Microb Health Dis 2025; 7: e1345

*Microbiota in Health and Disease*
A Journal of the European Helicobacter & Microbiota Study Group

European Helicobacter & Microbiota Study Group

# GUT MICROBIOTA DIVERSITY AND MENTAL HEALTH CONDITIONS: A SYSTEMATIC REVIEW

**A.A. Israel[1], G.P. Adeniyi[2], B.A. Adeniyi[1]**

[1]Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmacy, University of Ibadan, Nigeria
[2]Federal Neuropsychiatry Hospital Aro, Abeokuta, Ogun State, Nigeria

*Corresponding Author: Bolanle A. Adeniyi, Ph.D: email: bolaadeniyi06@gmail.com*

**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 cells[1-3]. 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 disorders[5]. The gut microbiome protects the host from pathogenic bacterial colonization through the production of essential metabolites and intestinal homeostasis throughout life[6,7].

This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License

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 reported[8]. 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 schizophrenia[18-21]. Additionally, gastrointestinal problems[22,23], immunological disorders[24-26], 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 system[29-31]. 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 SCFAs[36-38]. 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 reactions[32].

## Bile Acids

As signaling molecules, they contribute to various physiological procedures ranging from digestion, metabolism, to gut immune balance[43-45]. 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 gut[48-50]. 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-

flammatory 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 metabolites[49].

### 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 compounds[36]. 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 study[62]. 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 search[63]. 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 participants[66] to large sample size of 1135 per diagnostic group[70]. Four of the studies enrolled for this review are not controlled (Table 1).

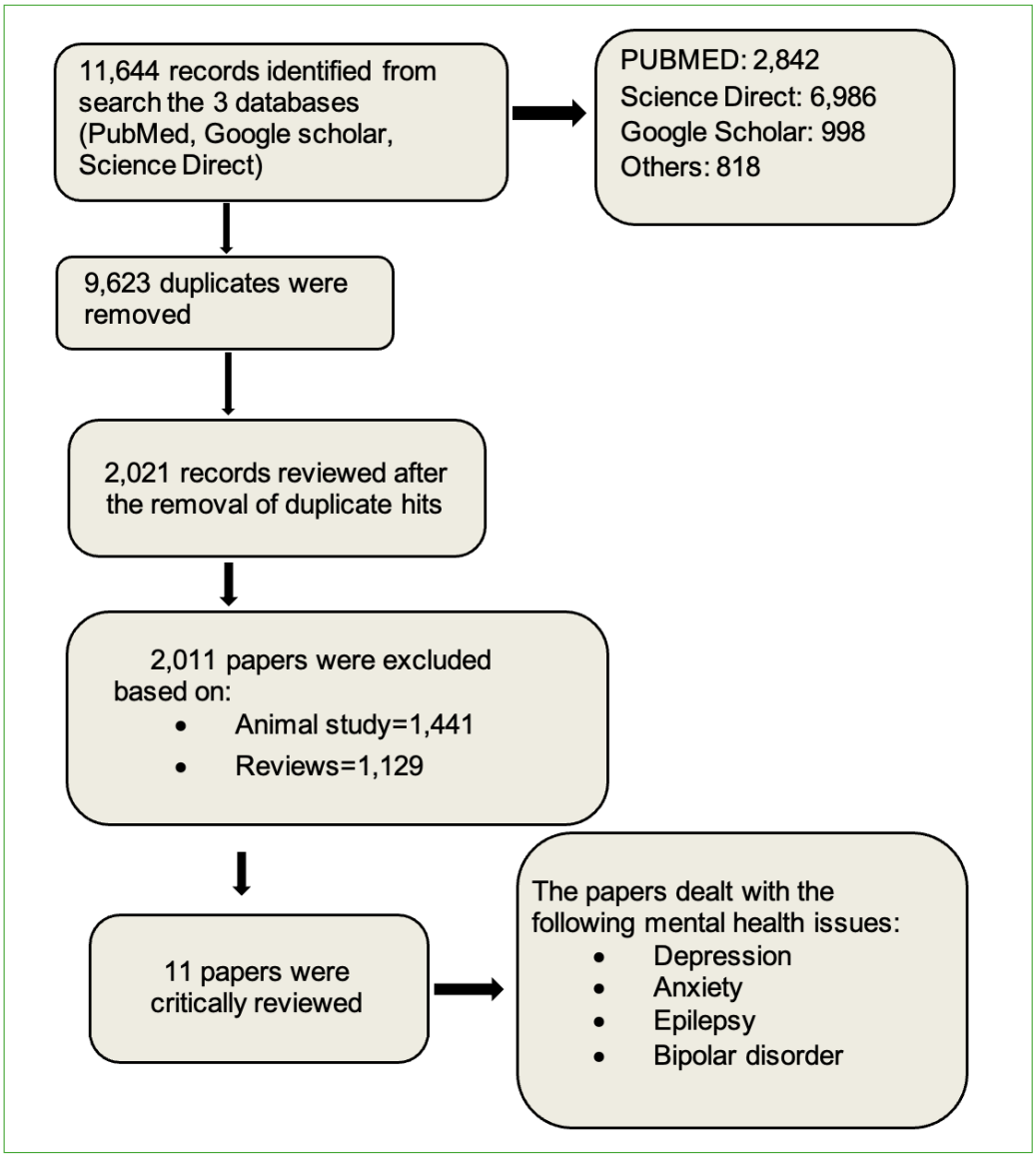


**Figure 1.** Standard preferred reporting item for systematic reviews. Major Depression Disorder (MDD), and other Mental Health Disorders.

