

GUT MICROBIOTA DIVERSITY AND MENTAL HEALTH CONDITIONS: A SYSTEMATIC REVIEW

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Abstract – Objective: Several mental disorders have been linked to imbalances in the diversity, composition, and function of the gut microbiota, regardless of the protection offered by the blood-brain barrier. This systematic review considered research that compared the gut microbial makeup of healthy volunteers and those with bipolar disorder, epilepsy, anxiety, and major depressive disorders (MDD).

Materials and Methods: To find human case-control studies and cohort-designed studies that examined the connections between mental health disorders and stool microbiota measurements, Medline *via* PubMed, Google Scholar, and Science Direct databases were searched using the phrases title: (Role of gut microbiota on mental health) AND title: (Role of gut microbiota on depression OR mental health OR anxiety).

Results: We analyzed the resulting research, concentrating on bacterial taxa that differed between MDD and healthy controls as well as between all recruited participants with psychiatric illnesses. *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Euryarchaeota*, *Proteobacteria*, *Spirochaetes*, *Nitrospirota*, and *Verrucomicrobia* were among the nine phyla that were represented. Seven of these phyla were found to be significant in both case-controlled and cohort-designed studies, but studies for all phyla produced different results. Ten of the nine taxa had lower MDD, seven had findings in both directions for case-controlled studies, and eleven had higher MDD. Thirteen genera were found to be less abundant in the MDD and Anxious Distress groups, whilst 28 genera were found to be significantly abundant in both groups.

Conclusions: There is no specificity on the bacterial taxa most frequently associated with mental health disorders based on the human research of mental health disorders and gut microbiota that are currently available.

Keywords: Gut, Microbiome, Microbiota, Depression, Mental health disorders, Gut-brain axis.

INTRODUCTION

Over 1,000 different species of bacteria found in the human gut exist with an individual gut carrying more than 160 species indicating that there are more microbial cells in the human body than the human cells¹⁻³. The human genome contains more microbial genes than human genes, and it was recently proposed that microbial signals regulate essential functions of the human body, ranging from host metabolic functions to brain functions^{1,4}. The gut microbiome plays a critical role in influencing the host physiology and brain development, and is involved in the pathophysiology of various physical, cognitive, and mental disorders⁵. The gut microbiome protects the host from pathogenic bacterial colonization through the production of essential metabolites and intestinal homeostasis throughout life^{6,7}.



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The vast majority of gut microbiota is dominated by phyla *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*. However, significant diversity at the species level and variation in their relative abundance have been reported⁸. While phylum Firmicutes includes butyrate-producing bacteria like *Eubacterium*, *Fecalibacterium*, and *Roseburia*, the phylum also includes other genera, such as *Clostridium*, *Lactobacillus*, and *Ruminococcus*. Members of the Bacteroidetes phylum, known for their ability to proficiently decompose dietary fiber, include genera such as *Bacteroides*, *Prevotella*, and *Xylanibacter*^{8,9}. Some of the phylum *Actinobacteria* (genus *Bifidobacterium*) are often used as probiotics. *Proteobacteria* contain *Escherichia* and *Desulfovibrio*, while *Verrucomicrobia* consists of mucus-degrading genus *Akkermansia*⁸⁻¹².

In spite of the blood-brain barrier's distant position and defense mechanism, the gut microbiota has been connected to a number of mental conditions, including major depressive disorder (MDD)¹³⁻¹⁷, diabetes, bipolar disorder, anxiety disorders, and schizophrenia¹⁸⁻²¹. Additionally, gastrointestinal problems^{22,23}, immunological disorders²⁴⁻²⁶, and metabolic or cardiovascular conditions^{27,28} have been linked to changes in the makeup and function of the gut microbiome. The gut-brain axis (GBA) is a complex network of communication routes between the gut microbiota and the central nervous system that connects the gastrointestinal system²⁹⁻³¹. Key processes like appetite and satiety, stress response, immunology, and intestinal motility are all regulated by the gut microbiota, which is known to have a direct impact on a number of regulatory mechanisms. These mechanisms include neuronal, immunological, endocrine, and metabolic pathways. Thus, bile acids, tryptophan, short-chain fatty acids (SCFAs), and neuroactive microbial metabolites are thought to be involved in this process^{32,33}. According to previous studies^{32,33}, these metabolites may impact blood-brain barrier (BBB) permeability, change gene expression, stimulate host immunological responses, and modify synaptic transmission, all of which can have an impact on brain-related functions.

Short-Chain Fatty Acids (SCFAs)

The colon's microbial fermentation of dietary fibers produces short-chain fatty acids (SCFAs), which are the main metabolites and an important conduit for gut-brain communication^{34,35}. The immune system is balanced, and the gut epithelial barrier is strengthened by SCFAs³⁶⁻³⁸. SCFAs, especially butyrate, can directly affect neuronal activity by passing through the blood-brain barrier (BBB)³⁹. It is also thought that SCFAs function as inhibitors of histone deacetylase (HDAC), which could be involved in neurobiological processes and gene regulation^{34,40}. These results highlight the crucial part SCFAs play in gut-brain connection by boosting afferent inputs to the vagus nerve^{36,41}. SCFAs play a major role in gut-brain interactions, causing enteroendocrine cells to release neuropeptides and initiate afferent nerve pathways^{32,42}. The hypothalamic-pituitary-adrenal (HPA) axis's development and function are facilitated by this mechanism which also is crucial for controlling stress reactions³².

Bile Acids

As signaling molecules, they contribute to various physiological procedures ranging from digestion, metabolism, to gut immune balance⁴³⁻⁴⁵. Their interaction with the gut microbiome is reciprocal, the gut microbiota controls the production of primary bile acids, their reabsorption, and the production of secondary bile acids, underlining the essential roles of both bile acids and gut bacteria in regulating intestinal and immune health^{44,46,47}.

Tryptophan

Tryptophan, primarily obtained from a protein diet, can cross the blood-brain barrier (BBB) when absorbed in the gut⁴⁸⁻⁵⁰. Tryptophan also plays a fundamental role in serotonin synthesis as a precursor^{49,51}. Tryptophan can be absorbed through the following pathways:

1. The Kynurenine Pathway: The majority of ingested tryptophan is metabolized through the kynurenine pathway by gut immune and intestinal epithelial cells. In subjects with active in-

inflammatory bowel disease (IBD), there are increased levels of kynurenine and kynurenic acid production due to elevated kynurenine pathway in their gut^{37,52}. Kynurenine can be further broken into neuroprotective kynurenic acid or excitotoxic quinolinic acid when it crosses the blood-brain barrier (BBB)⁴⁹.

