. However, studies on this topic are very limited and there is an immense need for empirical research before any conclusive solutions of broad communal intervention can be determined.

Researchers at the Social and Behavioral Research Branch, National Human Genome Research Institute, speculate that the bidirectional interaction of the gut-brain axis may be affected by psychosocial indicators in addition to the health status of the individual. Because the microbiome plays a role in immune functioning, the microbiomes of individuals in communities may be influenced by changes in the immune functions of other individuals (Findley et al., 2016). The potential intersection between microbiome composition and psychosocial behaviors may warrant more research through a public health context, although it would be difficult to gather human subjects for it due to the myriad of differences and socially determined health influences in individuals. The social aspect of microbiome composition remains an understudied facet of the gut-brain axis and public health intersection. However, it represents a new scope of population health intervention and shows the potential of new findings in the way people interpret the health of their communities.

## Conclusion

The gut-brain axis is an ever-expanding avenue for a deeper understanding of our physical health and mental health. As it continues to evolve, research shows its connection to be more profound than anticipated and calls for more studies on how gut imbalances and mood disorders have the potential to be mitigated through integrative medicine practices. It has become a new pathway for both medical practitioners and psychologists to create holistic intervention strategies for their patients.

With the expansive knowledge of the gut-brain pathway via the enteric nervous system and central nervous system, the axis connection becomes more apparent and relevant to understanding the intersection of gut and brain health. Studies continue to highlight this physiological connection as depression is now understood to be an inflammatory disease, mirroring the inflammatory nature of gut inflammation. The mechanisms shown through murine model research further illustrate the potential for psychobiotic intervention through the effects of increased probiotic intake to encourage microbiota diversity, and in turn, reduce depressive symptoms. Using a diet-oriented lens for interventions on inflammatory diseases shows a promising new understanding of how people can improve their gut health and mental health. Research shows that eating a healthy diet of foods rich in fiber, prebiotics, and probiotics reduces inflammation of the gut and may reduce depressive symptoms.

Considering this public health lens for the gut-brain axis brings a new approach to how the gut composition is impacted outside of the individual level. The gut microbiome of individuals has recently come into focus in the Western medical world, so research on a population level is not extensive. Nonetheless, the communities where people live, and the social influences in their environment may point to an interesting new realm of understanding and community interventions for gut and brain health. This emerging understanding not only paves the way for novel insights into communal wellbeing, but also holds promise for interventions of gut health and community health. As literature delves into this realm, the potential for deeper comprehension of the intersections of gut health, mental health, and community dynamics becomes increasingly apparent.

## References

Bastiaanssen, T. F. S., Cussotto, S., Claesson, M. J., Clarke, G., Dinan, T. G., & Cryan, J. F. (2020). Gutted! Unraveling the Role of the Microbiome in Major Depressive Disorder. Harvard review of psychiatry, 28(1), 26–39. https://doi.org/10.1097/HRP.0000000000000243

Bercik P, Denou E, Collins J, Jackson W, Lu J, Jury J, Deng Y, Blennerhassett P, Macri J, McCoy KD, Verdu EF, Collins SM. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology. 2011 Aug;141(2):599-609, 609.e1-3. doi: 10.1053/j.gastro.2011.04.052. Epub 2011 Apr 30. PMID: 21683077.

Berding, K., Vlčková, K., Marx, W., Schellekens, H., Stanton, C., Clarke, G., Jacka, F. N., Dinan, T. G., & Cryan, J. F. (2021). Diet and the Microbiota–Gut–Brain axis: sowing the seeds of good mental health. Advances in Nutrition, 12(4), 1239–1285. https://doi.org/10.1093/advances/nmaa181

Bonaz, B., Bazin, T., & Pellissier, S. (2018). The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Frontiers in neuroscience*, *12*, 49. https://doi.org/10.3389/fnins.2018.00049

Bull, M. J., & Plummer, N. T. (2014). Part 1: The Human Gut Microbiome in Health and Disease. Integrative medicine (Encinitas, Calif.), 13(6), 17–22.

Chen, Y., Xu, J., & Chen, Y. (2021). Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients*, *13*(6), 2099. https://doi.org/10.3390/nu13062099

Dinan TG, Stanton C, Cryan JF. Psychobiotics: a novel class of psychotropic. Biol Psychiatry. 2013 Nov 15;74(10):720-6. doi: 10.1016/j.biopsych.2013.05.001. Epub 2013 Jun 10. PMID: 23759244.

Eskandarzadeh, S., Effatpanah, M., Khosravi-Darani, K., Askari, R., Hosseini, A. F., Reisian, M., & Jazayeri, S. (2019). Efficacy of a multispecies probiotic as adjunctive therapy in generalized anxiety disorder: a double blind, randomized, placebo-controlled trial. Nutritional Neuroscience, 24(2), 102–108. https://doi.org/10.1080/1028415x.2019.1598669

Gururajan, A., Clarke, G., Dinan, T. G., & Cryan, J. F. (2016). Molecular biomarkers of depression. *Neuroscience & Biobehavioral Reviews*, *64*, 101–133. https://doi.org/10.1016/j.neubiorev.2016.02.011

Han, Y., & Xiao, H. (2020). Whole Food-Based Approaches to Modulating Gut Microbiota and Associated Diseases. Annual review of food science and technology, 11, 119–143. https://doi.org/10.1146/annurev-food-111519-014337

Han, Y., Wang, B., Gao, H., He, C., Hua, R., Liang, C., Zhang, S., Wang, Y., Xin, S., & Xu, J. (2022). Vagus Nerve and Underlying Impact on the Gut Microbiota-Brain Axis in Behavior and Neurodegenerative Diseases. Journal of inflammation research, 15, 6213–6230. https://doi.org/10.2147/JIR.S384949

Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., ... Sanders, M. E. (2014). Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology, 11(8), 506–514. https://doi.org/10.1038/nrgastro.2014.66

Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological out- comes in patients with major depressive disorder: a randomized clinical trial. Clinical Nutrition (Edinburgh, Scotland). 2019;38(2): 522–8. https://doi.org/10.1016/j.clnu.2018.04.010.