## Medication and Use of Probiotics/Prebiotics/Symbiotics

Four studies included participants taking psychiatric medications, including probiotics, prebiotics, symbionts, 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 al[68] permitted the use of Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) while people on other drugs were exempted from the study.

Chung et al[64] 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 infections[64].

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 al[67].

**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 al[12] excluded those who took probiotics or antibiotics in the month prior to enrollment and those who received any kind of antidepressant during the two weeks[12]. In Evans et al[20], 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 al[71].

## 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 al[66] 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 al[68] excluded participants diagnosed with comorbid schizophrenia, bipolar, or current substance misuse.

Liu et al[67] enrolled participants met the diagnostic criteria for a current major depressive episode and had PROMIS Depression scores > 21 in the MDD group.

Hu et al[10] enlisted patients of different depression severity classification categories of scores ranging from 8-16, 17-23, and ≥24. Hu et al[10] 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 al[65] 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 al[69]. Furthermore, thirty patients with idiopathic focal epilepsy who were followed up for at least six months were included by Şafak et al[69]. 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 group[69].

## 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], HDRS24[66], the Center for Epidemiologic Studies Depression Scale (CES-D)[70], and the HAMD-24 scale[65].

Clinical assessments Diagnostic methods for Ritchie et al[68] 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 al[64], were interviewed using a Huang et al[72] 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 level[64]. Liu et al[67], 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) psychopathology[67]. Zhang et al[12] 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 al[20] 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 V4[68], V3eV4 region and V4 region amplification[64], V4 hypervariable region[67], V3-V4 region[12], V4 region[20], V4 hypervariable regions[66], V3 region[69], V3-V4 region[70], V3-V4 region[65]. Hu et al[10] 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 demultiplexing[64-67] 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 al[68] 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 al[71] used UPARSE and R (version 3.6.0) as a quality filter. Şafak et al[69] 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 $1 \times 10\text{-}5$[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 Chao1[12]. Four of the enrolled studies conducted generic measures for evenness[10,66,68,71]. Hu et al[10] observed species richness[67] and Faith's phylogenetic diversity[66,67], Chung et al[64] observed OTUs and PD Whole Tree. Hu et al[10] 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 al[20], PCoA was done. While Şafak et al[69] narrated the beta diversity assessment, Yang et al[70] 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 function[67] and Principal Coordinates Analysis using the ordinate function of vegan[67], logistical regressions[20], 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 coefficient[66], analysis of similarity (ANOSIM)[12,71], linear discriminant analysis effect size (LEfSe) analysis[10,71], the linear discriminant analysis (LDA) score, partial correlation analysis[71], 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 analysis[65].

## Functional Analyses

Four out of the enrolled studies did a functional assessment of the gut microbiome obtained from their respective studies. Chung et al[64] and Liu et al[67] 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 al[67] 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 al[12] 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 al[10] 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 group[69]. 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, Tyzzerella 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 level[71]. *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 group[10].

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, Megamonas, 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 XlVa, 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.XlVa, 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 al[10] 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 al[67] 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 al[10] 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 significantly[67]. 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 al[69]. Nonetheless, PCoA was carried out, demonstrating the clear microbiota grouping between epileptic patients and healthy volunteers[69]. There was no diversity reported in the study results since Yang et al[70] did not describe or disclose alpha and beta diversity.

### Functional Analysis Result

Chung et al[64] 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 al[66] 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 al[12] 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 al[68] and severe, moderate, and mild depression symptoms as classified by Hu et al[10]). 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 study[10] 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 al[12] 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 tests[71].

## 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 makeup[75]. 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 factor[76]. 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 depression[75].

The confidence in study outcomes is limited by small sample sizes, with some as low as 20 participants[66]. 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 study[66] 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 studies[77-79].

## 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 taxa[67]. The gut microbiota is comparatively constant in the early stages of MDD[10], 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 food[66] and medicinal plants[19], likely because different taxa can fulfil the same metabolic functions[80], implying that individuals can host distinct but functionally comparable microbial communities. Microbial communities adapt to different environments and opportunities, taking up nutritional niches as needed[81]. 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 depression[64]. 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 depression[122]. Gut microbes provide many benefits to their host, including digesting carbohydrates, producing nutrients, and supporting immune function[82] as well as producing neuroactive molecules[83].

## 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 controls[64]. 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 baseline[66]. 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 quality[71]. 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 subjects[67]. 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 al[64], there is a moderate association between the genus *Holdemanian* 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 depression[70].

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 ammonia[93]. Genetic polymorphisms and dietary protein levels have been shown to interact to lower the risk of depression[97]. 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 inflammation[97].

