Review

Biological Psychiatry

# Mood Disorders: The Gut Bacteriome and Beyond

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**ABSTRACT**

Knowledge of the microbiome-gut-brain axis has revolutionized the field of psychiatry. It is now well recognized that the gut bacteriome is associated with, and likely influences, the pathogenesis of mental disorders, including major depressive disorder and bipolar disorder. However, while substantial advances in the field of microbiome science have been made, we have likely only scratched the surface in our understanding of how these ecosystems might contribute to mental disorder pathophysiology. Beyond the gut bacteriome, research into lesser explored components of the gut microbiome, including the gut virome, mycobiome, archaeome, and parasitome, is increasingly suggesting relevance in psychiatry. The contribution of microbiomes beyond the gut, including the oral, lung, and small intestinal microbiomes, to human health and pathology should not be overlooked. Increasing both our awareness and understanding of these less traversed fields of research are critical to improving the therapeutic benefits of treatments targeting the gut microbiome, including fecal microbiome transplantation, postbiotics and biogenics, and dietary intervention. Interdisciplinary collaborations integrating systems biology approaches are required to fully elucidate how these different microbial components and distinct microbial niches interact with each other and their human hosts. Excitingly, we may be at the start of the next microbiome revolution and thus one step closer to informing the field of precision psychiatry to improve outcomes for those living with mental illness.

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In a field struggling with stagnation with regard to biomarker and treatment discovery, the early 21st century has been promising for the field of psychiatry. The microbiome revolution has provided evidence that aspects of mental disorder pathophysiology are correlated (in humans) and causally related (in preclinical models) to our mutualistic microorganisms (1). While the foundational relationships between microbes and humans are often difficult to measure within the complex human ecosystem, evidence that microbiome-gut-brain mechanisms observed in animal models translate to mental health in people is emerging (2–6). Critical work uncovering the potential mechanistic pathways and processes including, but not limited to, inflammation and the immune system, oxidative stress and mitochondrial dysfunction, tryptophan-kynurenine metabolism, neuroendocrine metabolism, gut and blood-brain barrier integrity, and neurotransmitter production continues to shed light on these important relationships (1,7). Novel approaches and improved analytical tools are now allowing researchers to move beyond the many case-control studies that have investigated the associations between the gut bacteria and major depressive disorder (MDD) and, to a lesser extent, bipolar disorder (BD) (8,9). As much of the reviews to date have focused on gut bacteria, this review aims to shine a light on some of the other microorganisms and environmental niches that may be contributing to the microbiome-gut-brain axis and mood disorder pathophysiology.

## THINKING BEYOND THE BACTERIOME IN MOOD DISORDERS

Most gut microbiome research in relation to mood disorders, and indeed more broadly, has focused on bacteria and bacterial genomes (i.e., the gut bacteriome). Recent technological advances have provided evidence that lesser explored microorganisms—viruses, fungi, archaea, and parasites—are crucial in shaping the gut microbiome ecosystem through their interactions not only with the host, but also with each other and bacteria through complex inter- and intrakingdom microbe-microbe interactions (Figure 1) (10). While the study of other microorganisms is in its infancy, understanding their presence and mechanisms of action is likely critical for exploiting the potential of the gut microbiome to advance health outcomes. The following section will provide a brief overview of some of these lesser explored organisms and how they may relate to mood disorders.

### The Gut Virome

The gut virome comprises eukaryotic and prokaryotic viruses, as well as plant viruses largely derived from dietary intake, that can infect both human and other microbial cells (11). Viromes across body sites differ in composition; however, the greatest abundances of viruses reside within the gastrointestinal tract (12). These viruses are at least as abundant as bacteria, with estimates that they may outnumber bacteria up to a factor of 10:1 (11,13). Bacteriophages (i.e., viruses that selectively infect or target bacteria) are the most abundant, comprising potentially as much as 95% of the human gut virome (14–16). Phage diversity and richness is greatest at birth and decreases to a highly individualized, stable, adult-like state by two years of age; this contrasts with the initial assembly of the gut bacteriome, which starts with lower diversity that gradually increases (16). Viruses have been strongly implicated in the development