Liu, Y.-W., Liu, W.-H., Wu, C.-C., Juan, Y.-C., Wu, Y.-C., Tsai, H.-P., ... Tsai, Y.-C. (2016). Psychotropic effects of Lactobacillus plantarum PS128 in early life-stressed and naïve adult mice. Brain Research, 1631, 1–12. https://doi.org/10.1016/j.brainres.2015.11.018

Mayer, E. (2016). *The Mind-Gut Connection: How the hidden conversation within our bodies impacts our mood, our choices, and our overall health*. Harper Wave.

Mitrea, L., Nemeş, S. A., Szabo, K., Teleky, B. E., & Vodnar, D. C. (2022). Guts Imbalance Imbalances the Brain: A Review of Gut Microbiota Association With Neurological and Psychiatric Disorders. Frontiers in medicine, 9, 813204. https://doi.org/10.3389/fmed.2022.813204

Mittal, R., Debs, L. H., Patel, A. P., Nguyen, D., Patel, K., O'Connor, G., Grati, M., Mittal, J., Yan, D., Eshraghi, A. A., Deo, S. K., Daunert, S., & Liu, X. Z. (2017). Neurotransmitters: The Critical Modulators Regulating Gut-Brain Axis. Journal of cellular physiology, 232(9), 2359–2372. https://doi.org/10.1002/jcp.25518

Mörkl, S., Butler, M. I., Holl, A. K., Cryan, J. F., & Dinan, T. G. (2020). Probiotics and the Microbiota-Gut-Brain axis: Focus on psychiatry. Current Nutrition Reports, 9(3), 171–182. https://doi.org/10.1007/s13668-020-00313-5

Nguyen, T. L., Vieira-Silva, S., Liston, A., & Raes, J. (2015). How informative is the mouse for human gut microbiota research?. Disease models & mechanisms, 8(1), 1–16. https://doi.org/10.1242/dmm.017400

O'Riordan, K. J., Collins, M. K., Moloney, G. M., Knox, E. G., Aburto, M. R., Fülling, C., Morley, S. J., Clarke, G., Schellekens, H., & Cryan, J. F. (2022). Short chain fatty acids: Microbial metabolites for gut-brain axis signalling. Molecular and cellular endocrinology, 546, 111572. https://doi.org/10.1016/j.mce.2022.111572

Sandhu, K. V., Sherwin, E., Schellekens, H., Stanton, C., Dinan, T. G., & Cryan, J. F. (2017). Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry. Translational Research, 179, 223–244. https://doi.org/10.1016/j.trsl.2016.10.002

SEER Training Modules, General Structure of the Digestive System. U. S. National Institutes of Health, National Cancer Institute. 2023. https://training.seer.cancer.gov/anatomy/digestive/structure.html.

Sun, L. J., Li, J. N., & Nie, Y. Z. (2020). Gut hormones in microbiota-gut-brain cross-talk. *Chinese medical journal*, *133*(7), 826–833. https://doi.org/10.1097/CM9.0000000000000706

Ursell, L. K., Metcalf, J. L., Parfrey, L. W., & Knight, R. (2012). Defining the human microbiome. Nutrition reviews, 70 Suppl 1(Suppl 1), S38–S44. https://doi.org/10.1111/j.1753-4887.2012.00493.x

Vlasova, A. N., Kandasamy, S., Chattha, K. S., Rajashekara, G., & Saif, L. J. (2016). Comparison of probiotic lactobacilli and bifidobacteria effects, immune responses and rotavirus vaccines and infection in different host species. Veterinary immunology and immunopathology, 172, 72–84. https://doi.org/10.1016/j.vetimm.2016.01.003

Wu, J. (2011). Germ-Free Mice. NIH Intramural Research Project. https://irp.nih.gov/catalyst/19/4/germ-free-mice

Yang, J. (2012, July 16). The Human Microbiome Project: Extending the definition of what constitutes a human. National Human Genome Research Institute. https://www.genome.gov/27549400/the-human-microbiome-project-extending-the-definition-of-what-constitutes-a-human

Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., Nagler, C. R., Ismagilov, R. F., Mazmanian, S. K., & Hsiao, E. Y. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell, 161(2), 264–276. https://doi.org/10.1016/j.cell.2015.02.047

Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., Zeng, L., Chen, J., Fan, S., Du, X., Zhang, X., Yang, D., Yang, Y., Meng, H., Li, W., Melgiri, N. D., Licinio, J., Wei, H., & Xie, P. (2016). Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Molecular psychiatry, 21(6), 786–796. https://doi.org/10.1038/mp.2016.44