Short title: Gut microbiota and psychiatric disorders.

Full Title: Existing and future strategies to manipulate the gut microbiota with diet as a potential adjuvant treatment for psychiatric disorders.

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Abbreviations: BGM = brain-gut-microbiome, ASD = autism spectrum disorder, AD = Alzheimer's disease, MDD = major depressive disorder, Trp = tryptophan, BA = bile acid, CNS = central nervous system, RCT = randomized controlled trial, GI = gastrointestinal, SCFA = short chain fatty acid, ECC = enterochromaffin cell, IDO = indoleamine-2,3-dioxygenase, LPS = lipopolysaccharide, Microbe-associated molecular patterns = MAMPS, MCI = mild cognitive impairment, TNF-α = Tumor necrosis factor alpha, ADAS-Cog = The Alzheimer's Disease Assessment Scale-Cognitive subscale, HAM-D = The Hamilton Depression Rating Scale, MUC2 = mucin 2

ABSTRACT

Nutrition and diet quality play key roles in preventing and slowing cognitive decline and have been linked to multiple brain disorders. This review compiles available evidence from preclinical studies and clinical trials on the impact of nutrition and interventions regarding major psychiatric conditions and some neurological disorders. We emphasize the potential role of diet-related microbiome alterations in these effects and highlight commonalities between various brain disorders related to the microbiome. Despite numerous studies shedding light on these findings, there are still gaps in our understanding due to the limited availability of definitive human trial data firmly establishing a causal link between a specific diet and microbially mediated brain functions and symptoms. The positive impact of certain diets on the microbiome and cognitive function is frequently ascribed with the anti-inflammatory effects of certain microbial metabolites or a reduction of proinflammatory microbial products. We also critically review recent research on pro- and prebiotics and non-dietary interventions, particularly fecal microbial transplants. The recent focus on diet in relation to brain disorders could lead to improved treatment outcomes with combined dietary, pharmacological, and behavioral interventions.

Keywords: Brain-gut-microbiome (BGM) system/axis, Mediterranean diet, Nutritional Psychiatry, endotoxemia, dysbiosis, short-chain fatty acids, serotonin, tryptophan metabolites, dietary intervention, depression, cognitive decline, autism spectrum disorder.

INTRODUCTION

Psychiatric disorders have been perceived as diseases of the brain, with limited attention to the important role of diet and the gut microbiome in brain function. However, several epidemiological studies have suggested a correlation between nutritional intake and certain psychiatric disorders (1–4). Preclinical studies have demonstrated the influence of the gut microbiome on emotion-like behavior, and structural and biochemical brain measures. The potential role of major dietary components in modulating the brain through the microbiome has spurred investigations into the causal relationship between diet and the brain in the form of targeted dietary interventions and nutritional supplementation (5–7), as well as risk factors to guide the development of preventative strategies and better treatment approaches (8).

Evidence drawn from preclinical, cross-sectional, and epidemiological studies, and from microbiome science has enabled researchers to explore the connections between brain health, nutrition, and microbial function, encompassing the area of nutritional psychiatry. It has long been known that inadequate nutrient intake during early development can lead to impaired brain function and that sufficient quantities of dietary micro- and macronutrients are essential for optimal brain formation (9). Research thus far has predominantly focused on nutrients like amino acids, omega-3 fatty acids, and micronutrients, which are rapidly absorbed in the proximal small intestine. There is growing interest in large food molecules that surpass the capacity for complete digestion and are absorbed in the proximal gut. The absorption of these molecules heavily relies on the metabolic activity of the gut microbiota in the distal small intestine and colon. Microbial inflammatory, metabolic, and neuroactive metabolite production from dietary components represents a key mechanism whereby the gut microbiota impact the brain and consequently host health **(See Figure 1).**

Interventional and mechanistic studies provide evidence that diets rich in plant-based foods, fiber, polyphenols, and omega-3 fatty acids positively impact several aspects of health, including mental health. In this review, we delve into mechanisms involving diet-related gut microbial signaling and its impact on the brain. We explore bidirectional signaling within the BGM system and investigate how diet and microbial interventions affect psychiatric disorders like depression, autism spectrum disorder (ASD), and cognitive decline, including Alzheimer's disease (AD).