## 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 results[101]. 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 tasks[102].

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 symptoms[65]. 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 biomarkers[12]. 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 cytokines[103], leading to excitotoxic and neurotoxic effects[104].

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

According to Bhandari et al[97], 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 metabolism[10]. Ritchie et al[68] 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 past[109-111]. 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 studies[66]. Liśkiewicz et al[66] 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 acids[112].

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 studies[69]. The moderate and severe subgroups showed a considerable enrichment of *Bacteroides*, whereas the mild group showed no change[10].

According to Adamczyk-Sowa et al[116], 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 prevalent[118]. 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 etiology[71]. 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 axis[12]. 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 al[121], 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 changes[65].

According to Dong et al[65], Agidigbi et al[122], and Yamamura et al[123], 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 *Feacalibacterium* 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 controls[20].

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.

### Funding Statement

This review did not obtain any funding from public, commercial, or non-profit organization.

### 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.

### ORCID ID

Ayomide A. Israel: 0000-0002-0066-9463
Dr Grace P. Adeniyi: 0009-0008-3153-3906
Dr Bolanle A. Adeniyi: 0000-0001-9096-2235

### Conflict of Interest

The authors declare that there are no conflicts of interest.

## REFERENCES

1. Qin J. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010; 464: 59-65.
2. Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nat Med 2016; 22: 1079-1089.
3. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell 2016; 164: 337-340.
4. Turnbaugh PJ. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006; 444: 1027-1031.
5. Vinberg M, Ottesen NM, Meluken I, et al. Remitted affective disorders and high familial risk of affective disorders associate with aberrant intestinal microbiota. Acta Psychiatr Scand 2019; 139: 174-184.
6. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell 2014; 157: 121-141.
7. DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflamm Bowel Dis 2016; 22: 1137-1150.
8. Tamburini S, Shen N, Wu HC, Clemente JC. The microbiome in early life: implications for health outcomes. Nat Med 2016; 22: 713-722.
9. Arumugam M. Enterotypes of the human gut microbiome. Nature 2011; 473: 174-180.
10. Hu X, Li Y, Wu J, Zhang H, Huang Y, Tan X, Wen L, Zhou X, Xie P, Olasunkanmi OI, Zhou J, Sun Z, Liu M, Zhang G, Yang J, Zheng P, Xie P. Changes of gut microbiota reflect the severity of major depressive disorder: a cross sectional study. Transl Psychiatry 2023; 13: 137.
11. Yatsunenko T. Human gut microbiome viewed across age and geography. Nature 2012; 486: 222-227.
12. Zhang X, Hou Y, Li Y, Wei W, Cai X, Shao H, Yuan Y, Zheng X. Taxonomic and Metabolic Signatures of Gut Microbiota for Assessing the Severity of Depression and Anxiety in Major Depressive Disorder Patients. Neuroscience 2022; 496: 179-189.
13. Chen Z. Comparative metaproteomics analysis shows altered fecal microbiota signatures in patients with major depressive disorder. Neuroreport 2018; 29: 417-425.
14. Lai J, Li A, Jiang J, Yuan X, Zhang P, Xi C, Wu L, Wang Z, Chen J, Lu J, Lu S, Mou T, Zhou H, Wang D, Huang M, Dong F, Li MD, Xu Y, Song X, Hu S. Metagenomic analysis reveals gut bacterial signatures for diagnosis and treatment outcome prediction in bipolar depression. Psychiatry Res 2022; 307: 114326.
15. Lin P. Prevotella and Klebsiella proportions in fecal microbial communities are potential characteristic parameters for patients with major depressive disorder. J Affect Disord 2017; 207: 300304.
16. Rong H. Similarly in depression, nuances of gut microbiota: Evidences from a shotgun metagenomics sequencing study on major depressive disorder versus bipolar disorder with current major depressive episode patients. J Psychiatr Res 2019; 113: 90-99.