2. Aryl Hydrocarbon Receptor Ligands: Tryptamine and indole are produced by the degradation of tryptophan by the gut microbiota. Aryl hydrocarbon receptor (AhR) activation is triggered by these microbial metabolites, reduces inflammation in the CNS (Central Nervous System) in certain autoimmune^{53,54}.
3. Serotonin: Serotonin is produced from tryptophan by the host enterochromaffin cells. However, the availability of tryptophan for serotonin synthesis is limited by its concurrent metabolism into AhR ligands, kynurenine, and other metabolites⁴⁹.

Neuroactive Microbial Metabolites in Depression

Local functions like gut motility, secretion, and cell signaling in the Gastrointestinal-Tract (GIT) have been found to be influenced by central neurotransmitters^{55,56}. Various gut microbiota can synthesize neurotransmitters (for instance, *Lactobacilli* and *Bifidobacteria* are known to produce GABA)^{57,58}. *Escherichia coli* synthesizes serotonin (5-HT) and dopamine^{36,59}, *Lactobacilli* produce acetylcholine, and a variety of other microbial species contribute to the production of neuroactive compounds³⁶. Low levels of neurotransmitters, such as norepinephrine, 5-HT, and GABA, are associated with the absence of gut microbiota in the intestines^{60,61}. Additionally, several studies have compared the gut microbiome in individuals with major depressive disorder (MDD) vs. healthy controls. To examine this connection, we systematically reviewed cohort design and case-control studies analyzing gut microbiome impact on mental health.

REVIEW METHODOLOGY

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in the systematic literature search and analysis for this study⁶². We did not use a formal risk of bias scoring system or other related quantitative outcomes, and methodological features, such as sample size, study population, and use of an appropriate study design, were not evaluated. Instead, we concentrated on a narrative description of the eligible studies rather than effect sizes. The terms title: (Role of gut microbiota on mental health) AND title: (Role of gut microbiota on depression OR mental health OR anxiety) were used to search Medline using the PubMed, Google Scholar, and Science Direct databases from 2014 to February 17, 2024, to conduct this systematic review. For the review, original English research publications that described the role and interplay of gut microbiota in depression and mental health disorders, using case-control and cohort-design studies, were included. Publish or perish literature and citation mining algorithms were also used to supplement the literature search⁶³. Abstracts and article titles underwent independent screening and assessment.

RESULT

Literature Search and Literature and Synopsis of the Articles

11 studies met the search criteria^{10,12,20,64-71} involving a total of 2,234 research participants, 1,910 MDD participants, and 324 control (Figure 1).

Characteristics of the Study Sample

The sample sizes of the studies range from relatively small size of 20 participants⁶⁶ to large sample size of 1135 per diagnostic group⁷⁰. Four of the studies enrolled for this review are not controlled (Table 1).

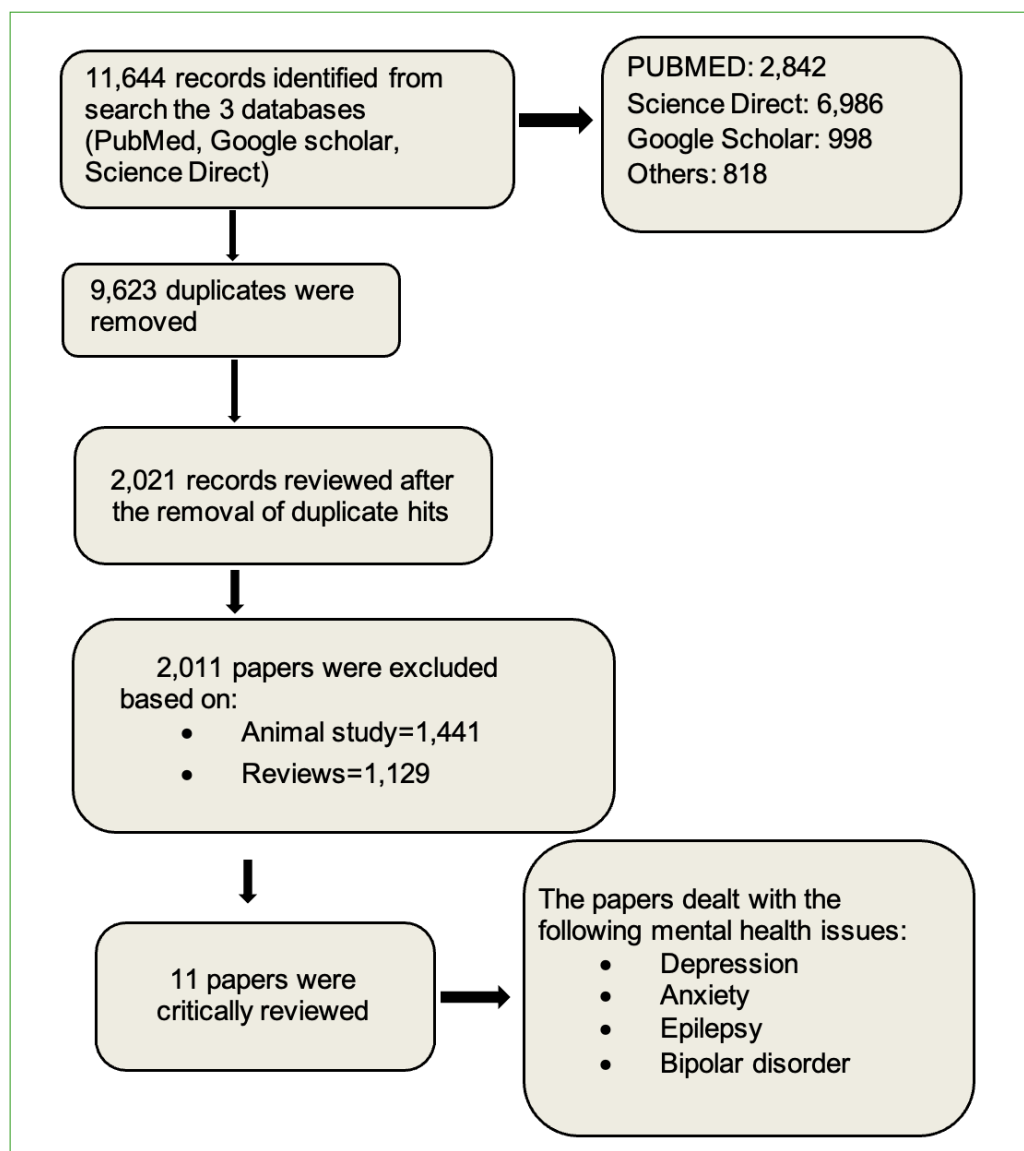


Figure 1. Standard preferred reporting item for systematic reviews. Major Depression Disorder (MDD), and other Mental Health Disorders.

