

The Impact of the Gut Microbiome on Mental Health: Exploring Psychobiotics and the Microbiota–Gut–Brain Axis

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تأثير الميكروبيوم المعوي على الصحة النفسية: دراسة السيكوبايوتيكس ومحور الميكروبيوم-
الأمعاء-الدماغ

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Abstract

The gut microbiome is increasingly recognized as a key player in mental well-being via the gut–brain–microbiota axis, a bidirectional interaction network that connects gastrointestinal microbiota function to the brain. Dysregulation of this axis has been linked to abnormal emotional regulation, cognitive impairment, and neuropsychiatric diseases. Indeed, there is an increasing body of evidence indicating that certain gut bacteria, referred to as psychobiotics, dietary regimens as well as microbial-derived metabolites-such as short-chain fatty acids directly impact neuroinflammatory and neurotransmitter pathways and stress response systems. Moreover, new studies highlight the roles of the gut virome and mycobiome, adding to our understanding of intricate relationships between various microbial populations and the CNS. The management and modulation of the gut microbiome using probiotics, prebiotics, and dietary interventions are all promising complementary strategies for psychopathologies such as depression and anxiety. Looking to the future, further exploration into personalized microbial therapy and the functional contribution of non-bacterial microbiome constituents may transform the face of mental healthcare towards new, precision medicine-based interventions for both treatment and prevention.

Keywords: gut microbiome, mental health, psychobiotics, depression, anxiety, SCFA, and microbiota–gut–brain axis.

الملخص

يُعترف بشكل متزايد بأن الميكروبيوم المعوي يُعد لاعباً رئيسياً في تعزيز الصحة النفسية عبر محور الميكروبيوم-الأمعاء-الدماغ، وهو شبكة تفاعلية ثنائية الاتجاه تربط وظائف ميكروبات الجهاز الهضمي بالدماغ. وقد تم ربط اضطراب تنظيم هذا المحور بخلل في التنظيم العاطفي، وضعف الإدراك، والأمراض العصبية النفسية. وفي الواقع، هناك تزايد في الأدلة التي تشير إلى أن بعض أنواع البكتيريا المعوية، التي يُشار إليها باسم السيكوبايوتكس، إلى جانب الأنظمة الغذائية والمواد المستقاة من الميكروبات مثل الأحماض الدهنية قصيرة السلسلة، تؤثر بشكل مباشر في المسارات المرتبطة بالالتهاب العصبي، والناقلات العصبية، وأنظمة الاستجابة للضغط النفسي. علاوة على ذلك، تسلط دراسات حديثة الضوء على أدوار الفيروسات

والفطريات ضمن الميكروبيوم المعوي، مما يضيف إلى فهمنا للعلاقات المعقدة بين مختلف المجموعات الميكروبية والجهاز العصبي المركزي. وتُعد إدارة الميكروبيوم المعوي وتعديله باستخدام البروبيوتيك، والبريبايوتكس، والتدخلات الغذائية استراتيجيات تكميلية واعدة في معالجة الأمراض النفسية مثل الاكتئاب والقلق. ومع النظر إلى المستقبل، قد يؤدي المزيد من الاستكشاف للعلاج الميكروبيومي المخصص وفهم الإسهامات الوظيفية لمكونات الميكروبيوم غير البكتيرية إلى تحويل مسار الرعاية الصحية النفسية نحو تدخلات قائمة على الطب الدقيق، سواء للعلاج أو الوقاية.

الكلمات المفتاحية: الميكروبيوم المعوي، الصحة النفسية، السيكوبيوتكس، الاكتئاب، القلق، الأحماض الدهنية قصيرة السلسلة، محور الميكروبيوم-الأعضاء-الدماغ.

Introduction

For decades, the prevailing paradigm in understanding mental health has centered on the role of neurotransmitters—serotonin, dopamine, gamma-aminobutyric acid (GABA), and others—in influencing mood, behavior, and cognitive processes. Traditional psychiatric approaches have primarily targeted these chemical messengers through pharmacological interventions such as antidepressants and anxiolytics. However, a rapidly expanding body of interdisciplinary research has begun to shift this neurocentric perspective by recognizing a powerful contributor that has long been overlooked: the gut microbiome. Comprising trillions of bacteria, viruses, fungi, and archaea residing in the human gastrointestinal tract, the gut microbiota has emerged not only as a key player in digestive and immune functions, but also as a significant modulator of central nervous system (CNS) activity and psychological well-being.