17. Valles-Colomer M. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol 2019; 4: 623-632.
18. Coello K. Gut microbiota composition in patients with newly diagnosed bipolar disorder and their unaffected first-degree relatives. Brain Behav Immun 2018; 75: 112-118.
19. Adeniyi GP, Igbokwe CO, Mahady GB, and Adeniyi, BA. The Role of Plants Having Antimicrobial Properties in the Management of Mental Health Disorders: A Review. Journal of Complementary and Alternative Medicine Res 2024; 25: 125-146.
20. Evans SJ, Bassis CM, Hein R, Assari S, Flowers SA, Kelly MB, Young VB, Ellingrod VE, McInnis MG. The gut microbiome composition associates with bipolar disorder and illness severity. J Psychiatr Res 2017; 87: 23-29.
21. Nguyen TT, Kosciolek T, Eyler LT, Knight R. Jeste DV Overview and systematic review of studies of microbiome in schizophrenia and bipolar disorder. J Psychiatr Res 2018; 99: 50-61.
22. Ahn J, Sinha R, Pei Z, Dominianni C, Wu J, Shi J, Goedert JJ, Hayes RB, Yang L. Human gut microbiome and risk for colorectal cancer. J Natl Cancer Inst 2013; 105: 19071911.
23. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. Gastroenterology 2014; 146: 1489-1499.
24. Huang Y, Shi X, Li Z, Shen Y, Shi X, Wang L, Li G, Yuan Y, Wang J, Zhang Y, Zhao L, Zhang M, Kang Y, Liang Y. Possible association of Firmicutes in the gut microbiota of patients with major depressive disorder. Neuropsychiatr Dis Treat 2018; 14 :3329-3337.
25. Kasselman LJ, Vernice NA, DeLeon J, Reiss AB. The gut microbiome and elevated cardiovascular risk in obesity and autoimmunity. Atherosclerosis 2018; 271: 203-213.
26. Scher JU, Littman DR, Abramson SB. Microbiome in Inflammatory Arthritis and Human Rheumatic Diseases. Arthritis Rheumatol 2016; 68: 35-45.
27. Arora T, Bäckhed F. The gut microbiota and metabolic disease: current understanding and future perspectives. J Intern Med 2016; 280: 339-349.
28. Jie Z, Xia H, Zhong SL, Feng Q, Li S, Liang S, Zhong H, Liu Z, Gao Y, Zhao H, Zhang D, Su Z, Fang Z, Lan Z, Li J, Xiao L, Li J, Li R, Li X, Li F, Ren H, Huang Y, Peng Y, Li G, Wen B, Dong B, Chen JY, Geng QS, Zhang ZW, Yang H, Wang J, Wang J, Zhang X, Madsen L, Brix S, Ning G, Xu X, Liu X, Hou Y, Jia H, He K, Kristiansen K. The gut microbiome in atherosclerotic cardiovascular disease. Nat Commun 2017; 8: 845.
29. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiol Stress 2017; 7: 124-136.
30. Kelly JR, Borre Y, O' Brien C, Patterson E, El Aidy S, Deane J, Kennedy PJ, Beers S, Scott K, Moloney G, Hoban AE, Scott L, Fitzgerald P, Ross P, Stanton C, Clarke G, Cryan JF, Dinan TG. Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res 2016; 82: 109-118.
31. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The Central Nervous System and the Gut Microbiome. Cell 2016; 167: 915-932.
32. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the Manipulation of Bacteria-Gut-Brain Signals. Trends Neurosci 2016; 39: 763-781.
33. Kelly J. Breaking down the barriers: the gut microbiome, intestinal permeability and stressrelated psychiatric disorders. Front Cell Neurosci 2015; 9: 392.
34. Koh A, Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell 2016; 165: 1332-1345.
35. Sun J, Chang EB. Exploring gut microbes in human health and disease: Pushing the envelope. Genes Dis 2014; 1: 132-139.
36. Caspani G, Kennedy S, Foster JA, Swann J. Gut microbial metabolites in depression: understanding the biochemical mechanisms. Microb Cell 2019; 6: 454-481.
37. Meckel KR, Kiraly DD. A potential role for the gut microbiome in substance use disorders. Psychopharmacology (Berl) 2019; 236: 1513-1530.
38. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes 2016; 7: 189-200.
39. Joseph J, Depp C, Shih PB, Cadenhead KS, Schmid-Schönbein G. Modified Mediterranean Diet for Enrichment of Short Chain Fatty Acids: Potential Adjunctive Therapeutic to Target Immune and Metabolic Dysfunction in Schizophrenia? Front Neurosci 2017; 11: 155.
40. Stilling RM, Dinan TG, Cryan JF. Microbial genes, brain & behaviour - epigenetic regulation of the gut-brain axis. Genes Brain Behav 2014; 13: 69-86.
41. Bonaz B, Sinniger V, Pellissier S. Vagus Nerve Stimulation at the Interface of Brain-Gut Interactions. Cold Spring Harb Perspect Med 2019; 9: a034199.
42. Raybould HE. Gut chemosensing: interactions between gut endocrine cells and visceral afferents. Auton Neurosci 2010; 153: 41-46.
43. Li Z, Quan G, Jiang X, Yang Y, Ding X, Zhang D, Wang X, Hardwidge PR, Ren W, Zhu G. Effects of Metabolites Derived From Gut Microbiota and Hosts on Pathogens. Front Cell Infect Microbiol 2018; 8: 314.
44. van de Wouw M, Schellekens H, Dinan TG, Cryan JF. Microbiota-Gut-Brain Axis: Modulator of Host Metabolism and Appetite. J Nutr 2017; 147: 727-745.
45. Chiang JY. Bile acid metabolism and signaling. Compr Physiol 2013; 3: 1191-212.
46. Sayin SI, Wahlström A, Felin J, Jäntti S, Marschall HU, Bamberg K, Angelin B, Hyötyläinen T, Orešič M, Bäckhed F. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist. Cell Metab 2013; 17: 225-235.
47. Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. Cell Metab 2016; 24: 41-50.