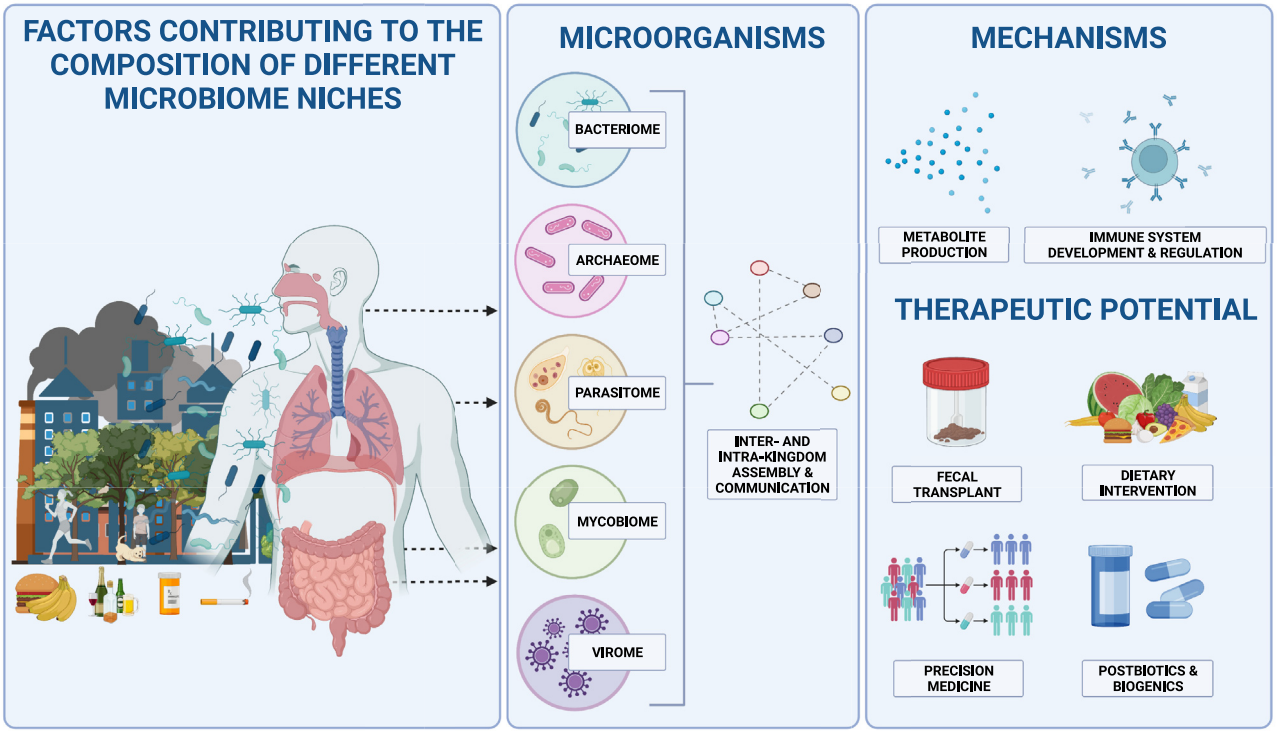


**Figure 1.** Beyond the bacteriome in mood disorders. Numerous factors, including environmental (i.e., air pollution, green space, and pets) and lifestyle (e.g., diet, alcohol consumption, medication use, tobacco use) factors, can contribute to the assembly and compositions of different human microbiomes, including the oral, lung, and small intestinal microbiomes. These microbiomes consist of different types of microorganisms, including bacteria, archaea, parasites, fungi, and viruses, which communicate with each other and may impact human health through mechanisms such as metabolite production and influencing the development and regulation of the human immune system. Understanding the contribution and function of these environmental niches and different microorganisms to human health may afford the opportunity to further exploit microbiomes to improve human health, including mood disorders, through novel therapies such as fecal microbiome transplantation, dietary interventions, postbiotic and biogenic supplementation, and precision medicine.

and regulation of the human immune system (17), which is a primary mechanism involved in the pathophysiology of mood disorders (18). Phages also shape the gut bacteriome and influence bacterial metabolism (19), which may also contribute to mood disorder pathophysiology.