Despite promising animal model research, we highlight the need for more clinically relevant human studies. We also discuss integrative approaches encompassing dietary interventions, such as probiotics, prebiotics, and fecal microbiota transplantation (FMT).

The Brain-Gut-Microbiome System

In contrast to the traditional concept of linear interactions involving the central nervous system (CNS), the gut, individual microbes, and their metabolites (10), the interactions between these components involving multiple feedback loops is best described in systems biological terms as the BGM system**.**

Role of diet in influencing communication between the gut microbiome and the brain.

Three main pathways (neuronal, endocrine, and immunoregulatory) facilitate communication between the gut microbes and the brain (11). A less well studied communication pathway may be the transportation of microbiota-derived extracellular vesicles from the gut to the brain (12,13). In addition, the CNS can directly modulate the function/composition of the gut microbiota through the autonomic nervous system. Indirect pathways can facilitate this top-down modulation, such as: 1) luminal release of neurotransmitters, 2) permeability of the intestinal barrier and secretion of mucus, and 3) regional regulation of gastrointestinal (GI) transit and motility. Furthermore, norepinephrine, serotonin, and additional neurotransmitters are emitted from postsynaptic sympathetic terminals and can exert a direct influence on gene expression and function of the gut microbiota (14). As shown in Figure 1, the metabolic function of the gut microbial community is largely diet-dependent and likely plays a vital role in its influence on behavior via the BGM system (15).

The role of dietary tryptophan in gut to brain signaling

One of the best-characterized gut microbe and diet-dependent gut-to-brain signaling pathways is related to metabolism of the essential amino acid tryptophan (Trp), necessary to produce serotonin and other key molecules involved in neuroendocrine signaling and pathology. An important role of serotonin as a pathophysiological factor in certain psychiatric disorders is the widespread use of serotonin reuptake inhibitors in treating depression, and in the increased plasma serotonin levels in a subset of patients with ASD (16). Certain gut microbes modulate Trp into various metabolites,

such as kynurenine, tryptamine and indoles (17–19). Trp metabolites play a significant role in neuroendocrine and neuroimmune processes, as they can affect the CNS via the bloodstream or by activating vagal afferents **(See Figure 2)** (14)**.** By managing the serotonergic system, the gut microbiota can directly impact their environment (14). The functional implications of serotonin released into the gut lumen are not yet fully understood.

Lactobacilli generate hydrogen peroxide, a reactive oxygen species known to impede host kynurenine metabolism by suppressing the expressing the indoleamine-2,3-dioxygenase (IDO1) enzyme. In the GI tract, IDO1 participates in the conversion of Trp to kynurenine (20). In a rodent model of chronic variable stress, reduced *Lactobacillus* abundance led to decreased ability of hydrogen peroxide to inhibit IDO1, resulting in elevated kynurenine synthesis from Trp (21,22). In these studies, elevated brain kynurenine levels were associated with increased depression-like behavior, which was alleviated by administering *Lactobacillus* (23). Similar psychobiotic effects in humans have not been demonstrated.

While numerous indoles have been shown to benefit both intestinal and systemic homeostasis (24), preclinical investigations have demonstrated that specific indole metabolites are involved in depression-like behavior (25). Although gut microbes have limited involvement in the synthesis of serotonin and kynurenine from Trp, the production of indoles from Trp relies exclusively on specific gut microbes that harbor the enzyme tryptophanase, crucial for their synthesis via the indole pathway (26). The indole metabolite indoxyl sulfate is produced from microbiota-derived indols in the liver and may be involved in the development of various neurological conditions, such as ASD, AD, and depression (11).