Medication and Use of Probiotics/Prebiotics/Symbiotics

Four studies included participants taking psychiatric medications, including probiotics, prebiotics, symbiotics, etc^{20,68,10,70} while 6 of the studies excluded participants who had taken antibiotics, probiotics, prebiotics, and substance misuse prior to enrolment^{65,66,64,69,12,71}. Ritchie et al⁶⁸ permitted the use of Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin Nor-epinephrine Reuptake Inhibitors (SNRIs) while people on other drugs were exempted from the study.

Chung et al⁶⁴ recruited major depressive disorder patients on antidepressants and excluded participants who had undergone gastrointestinal surgery within the preceding two months, and those who had utilized antibiotics, probiotics, prebiotics, symbiotics, or had known active microbial infections⁶⁴.

Patients who had smoked cigarettes or cigars within the previous 12 months, were vegans, had experienced gastrointestinal illness within the previous 6 months, had diarrhea within the last 2 weeks, had taken anti-diarrhea medication within the previous 6 weeks, or had taken antibiotics within the previous 3 months were not included in a study by Liu et al⁶⁷.

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TABLE 1. REVIEW POPULATION CHARACTER.

Study	Controlled? (yes/no)	Country	Sample size		Male		Female		AGE		BMI	
			MDD	HC	MDD	HC	MDD	HC	MDD	HC	MDD	HC
Ritchie et al ⁶⁸	No	Australia and New Zealand	117	-	36	-	79	-	18-72	-	57.32 (13.69)	-
Chung et al ⁶⁴	Yes	Taiwan	36 (86%)	37	8	14	28	23	20-65	20-65	22.80 (4.21)	23.95 (3.92)
Zhang et al ¹²	No	China	45	-	-	-	-	-	-	-	-	-
Zhang et al ⁷¹	Yes	China	36	45	21	19	15	26	36.81±13.52	39.29±11.44	24.47 ± 4.16	23.94 ± 3.05
Liu et al ⁶⁷	Yes	United States of America	43	47	5	13	38	34	21.9±2.1	22.1±1.8	-	-
Evans et al ²⁰	Yes	United States of America	115	64	32	24	83	40	50.2 (12.8)	48.6 (16.6)	29.3 (7.2)	26.0 (4.6)
Şafak et al ⁶⁹	Yes	Turkey	30	10	16	2	14	8	-	-	-	-
Liśkiewicz et al ⁶⁶	No	Poland	16	-	8	-	8	-	21-64	-	25.0	-
Dong et al ⁶⁵	Yes	China	63	30	20 (31.7)	10 (33.3)	43 (68.3)	20 (66.7)	28.34 ± 8.63	29.23 ± 6.59	21.67 ± 3.91	21.49 ± 2.23
Hu et al ¹⁰	Yes	China	138	155	-	-	-	-	29.28 ± 7.10	29.13 ± 8.03	22.44 ± 3.41	22.38 ± 3.34
Yang et al ⁷⁰	No	Japan	2192	-	956	-	1236	-	52.4 ± 15.2	-	-	-

Zhang et al¹² excluded those who took probiotics or antibiotics in the month prior to enrollment and those who received any kind of antidepressant during the two weeks¹². In Evans et al²⁰, the majority of bipolar participants were on multiple psychiatric medications. On the other hand, recent use of probiotics or synbiotics within 30 days of study participation was not included by Zhang et al⁷¹.

Medical and Mental Health Conditions

The 11 studies have different exclusion criteria for medical and mental health conditions. Six studies either excluded a broad range of specific diseases or required that even healthy control participants have no active medical conditions^{10,12,64,65,68,71}. Four of the enrolled studies did not specifically indicate such exclusion^{20,67,70}. Liśkiewicz et al⁶⁶ examined each participant by a gastroenterologist and excluded patients suffering from GIT disorders that can influence the gut microbiota, such as irritable bowel syndrome. Some of the studies specified the exclusion of individuals with other psychiatric histories. Ritchie et al⁶⁸ excluded participants diagnosed with comorbid schizophrenia, bipolar, or current substance misuse.

Liu et al⁶⁷ enrolled participants met the diagnostic criteria for a current major depressive episode and had PROMIS Depression scores > 21 in the MDD group.

Hu et al¹⁰ enlisted patients of different depression severity classification categories of scores ranging from 8-16, 17-23, and ≥ 24 . Hu et al¹⁰ excluded patients with bipolar disorder, alcohol, and substance abuse, acute intoxication, antibiotic use within a month prior to sampling, schizophrenic, schizoaffective, or other Axis I psychiatric disorders, as well as serious chronic somatic disorders like thyroid disease, cardiovascular disease, diabetes, cancer, etc.

Patients with an organic etiology who were younger than 18 or older than 45 years old were rejected by Dong et al⁶⁵ due to their intellectual incapacity, psychotic traits, or psychiatric symptoms. Patients with cerebrovascular disease, tumors, brain injuries, central nervous system malformations, neurocutaneous disorders, and organ failure were not allowed to enroll in the study by Şafak et al⁶⁹. Furthermore, thirty patients with idiopathic focal epilepsy who were followed up for at least six months were included by Şafak et al⁶⁹. Ten volunteers in good health who had never experienced epileptic seizures made up the control group, while individuals with gastrointestinal disorders and those who had received antibiotic or anti-inflammatory medication during the previous two months were not allowed to participate in the study for either group⁶⁹.