In preclinical studies, differences in gut virome composition have been observed in a chronic restraint stress-induced rodent model of depression, and these differences correlated with differences in fecal neurotransmitters and metabolites, particularly those involved in tryptophan metabolism (20). Differences in gut virome composition have also been observed in a nonhuman primate model of depression compared with control nonhuman primates, which correlated with altered lipid metabolism in both the brain and periphery (21). In humans, differential abundances of gut viruses have been observed in MDD, and combining these viral data with those of bacteria and metabolites was able to better discriminate MDD from healthy control individuals (22). To date, there are no studies that have investigated the gut virome in BD, and the functional impacts of differences in the virome in individuals with mood disorders is yet to be considered.

## The Gut Mycobiome

The gut mycobiome, which refers to the fungal components of the gut microbiome, is also receiving increasing attention (23). Although fungi comprise only 0.1% of the microbes present in the gut, they can be up to 100 times larger than bacteria, thus contributing substantial biomass (24). The gut mycobiome is colonized with fungal species at birth, with key changes observed with the transition to solid foods, suggesting that diet is an important determinant of gut mycobiome composition (25). Maturation of the gut mycobiome has been associated with both maternal and early-life factors, including both maternal and infant body mass index (26), which are factors that are also important to mental health (27). In adulthood, gut mycobiomes show high interindividual variability, and potentially a core mycobiome, that continues to be shaped by environmental factors, especially diet (28,29). Cross-kingdom analyses provide evidence of intra- and interkingdom communication between the gut bacteria and fungi, and correlations with fecal metabolites (28). The gut mycobiome appears to modulate both the human immune system and gut bacteriome assembly and composition (23) and thus may plausibly play a role in mood disorder pathogenesis.

Commensal gut fungi have previously been implicated in disease. Blood antibodies to the fungus *Saccharomyces cerevisiae*, a common gut commensal (30), have been observed in Crohn's disease, especially in children (31,32). It is hypothesized that increased inflammation and permeability of the gut results in translocation of this fungus into systemic circulation;

however, this idea is controversial (33,34). Increased levels of *Saccharomyces cerevisiae* antibodies have also been observed in the neurological conditions Parkinson's disease (35), schizophrenia (36), and BD (37). Higher levels of antibodies to the fungal species *Candida albicans* have also been observed in schizophrenia and BD (38). In MDD, reduced alpha diversity of the gut mycobiome and alterations in composition, including increased *Candida albicans*, have been observed compared with control participants (39). Disruptions in community networks, including bacteria-fungal interconnections, were also observed, and combining data on both the gut bacteriome and mycobiome improved the ability to discriminate MDD participants from healthy control participants (39). Disrupted bacteria-fungi networks have also been reported in schizophrenia (40); however, to date, no studies have explored gut mycobiome composition and function in BD, nor the functional consequences of these differences within the context of mood disorders.

### The Gut Archaeome

Archaea are prokaryotic microorganisms with structural and functional differences to bacteria, thus forming their own domain (41). Archaea are primarily known for their methane production and their ability to live in harsh conditions like hot springs or salt lakes (42,43). Like other components of the gut microbiome, the archaeome is influenced by environmental factors including urbanization and diet (44). Methanogens, such as the genus *Methanobrevibacter*, are the most predominant archaea in the gut, and can utilize hydrogen produced by bacterial fermentation to form methane (45). Methane has been shown to influence gut transit time and have inhibitory effects on the gut bacteriome, and thus archaea have been implicated in the pathogenesis of inflammatory bowel disease and irritable bowel syndrome (46). Some studies in mental disorders have reported higher levels of methanogens, as well as enrichment of pathways associated with methanogenesis and methane metabolism (8). While there are few studies directly linking archaea to mood disorders, these microorganisms have been implicated in relevant mechanisms, such as bile salt metabolism (46) and the metabolism of trimethylamine and TMAO (trimethylamine *N*-oxide) (47). Bile acids have a potential protective effect in mood disorders, whereas TMAO can cross the blood-brain barrier, and its abundance has been positively associated with MDD severity (48); therefore, gut archaea may be able to influence mood disorder pathophysiology through disruptions to metabolite production.

