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Association Between Gut Microbiome and Major Depressive Disorder, Bipolar Disorder and Schizophrenia: A Systematic Review

Imran Rangraze[1], Shehla Shafi Khan[2], Adil Farooq wali[3], Godfred Menezes[4], Manjunatha Goud[5], Muhammad Jabran[6]

Abstract

Background: Gut bacteria have been shown to disrupt homeostatic balance and influence the pathophysiology of a broad variety of psychological diseases, even though they play a significant role in normal health maintenance. It has long been assumed that the gut microbiota plays a crucial role in the pathophysiology of major depression disorder (MDD), bipolar disorder (BD), and schizophrenia (SZ). A definite cause-and-effect connection has not, however, been demonstrated. Microbial dysbiosis, which is linked to MDD, BD and SZ is characterised as an imbalance in microbial diversity brought on by the disruption of the microbiota's delicate balance and the ensuing psychological abnormalities.

Therefore, we recently conducted a systematic review of the observational literature comparing the composition of gut microbiota in persons with MDD, SZ, BD with healthy controls.

Methods: This review was written according to the guidelines established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Pubmed, Scopus, Embase, Web of Science, Ovid, Global Health, PsycINFO, etc. were searched thoroughly using the phrases "gut microbiota, psychological disorders, composition, major depressive disorder, bipolar disorders, schizophrenia, etc."

Results: For this comprehensive assessment, 26 articles were chosen. Our analysis showed an increase in lactic acid-producing bacteria in all three psychological disorders (MDD, BD, and SZ). Cases of the three psychological disorders had a greater prevalence of the genus Lactobacillus. Other lactic acid manufacturers, such as Enterococcus and Streptococcus and Bifidobacterium were also observed to be more abundant in patients with MDD, BD, SZ respectively. Our analysis also revealed that all three psychological disorders shared an increase in the abundance of bacteria involved in the metabolism of glutamate and aminobutyric acid (GABA). It was observed that number of butyrate producing gut microbiota was lower in these psychological disorders.

[1] Associate professor, Department of Internal medicine, RAK Medical and Health Science University, RAK, UAE, imranrashid@rakmhsu.ac.ae
[2] Senior Instructor, Department of Psychiatry, RAK Medical and Health Science University, RAK, UAE
[3] Associate Professor, Department of Phramaceutical chemistry, RAK Medical and Health Science University, RAK, UAE
[4] Professor, Department of Microbiology, RAK Medical and Health Science University, RAK, UAE
[5] Professor, Department of Biochemistry, RAK Medical and Health Science University, RAK, UAE
[6] Medical Intern, RAK Medical and Health Science University, RAK, UAE

Conclusion: There was a general trend toward increased abundances of bacteria involved in glutamate and GABA metabolism, and lower abundances of butyrate-producing bacteria in psychological disorders namely MDD, BD and SZ.

Keywords: *Major Depression Disorder, Bipolar Disorder, Schizophrenia, gut microbiome.*

Introduction

Gut microbiome i.e symbiotic bacteria in the human gastrointestinal (GI) tract is part of essential “metabolic machinery” for human bodies. Some define the gut microbiome as a 'virtual organ' [1] due to the extent to which it affects numerous facets of physiology through neurological, hormonal, and immunological pathways. The link between the intestinal microbiota and the central nervous system is referred to as the “bacteria-gut-brain axis” [2]. Even though they play a significant role in health maintenance, gut bacteria have been shown to disrupt homeostatic balance and influence the pathophysiology of a broad variety of diseases [3,4].

“Psychological disorders are the most frequent mental comorbidity in people with functional GI difficulties [5,6], and abdominal discomfort is one of the most known physical signs of sadness [7,9]. There is growing evidence that the gut microbiota plays a role in irregularity of inflammation [8], oxidative stress [9], tryptophan metabolism [10], mitochondrial dysfunction [11], neurotransmitters physiology [12], regulation of brain plasticity and neurotrophic factors [13], and metabolic processes [14]. All these events can be linked to pathophysiology of psychological disorders like MDD, BD and SZ. [15, 20-22]. Now, there are a number of observational studies that have looked at whether or not the gut microbiota of persons with these psychological problems differs from that of healthy controls.

There are many significant mediators that play a role in the interactions between the gut microbiota and the host, including microbial metabolites that are created by the bacteria themselves, bacterially-modified host molecules like bile acids (BAs), and products that are directly produced by the bacteria themselves. [15-19] The microbial metabolome changes as a result of changes in the gut microbiota in MDD, which contribute to the disease's etiology.