Methodological approach of the studies

The patients enrolled were clinically assessed according to the HAMD-17 scale (Hamilton Depression Rating Scale), International Classification of Diseases (ICD-10) criteria (F32.1, F32.2, F33.1, F33.2)⁷¹, HDRS²⁴⁶⁶, the Center for Epidemiologic Studies Depression Scale (CES-D)⁷⁰, and the HAMD-24 scale⁶⁵.

Clinical assessments Diagnostic methods for Ritchie et al⁶⁸ included Beck Depression Inventory (BDI-II), generalized anxiety (GAD-7), and Perceived stress scale (PSS). To evaluate demographics, physical characteristics, and a preliminary diagnosis of psychiatric illnesses, subjects enrolled by Chung et al⁶⁴, were interviewed using a Huang et al⁷² modified Chinese version of the Schedule for Affective Illnesses and Schizophrenia-Lifetime (SADS-L). The participants were clinically assessed by the Beck Depression Inventory (BDI) to obtain levels of depressive severity and the Beck Anxiety Inventory (BAI) assessed anxiety levels, while the Perceived Stress Scale (PSS) was used to measure patients' stress level⁶⁴. Liu et al⁶⁷, clinically assessed the participants with The PROMIS Depression form and C-SSRS137 and SITBI138 to evaluate the participants' lifetime histories of suicidal thoughts and actions and non-suicidal self-harm, respectively while SCID-V139 was used to assess current and lifetime DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders) psychopathology⁶⁷. Zhang et al¹² assessed the severity of symptoms in patients based on the Hamilton depression scale-17 (HAMD-17) and Hamilton anxiety scale-14 (HAMA-14) scores. Patients enrolled by Evans et al²⁰ were clinically screened using the following methods; Patient Health Questionnaire-9 (PHQ-9) for severity and frequency of depressive states, the Altman Self Rating Mania Scale

(ASRM) for severity and frequency of manic states, the Short Form Health Survey (SF-12) assess physical (PCS) and mental (MCS) health, the Generalized Anxiety Disorder Assessment (GAD-7) to assess severity and frequency of anxiety symptoms and the Pittsburg Sleep Quality Index (PSQI) to measures sleep quality.

Microbiome Quantification

All but one of the studies included in this review used 16S rRNA gene sequencing, but different region specifications were sequenced: region V3 and V4⁶⁸, V3eV4 region and V4 region amplification⁶⁴, V4 hypervariable region⁶⁷, V3-V4 region¹², V4 region²⁰, V4 hypervariable regions⁶⁶, V3 region⁶⁹, V3-V4 region⁷⁰, V3-V4 region⁶⁵. Hu et al¹⁰ employed Whole Genome Sequencing with the E.Z.N.A. Soil DNA Kit.

For pipeline analysis, four studies enrolled for this review used Quantitative Insights into Microbial Ecology (QIIME) of which three used QIIME2 for demultiplexing⁶⁴⁻⁶⁷ while two of the studies^{20,70} used Ribosomal Database Project (RDP). Two studies^{12,71} used UPARSE (version 3, 7.1) for Operational Taxonomic Units (OTUs) clustering. The study conducted by Ritchie et al⁶⁸ used Calypso [Version 88.84] to analyze taxonomic information from 16S rDNA datasets. One study used USEARCH 8.0 for demultiplexing and quality filters. The study by Zhang et al⁷¹ used UPARSE and R (version 3.6.0) as a quality filter. Şafak et al⁶⁹ used Scythe (v0.994 BETA) and Sickle programs to extract non-specific adaptor sequences from reading results. One of the studies did metagenomic analysis such that each gene was assigned to the highest-scoring taxonomy based on a unified database to assess the gut microbiota species of MDD patients, followed by the alignment of the Nonredundant gene set against the KEGG database with an e-value cutoff of 1×10^{-5} ¹⁰.

Diversity Assessments

All eight studies assessing α -diversity (within-sample diversity) used the Shannon index and Simpson diversity index^{10,12,64-68,71}. Two studies^{65,68} additionally estimated richness with abundance-based estimators, the Abundance-based Coverage Estimator (ACE) and Chao1¹². Four of the enrolled studies conducted generic measures for evenness^{10,66,68,71}. Hu et al¹⁰ observed species richness⁶⁷ and Faith's phylogenetic diversity^{66,67}, Chung et al⁶⁴ observed OTUs and PD Whole Tree. Hu et al¹⁰ reported α -diversity indexes higher than 4.0.

Estimates of β -diversity (diversity of microbial community structure) employed included weighted Bray-Curtis similarity^{10,12,65-68,71}, and principal coordinate analysis (PCoA) of weighted^{10,12,65,71}, Principal coordinate analysis (PCoA) in weighted UniFrac distance^{64,67-69,71} and unweighted^{64,66,67} UniFrac distances. Two of the enrolled studies^{65,71} mentioned Analysis of similarity (ANOSIM). Although the Alpha diversity and beta diversity were not specified by Evans et al²⁰, PCoA was done. While Şafak et al⁶⁹ narrated the beta diversity assessment, Yang et al⁷⁰ did not provide details regarding the alpha and beta diversity of the study participants.

Summary of Statistical Approaches in Included Studies

Various techniques were used to distinguish MDD from control groups, ranging from classical statistics to machine learning approaches. These included the following: independent samples *t*-tests^{68,71} and Chi-Square analyses^{10,68,69,71}, permutational analysis of variance (PERMANOVA)^{64,66}, analysis of composition of microbiomes (ANCOM)⁶⁴, Adonis function⁶⁷ and Principal Coordinates Analysis using the ordinate function of vegan⁶⁷, logistical regressions²⁰, linear regression analyses^{12,20,65,71}, false-discovery rate (FDR, Benjamin Hochberg) multiple testing correction^{20,65,69,71}, Wilcoxon signed-rank or rank sum tests^{66,71}, Spearman's rank correlation coefficient⁶⁶, analysis of similarity (ANOSIM)^{12,71}, linear discriminant analysis effect size (LEfSe) analysis^{10,71}, the linear discriminant analysis (LDA) score, partial correlation analysis⁷¹, Mann-Whitney U test^{12,69,71}, one-way ANOVA test, LSD's multiple comparisons or non-parametric factorial Kruskal-Wallis sum-rank test, Kruskal-Wallis sum-rank test^{10,12}, Welch's *t*-tests, and correlation analysis⁶⁵.