In summary, based on largely preclinical studies, dietary Trp and its microbe-dependent metabolites play a major role in modulating functions of the peripheral and CNS. However, a causal role(s) of dietary Trp and its metabolites in the development of human psychiatric diseases remains to be established.

The role of diet in inflammatory gut to brain signaling

Gram-negative microbes contain cell wall components called Microbe-Associated Molecular Patterns (MAMPs) such as bacterial lipopolysaccharide (LPS), flagellin, lipoproteins, and peptidoglycans. MAMPs can engage with toll-like receptors on enteric neurons or vagal afferents, immune cells in the gut, or elicit their effects systemically throughout the body and brain. Dietary influences on the gut microbiota can regulate the intestinal gut-based immune system by influencing the permeability of the epithelial barrier and enabling the translocation of microbial membrane components and even intact microbes into systemic circulation. This translocation and systemic immune activation can lead to metabolic endotoxemia (27–29). Studies have explored intricate connections between immune activation in the CNS and gut microbiota. Specific gut microbes can affect the body's immune system by directly activating immune cells in the gut, leading to pro- and anti-inflammatory systemic immune responses (30). The potential association of neurodegenerative and neuroinflammatory mechanisms associated with the BGM system in various brain disorders was recently explored (31).

Although cell wall components from gut microbes are essential for neuroinflammation, other microbes can be instrumental in inhibiting and preventing immune activation within the gut, such as Akkermansia mucinophilia. Akkermansia colonizes the outer compartment of the mucus layer and improves intestinal barrier function by breaking down and utilizing mucin (MUC2) in the intestinal mucus layer, while upregulating the synthesis of MUC2 by goblet cells through metabolites (32). This dual effect on degradation and new synthesis of mucus strengthens the intestinal barrier function with benefits for metabolic and immune homeostasis (33). Additionally, a distinct group of microbial metabolites, specifically SCFAs, have strong peripheral and central anti-inflammatory properties. Synthesis of SCFAs, particularly butyrate, is performed by several species of gut microbes that ferment complex carbohydrates, including *Eubacterium rectale, E. hallii, Faecalibacterium prausnitzii,* and *Ruminococcus bromii*. These microbes facilitate their anti-inflammatory effects by promoting the production of IL-10 via G-protein coupled receptor 43. Furthermore, butyrate can directly reduce the expression of genes related to inflammatory pathways in healthy intestinal tissue (34). The majority of butyrate within the colon (95%) acts as an energy source through absorption by colonocytes via the tricarboxylic acid system and β-oxidation. Absorption can also occur by small intestinal enterocytes from glutamate and glucose (35). Moreover, butyrate can induce the differentiation of regulatory T cells, thus demonstrating

mechanisms in which intestinal homeostasis can be established (36,37). Microbially generated butyrate not only has beneficial effects on immune and epithelial cells in the gut, has been shown to have anti-inflammatory effects in the brain (38).

Neuroinflammation in the brain is closely linked to immune activation in the gut. Dietary influences on the composition and function of the gut microbiome can indirectly act as a regulator of microglia in the CNS, affecting their maturation and functioning through immunoregulatory pathways (36,37). Microglia are the predominant immune cells in the brain, and the presence of beneficial gut bacteria is essential for their optimal functioning (39). Administration of SCFAs resulted in restored microglia function in cases of impairment (40). Based on extensive preclinical evidence, microglia dysfunction and diet-related gut microbial dysbiosis have been linked to a variety of psychiatric disorders, including anxiety, depression, neurodevelopmental disorders, including ASD and neurodegenerative disorders (41,42).

Based on preclinical studies, diet-related gut changes can result in metabolic endotoxemia affecting neuroinflammation. However, to establish causality between diet, metabolic endotoxemia, and impaired brain function in psychiatric diseases, well-controlled human intervention trials are essential.