48. Agus A, Planchais J, Sokol H. Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. Cell Host Microbe 2018; 23: 716-724.
49. O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav Brain Res 2015; 277: 32-48.
50. Roager HM, Licht TR. Microbial tryptophan catabolites in health and disease. Nat Commun 2018; 9: 3294.
51. Waclawiková B, El Aidy S. Role of Microbiota and Tryptophan Metabolites in the Remote Effect of Intestinal Inflammation on Brain and Depression. Pharmaceuticals (Basel) 2018; 11: 63.
52. Sofia MA, Ciorba MA, Meckel K, Lim CK, Guillemin GJ, Weber CR, Bissonnette M, Pekow JR. Tryptophan Metabolism through the Kynurenine Pathway is Associated with Endoscopic Inflammation in Ulcerative Colitis. Inflamm Bowel Dis 2018; 24: 1471-1480.
53. Levy M, Thaiss CA, Elinav E. Metabolites: messengers between the microbiota and the immune system. Genes Dev 2016; 30: 1589-1597.
54. Rothhammer V, Mascanfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, Chao CC, Patel B, Yan R, Blain M, Alvarez JI, Kébir H, Anandasabapathy N, Izquierdo G, Jung S, Obholzer N, Pochet N, Clish CB, Prinz M, Prat A, Antel J, Quintana FJ. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. Nat Med 2016; 22: 586-597.
55. Berger M, Gray JA, Roth BL. The Expanded Biology of Serotonin. Annu Rev Med 2009; 60: 355-366.
56. Hyland NP, Cryan JF. A Gut Feeling about GABA: Focus on GABA(B) Receptors. Front Pharmacol 2010; 1: 124.
57. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. J Appl Microbiol 2012; 113: 411-417.
58. Pokusaeva K, Johnson C, Luk B, Uribe G, Fu Y, Oezguen N, Matsunami RK, Lugo M, Major A, Mori-Akiyama Y, Hollister EB, Dann SM, Shi XZ, Engler DA, Savidge T, Versalovic J. GABA-producing Bifidobacterium dentium modulates visceral sensitivity in the intestine. Neurogastroenterol Motil 2017; 29: e12904.
59. Shishov VA, Kirovskaia TA, Kudrin VS, Oleskin AV. [Amine neuromediators, their precursors, and oxidation products in the culture of Escherichia coli K-12]. Prikl Biokhim Mikrobiol 2009; 45: 550-554. Russian.
60. Asano Y, Hiramoto T, Nishino R, Aiba Y, Kimura T, Yoshihara K, Koga Y, Sudo N. Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice. Am J Physiol Gastrointest Liver Physiol 2012; 303: G1288-95.
61. Matsumoto M, Kibe R, Ooga T, Aiba Y, Sawaki E, Koga Y, Benno Y. Cerebral low-molecular metabolites influenced by intestinal microbiota: a pilot study. Front Syst Neurosci 2013; 7: 9.
62. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
63. Harzing A. Publish or Perish; Harzing Resources. Available online at: https://harzing.com/resources/publish-or-perish.
64. Chung YE, Chen HC, Chou HL, Chen IM, Lee MS, Chuang LC, Liu YW, Lu ML, Chen CH, Wu CS, Huang MC, Liao SC, Ni YH, Lai MS, Shih WL, Kuo PH. Exploration of microbiota targets for major depressive disorder and mood related traits. J Psychiatr Res 2019; 111: 74-82.
65. Dong Z, Shen X, Hao Y, Li J, Xu H, Yin L, Kuang W. Gut microbiome: A potential indicator for predicting treatment outcomes in major depressive disorder. Front Neurosci 2022; 16: 813075.
66. Liśkiewicz P, Kaczmarczyk M, Misiak B, Wroński M, Bąba-Kubiś A, Skonieczna-Żydecka K, Marlicz W, Bieńkowski P, Misera A, Pełka-Wysiecka J, Kucharska-Mazur J, Konopka A, Łoniewski I, Samochowiec J. Analysis of gut microbiota and intestinal integrity markers of inpatients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2021; 106: 110076.
67. Liu RT, Rowan-Nash AD, Sheehan AE, Walsh RFL, Sanzari CM, Korry BJ, Belenky P. Reductions in anti-inflammatory gut bacteria are associated with depression in a sample of young adults. Brain Behav Immun 2020; 88: 308-324.
68. Ritchie G, Strodl E, Parham S, Bambling M, Cramb S, Vitetta L. An exploratory study of the gut microbiota in major depression with anxious distress. J Affect Disord 2023; 320: 595-604.
69. Şafak B, Altunan B, Topçu B, Eren Topkaya A. The gut microbiome in epilepsy. Microb Pathog 2020; 139: 103853.
70. Yang Y, Mori M, Wai KM, Jiang T, Sugimura Y, Munakata W, Mikami T, Murashita K, Nakaji S, Ihara K. The Association between Gut Microbiota and Depression in the Japanese Population. Microorganisms 2023; 11: 2286.
71. Zhang Q, Yun Y, An H, Zhao W, Ma T, Wang Z, Yang F. Gut Microbiome Composition Associated With Major Depressive Disorder and Sleep Quality. Front Psychiatry 2021; 12: 645045.
72. Huang TT, Lai JB, Du YL, Xu Y, Ruan LM, Hu SH. Current Understanding of Gut Microbiota in Mood Disorders: An Update of Human Studies. Front Genet 2019; 10: 98.
73. Madan A, Thompson D, Fowler JC, Ajami NJ, Salas R, Frueh BC, Bradshaw MR, Weinstein BL, Oldham JM, Petrosino JF. The gut microbiota is associated with psychiatric symptom severity and treatment outcome among individuals with serious mental illness. J Affect Disord 2020; 264: 98-106.
74. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011; 334: 105-108.
75. McDonald D, Hyde E, Debelius JW, Morton JT, Gonzalez A, Ackermann G, Aksenov AA, Behsaz B, Brennan C, Chen Y, DeRight Goldasich L, Dorrestein PC, Dunn RR, Fahimipour AK, Gaffney J, Gilbert JA, Gogul G, Green JL, Hugenholtz P, Humphrey G, Huttenhower C, Jackson MA, Janssen S, Jeste DV, Jiang L, Kelley ST, Knights D, Kosciolek T,