Functional Analyses

Four out of the enrolled studies did a functional assessment of the gut microbiome obtained from their respective studies. Chung et al⁶⁴ and Liu et al⁶⁷ analyzed the functional pathways by Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt, version 1.1.2, and PICRUSt2, respectively) to understand the potential functional properties of the microbiome obtained from the depressed patients. Lui et al⁶⁷ further discovered that pathways associated with the MDD subjects are related to vitamin (folate and thiamine) biosynthesis, LPS biosynthesis, and long-chain fatty acid biosynthesis, while pathways associated with the healthy subjects seemed to be related to fermentation to short-chain fatty acids, phospholipid biosynthesis, nucleic acid metabolism, and aliphatic amino acid biosynthesis. Zhang et al¹² analyzed tryptophan/phenylalanine/tyrosine-derived metabolites and neuroactive metabolites by performing high-performance liquid chromatography followed by mass spectrometry for the detection of specific metabolites. Hu et al¹⁰ conducted LDA Effect Size (LEfSe) analysis on bacteria between HCs and MDD subgroups (LDA > 2.5, $p < 0.05$) to understand the alterations in gut microbiota and the consequence of the profound bacteria derangement on metabolic function.

Synthesized Findings

The following phyla were found to be significantly different between the two groups by seven studies that reported a significant difference in taxa between MDD and controls: *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Euryarchaeota*, *Proteobacteria*, and *Spirochaetes*. The phylum *Firmicutes* had the largest number of taxa (six families) found to be significantly different between MDD and controls. *Proteobacteria* phylum was higher in patients with epilepsy than in healthy volunteer group⁶⁹. On the family level, *Lachnospiraceae* was reported to be significantly different between the two groups in four studies^{10,64,67,71}. All studies identified taxa at the genus level, finding 30 genera that distinguished the diagnostic groups, as follows: 11 genera were higher in MDD (*Adlercreutzia*, *Bifidobacterium*, *Clostridium XI*, *Eggerthella*, *Holdemania*, *Meganomas*, *Sutterella*, *Flavonifractor*, *Sellimonas*, *Enterococcus*, *Escherichia*), 10 were lower (*Blautia*, *Ruminococcus*, *Faecalibacterium*, *Parabacteroides*, *Bacteroides*, *Anaerostipes*, *Fusicatenibacter*, *Tyzzereella 3*, *Hungatella*, *Collinsella*) and seven had findings in both directions (*Bacteroides*, *Prevotella*, *Parabacteroides*, *Ruminococcus*, *Blautia*, *Faecalibacterium*, *Bifidobacterium*). Genera identified by more than one report as elevated in MDD were *Bifidobacterium*, *Blautia*, *Prevotella*, and *Parabacteroides*, although *Blautia* also had one report found to be low in MDD. Only *Faecalibacterium* had two reports of being lower in MDD, and one report of being lower in bipolar disorder. Regardless of the severity of depression, *Coprococcus* and *Intestinibacter* were linked to better sleep at the genus level⁷¹. *Bacteroidetes* were shown to be more abundant in the gut microbiota of moderate and severe MDD patients, whereas *Ruminococcus* and *Eubacterium* were found to be less prevalent in the latter group¹⁰.

However, the following results were reported by cohort-designed studies that lacked control groups and concentrated on individuals with particular mental health conditions: these seven investigations found that there were substantial differences between the two groups in the following phyla at the phylum level: *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Fusobacteria*, *Nitrospirota*, *Proteobacteria*, *Verrucomicrobia*. The phylum *Firmicutes* had the largest number of taxa (two families, 18 genera) found to be significantly different in taxa. On the family level, Enterobacteriaceae was found to be significantly different among the patients. All studies identified taxa at the genus level, finding 50 genera that distinguished the diagnostic groups, as follows: four genera were higher in MDD (*Veillonella*, *Bifidobacterium*, *Clostridium*, *Prevotella*), 28 genera were reported to be abundant in MDD group and Anxious Distress group (*Clostridium*, *Serratia*, *Escherichia*, *Veillonella*, *Phascolarctobacterium*¹², *Akkermansia*, *Limnobacter*, *Meganomas*, *Thermodesulfovibrio*, *Catenibacterium*, *Cetobacterium*, *Fusobacterium*, *Megasphaera*, *Ruminococcus*, *Roseburia*, *Oscillospira*, *Lachnospira*, *Gemmiger*, *Dorea*, *Coprococcus*, *Collinsella*, *Blautia*, *Enterococcus*, *Parabacteroides*, *Bacteroides*, *Desulfovibrio*, *Streptococcus*, and *Prevotella* (excluding *Prevotella stercorea*), 13 genera were reported to be less abundant in MDD group and Anxious Distress group (*Prevotella stercorea*⁶⁸, *Bifidobacterium*¹², *Paraprevotella*, *Alistipes*, *Butyricimonas*, *Eggerthella*, *Holdemania*, *Flavonifractor*, *Anaerostipes*, *Olsenella*, *Sub-*

doligranulum, *Sutterella*, and *Haemophilus*), six genera were reported to have no significant difference in abundance (*Candidatus amobophilus*, *Faecalibacterium*, *Clostridium XI*, *Clostridium XIVa*, *Mitsuokella*, and *Eubacterium*). Four genera were reported to be more abundant in MDD by more than one report (*Bifidobacterium*, *Phascolarctobacterium*, *Veillonella*, *Clostridium*), one genus was reported to be less abundant in MDD by more than one report (*Prevotella*), and five genera were reported to have no significant difference in abundance by more than one report (*Eubacterium*, *Faecalibacterium*, *Clostridium XI*, *Clostridium XIVa*, *Mitsuokella*).

Studies assessing microbial diversity in patients with Major Depressive Disorder (MDD) compared to healthy controls (HCs) have yielded mixed results regarding alpha and beta diversity. Of the two studies^{10,20} that reported significant differences in alpha diversity, Hu et al¹⁰ observed a significant decrease in Simpson's index, indicating lower alpha diversity in more severe MDD groups compared to milder cases. There were no significant variations in alpha diversity, according to six of the enrolled research^{12,64-66,68,71}. Three studies reported no significant difference in beta diversity^{12,65,66}. Four studies reported significant differences in beta diversity^{10,20,64,67}, of which Liu et al⁶⁷ reported statistically significant differences in community composition based on Bray-Curtis Dissimilarity and Unifrac Distance, which do not consider the phylogenetic relatedness of taxa in a sample. Hu et al¹⁰ reported that the PERMANOVA test revealed that the general characteristics of microbiota in moderate and severe groups were significantly different from HCs, while the mild group and HCs did not differ significantly⁶⁷. Alpha and beta diversity did not differ significantly, according to three studies^{12,65,66}.