### The Gut Parasitome

Humans have commensal parasites that reside in the gut, including protozoa (e.g., amoebozoa) and eukaryotic parasites (e.g., helminths, also known as worms), which have been proposed to be beneficial for health (49,50). While counterintuitive, as they are generally associated with disease, parasites have been shown to be important in the regulation of the immune system (51). Cross-kingdom interactions suggest that the presence of parasites can influence bacterial composition (49,50,52), and lower abundances of parasites in developed nations has been hypothesized to have contributed to the reduced gut bacterial diversity observed in these countries (49).

In humans, the prevalence of helminths appears to be inversely associated with immunological diseases (53,54). Numerous clinical trials have been conducted or are currently underway to determine the safety and feasibility of helminth therapy for conditions such as allergy, inflammatory bowel diseases, multiple sclerosis, and rheumatoid arthritis (53,54), and the application of helminth therapy to mental disorders has been proposed (53). In common with fecal microbiome transplantation, people are self-treating with helminths (55), highlighting the imperative for clinical trials of helminth therapy to better understand safety, potential causal pathways, and efficacy (55). This is particularly important, as parasitic infection—as opposed to mutualism—has been linked to higher prevalence of mental illnesses (56) and may even increase the risk of psychiatric disorders (57). Further, while the deworming of individuals in areas endemic with parasitic infections that result in mortality is considered essential, there are now concerns that such interventions may contribute to the rise in inflammatory and autoimmune conditions in these countries over time (54). Considering the potential of helminth therapy for immunological conditions, the contribution of parasites to human health, including mental health, is an important research focus.

### Challenges in Measuring Other Microorganisms

While reference databases for these other microorganisms are less developed than for the gut bacteriome, groups are developing and curating databases specifically focusing on human gut viruses (16,58,59), fungi (30), and archaea (45); however, such initiatives for the gut parasitome are still required (60). Each of these different microorganisms comes with their own unique characteristics that require different collection, processing, sequencing, and bioinformatic methodologies (61–63). Recent guidelines for the standardized reporting of microbiome research are a promising step toward improving approaches to the science (64). However, the challenges of trying to also understand the role of the other microorganisms of the gut microbiome are daunting and will require substantial interdisciplinary collaboration.

## THINKING BEYOND THE LARGE INTESTINE IN MOOD DISORDERS

To date, most microbiome-related research has focused on the gut; however, numerous microbiomes have a role to play in human health. In the following section, we highlight some advances in research pertaining to the oral, small intestinal, and lung microbiomes, notwithstanding the myriad other microbiomes that are likely contributing to health and disease and whose role in mood disorders may be of relevance.

### The Oral Microbiome

The oral microbiome comprises a less diverse microbiome than the large intestine, with over 700 microbial taxa—mostly bacteria—in the distinct niches of the tongue, plaque, cheek, gingiva, and oral mucosa (65). The composition of the oral microbiome appears to have changed alongside major dietary shifts in history, particularly with the industrialization of food

systems (66). The oral microbiome also appears to be relatively resilient (67,68); however, it is particularly susceptible to the intake of highly fermentable carbohydrates (69). Similar to the gut microbiome, the oral microbiome has been implicated in mood disorders and other brain conditions. Two small studies have reported associations between the abundances of taxa in the saliva of young people with depression and anxiety symptoms (70,71), with potential mediation via basal C-reactive protein and cortisol levels (70). Differences in oral bacterial taxa have also been observed in subgingival samples of those with BD compared with healthy control individuals (72).

Although replication is required and causality remains unclear, there are theoretically plausible mechanisms to support further investigation of the oral microbiome in mood disorders. These include direct microbial translocation from the oral cavity into the central nervous system via the facial nerves and olfactory bulb (73), which has also been implicated as a mechanism contributing to the pathogenesis of Alzheimer's disease (74), and disruption of the oral-gut microbiome axis, which may contribute to neuroinflammatory processes (75). Moreover, the immunomodulatory abilities of oral microbiota, as per gut microbiota, can activate proinflammatory cytokines and cause systemic inflammation (76).