Diet, the BGM System and Brain Disorders

Alterations in the interaction between the BGM system and diet have been associated with various psychiatric and neurological disorders. In the following sections, we will explore a number of these disorders for which there is significant clinical evidence supporting this relationship.

Diet and depression.

The prevalence of depression is rising globally, particularly amongst younger populations (43). While traditional treatments involve centrally acting medications along with cognitive-behavioral techniques or other psychological interventions, dietary interventions have emerged as a promising adjuvant treatment approach (**Table 1**).

Systemic immune activation has been identified as a contributing factor in the development and progression of depression (44). The Standard American Diet and other diets associated with metabolic endotoxemia can have an effect on numerous biological systems linked to depression, while a healthy diet was positively associated with self-reported happiness and mental well-being (45–47). The relationship between diet and depression has been supported by multiple studies (summarized in **Table 1**), some of which provide the best evidence to date to support a causal relationship between a Mediterranean-style diet and beneficial effects in patients with depression. Numerous studies suggest that higher consumption of fish, fruits, vegetables, and whole grains, as well as a Mediterranean diet, is associated with a lower risk of depression (48,49). A correlation was revealed between unhealthy dietary patterns and compromised mental health, while optimal nutrition showed a positive association with improved mental health in children and adolescents (50).

Although these studies provide insight into the relationship between diet and mental health, conclusions cannot be drawn regarding the causality of diet and mental health. One explanation is that individuals with depression resort to unhealthy comfort foods as self-medication, which can temporarily improve mood and stress response. Other lifestyle factors, such as physical exercise and social connection, may confound the results of these studies. Furthermore, early dietary patterns and nutrient intake may influence brain development, and deficiencies in essential nutrients due to poor-quality diets have been linked to mental health issues (51,52). Magnesium, folate, zinc, and omega-3 fatty acids have been inversely associated with depression and anxiety disorders. Despite methodological limitations of many studies looking at the correlation between dietary patterns and depression, existing evidence strongly supports the benefits a diet high in plant-based foods (e.g., Mediterranean-type diet) for improved mental health. One possible explanation is the role of the gut microbiome in converting food components, such as fiber and polyphenols, into anti-inflammatory molecules and signals that positively impact the brain.

Large European population-based studies utilizing data from the Flemish Gut Flora Project (53,54) have strengthened the evidence linking an altered gut microbiome to depression. Among these studies, one revealed a positive association between the bacterial taxa *Dialister* and *Coprococcus* with quality-of-life (QoL) measures, while lower presence of *Bacteroides* was linked to both

reduced QoL scores and elevated rates of depression (55). In a recent large-scale study examining microbiome data from the HELIUS and Rotterdam Study, the relationship between microbial composition and depression was investigated. Twelve genera and one microbial family (*Ruminococcaceae*) was found to be linked with depressive symptoms, including *Coprococcus, Eggerthella,* and *Subdoligranulum* (53). Another study within the HELIUS cohort, focusing on different ethnic groups, also found an association between certain microbiota and depression levels that could be generalized among ethnic groups. This suggests that ethnic variations in the gut microbiota might partially contribute to disparities in depression (54). Both studies (53,54) showed alterations in GABA, glutamate, and tryptophan metabolites, which have been implicated in mouse models of depression, leading the authors to suggest a role of these microbial changes in the pathophysiology of depressive symptoms. However, other factors such as dietary habits and other lifestyle factors may have contributed to the results.

In summary, despite considerable epidemiological evidence to demonstrate an association between a healthy diet and lower rates of depression, as well as both preclinical and clinical evidence implicating alterations in the gut microbiome in depression, high-quality clinical trials in well-controlled study populations are needed to prove causality.

Diet and cognitive decline. AD is a progressive neurodegenerative disorder affecting over 40 million people globally. The disease is characterized by impaired executive brain function and memory loss, and may coincide with anxiety, insomnia, and depression (56). Several clinical studies have investigated the impact of diet on cognitive decline, some of which are summarized in **Table 2**.