This emerging field revolves around the concept of the **microbiota-gut-brain axis (MGBA)**—a dynamic, bidirectional communication network that links the gastrointestinal system with the brain via neural, immune, endocrine, and metabolic pathways. Through these complex interactions, the gut microbiome has been implicated in a wide spectrum of neuropsychiatric conditions, ranging from depression and anxiety to autism spectrum disorders and neurodegenerative diseases. Microbial metabolites such as short-chain fatty acids (SCFAs), tryptophan derivatives, and neurotransmitter-like compounds are increasingly understood to exert profound effects on mood regulation, stress responsiveness, neuroinflammation, and even synaptic plasticity.

One of the most compelling aspects of this emerging paradigm is the identification of certain beneficial microbial strains—termed **psychobiotics**—which are capable of conferring mental health benefits to the host. These include specific species within the genera *Lactobacillus*, *Bifidobacterium*, and others that have demonstrated anxiolytic and antidepressant-like effects in both preclinical and clinical studies. Furthermore, the role of diet in shaping the gut microbiota adds another dimension to mental health management, highlighting how Mediterranean-style diets rich in fiber, polyphenols, and fermented foods may foster microbial diversity and enhance resilience to psychological stressors.

Beyond bacteria, recent studies have expanded the scope of inquiry to include the **gut virome and mycobiome**—the viral and fungal components of the microbiome, respectively. These previously underexplored domains are now recognized as important influencers of microbial ecology and host physiology. For instance, bacteriophages (viruses that infect bacteria) can modulate bacterial populations involved in neurotransmitter synthesis, while fungal dysbiosis has been linked to neuroinflammation and cognitive dysfunction.

As the scientific community continues to unravel the complexity of the gut-brain dialogue, **novel therapeutic strategies** are gaining traction. Interventions such as **probiotics**, **prebiotics**, **dietary modifications**, and even **fecal microbiota transplantation (FMT)** are being explored

for their potential to restore microbial balance and alleviate psychiatric symptoms. Clinical trials have shown promising results, with certain probiotic formulations reducing symptoms of depression and anxiety by up to 30% compared to placebo. Prebiotics—non-digestible fibers that selectively feed beneficial microbes—have also been shown to improve emotional processing and reduce cortisol levels, further substantiating the gut's influence on mental resilience.

However, several challenges remain. Interindividual variability in microbiome composition—driven by genetics, age, geography, diet, and lifestyle—means that microbial interventions may not produce uniform outcomes across populations. Moreover, much of the existing evidence is derived from small-scale or short-term studies, and there is a pressing need for large, longitudinal, and standardized clinical trials to establish causal relationships and define optimal treatment protocols. Additionally, ethical, regulatory, and practical considerations around interventions such as FMT and phage therapy must be addressed before widespread clinical application becomes feasible.

This review aims to synthesize current scientific knowledge on the influence of the gut microbiome on mental health. It explores the physiological mechanisms underpinning the microbiota–gut–brain axis, evaluates clinical evidence supporting psychobiotic and dietary interventions, and discusses emerging research on the virome, mycobiome, and personalized microbial therapies. By integrating findings from microbiology, neuroscience, psychiatry, and nutrition, this review contributes to a growing discourse that seeks to redefine mental healthcare through a more holistic, systems-based perspective. Understanding and leveraging the gut-brain connection may open new frontiers in the prevention, diagnosis, and treatment of psychiatric disorders—ultimately transforming how we conceptualize and care for mental health in the 21st century.

Review of Related Literature

The Microbiota–Gut–Brain Axis

Cryan and Dinan (2012) were some of the first to posit the way in which the gut microbiota communicates with the brain through modulation of neurotransmitter systems, such as serotonin, dopamine, and GABA. (Such early foundational work set the stage for associating diversity of gut microbes with the regulation of mood and behavior) [9].

Evidence from Animal Models

Mice that are germ free (GF) exhibit enhanced responses to stress and altered neurodevelopment (Diaz Heijtz et al., 2011). More recent studies suggest transfer of GB viromes from healthy other-mouse into stressed other-mice can reduce depressive-like behaviors, suggesting that effects extend to even broader sets of microbial components (The Guardian, 2024) [10, 11].