Alpha and beta diversity were not specified in the methods of the Safak et al⁶⁹. Nonetheless, PCoA was carried out, demonstrating the clear microbiota grouping between epileptic patients and healthy volunteers⁶⁹. There was no diversity reported in the study results since Yang et al⁷⁰ did not describe or disclose alpha and beta diversity.

Functional Analysis Result

Chung et al⁶⁴ found that 31 pathways were enriched for MDD including compound metabolism (such as Amino acid, carbohydrate, starch, sucrose and galactose metabolism, etc.), biosynthesis processes (such as lysine, primary and secondary bile acid, phenylalanine, tyrosine and tryptophan) and degradation (such as bisphenol and nitrotoluene, etc.) pathways.

After adjusting for multiple testing, Liśkiewicz et al⁶⁶ discovered that none of the 347 MetaCyc pathways were differentially abundant between the two groups, confirming the relationship between changes in bacterial abundance, SCFA production, and MDD severity in the microbial metabolic potential between the groups^{66,67,73}. Zhang et al¹² found that whereas norepinephrine levels were similar in MDD patients with severe anxiety, both indole-3-acetate and indole-3-carboxaldehyde were considerably enriched in these patients. Patients with severe depression showed norepinephrine depletion.

DISCUSSION

Main Findings

Significant differences in taxa were found between the MDD and control groups, as well as within the specific groups, in all seven controlled studies and two grouped studies (MDE with and without anxious diversity as classified by Ritchie et al⁶⁸ and severe, moderate, and mild depression symptoms as classified by Hu et al¹⁰). However, some interaction has been observed between the relative abundance, microbial diversity and change in microbial composition in those with or without.

Disparities in Method

Discrepancies are probably the cause of the discordance between the research. Comparability of all reviewed studies based on their sequence methods was affected by the use of metagenom-

ic analysis of fecal samples in one study¹⁰ while others used 16S rRNA quantification. Furthermore, varying outcomes can be influenced by different analytical techniques, such as differences in variable regions, pipelines, databases, and other quality criteria, despite the common use of 16S rRNA high-throughput sequencing by the studies.

Additionally, there were considerable differences in the analytical approaches used in each study. Zhang et al¹² used metabolomics to examine tryptophan-derived metabolites and neuroactive metabolites, while two studies^{64,67} used marker gene data and a group of known genomes to estimate the functional gene profile of a metagenome using an advanced statistical methodology called PICRUST.

None of the reviewed studies mentioned any means of statistical standardization for microbiome analysis. Nonetheless, the diversity of the statistical tools used across the studies has a high propensity for FDR, which was addressed in only 5 of the reviewed studies^{10,20,65,66,71}. Even after numerous corrections, false discovery rates (FDR) failed numerous tests⁷¹.

Disparities in the Sample

Although the research's high level of demographic homogeneity was a noteworthy strength, comparability is hindered by differences in study population characteristics. The microbial diversity and richness of the GIT is likely to be directly impacted by several factors, including variations in host genetics, host immune profiles, and behavioral factors, ethnicity, unmeasured confounding factors unique to each geographic group, and differences in geographic location and diet^{67,71,74}. Geographical location has a substantial impact on the microbial makeup⁷⁵. Based on research conducted with a large sample size (N = 7,009) from a single Chinese province, the biggest factor affecting microbiome variability is geographical variation, which explains five times as much variance among people of identical ancestry (99% Han Chinese) as the next most important factor⁷⁶. As a result, any signal associated with depression would have to take into consideration enough variance to be discernible among other contributing factors. Interestingly, a study using participants from several geographical areas did find a signal linked to mental illness that could be replicated across regional groupings. However, the status of mental illness was determined by self-reports and included more than just depression⁷⁵.

The confidence in study outcomes is limited by small sample sizes, with some as low as 20 participants⁶⁶. Differences in exclusion criteria regarding medical conditions across the 11 studies may have introduced variability in the control groups, as conditions causing systemic inflammation that could affect microbiota differences among individuals. Except for one study⁶⁶ that enforced a 7-day medication washout for all participants, and two other studies^{65,66} that assessed the role of gut microbiota in administered drugs, four other studies^{20,64,65,67} allowed the use of medication and other antipsychotic drugs, which likely impacted gut microbiome results. The inclusion of participants on antipsychotics in four of these studies complicates comparisons across studies. Antipsychotic medications, in particular, are known to influence microbial composition, with atypical antipsychotics altering gut microbiota in several studies⁷⁷⁻⁷⁹.

The Gut Microbiota's Function in Psychopathology

Many studies on the microbiome, including the 11 articles examined here, focused on the relative abundance of specific OTUs and their impact on health outcomes. Although there is individual variation, people who experienced more severe depressive symptoms often showed more noticeable alterations in microbial taxa⁶⁷. The gut microbiota is comparatively constant in the early stages of MDD¹⁰, but alterations in a few important taxa are correlated with the severity of symptoms^{10,67}. Although the gut is home to a vast array of microbial taxa, only a small number of these species hold niches within any given person. Notably, microbial composition hardly overlaps or converges, even among people who consume the same food⁶⁶ and medicinal plants¹⁹, likely because different taxa can fulfil the same metabolic functions⁸⁰, implying that individuals can host distinct but functionally comparable microbial communities. Microbial communities adapt to different environments and opportunities, taking up nutritional niches as needed⁸¹. When studying the microbiome's role in depression, focusing on the functional roles of the microbiome may

be more informative than simply tracking changes in taxonomic abundance. Stronger evidence is needed to identify reliable microbial biomarkers for depression⁶⁴. Microbial activity, including substrate utilization and metabolite production, can reveal how bacteria thrive in specific environments and influence health. Of particular interest are the metabolites that affect the nervous system and immune responses, such as inflammation, which may play a role in depression¹²². Gut microbes provide many benefits to their host, including digesting carbohydrates, producing nutrients, and supporting immune function⁸² as well as producing neuroactive molecules⁸³.