Various hypotheses have been proposed to explain the biochemical mechanisms underlying AD including the concept of diet-related endothelial inflammation (57) and reduction of flow-mediated vasodilation, as likely factors in early cognitive decline (58). Consumption of a healthier diet during adulthood has been linked to a decreased risk of cognitive decline (59–61). Polyphenol intake, through diet or supplementation, among elderly individuals has also been linked to enhanced cognitive functioning (62,63). A recent study showed these benefits, however only in

subjects with a low baseline intake of flavonoid-rich foods (64). Human studies support earlier preclinical research by demonstrating that polyphenol-rich diets, such as Mediterranean-style diets are linked to better cognitive function (65).

A possible role of the gut microbiota in translating such diets into brain healthy molecules has been supported by several preclinical and clinical studies (66). Vagal input is received by brain regions such as the locus coeruleus and the nucleus solitarius, suggesting a possible neural connection between the gut microbiome and brain regions impacted by AD, as demonstrated in postmortem investigations (67). The composition of gut microbiota influences the interplay between cognitive decline, neuroinflammation, and the onset of AD (68). Diet-induced endothelial neuroinflammation can be inhibited by consuming dietary components like omega-3 fatty acids and polyphenols, particularly cocoa flavanols.

Dietary intake of polyphenols can change the gut microbiota community structure and gut microbial metabolites, by altering the composition of secondary BAs through modulation of bacterial 7α-dehydroxylation of de-conjugated primary BAs into secondary BAs. In view of BAs regulatory and signaling functions throughout the CNS (69), alterations in this system have been implicated in AD. An increased ratio of cholic acid to deoxycholic acid, reflecting 7α-dehydroxylation of cholic acid by gut bacteria, has been correlated with cognitive decline (70,71). In individuals with AD, there is a reduction in systemic primary BAs and an increase in specific secondary BAs that are synthesized by gut microbes and have also been detected in postmortem brains of AD patients (70). This suggests that changes in the ratio of primary to secondary BAs are influenced by dietary factors and gut microbiota composition. The progression of AD symptoms from moderate to severe is associated with secondary BA levels, with higher concentrations of secondary BAs correlating with poorer cognitive function (70). In a study comparing metabolic profiles of AD patients and healthy controls, deoxycholic acid, a bile acid, was identified as a distinguishing metabolite for early detection of AD (72). Nho *et al*. also found an association between certain BAs, changes in brain structure, and cerebrospinal fluid biomarkers, suggesting the involvement of the gut-liver-brain axis in cognitive decline related to AD (71). The

accumulation of amyloid-beta and tau protein aggregates in the CNS is considered a hallmark of AD pathology.

Despite the proven benefits of Mediterranean-style diets, like the MIND diet (2,62,73), there is increasing evidence supporting the potential therapeutic potential of a ketogenic diet for individuals with AD or mild cognitive impairment (74–76). Several clinical studies, consistent with preclinical findings (76–78), revealed that diets which increase blood ketone levels may improve memory functioning and cognition in AD patients, as well as changes in gut microbial composition (79–82). Numerous clinical trials have demonstrated the beneficial impact of a medium chain triglyceride diet on the results of the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) in mild-to-moderate AD patients, indicating an immediate improvement on the ADAS-cog (83), as well as prolonged and notable enhancements in digit-symbol coding tests and immediate and delayed logical memory (79). Furthermore, improvements in the Memory Composite Score, ADAS-cog, and a range of cognitive domains, such as processing speed, episodic memory, executive function, and language were observed (80,84).

In view of current evidence supporting diets with very different composition and effects on the gut microbiome and AD symptoms, no clinical dietary recommendations can currently be made. While neither diet is likely to benefit patients with advanced disease, future well-designed clinical trials are needed to identify the most effective dietary interventions to slow the progression of mild cognitive impairment.