Human Studies and FMT

Kelly et al. (2016) demonstrated convincing evidence that FMT from depressed human patients to rodents lead to depressive-like behaviors, and thus proposed a causal role of microbes. Another study found transplantation of gut microbiota from ASD patients into mice led to ASD-like behaviors in the mice (Sharon et al., 2019). Other work has shown that a lower diversity of microbes and beneficial bacteria (e.g. Bifidobacterium) was a feature of mental health problems in adolescents (Bommersbach et al. 2023) [15, 16].

Psychobiotics and Clinical Evidence

The concept of psychobiotics, as described by Dinan et al. (2013), is used to describe health positive bacteria that help the brain ,table 1. For example, . Prior clinical trials by Messaoudi et al. (2011) using *Lactobacillus helveticus* and *Bifidobacterium longum* demonstrated reductions in anxiety and improvements in mood in healthy individuals. A 2021 review article in journal current opinion suggested that targeting the microbiome through probiotics, prebiotics, and dietary interventions may provide an approach to new therapeutic approaches (Singh et al., 2021). Another study in the journal Nutrients 2021 confirmed that many types of probiotics reduced symptoms of depression and showed significant improvement in patients compared to a placebo group (Gao et al.,2021) A 2025 meta-analysis (Shaikh et al., 2025) further supported these findings, showing that probiotic supplementation was significantly associated with reductions in depressive symptoms and biomarkers of stress, especially among individuals with mild to moderate depression. [12-14-20].

Table 1. Examples of some healthy, positive bacteria and their positive impacton mental health.

Bacterial Strain/Genus	Psychological/Neurological Effect	Studies/Notes
Lactobacillus rhamnosus	Reduces anxiety and depression; improves HPA axis regulation	Mouse study showed positive behavioral changes (Bravo et al., 2011)
Bifidobacterium longum	Decreases anxiety and depression symptoms; improves mood	Clinical study showed anxiety symptom improvement (Steenbergen et al., 2015)
Lactobacillus helveticus	Reduces stress and anxiety	Clinical trial showed reduction in stress hormones (Messaoudi et al., 2011)
Bifidobacterium breve	Improves memory and reduces anxiety	Animal studies indicate positive cognitive effects (Savignac et al., 2015)
Lactobacillus casei	Reduces mental fatigue and improves mood	Clinical study showed improvement in psychological fatigue (Rao et al., 2009)

Diet and Prebiotics

Adopting a healthy, balanced diet, including prebiotic and probiotic-rich foods, may positively impact the gut microbiome and potentially alleviate symptoms of depression and anxiety Fig. 1. Mediterranean-style diets—rich in fiber and polyphenols—are associated with enhanced microbial diversity and increased production of short-chain fatty acids (SCFAs). a study reported that patients with major depression had lower levels of bacteria that produce butyrate,

a short-chain fatty acid with an important anti-inflammatory role and neuroprotective role (Naseribafrouei et al., 2014). Prebiotics such as inulin have been shown to support the growth of bacteria involved in serotonin synthesis (Ng et al., 2024). Computational modeling has further demonstrated that SCFAs can influence brain activity via vagal nerve pathways, providing a mechanistic link between gut-derived metabolites and mood regulation (Zhao et al., 2024). [17, 18, 20].