Ladau J, Leach J, Marotz C, Meleshko D, Melnik AV, Metcalf JL, Mohimani H, Montassier E, Navas-Molina J, Nguyen TT, Peddada S, Pevzner P, Pollard KS, Rahnavard G, Robbins-Pianka A, Sangwan N, Shorenstein J, Smarr L, Song SJ, Spector T, Swafford AD, Thackray VG, Thompson LR, Tripathi A, Vázquez-Baeza Y, Vrbanac A, Wischmeyer P, Wolfe E, Zhu Q; American Gut Consortium; Knight R. American Gut: an Open Platform for Citizen Science Microbiome Research. mSystems 2018; 3: e00031-18.
76. He Y, Wu W, Zheng HM, Li P, McDonald D, Sheng HF, Chen MX, Chen ZH, Ji GY, Zheng ZD, Mujagond P, Chen XJ, Rong ZH, Chen P, Lyu LY, Wang X, Wu CB, Yu N, Xu YJ, Yin J, Raes J, Knight R, Ma WJ, Zhou HW. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. Nat Med 2018; 24: 1532-1535.
77. Bahr SM, Weidemann BJ, Castro AN, Walsh JW, deLeon O, Burnett CM, Pearson NA, Murry DJ, Grobe JL, Kirby JR. Risperidone-induced weight gain is mediated through shifts in the gut microbiome and suppression of energy expenditure. EBioMedicine 2015; 2: 1725-1734.
78. Macedo D, Filho AJMC, Soares de Sousa CN, Quevedo J, Barichello T, Júnior HVN, Freitas de Lucena D. Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. J Affect Disord 2017; 208: 22-32.
79. Morgan AP, Crowley JJ, Nonneman RJ, Quackenbush CR, Miller CN, Ryan AK, Bogue MA, Paredes SH, Yourstone S, Carroll IM, Kawula TH, Bower MA, Sartor RB, Sullivan PF. The antipsychotic olanzapine interacts with the gut microbiome to cause weight gain in mouse. PLoS One 2014; 9: e115225.
80. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012; 486: 207-214.
81. Tannock GW. Understanding the Gut Microbiota. John Wiley & Sons; 2017.
82. Kamada N, Chen GY, Inohara N, Núñez G. Control of pathogens and pathobionts by the gut microbiota. Nat Immunol 2013; 14: 685-690.
83. Lyte M. Microbial endocrinology in the microbiome-gut-brain axis: how bacterial production and utilization of neurochemicals influence behavior. PLoS Pathog 2013; 9: e1003726.
84. Cheung SG, Goldenthal AR, Uhlemann AC, Mann JJ, Miller JM, Sublette ME. Systematic Review of Gut Microbiota and Major Depression. Front Psychiatry 2019; 10: 34.
85. Boets E, Gomand SV, Deroover L, Preston T, Vermeulen K, De Preter V, Hamer HM, Van den Mooter G, De Vuyst L, Courtin CM, Annaert P, Delcour JA, Verbeke KA. Systemic availability and metabolism of colonic-derived short-chain fatty acids in healthy subjects: a stable isotope study. J Physiol 2017; 595: 541-555.
86. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, Pettersson S. Host-gut microbiota metabolic interactions. Science 2012; 336: 1262-1267.
87. Valido E, Bertolo A, Fränkl GP, Itodo OA, Pinheiro T, Pannek J, Kopp-Heim D, Glisic M, Stoyanov J. Systematic review of the changes in the microbiome following spinal cord injury: animal and human evidence. Spinal Cord 2022; 60: 288-300.
88. Wang K, Wu S, Li P, Xiao N, Wen J, Lin J, Lu S, Cai X, Xu Y, Du B. Sacha Inchi Oil Press-Cake Protein Hydrolysates Exhibit Anti-Hyperuricemic Activity via Attenuating Renal Damage and Regulating Gut Microbiota. Foods 2022; 11: 2534.
89. Yang C, Deng Q, Xu J, Wang X, Hu C, Tang H, Huang F. Sinapic acid and resveratrol alleviate oxidative stress with modulation of gut microbiota in high-fat diet-fed rats. Food Res Int 2019; 116: 1202-1211.
90. Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, Thangaraju M, Prasad PD, Manicassamy S, Munn DH, Lee JR, Offermanns S, Ganapathy V. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity 2014; 40: 128-139.
91. Takahashi K, Nishida A, Fujimoto T, Fujii M, Shioya M, Imaeda H, Inatomi O, Bamba S, Sugimoto M, Andoh A. Reduced Abundance of Butyrate-Producing Bacteria Species in the Fecal Microbial Community in Crohn's Disease. Digestion 2016; 93: 59-65. doi: 10.1159/000441768. Epub 2016 Jan 14. Erratum in: Digestion 2016; 93: 174.
92. Caminero A, Herrán AR, Nistal E, Pérez-Andrés J, Vaquero L, Vivas S, Ruiz de Morales JM, Albillos SM, Casqueiro J. Diversity of the cultivable human gut microbiome involved in gluten metabolism: isolation of microorganisms with potential interest for coeliac disease. FEMS Microbiol Ecol 2014; 88: 309-319.
93. Kaur H, Das C, Mande SS. In Silico Analysis of Putrefaction Pathways in Bacteria and Its Implication in Colorectal Cancer. Front Microbiol 2017; 8: 2166.
94. McLuskey K, Grewal JS, Das D, Godzik A, Lesley SA, Deacon AM, Coombs GH, Elsliger MA, Wilson IA, Mottram JC. Crystal Structure and Activity Studies of the C11 Cysteine Peptidase from Parabacteroides merdae in the Human Gut Microbiome. J Biol Chem 2016; 291: 9482-9491.
95. Boolani A, Gallivan KM, Ondrak KS, Christopher CJ, Castro HF, Campagna SR, Taylor CM, Luo M, Dowd SE, Smith ML, Byerley LO. Trait Energy and Fatigue May Be Connected to Gut Bacteria among Young Physically Active Adults: An Exploratory Study. Nutrients 2022; 14: 466.
96. Tettamanzi F, Bagnardi V, Louca P, Nogal A, Monti GS, Mambrini SP, Lucchetti E, Maestrini S, Mazza S, Rodriguez-Mateos A, Scacchi M, Valdes AM, Invitti C, Menni C. A High Protein Diet Is More Effective in Improving Insulin Resistance and Glycemic Variability Compared to a Mediterranean Diet-A Cross-Over Controlled Inpatient Dietary Study. Nutrients 2021; 13: 4380.
97. Bhandari S, Larson ME, Kumar N, Stein D. Association of Inflammatory Bowel Disease (IBD) with Depressive Symptoms in the United States Population and Independent Predictors of Depressive Symptoms in an IBD Population: A NHANES Study. Gut Liver 2017; 11: 512-519.
98. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. J Clin Invest 2015; 125: 926-938.
99. Wang HX, Wang YP. Gut Microbiota-brain Axis. Chin Med J (Engl) 2016; 129: 2373-2380.