Diet and autism spectrum disorder. ASD is distinguished by impaired social communication and persistent, repetitive behaviors that emerge during early development and significantly hinder normal social function (85). Incidence of ASD has surged in recent years, with one in 36 children in the US currently being affected (86). ASD is associated with GI issues, immune dysregulation, and anxiety, with common GI symptoms including changes in bowel habits, gastric reflux, abdominal pain, and diarrhea (87).

Although the genetic risk factors for ASD have not changed significantly in recent years, environmental factors such as dietary habits and exposure to toxins of the affected individuals have been identified as potential contributors to its etiology, while maternal obesity, maternal immune activation, and metabolic syndrome are underappreciated risk factors. Several preclinical and clinical studies have revealed that individuals with ASD have elevated levels of inflammatory markers in their bloodstreams compared to neurotypic controls, including heightened systemic tumor necrosis factor-alpha (TNF-α) (88–90) and increased IL-1B (88,91). Postmortem analysis of ASD patients has indicated increased intestinal permeability (92). The presence of GI symptoms and anxiety in conjunction with these observations implies that gut dysbiosis may be a contributing factor to the underlying pathophysiology of ASD.

Several clinical studies (93–95) corroborate preclinical findings (96,97) in revealing changes to the gut microbiota in ASD patients and proposing that the gut microbiome may be involved in its pathophysiology. Multiple small-scale dietary intervention studies examined the potential of using diet as a treatment for ASD (**see Table 3**). However, many of these studies are of insufficient quality to support the benefit of a particular diet in patients with ASD. For example, two separate studies found no significant changes in behavior or beta-casomorphin concentrations in urine between a gluten-free, casein free diet and ASD symptoms (98,99). Tryptophan-based treatments have been proposed in treating ASD symptoms, as lack of dietary tryptophan has been shown to exacerbate ASD behaviors (100). However, no clinical evidence can support an association between hyperserotonemia and ASD symptom alleviation, either through dietary tryptophan intervention or selective serotonin reuptake inhibitor administration (101,102).

Preclinical and clinical evidence suggests a role of maternal immune activation as a result of infections or diet-induced immune activation in increasing the risk for ASD in the offspring (103–105). Further studies including placebos, binding elements, and long follow-up periods are required to better understand the effect of maternal and offspring diet in preventing and treating ASD symptoms.

Interventions targeting the microbiome:

Supplementation with probiotics and prebiotics has become increasingly popular in the treatment of psychiatric disorders, some of which are discussed in Table 4. Probiotics are 'live microorganisms which, when administered in adequate amounts, confer a health benefit to the host' (106). For example, probiotic supplementation on depression was studied in 47 participants which showed that probiotic administration was associated with a decrease in The Hamilton Depression Rating Scale (HAM-D) scores and an increase in *Lactobacillus,* which was associated with significantly reduced depressive symptoms. This study suggests a possible association between the gut microbiome and depression, but does not provide evidence for a causal relationship (107).

Prebiotics are substrates that increase the growth of health-promoting microorganisms, thus improving host health (108,109). Prebiotics enhance the relative abundance and metabolic function of gut microbial taxa, which release SCFAs into the circulatory system, affecting the GI tract and other organs (110). Clinical evidence supports the advantages of a prebiotic-rich diet in promoting gut microbiome richness and diversity and in reducing systemic immune activation (8,111).

FMT, involving the transfer of gut microbiota from a healthy donor into a patient, shows potential as a therapeutic strategy for a number of psychiatric disorders. Evidence in support of such a gut microbial role comes from earlier preclinical studies (112) and from several studies demonstrating that FMT from patients with a clinical diagnosis of MDD into a rodent can lead to depressive-like behaviors in the recipient, suggesting a possible causal relationship (113,114). Definitive evidence for a therapeutic benefit of FMT remains limited to *Clostidioides difficile* colitis and multiple clinical studies have failed to provide such evidence for the effectiveness of FMT in the treatment of psychiatric disorders. One exception is a study in children with ASD receiving FMT revealed a significant prolonged reduction in GI and ASD symptoms, as well as changes in the abundance of

specific beneficial bacterial taxa, such as *Bifidobacterium*, *Desulfovibrio,* and *Prevotella* (94,115). Even though not replicated by other published studies, these findings provide evidence that the gut microbiome contributes to the pathophysiology of ASD.