The trillions of bacteria, viruses, archaea, and fungus that live in our digestive tract contribute to human health. However, a conclusive causal relationship has not been conclusively established. Microbial dysbiosis, associated with Major Depressive Disorder (MDD),Schizophrenia (SZ) and Bipolar disorder (BD), is characterized by an imbalance in microbial diversity resulting from the disruption of the microbiota's delicate equilibrium and the subsequent emergence of psychological abnormalities. [23-29].

Consequently, we have recently undertaken a systematic review of observational literature to compare the gut microbiota composition of individuals with MDD, Schizophrenia (SZ), Bipolar Disorder (BD), and healthy controls in order to elucidate potential associations.

Methods

This review was written according to the guidelines established by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Not a single rule was broken, yet a more thorough search strategy did provide more relevant results. (figure1).

Sources of information

Pubmed, Scopus, Embase, Web of Science, Ovid, Global Health, PsycINFO, etc. were searched thoroughly using the phrases “gut microbiota, psychological disorders, composition, major depressive disorder, bipolar disorders, schizophrenia, etc.” Extensive searches were performed for all publications using inclusion and exclusion criteria.in the range of June 28th, 2018 and June 28th, 2023.

Eligibility criteria for selection

Included were original studies, literature reviews, scientific communications, systematic reviews, letters to the editor, and many additional preprints addressing the following areas related to gut microbiota and psychiatric disorders: (1) The role of the gut microbiome in depression (2) The role of the gut microbiome in bipolar disorder (3) Schizophrenia risk factors: the gut microbiome, (4) A link may be seen between the diversity of gut microbiota and personal disorders. Exclusion criteria were outlined as follows: Publications discovered in newspapers, magazines, blogs, and other non-academic venues; (1) written materials not in English; (2) documents related to issues not included in the inclusion requirements; (3) publications not written for an academic audience

Reviewing process

Before being tasked with the screening activity, reviewers received training in both full-text evaluation and assessment of simply the abstracts. The test was executed in an abstract manner using the Rayyan program. While one observer (AB) looked through all of the search results, three researchers (XX, HH, and JJ) independently reviewed 33.33 percent of the total hits twice. After reading the abstracts, the review committee got together to resolve their differences and create the final list of articles that needed to be evaluated in full. A full-text review was conducted using the Covidence program. Two independent reviewers, WW and YY, read the whole articles and rated them according to the criteria. When researchers weren't sure whether or not a certain method was employed in an article, they went straight to the authors to ask for clarification. Members of the panel and reviewers from the scientific committee reached consensus on the final list of articles to be considered for review.

Evaluation of the quality of the included studies

The effectiveness of the chosen studies was evaluated using the "risk of bias" technique developed by the Cochrane Collaboration. Each of the seven bias risk domains—random sequence generation, allocation concealment, participant and staff blinding, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias—was subjected to an individual critical examination. Each domain was categorised as having a low, unclear, or high risk of bias. Two independent researchers extracted the qualitative and quantitative data, evaluated the risk of bias, and extracted the information. Discussions amongst the evaluators were used to settle disagreements.

Results

Results of search of study

189 papers were discovered through a literature search using search criteria. There were 124 publications that were excluded because they were duplicates or similar. 65 different articles were first chosen. Following an examination of the titles and abstracts, thirty publications were removed. For 35 articles, full text management was done. Extra two papers were manually retrieved from references. There were 37 articles with full texts that could be read. 11 subpar articles were eliminated from the final evaluation. Finally, for this comprehensive assessment, 26 articles were chosen. (figure 1) (Table 1)