The Function of Gut Microbiota in Protein and Carbohydrate Metabolism

Important roles are played by the gut bacteria in the metabolism of food ingredients and nutrients. Several glucose metabolic pathways, specifically the starch, sucrose metabolism pathway, and the pentose phosphate pathway are implicated in the enriched microbiome functional pathways for depression, which may not be surprising given that MDD patients have been found to ingest more carbohydrates than controls⁶⁴. Gut bacteria frequently use dietary carbohydrates, particularly indigestible oligosaccharides, as a substrate to convert them into short-chain fatty acids (SCFAs), such as butyrate, valerate, propionate, and acetate. These compounds provide the host and other bacterial species with energy^{4,84}. Butyrate, propionate, and acetate are some of the primary metabolites that gut bacteria create. The absence of SCFA-producing bacteria was found to be linked to the severity of MDD^{67,69,73}.

The genera reduced in MDD generally have a broad capacity to metabolize carbohydrates, especially mono- and disaccharides and their derivatives *Bifidobacterium*, *Faecalibacterium*, *Eubacterium*, *Oscillibacter*, and *Ruminococcus*^{10,70,85-89}. The abundance of bacteria in the taxonomic ranks responsible for producing SCFAs, such as the phylum *Firmicutes*, class *Clostridia*, and order *Clostridiales*, was reported to be inversely significantly correlated with the severity of depressive symptoms at baseline⁶⁶. According to reports, *Dorea* is linked to both MDD and the quality of sleep^{24,71}. Sleep deficiencies in MDD may be mediated by *Dorea* because it is known to ferment polysaccharides into short-chain fatty acids (SCFAs)⁹⁰, and SCFAs, such as butyrate and acetate, are critical for clock gene expression, which is intimately linked to circadian rhythm and sleep quality⁷¹. In comparison to healthy controls, *Faecalibacterium* was found to be lower in MDD participants. Several related species within the family *Ruminococcaceae* also showed lower levels of *Faecalibacterium* in MDD subjects⁶⁷. Anxiety was quite high in conjunction with reduced *Bifidobacterium* and *Faecalibacterium*¹². Reduced levels of *Clostridium*, *Eubacterium*, and *Ruminococcus* dominated the highly concentrated clusters in severe MDD, in contrast to mild and intermediate patients; nonetheless, all recruited MDD patients shared depletion of *Blautia* and *Eubacterium*¹⁰. *Oscillibacter*, also referred to as butyrate-producing and inflammation-related gut microbiota taxa, were found to be negatively associated with the presence of depression^{70,87,88,91}.

However, it may be important to note that a number of the genera identified as elevated in MDD are also capable of metabolizing proteins and amino acids, including *Clostridium*, *Klebsiella*, *Parabacteroides*, *Streptococcus*, *Oscillibacter*, and *Alistipes*⁹²⁻⁹⁴. Processed meat consumption was positively correlated with *Holdemania* abundance^{70,95}. According to Chung et al⁶⁴, there is a moderate association between the genus *Holdemania* in depression, anxiety ($r = 0.22$), and perceived stress levels ($r = 0.38$)⁶⁴. Genus *Coprococcus* has been shown to have a favorable effect on blood glucose fluctuations after eating a high-protein diet^{70,96}. Additionally, according to one of the reviewed studies, butyrate production is a function of most of the bacterial species that are strongly linked to depression⁷⁰.

The microbiota's increased protein metabolism includes fermentation, also known as bacterial putrefaction, which can transfer vital host amino acids to the microorganisms and produce harmful byproducts such as phenol, putrescine, and ammonia⁹³. Genetic polymorphisms and dietary protein levels have been shown to interact to lower the risk of depression⁹⁷. Therefore, even if the research discussed here cannot be statistically tested, we can hypothesize that dysbiosis, which results in a comparatively lower capacity to metabolize carbohydrates and a higher capacity for protein metabolism, may have a role in the pathophysiology of MDD. Since inflammatory bowel disorders have been linked to a high co-morbidity with anxiety and depression, lower SCFA may contribute to symptomatology due to altered neurotransmission and decreased energy. Additionally, both lower SCFA and higher putrefaction products are implicated in intestinal inflammation⁹⁷.

Function in Communication of the Gut-Brain Axis

The bidirectional communication network of the gut-brain axis affects the brain through metabolites, including serotonin, GABA, and SCFAs^{98,99}. Research has demonstrated associations between the composition of the gut microbiota and the structure and activity of the brain as seen by MRI scans^{100,101}. For example, two bacterial profile clusters, one dominated by *Bacteroides* and the other by *Prevotella*, were found in studies including healthy female volunteers. These clusters were associated with variations in brain imaging results¹⁰¹. According to a randomized study, probiotics with several bacterial species decreased the way the insula and sensory processing regions of the brain responded to emotional tasks¹⁰².

Additionally, it has been observed that increased lipid metabolism and its byproducts support intestinal barrier maintenance and may improve probiotics' ability to treat anxiety and depression symptoms⁶⁵. The degree of anxiety and depression in MDD has been linked to biomarkers such as indole-3-carboxyaldehyde and *Veillonella parvula*, which shed light on the variety of MDD symptoms and connect clinical symptoms to gut-brain axis biomarkers¹². Since gut dysbiosis-induced inflammation can activate CNS pathways connected to depression, this linkage may help explain the frequent association between inflammatory GI illnesses and depression. Tryptophan can be diverted from serotonin synthesis to the kynurenine pathway by elevated inflammatory cytokines¹⁰³, leading to excitotoxic and neurotoxic effects¹⁰⁴.

The Gut Microbiota's Function in Autoimmune Disease and Inflammatory Regulation

According to Bhandari et al⁹⁷, 49% of patients with inflammatory bowel disease experience depressed symptoms. Several taxa, including *Prevotella*, *Enterobacteriaceae*, *Enterobacteriales*, and bacteria belonging to the family *Clostridiaceae* (i.e., species *Sarcina maxima*, *Clostridium fallax*, and *Clostridium cadaveris*) have been linked to increased intestinal permeability and inflammation^{68,105,106}. The abundance of these taxa has also been inversely correlated with some indicators of inflammation^{68,107}. However, through cross-feeding with other bacteria, *Blautia* has been shown to reduce obesity-related disorders, trigger an anti-inflammatory peripheral immune response, and control metabolism¹⁰. Ritchie et al⁶⁸ stated that individuals with MDD have higher levels of *Enterobacteriaceae*.