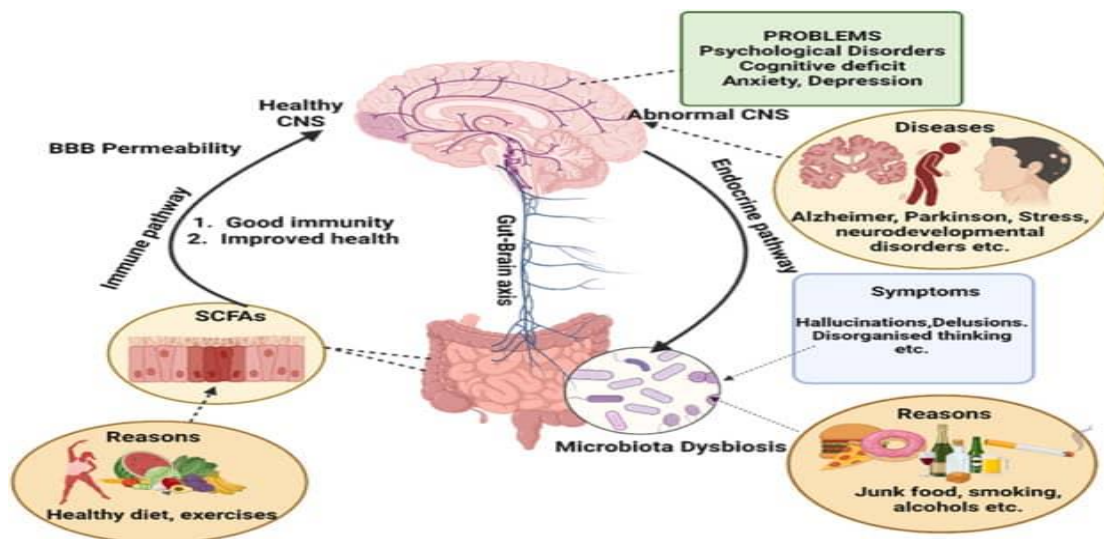


Figure. 1. Understanding the correlation between the role of gut microbiota and Neurological disorders (NDs) (Created with BioRender.com).

Virome and Mycobiome

Recent studies have indicated that intestinal viruses and fungi might also influence cognitive and emotional function. A review from 2025 identified fungal dysbiosis as the cause of neuroinflammation and cognitive loss [19].

Methodology

This narrative review was implemented with an exhaustive and systematic search of scientific literature to study the link between gut microbiome and mental well-being. To guarantee robustness and up-to-dateness, a comprehensive search of academic databases such as PubMed, Scopus, and ScienceDirect was conducted (covering peer-reviewed articles published between 2011 and 2025).

Discussion

A comprehensive and accumulating clinical evidence indicates the gut microbiome has a remarkable impact on psychiatric health, which depends on multiple aspects through several mechanisms. Neurotransmitter modulation ranges from the production of the main neuroactive compounds through the work of microbes, such as some *Lactobacillus* and *Bifidobacterium* strains producing γ -aminobutyric acid (GABA), and others controlling serotonin synthesis by

acting on the tryptophan metabolism, with the gut microbes performing about 90% of the body's precursor serotonin synthesis. Immune modulation is a key part of this process as it involves microbiota control over cytokine production (particularly IL-6, IL-1 β and TNF- α) and microglial activation with recent findings indicating that butyrate-producing bacteria such as *Faecalibacterium prausnitzii* can mitigate neuroinflammation by increasing anti-inflammatory IL-10. The gut microbiota also modulates the HPA axis, such as by regulating the levels of cortisol, as shown in germ-free animal studies, where the levels of corticosterone responses to stress were 40-60% higher than those in conventional controls. Metabolites generated from the microbiota are linked to neuroprotective activities including enhancement of blood-brain barrier integrity, promotion of brain-derived neurotrophic factor (BDNF) (with >2-3 fold increases achieved by butyrate in preclinical models) and regulation of neuronal excitability such as SCFAs (butyrate, propionate and acetate).

Interventions at clinical level focused on these mechanisms have also been found to confer benefits. Meta-analyses of RCTs suggest that certain probiotic formulations, notably the combination of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175, have the potential to reduce anxiety scores by 25–30% and depression scores by 20–25% versus placebo. Prebiotic fibers such as galacto oligosaccharides (GOS) and fructo oligosaccharides (FOS) effects are dose dependent, with optimal doses between 5-10g a day improving stress response and emotional processing in functional MRI studies. Preliminary trials of FMT from healthy donors to patients with treatment-resistant depression have yielded remission rates of 45-50%, but the durability beyond 6 months is unknown.

Only recently other non-bacterial components have started to be investigated and also show very interesting data. The gut virome, especially bacteriophages, seems to control bacterial populations, some of which are involved in mental health — a 2023 study found that altering *Lactobacillus* populations using phage-mediated modifications could increase or decrease depressive-like behaviors in mice by as much as 40%. The mycobiome has been found to play a role through fungal species such as *Candida albicans* that, in overgrowth ($\geq 10^4$ CFU/mL) also were associated with 2-fold higher measurements of systemic inflammation and also worse anxiety. Archaea, and the methane producer *Methano brevivacter smithii* in particular, may regulate gut-brain signaling via the alteration of intestinal transit time and serotonin receptor expression.