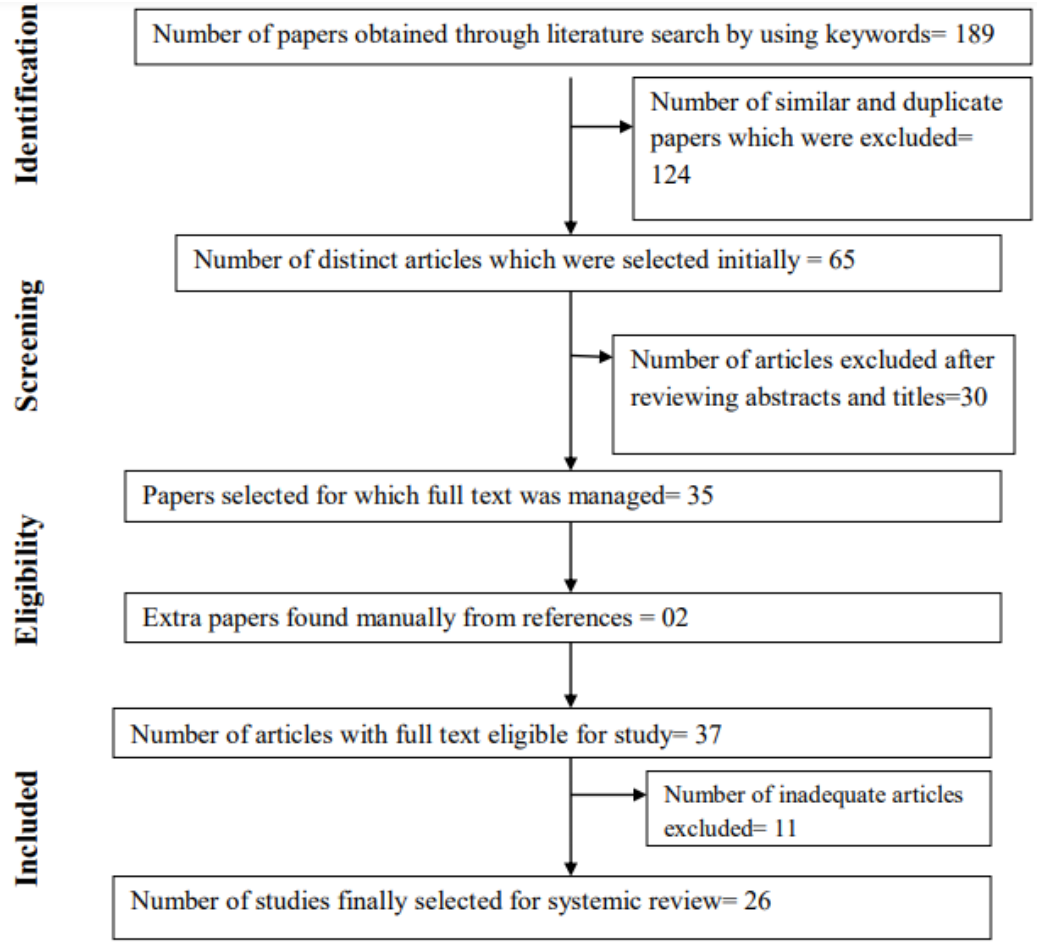

Figure 1: PRISMA flowchart for selection of studies in systematic review

Table 1: Important features of studies included in systematic review

S. No	Authors with year	Intension and motive	Psychological disorder evaluated and basic methodology	Results and Conclusion
1	Bai S et al 2021 [31]	This study set out to test the hypothesis that inflammatory blood metabolites produced by the gut microbiota may act as biomarkers for clinical depression	MDD	The results suggested that disruption of the phylum Firmicutes may play a role in the onset of depression by regulating the host's inflammatory response. Five inflammation-related metabolites were identified as potential biomarkers that could be useful in future as investigation for diagnosing MDD.

2	Chen JJ et al, 2018 [32]	The purpose of this research was to learn about the alterations in gut microbiota that occur in persons with MDD.	MDD	It was discovered that Firmicutes was significantly lower in young MDD patients compared to young healthy controls (HC) and Bacteroidetes being significantly lower in middle-aged MDD patients compared to middle-aged HCs
3	Chen YH et al, 2020 [33]	The purpose of this research was to evaluate gut microbiota and their functions in major depressive illness in females.	MDD	Bacteroidetes, proteobacteria, and Fusobacteria were greater in the microbiomes of female patients with MDD, whereas Firmicutes and Actinobacteria were consistently low in the microbiomes
4	Chen JJ et al ,2018 [34]	The study's authors aimed to determine if there were gender differences in the gut microbiome of people with MDD.	Female and male MDD patients were compared to healthy controls.	The most notable differences in bacterial taxa between female and male MDD patients were seen in the phyla Actinobacteria and Bacteroidia.
5.	Dong Z et al,2021 [35]	To examine the variations in gut microbiota between cases of MDD and general anxiety disorders (GAD)	MDD, GAD	GAD had a higher prevalence of Sutterella than MDD, but Faecalibacterium was much less common
6.	Huang Y et al,2018 [36]	Researchers studied the impact of Firmicutes in people with MDD	MDD	The MDD samples show the most dramatic reduction in the phylum Firmicutes. Thirteen taxonomic biomarkers from firmicutes have been