### The Small Intestinal Microbiome

The small intestinal microbiome has received somewhat less attention, likely due to its relatively inaccessible nature that limits measurement (77). Although bacterial composition appears to be less diverse than that of the large intestine (78), the small intestinal microbiome shows greater and more dynamic temporal variation, likely due to factors such faster transit time and the need to rapidly respond to changing dietary factors (77).

Considering most digestion and nutrient absorption occurs within the small intestine, the composition of the small intestinal microbiome may be extremely important to human health. Preclinical studies have suggested that the small intestinal microbiome is involved in nutrient and bile acid metabolism, as well as mucosal immunity (79). In humans, samples from participants with ileostomy have revealed that the small intestinal microbiome is enriched with genes related to carbohydrate metabolism, more so than that of the fecal microbiome (78). Metagenomic analysis of human duodenal samples has shown lower levels of genes associated with carbohydrate metabolism, and higher levels of genes associated with lipid metabolism, in individuals with obesity compared with lean individuals (80). Moreover, change from a high-fiber diet to a diet low in fiber and high in simple sugars reduced small intestinal microbiome diversity and increased gastrointestinal symptoms in patients undergoing esophagogastroduodenoscopy (81).

A healthy dietary pattern has consistently been shown to associate with reduced risk for depression (82,83), and dietary interventions have been shown to improve depressive symptoms (84), even in moderate-to-severe MDD (85,86). Epidemiological evidence suggests that those with BD have poorer dietary patterns than healthy control individuals (87), and there is evidence of improvements in BD symptoms with dietary intake or supplementation of unsaturated fatty acids (88). Interventions of whole diet and dietary components have also been shown to change fecal microbiome composition and function (89,90), and thus the gut microbiome is hypothesized to be a mediating factor in the diet-mental health relationship (91). As we continue to unravel the diet-microbiome-mental health interactions, it is possible that the small intestinal microbiome will emerge as a key player; however, technological advances are required to further understand its role in health, including mental health.

### The Aerobiome

The air we breathe contains its own microbiome—termed the aerobiome—comprising microorganisms from our surrounding environments arising from natural sources and human activities (92). The average human adult breathes in approximately 11,000 L of air per day, and an estimated $10^8$ bacterial genomes (93), which can modulate the composition of human bodily microbiomes, particularly the lung microbiome. Research has also linked the aerobiome to the pathophysiology of mental disorders and, indeed, there is increasing interest in what is termed the lung-brain axis (94). For example, rodents exposed to dust from a more biodiverse soil had an increased abundance of a soil-derived butyrate-producing gut bacterium, which negatively correlated with anxiety-like symptoms (95).

The lung and other respiratory system microbiomes have been implicated in neurological diseases (96). In preclinical models, exposure to air pollutants has been shown to influence neuroinflammation and microglial activation (97) and increase amyloid-β plaque load in mice, a hallmark of Alzheimer's disease (98). In humans, exposure to air pollution has been associated with an increased risk of cognitive decline and neurodegenerative disease, increases in depression and anxiety symptoms, and changes in brain structure and function (99,100). However, to what extent these effects are mediated by microbes is unclear. There is also evidence demonstrating a role for the lung microbiome in modulating brain autoimmunity in humans (101). Moreover, interactions between the gut and the lungs—termed the gut-lung axis—and their respective microbiomes have also been implicated in disease, particularly through immune-mediated mechanisms (102). Finally, increased exposure to nature-rich urban spaces (e.g., parks), forests, or seascapes—commonly referred to as green and blue spaces—have been associated with reduced depression symptoms in observational studies, as well as with improvements in mood in intervention studies (103,104). Again, whether these associations or outcomes involve the aerobiome is, as yet, uncertain, and several other causal explanations have been demonstrated including physical activity, reduced stress, and natural light (104). Future research in this area may facilitate important information linking the environment and human mental health and explore therapeutic possibilities that harness the aerobiome.