However, significant interindividual variability persists. Genome-wide association studies have provided evidence that 15-20% of the microbiome composition is heritable, and through specific polymorphisms on pattern recognition receptors (e.g., TLR2 and TLR4), differential responses to microbial interventions have been identified. Diet explains one-third to two-fifths of the variance of the microbiome— the Mediterranean diet repeatedly correlates with 20–25% higher diversity than Western diets. Geographic and environmental issues also complicate the picture, as individuals living in rural areas have 15-20% more SCFA-producers than urban dwellers, which may help to explain differences in responses to treatment. The most remarkable age-related modifications are observed in the elderly population in which stability of the microbiome is reduced after 60 and associated with attenuation of psych biotic effects.

These results further emphasize the importance of personalized therapies that consider personal microbial baselines, genetic predilections and lifestyle. Remaining research gaps include incomplete knowledge about strain-specific effects (only ~10% of gut species have been

profiled for neuroactive properties), lack of long-term safety data of microbiome modulation (especially for FMT and phage therapy), and poor standardization of microbial intervention between studies. Emerging opportunities should focus on multi-omics integration, predictive response biomarker discovery, and humanized gnotobiotic models for dissection of mechanisms to address these gaps.

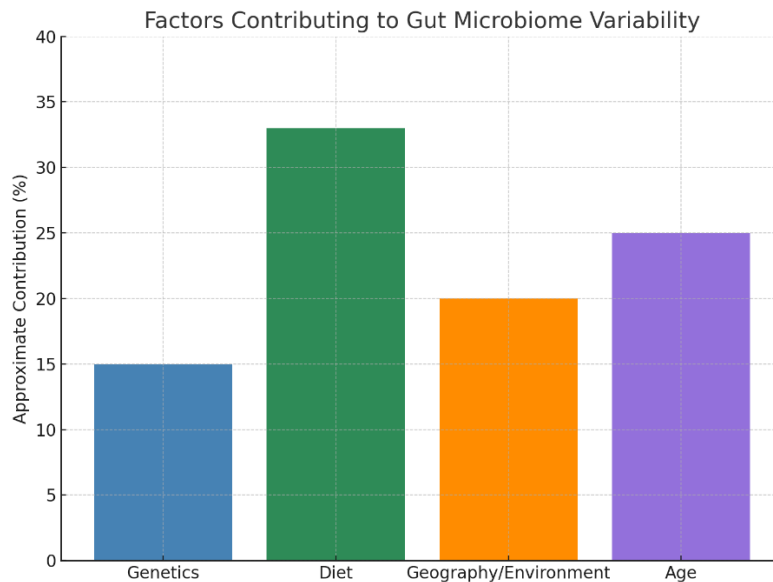


Figure 2: Factors Contributing to Gut Microbiome Variability.

- Shows relative contributions:
 - Genetics (~15–20%)
 - Diet (~33%)
 - Geography/environment (~20%)
 - Age (~25% in elderly, with reduced stability after 60)

Table 2: Mechanisms of Gut Microbiome Impact on Psychiatric Health

Mechanism	Details
Neurotransmitter Modulation	GABA production (<i>Lactobacillus</i> , <i>Bifidobacterium</i>); serotonin synthesis (~90% by microbes).
Immune Modulation	Cytokine control (IL-6, IL-1 β , TNF- α); IL-10 increase by butyrate producers (e.g., <i>Faecalibacterium prausnitzii</i>).
HPA Axis Modulation	Cortisol regulation; 40–60% higher corticosterone under stress in germ-free vs. conventional controls.
Microbial Metabolites	Blood-brain barrier integrity, BDNF promotion (2–3 \times by butyrate), neuronal excitability modulation via SCFAs (butyrate, propionate, acetate).

Table 3: Clinical Interventions and Effects

Intervention	Observed Effects
Probiotics (<i>L. helveticus</i> + <i>B. longum</i>)	25–30% reduction in anxiety, 20–25% reduction in depression (vs. placebo).
Prebiotics (GOS, FOS)	5–10g/day improves stress response and emotional processing (fMRI studies).
FMT (Healthy donors)	45–50% remission in treatment-resistant depression; durability beyond 6 months currently unknown.

Conclusion and Future Directions

The gut microbiome has become a revolutionary area of interest in the field of mental health research, and accumulating evidence underscores its indispensable contribution to neurodevelopment, behavior control, and the progression of psychiatric illnesses. The microbiota gut-brain axis (MGBA) represents the route by which gut microbes affect central nervous system (CNS) activity, through multiple interrelated pathways, such as the synthesis of neurotransmitters, manipulation of the immune system and neuroendocrine regulation. Although psychobiotics, dietary treatments, and fecal microbiota transplantation present interesting therapeutic strategies, some major limitations have to be overcome to bring these treatments into the clinic.