				shown to have significant reduction in patients with MDD.
7.	Kelly JR e al,2016 [37]	To determine whether or not changes in the gut microbiota's composition and function are involved in pathways for MDD	MDD	Anxiety-like behaviors and alterations in tryptophan metabolism associated with gut microbiota.
8.	Lin P et al 2017 [38]	Authors looked at the possibility that the relative abundance of Prevotella and Klebsiella in the gut microbiome might serve as a diagnostic marker for individuals with severe depressive disorder.	MDD	There was a decrease in Bacteroidetes, as well as an increase in the numbers of bacteria belonging to the genera Prevotella, Klebsiella, Streptococcus, and Clostridium XI. Prevotella and Klebsiella in the gut microbiome might serve as a diagnostic marker for individuals with severe depressive disorder.
9.	Liu RT et al, 2020 [39]	This study tried to found that among young individuals, depression was linked to a decline in anti-inflammatory gut flora.	The scientists compared the gut microbiota of 43 persons with MDD and 47 healthy controls, analyzing the gut microbiota of 90 young Americans in total	The results support the idea that a lack of butyrate-producing anti-inflammatory bacteria contributes to MDD, and they point to a connection between the gut microbiota and the chronic, low-grade inflammation

				experienced by those with MDD. Similarly, the levels of Faecalibacterium and other members of the family Ruminococcaceae were lower in the MDD group compared to the healthy control group.
10.	Liu Y et al,2016 [40]	Clinical and pathophysiological features of irritable bowel syndrome (IBS), major depressive disorder (MDD), and IBS/MDD co-occurrence were analyzed in relation to fecal microbiota profiles	Immunohistochemical analyses of sigmoid tissue biopsy specimens to assess colonic mucosal inflammation	The etiology of both IBS-D and depression may be linked to changes in the fecal microbiota shared by patients with both disorders. There was a correlation between the degree of inflammation in the colon and the intensity of IBS symptoms.
11	Mason BL et al,2020 [41]	To investigate the gut microbiota distributions of persons with co-occurring depression and anxiety, along with those with just depression or only anxiety, to see whether gut bacteria differently corresponds with unique clinical presentations.	MDD	Decreased Bacteroides may be more strongly linked to anxiety even in the absence of depression.
12	Coello K et al, 2019 [42]	To analyse the gut microbiota diversity in freshly diagnosed BD individuals, unaffected immediate family members, and	The gut microbiota composition was compared between 113 BD patients, 39 unaffected first-degree relatives, and 77 healthy persons by collecting stool	The bacterial genus Flavonifractor has been found to play a role in oxidative stress, inflammation, and host immune system dysfunction causing BD

		healthy people.	samples from each group and profiling the microbiome using 16S rRNA gene amplicon sequencing.	
13	Evans SJ et al, 2017 [43]	Researchers studied the gut microbiota of people with bipolar illness and compared them to normal control	BD	Higher representation of Faecalibacterium among people with bipolar disorder . The findings lend credence to the theory that focusing on the microbiota might be a useful approach to treating bipolar illness
14.	Hu S et al,2019 [44]	The researchers wanted to see if they could use changes in gut microbiota caused by quetiapine treatment as a biomarker for BD diagnosis and treatment success, and they also wanted to compare the microbiota of depressed patients with BD to that of healthy controls.	BD	The phylum Bacteroidetes predominates in the bacterial communities of patients with BD, whereas the phylum Firmicutes predominates in those with HCs. Butyrate-producing bacteria are present in lower numbers in untreated patients. The microbiota composition of persons with BD is changed by quetiapine treatment.
15	Lai WT et al 2021 [45]	The goal of the study was to see whether changes in the gut microbiota in people with bipolar illness experiencing a severe depressive episode might be disclosed by using shotgun	BD	Changes in the microbiome have been suggested as a biomarker that might be used to distinguish BPD sufferers from HCs.

		metagenomics		
16	McIntyre RS et al, 2021 [46]	To better understand the gut microbiome of persons with bipolar illness	Subjects (aged 18-65) who met DSM-5 criteria for BD and healthy controls (HC) of the same age and sex but without a history of mental or serious medical illnesses both provided fecal samples. We employed microbial community analysis (ANCOM) and cluster analysis to look at how different types of microorganisms in the gut are related to each other, as well as how food affected the microbiome overall	According to the results of this research, the gut microbiota of people with BD may be different from that of those without the condition, namely due to a higher abundance of Clostridiaceae and Collinsella
17	Rong H et al,2019 [47]	Researchers conducted a study on the gut microbiota of persons with major depressive disorder, bipolar disorder who are now experiencing a major depressive episode, and healthy controls.	BD	The phyla Firmicutes and Actinobacteria had substantial increases in abundance in the MDD and BPD groups, whereas the phylum Bacteroidetes saw a major decrease
18	Zheng P et al,2020 [48]	Researchers conducted a study on the markers of the gut microbiota to distinguish unipolar from bipolar disorder	BD	It was discovered that MDD is distinguished from BD and HCs by its distinctive gut microbial composition, and authors provided a novel marker panel for distinguishing MDD from BD based on patterns in the gut microbiome