## THINKING BEYOND CURRENT TREATMENT OPTIONS

### Fecal Microbiome Transplantation

The process of therapeutic fecal microbiome transplantation (FMT) involves transfer of the fecal microbiome, including all

aspects of microorganisms and metabolites, of a healthy person into an unwell recipient; this process is commonly used and highly efficacious for *Clostridioides difficile* gut infection (105). Seminal studies in rodent models have shown that FMT from those with MDD into rodents can result in a depressive phenotype (106–110). In humans, FMT has been shown to improve depression symptoms in those with irritable bowel syndrome; however, understanding whether this effect is mediated by improvements in bowel symptoms requires further exploration (111). More recently, FMT in those with moderate-to-severe MDD has been shown to be feasible and safe, with improvements in gastrointestinal symptoms and quality of life observed, setting the scene for large randomized controlled trials (112,113). Case studies of FMT in BD have reported substantial improvements in symptoms (114,115). However, fully powered randomized controlled trials are required; promisingly, there is a large trial of FMT for BD depression currently underway (116).

The contributions of the virome and mycobiome have also been linked to the success of FMT. Indeed, sterile fecal filtrate (including the viruses, metabolites, and other bioactive molecules, but not bacteria) is showing some success for treating conditions such as *C. difficile* infection, obesity, type 2 diabetes mellitus, and necrotizing enterocolitis (117). How these other microorganisms influence FMT, or if this fecal filtrate is a sufficient alternative to FMT, is yet to be determined. More randomized controlled trials are required to answer these questions in order to fully leverage the capacity of FMT as a treatment strategy for mood disorders.

## Postbiotics and Biogenic Metabolites

A postbiotic is a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host" (118). This definition differs from that of a probiotic, in which the microorganisms must be viable. These nonviable microbes and their cell components are proposed to influence health through modulation of resident gut microorganisms, enhancing gut barrier integrity and function, modulation of local and systemic immune responses, modulation of systemic metabolic responses, and systemic signaling via the nervous system (118).

Postbiotics have been shown to improve sociability and have a potential anxiolytic effect in healthy mice, with only modest changes in gut microbiota composition (119). In rodent models, the use of postbiotics has been shown to prevent (120) and improve (121–123) depression- and anxiety-like behaviors. In humans, two randomized controlled trials of postbiotic supplementation have been conducted in medical school students during periods of stress (124,125), and improvements in general health, sleep, and gastrointestinal symptoms, but not anxiety and depression symptoms, were reported.

Closely related to the concept of postbiotics are bioactive metabolites, sometimes referred to as biogenics, which are produced by bacteria during fermentation processes. These metabolites contribute to the functional activity of foods such as sauerkraut, kombucha, kefir, and yogurt. These fermentation products include, but are not limited to, vitamins (such as B vitamins), bioactive peptides (such as lactotripeptides), bacteriocins (which aid with bacterial survival), short-chain fatty acids (such as butyric acid), and neurotransmitters (such as GABA [gamma-aminobutyric acid] and serotonin) (126). These metabolites are thought to have numerous direct health effects, including having neuroactive potential (127), that are not always mediated through the gut microbiome (128). The possibility that fermented foods can be used as therapeutics in mood and anxiety disorders is generating research interest, with trials investigating the impact of fermented foods on brain structure and function currently underway (ACTRN12622000622707).

## Dietary Interventions

There is a consistent and growing body of evidence that diet matters to the risk of depressive disorders (82) and across the life course (129). Indeed, dietary interventions are showing promise as efficacious adjunctive treatment options for clinical MDD (85,86). Mechanistic pathways that are postulated to mediate the diet-mental health relationship include the immune system, brain plasticity, neurotransmitters, stress response systems, gene expression, mitochondrial function, and gut microbiota (91). Many of these mechanistic processes are influenced by the microbiome-gut-brain axis. However, at present there are no studies that have examined these mechanisms within the context of a dietary intervention trial for MDD, and it is still unknown just how much of the apparent positive impact of dietary improvement on depressive symptoms are due to changes in gut microbiome composition and/or function. Incorporating measures of both gut microbiome composition and—critically—function and microbiome-diet–related metabolites in intervention studies is needed.