The assessment of the possible therapeutic benefits of FMTs in brain disorders, emulating the outcomes observed in animal models, has achieved limited and short-lived success (116). Even so, it is essential to confirm these results through well-designed RCTs before proposing it as a viable treatment option. It remains to be demonstrated whether personalized and targeted dietary and supplement advice based on stool microbiome assessments is effective, although this method combined with genetic risk factor analysis has the potential to emerge as a valuable approach in the future.

Challenges, **Clinical Implications and Future Directions**

A wealth of clinical epidemiological research suggests that nutritional interventions offer therapeutic benefits for chronic brain disorders, while preclinical studies have provided mechanistic evidence supporting a role of the microbiome in mediating some of these benefits (117). However, there are still major hurdles to overcome before the effectiveness of dietary approaches in treating cognitive decline, depression, anxiety, ASD, and AD can be fully understood. Important questions include the specificity of certain diets and their individual components providing mental health benefits. In the case of neurodegenerative diseases, i.e. can a particular diet delay the onset of the disease, slow progression, or alleviate symptoms once fully developed? In the case of depression, can a dietary intervention replace pharmacological therapy in mild forms of the disorder, or should it be used as an adjuvant therapy, reducing symptoms, and medication side effects? In the case of ASD, is the most effective strategy to change the diet of the pregnant mother, thereby preventing the generation and transmission of inflammatory or neuroactive molecules to the fetal brain?

An ongoing query involves the specificity of gut microbiome changes in various mental disorders. The American Gut Project identified similar gut microbiomes in individuals with conditions like

depression, schizophrenia, and post-traumatic stress disorder (PTSD) across both US and UK populations, despite gender differences. (118). This review highlights how various chronic brain disorders may stem from systemic low-grade immune activation, linked to diet-related increased gut permeability and the prevalence of pro-inflammatory microbial molecules (LPS, MAMPs) over anti-inflammatory mechanisms like SCFA and IL-10. Elevated gut permeability, leading to immune activation and metabolic endotoxemia, is suggested as a shared factor in mental disorders and other medical conditions (119). As such, promoting the growth of SCFA-producing microbes, particularly butyrate-producers in the gut could represent a promising therapeutic approach with broad applications (120).

We propose a model where the gut microbial ecosystem's health and interactions with the host's immune system profoundly impact the BGM system's homeostasis, and that chronic disturbances in this equilibrium result in varied mental disorders, influenced by genetic predisposition and exposome factors like perinatal influences, stress, viral infections, and environmental toxins. Additionally, we propose a model where diet, gut microbes, and gut interactions create a proinflammatory environment in the gut and the brain, potentially shared across psychiatric disorders influenced by genetics, sex, and exposome factors. While specific dietary interventions await stronger evidence for certain psychiatric disorders, practical advice emphasizes a healthy, plant-based diet like the traditional Mediterranean diet.

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Figure Legends

Figure 1. Diet-related and microbial signaling molecules influencing brain function. Neuroactive, inflammatory and anti-inflammatory molecules interact on brain targets to modify brain networks. Diet influences composition and function of the gut microbes, and microbes metabolize large diet-derived molecules (polysaccharides and polyphenols) and amino acids into neuroactive substances.
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Figure 2. Tryptophan effects on the brain. 3 Illustrates the 4 different pathways (tryptophan, serotonin, kynurenine, and indoles) through which Trp can influence brain function. Three of these pathways are dependent on gut microbial metabolism, in the other one, Trp, reaches the raphe nuclei through the systemic circulation, without microbial modifications.
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