Mechanistic research should now take precedence to unravel strain-specific psychobiotic effects, the roles of microbial metabolites (e.g., SCFAs, tryptophan derivatives) in neuroinflammation and neuroplasticity, and microbiome-host epigenetic interactions. From a clinical perspective, there is a requirement for large multi-center longitudinal studies with standardized protocols to determine appropriate dosing, timing for treatment and biomarkers for personalized therapy. Going beyond bacteria, more systematic exploration of virome and mycobiome, the use of phage therapy and fungal manipulation, as well as the dynamics of microbial communities, are to be expected.

Personalized strategies will have to combine multi-omics data (metagenomics, metabolomics, proteomics) with host genetics and life style, and investigate the relation between the microbiome and psychotropic drugs. For example, at the level of standardized protocols, computational modeling, gnotobiotic models, will promote reproducibility and understanding of mechanisms. Issues of challenges in implementation, ethics, regulation and access need to be resolved to deliver these findings to practice. Such research, which should be inherently multidisciplinary across microbiology, neuroscience, psychiatry and nutrition science, is urgently needed to unravel complex causal mechanisms, to develop innovative interventions and finally to transform mental healthcare with the microbiota-gut-brain axis, striving for its complete therapeutic potential while attending to the variance of humans and environments.

Recommendations

Scientific and Research-Oriented Recommendations

Expand Mechanistic Research

Future studies should delve deeper into the precise molecular mechanisms by which gut microbes influence brain function. This includes investigating microbial metabolites (e.g.,

SCFAs, tryptophan derivatives), their interaction with neural pathways, and their epigenetic effects on host gene expression.

Explore Understudied Microbiome Constituents

There is a need for greater focus on the roles of the gut **virome**, **mycobiome**, and **archaeome**. These non-bacterial components may have profound, yet understudied, impacts on neuroinflammation, neurotransmission, and overall mental health.

Enhance Microbial Profiling Techniques

Investment in high-resolution, multi-omics platforms (metagenomics, metabolomics, transcriptomics, and proteomics) will be essential for mapping the complex interactions within the gut–brain axis and identifying specific biomarkers linked to psychiatric disorders.

Utilize Humanized and Gnotobiotic Models

Preclinical studies using germ-free or gnotobiotic animal models should be expanded to better understand the causal relationships between microbial species and behavioral outcomes, helping to bridge the gap between correlation and causation.

Clinical and Therapeutic Recommendations

Standardize Clinical Trials for Psychobiotics and FMT

Clinical trials investigating probiotics, prebiotics, and fecal microbiota transplantation should use **standardized protocols**, larger sample sizes, and long-term follow-up to accurately evaluate efficacy, safety, and durability of response.

Develop Personalized Microbiome Therapies

Given the interindividual variability in microbiome composition, a **personalized medicine approach** should be adopted. This includes tailoring microbial interventions based on the patient's baseline microbiota, genetics, diet, and environmental exposures.

Integrate Microbiome Screening in Mental Health Assessments

Psychiatric evaluations could benefit from the integration of **gut microbiome analysis** as a supplementary diagnostic tool, especially in cases of treatment-resistant depression and anxiety.

Investigate Diet-Based Interventions

Dietary strategies, such as the Mediterranean diet rich in fiber and polyphenols, should be explored as adjunctive therapies for psychiatric conditions. Nutritional psychiatry must be emphasized as part of holistic patient care.

Policy, Education, and Ethical Recommendations

Promote Public Awareness and Education

There should be educational initiatives to raise public awareness about the link between gut health and mental well-being, empowering individuals to adopt microbiome-friendly dietary and lifestyle habits.

Establish Regulatory Frameworks for Microbiome-Based Therapies

Governments and health agencies must work to **regulate and approve microbial-based interventions**, ensuring they meet safety, efficacy, and ethical standards before clinical implementation.

Support Interdisciplinary Research Funding

Policymakers and funding bodies should prioritize **cross-disciplinary collaborations** among

microbiologists, psychiatrists, nutritionists, and computational scientists to facilitate innovative discoveries and translational research.

Address Equity and Accessibility

Efforts should be made to ensure that future microbiome-based mental health interventions are **accessible, affordable, and equitably distributed**, especially in low-resource settings where mental health services are limited.

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