## Precision Medicine and Treatment Response

Leveraging the gut microbiome to inform and strengthen precision medicine strategies is an exciting area of research and holds much promise for the field of psychiatry. Mood disorders are consistently associated with differences in gut microbiome composition compared with healthy control individuals (8,9). A large population study reported an association between the gut microbiome and quality of life and depression (130). Higher relative abundances of *Faecalibacterium* and *Coprococcus* were associated with higher quality of life, and lower abundances of *Coprococcus* and *Dialister* were linked to depression, an observation that was validated in a second cohort (130). Similar associations have also been observed in a recent clinical study of female MDD individuals compared with healthy volunteers; this study used random forest models to identify bacterial genera that were enriched in healthy individuals compared with people with MDD that included *Faecalibacterium* and *Coprococcus* (131). This study also identified bacterial genera enriched in MDD including *Escherichia-Shigella* and *Alistipes*, taxa that are associated with increased inflammation (131), implicating microbiota-immune-brain signaling in MDD. These associations were also supported by findings from a large systematic review of gut microbiome composition in psychiatric disorders, which included 24 studies in MDD and 7 studies in BD (8). This review reported consistently lower *Coprococcus* and

*Faecalibacterium* in both disorders and higher *Escherichia-Shigella* and *Alistipes* in MDD (8).

While the observation of some overlapping taxa observed across studies is promising, there are no taxa whose differential abundance in mood disorders is ubiquitously observed across all studies (8). Further, to date, most studies investigating differences in gut microbiome composition between those with and without mood disorders have only measured genus-level differences; species and strains within a genus can exert different functions (132), which makes the biological relevance of differences at the genus level difficult to interpret. Mood disorders have high clinical heterogeneity, and their causes are likely multifactorial and differ widely across individuals. As such, it is highly probable that there is no singular biological cure for these conditions, and individuals will benefit from different treatment approaches specifically tailored to them, as is the case within the spectrum of evidence-based psychotherapeutic approaches (133). Thus, while the use of specific signatures as a diagnostic tool for mood disorders may be premature, gut microbiome profiles may be used to identify individual risk, inform treatments, and predict treatment responses, affording the development of personalized recommendations.

Relatedly, it is becoming increasingly apparent that an individual's gut microbiome composition influences their response to treatments, for example, cancer therapies and antibiotics (131,132). Differences in baseline gut microbiome composition have been observed in responders and non-responders to antidepressant treatment in MDD (133), and changes in gut bacteriome composition have also been reported after commencing psychotropic medication in both MDD and BD (8). There also appear to be reciprocal interactions between psychiatric medications and the gut microbiome; the gut bacteriome has been implicated as influencing the bioavailability of drugs and influencing drug metabolism (134), including psychiatric medications (135–137), while psychiatric medications have been shown to have antimicrobial effects (138). Indeed, medication use has been identified as one of the greatest confounders of gut microbiome composition (139–142). Medication use thus poses a significant challenge in clinical trials of microbiome-modulating therapies within psychiatry. However, understanding how these medications may influence adjunctive treatments targeting the microbiome, such as biotics or FMT, may provide critical insights enhancing therapeutic success. Moreover, an understanding of the role of gut microbes in mediating individual variability in drug metabolism will be valuable in informing personalized dosage recommendations.

## CONCLUSIONS

The microbiome revolution has been a welcomed addition to the field of psychiatry. Research conducted to date has been critical in developing our understanding of the microbiome-gut-brain axis and its contribution to mood disorder pathophysiology. New frontiers in microbiome science, including the contribution of other organisms, as well as the biological relevance of other microbial niches, are avenues of research that hold promise to further reveal how these mutualistic microorganisms influence mental disorders. We believe that harnessing this knowledge to inform future therapies and precision psychiatry holds huge promise, although interdisciplinary collaboration and the use of systems biology will be essential in bringing this vision to fruition.

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## ARTICLE INFORMATION

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