Intestinal fatty-acid binding protein I-FABP, IL-6 cytokine, LPS-binding protein (LPB), Calprotectin, and Zonulin are among the intestinal barrier and inflammatory indicators described in the reviewed studies^{66,108}. According to reports, I-FABP is directly correlated with the degree of suicidal symptoms in depressive patients as well as with IL-6, a cytokine that has been linked to suicide in the past¹⁰⁹⁻¹¹¹. Fecal calprotectin (dCalp), a gastrointestinal inflammatory and gut integrity marker, was found to be significantly positively correlated with a decrease in depressive symptoms in one of the reviewed studies⁶⁶. Liśkiewicz et al⁶⁶ reported that a higher baseline concentration of protein I-FABP, a marker of intestinal barrier integrity, was significantly linked to a greater reduction in depressive symptoms as measured after treatment. Since the LPS of *Bacteroides* and Gamma *proteobacteria* species is known to be immunogenic, it has been noted that the MDD group's enrichment in LPS biosynthesis pathways correlates with elevated serum immunoglobulin A and M, which are responses to the LPS of these species^{67,72}.

Gut Microbiota's Function in Relation to Autoimmune Disorders

In addition to their general effects, like maturing microglia, which are linked to the immune defense of the central nervous system and the reduction of blood-brain barrier permeability, short-chain fatty acids have been shown to have a number of specific positive effects, including lowering the incidence of colon cancer, reducing asthma, and improving the intestinal immune system when butyrate is consumed. While *Campylobacter* and *Haemophilus* have been implicated in

causing inflammation and autoimmune disorders like Graves' disease and inflammatory bowel disease, the phyla of *Proteobacteria* and *Fusobacteria* have also been linked to autoimmune disorders and inflammation (such as ulcerative colitis (UC) and inflammatory bowel disorders like CD)^{69,112-114}. *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* have also been found to have favorable effects on the central nervous system and intestinal immune systems by generating short-chain fatty acids¹¹².

By altering T cell function and enhancing cognitive impairment disease pathology by activating microglia, *Bacteroides* has been implicated in immune system maturation, tumor development, and autoimmune disease activation^{115,116}. *Proteobacteria* and *Fusobacteria* were found to be significantly more prevalent in epileptic subjects than in the healthy group, while *Firmicutes*, *Bacteroidetes*, and *Actinobacteria* were found to be significantly less prevalent in epileptic patients than in the healthy group, according to one of the reviewed studies⁶⁹. The moderate and severe subgroups showed a considerable enrichment of *Bacteroides*, whereas the mild group showed no change¹⁰.

According to Adamczyk-Sowa et al¹¹⁶, multiple sclerosis (MS) is an autoimmune illness that is typified by immune cells (such as CD4 and CD8 T cells, B cells, and activated monocytes) invading the central nervous system, demyelinating neurons, and causing subsequent pathology¹¹⁷. According to reports, certain *Bacteroides* (such as *B. stercoris*, *B. coprocola*, and *B. coprophilus*), *Faecalibacterium*, and SCAF-producing bacteria are less common in MS patients, while *Methanobrevibacter*, *Enterobacteriaceae*, and *Akkermansia* are more prevalent¹¹⁸. On the contrary, compared to individuals who are not treated, those who get disease-modifying medication had higher levels of *Prevotella*¹¹⁹.

Neurotransmitter Synthesis

Finding new pathophysiologic pathways underpinning MDD is urgently needed due to its complex etiology⁷¹. Neurotrophic changes, neurotransmission deficiencies, and endocrine-immune system disorders are among the major pathogenic events of MDD that have been strongly linked to disruption of the gut microbiota-brain axis¹². Precursors to neurotransmitters, including GABA, serotonin, norepinephrine, and dopamine^{57,120-122}.

The Function of Nutrition

Adults' self-reported long-term dietary patterns have been linked to the composition of their gut microbiota. According to Wu et al¹²¹, people who report consuming more carbohydrates and simple sugars have a higher prevalence of *Prevotella*, while people who report consuming more animal protein and saturated fats have a higher prevalence of *Bacteroides*⁷⁴. Both the microbial makeup and metabolic pathways of the gut microbiota of the responder and non-responder MDD groups showed notable changes⁶⁵.

According to Dong et al⁶⁵, Agidigbi et al¹²², and Yamamura et al¹²³, increased lipid metabolism has been shown to impact host systemic inflammation further and impact probiotics' ability to treat anxiety and depression symptoms by preserving the intestinal barrier and producing short-chain fatty acids, respectively^{65,122,123}. Habitual dietary data revealed strong positive correlations between *Faecalibacterium* fractional representation and habitual intake of several polyunsaturated fatty acids (PUFA)²⁰. *Eggerthellaceae* abundance has been shown to have a negative impact on 11-deoxy-PGE1 in the responder group and to influence lipid metabolism in radiation enteritis patients, according to Dong et al^{65,124}. Furthermore, indole produced by *Alistipes* has been shown to affect tryptophan metabolism, which is essential for controlling emotions^{71,125}. *Faecalibacterium* may be enhanced by dietary methods in circumstances where a small sample of actively depressed individuals and bipolar subjects had lower fractional representation of *Faecalibacterium* in comparison to controls²⁰.

At the genus level, one of the reviewed studies found that MDD subjects had higher levels of *Bacteroides*, *Parabacteroides*, and *Alistipes* and lower levels of *Prevotella* and *Eggerthella*^{20,70,71}.

CONCLUSIONS

Numerous human studies on mental health conditions and gut microbiota have reported psychological findings (specific to epilepsy, bipolar disorder, stress, anxiety, depression, and sleep quality) regarding microbiota proportions. However, most of these studies have small sample sizes, and no conclusions have been drawn about which bacterial taxa are most relevant to mental health conditions. As a result, the magnitude of the impact of microbial variations linked to mental health disorders is still unknown.

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Authors' Contribution

BAA initiated the topic and supervised the process. AAI did data collection, study review, and manuscript drafting. GPA did some data collection, drafting, and professional review. All three authors contributed by reviewing, offering critical amendments to the article, and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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