100. Fernandez-Real JM, Serino M, Blasco G, Puig J, Daunis-i-Estadella J, Ricart W, Burcelin R, Fernández-Aranda F, Portero-Otin M. Gut Microbiota Interacts With Brain Microstructure and Function. J Clin Endocrinol Metab 2015; 100: 4505-4513.
101. Tillisch K, Mayer EA, Gupta A, Gill Z, Brazeilles R, Le Nevé B, van Hylckama Vlieg JET, Guyonnet D, Derrien M, Labus JS. Brain Structure and Response to Emotional Stimuli as Related to Gut Microbial Profiles in Healthy Women. Psychosom Med 2017; 79: 905-913.
102. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, Ebrat B, Guyonnet D, Legrain-Raspaud S, Trotin B, Naliboff B, Mayer EA. Consumption of fermented milk product with probiotic modulates brain activity. Gastroenterology 2013; 144: 1394-401, 1401.e1-4.
103. Miura H, Ozaki N, Sawada M, Isobe K, Ohta T, Nagatsu T. A link between stress and depression: shifts in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression. Stress 2008; 11: 198-209.
104. Guillemin GJ. Quinolinic acid, the inescapable neurotoxin. FEBS J 2012; 279: 1356-1365.
105. Larsen JM. The immune response to Prevotella bacteria in chronic inflammatory disease. Immunology 2017; 151: 363-374.
106. Pedersen C, Ijaz UZ, Gallagher E, Horton F, Ellis RJ, Jaiyeola E, Duparc T, Russell-Jones D, Hinton P, Cani PD, La Ragione RM, Robertson MD. Fecal Enterobacteriales enrichment is associated with increased in vivo intestinal permeability in humans. Physiol Rep 2018; 6: e13649.
107. Chen YH, Bai J, Wu D, Yu SF, Qiang XL, Bai H, Wang HN, Peng ZW. Association between fecal microbiota and generalized anxiety disorder: Severity and early treatment response. J Affect Disord 2019; 259: 56-66. doi: 10.1016/j.jad.2019.08.014. Epub 2019 Aug 13. Erratum in: J Affect Disord 2020; 260: 489.
108. Beşer OF, Sancak S, Erkan T, Kutlu T, Cokuğraş H, Cokuğraş FÇ. Can Fecal Calprotectin Level Be Used as a Markers of Inflammation in the Diagnosis and Follow-Up of Cow's Milk Protein Allergy? Allergy Asthma Immunol Res 2014; 6: 33-38.
109. Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, Minthon L, Hansson O, Björkqvist M, Träskman-Bendz L, Brundin L. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biol Psychiatry 2009; 66: 287-292.
110. Niculescu AB, Levey DF, Phalen PL, Le-Niculescu H, Dainton HD, Jain N, Belanger E, James A, George S, Weber H, Graham DL, Schweitzer R, Ladd TB, Learman R, Niculescu EM, Vanipenta NP, Khan FN, Mullen J, Shankar G, Cook S, Humbert C, Ballew A, Yard M, Gelbart T, Shekhar A, Schork NJ, Kurian SM, Sandusky GE, Salomon DR. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. Mol Psychiatry 2015; 20: 1266-1285.
111. Ohlsson L, Gustafsson A, Lavant E, Suneson K, Brundin L, Westrin Å, Ljunggren L, Lindqvist D. Leaky gut biomarkers in depression and suicidal behavior. Acta Psychiatr Scand 2019; 139: 185-193. doi: 10.1111/acps.12978. Epub 2018 Nov 1. Erratum in: Acta Psychiatr Scand 2020; 142: 423.
112. Brusaferro A, Cavalli E, Farinelli E, Cozzali R, Principi N, Esposito S. Gut dysbiosis and paediatric Crohn's disease. J Infect 2019; 78: 1-7.
113. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. Clin Exp Immunol 2019; 195: 74-85.
114. Mohebali N, Ekat K, Kreikemeyer B, Breitrück A. Barrier Protection and Recovery Effects of Gut Commensal Bacteria on Differentiated Intestinal Epithelial Cells In Vitro. Nutrients 2020; 12: 2251.
115. Nakajima A, Sasaki T, Itoh K, Kitahara T, Takema Y, Hiramatsu K, Ishikawa D, Shibuya T, Kobayashi O, Osada T, Watanabe S, Nagahara A. A Soluble Fiber Diet Increases Bacteroides fragilis Group Abundance and Immunoglobulin A Production in the Gut. Appl Environ Microbiol 2020; 86: e00405-20.
116. Adamczyk-Sowa M, Medrek A, Madej P, Michlicka W, Dobrakowski P. Does the Gut Microbiota Influence Immunity and Inflammation in Multiple Sclerosis Pathophysiology? J Immunol Res 2017; 2017: 7904821.
117. Miyake S, Kim S, Suda W, Oshima K, Nakamura M, Matsuoka T, Chihara N, Tomita A, Sato W, Kim SW, Morita H, Hattori M, Yamamura T. Dysbiosis in the Gut Microbiota of Patients with Multiple Sclerosis, with a Striking Depletion of Species Belonging to Clostridia XIVa and IV Clusters. PLoS One 2015; 10: e0137429.
118. Mete A, Garcia J, Ortega J, Lane M, Scholes S, Uzal FA. Brain lesions associated with clostridium perfringens type D epsilon toxin in a Holstein heifer calf. Vet Pathol 2013; 50: 765-768.
119. Williams BB, Van Benschoten AH, Cimermancic P, Donia MS, Zimmermann M, Taketani M, Ishihara A, Kashyap PC, Fraser JS, Fischbach MA. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. Cell Host Microbe 2014; 16: 495-503.
120. Wall R, Cryan JF, Ross RP, Fitzgerald GF, Dinan TG, Stanton C. Bacterial neuroactive compounds produced by psychobiotics. Adv Exp Med Biol 2014; 817: 221-239.
121. Wu L, Shen F, Wang W, et al. The effect of multispecies probiotics on cognitive reactivity to sad mood in patients with Crohn's disease. J Funct Foods 2021; 82: 104431.
122. Agidigbi TS, Adeniyi GP, Adeniyi BA, Majekodunmi OE and Mahady, GB. Inflammatory Pathways: A Review of the Complex Interaction between Infection, Chronic Disorders and Psychiatric Disorders. Asian Journal of Research & Reports in Neurology 2025; 8: 27-51.
123.Yamamura R, Okubo R, Katsumata N, Odamaki T, Hashimoto N, Kusumi I, Xiao J, Matsuoka YJ. Lipid and Energy Metabolism of the Gut Microbiota Is Associated with the Response to Probiotic Bifidobacterium breve Strain for Anxiety and Depressive Symptoms in Schizophrenia. J Pers Med 2021; 11: 987.
124. Zhao K, Li W, Kang C, Du L, Huang T, Zhang X, Wu M, Yue B. Phylogenomics and evolutionary dynamics of the family Actinomycetaceae. Genome Biol Evol 2014; 6: 2625-2633.
125. Song Y, Könönen E, Rautio M, Liu C, Bryk A, Eerola E, Finegold SM. Alistipes onderdonkii sp. nov. and Alistipes shahii sp. nov., of human origin. Int J Syst Evol Microbiol 2006; 56: 1985-1990.