19	Li S et al, 2020 [49]	Scientists investigated whether or not there was a link between alterations in gut flora and the manifestation of schizophrenia	Authors evaluated the associations between changed gut microbiota and the severity of symptoms in 82 SZ patients by comparing their fecal microbiota with that of 80 demographically comparable normal controls (NCs) using 16S rRNA sequencing	It showed that Succinvibrio and Corynebacterium were linked to more severe symptoms, suggesting that these bacteria might serve as useful novel biomarkers in the diagnosis of SZ. Results showed that the SZ group had a different microbiota in their digestive tract
20	Li S et al, 2021 50]	Researchers set out to learn more about how the composition of one's gut microbiota might affect cognitive performance	SCZ	They found that the abundance of Veillonella was much higher in SZ patients compared to NCs, but the abundance of Ruminococcus and Roseburia was much lower in SZ patients.
21	Ma X et al,2020 [51]	The pathophysiology of schizophrenia (SCZ) was investigated by authors who looked into possible links between the gut microbiota and SCZ	SCZ	Significant changes were seen for the families Christensenellaceae, Enterobacteriaceae, Pasteurellaceae, and Turicibacteraceae, and genus Escherichia among SCZ patients
22	Manchia M et al,2021 [52]	Authors looked at the connection between changes in the gut microbiota and the emergence of antipsychotic drug resistance in patients with schizophrenia.	Determine whether there were any differences in the gut microbiota composition of SCZ patients who responded differently to antipsychotics (18 patients with treatment-resistant schizophrenia (TRS) and 20 patients who responded to antipsychotics).	Findings showed that SCZ and HC had distinct gut microbiota. with some taxonomic levels of bacteria being exclusive to one group or the other.

23	Miao Y et al,2021 [53]	Authors. examined the relationship between gut microbiota and blood folic acid level in first-episode, drug-free individuals with schizophrenia (SCZ).	SCZ	Psychiatric symptoms in first-episode, antibiotic free patients were linked to low blood folic acid levels and a high abundance of Bifidobacterium
24	Nguyen TT et al, 2019 [54]	To compare people with chronic schizophrenia and non-psychiatric controls (NCs) with similar demographics	In this research, 50 people were analyzed, including 25 people with chronic schizophrenia and 25 non-psychiatric controls (NCs) with similar demographics	Schizophrenia was associated with an increase in the species Anaerococcus and a reduction in the genera Haemophilus, Sutterella, and Clostridium.
25	Nguyen TT et al,2021 [55]	Using 16S rRNA sequencing, authors examined the gut microbiota composition and functional capacity in 48 people with chronic schizophrenia and 48 healthy controls (NCs) who were similar to the patients in terms of sequencing plate, age, sex, body mass index (BMI), and antibiotic usage.	In order to find differentially abundant microorganisms and pathways, authors used a novel compositionally-aware approach that included reference frames	Results suggested that Lachnospiraceae is linked to schizophrenia
26.	Pan R et al,2020 [56]	In order to investigate the potential of the gut microbiome as a non-invasive biomarker for schizophrenia (SCZ), authors undertook a research comparing the gut microbiota	SCZ	SCZ-specific gut microbiota characteristics provide insights into disease prognosis and enable more precise treatment

		features of individuals with acute and remission SCZ		

Association of Gut microbiota with different psychiatric disorders

1. Gut microbiota and MDD patients

Bai S et al 2021 [31] suggested that disruption of the phylum Firmicutes may play a role in the onset of depression by regulating the host's inflammatory response. Five inflammation-related metabolites were identified as potential biomarkers that could be useful for future investigation into objective methods for diagnosing MDD. [31]

It was discovered by Chen JJ et al, 2018 [32] that the relative abundance of Firmicutes being significantly lower in young MDD patients compared to young healthy controls (HCs) and the relative abundance of Bacteroidetes being significantly lower in middle-aged MDD patients compared to middle-aged HCs. They concluded that the results of their study will provide a new perspective to the quest for the root causes of MDD. [32]

Bacteroidetes, proteobacteria, and Fusobacteria were in greater numbers in the microbiomes of female patients with MDD, whereas Firmicutes and Actinobacteria were consistently lower in the microbiomes. The etiology of major depressive illness in women may include microbiota and microbial metabolite alterations as possible microbiological targets and diagnostic indicators, respectively. [33] (Figure 2a, 2b)

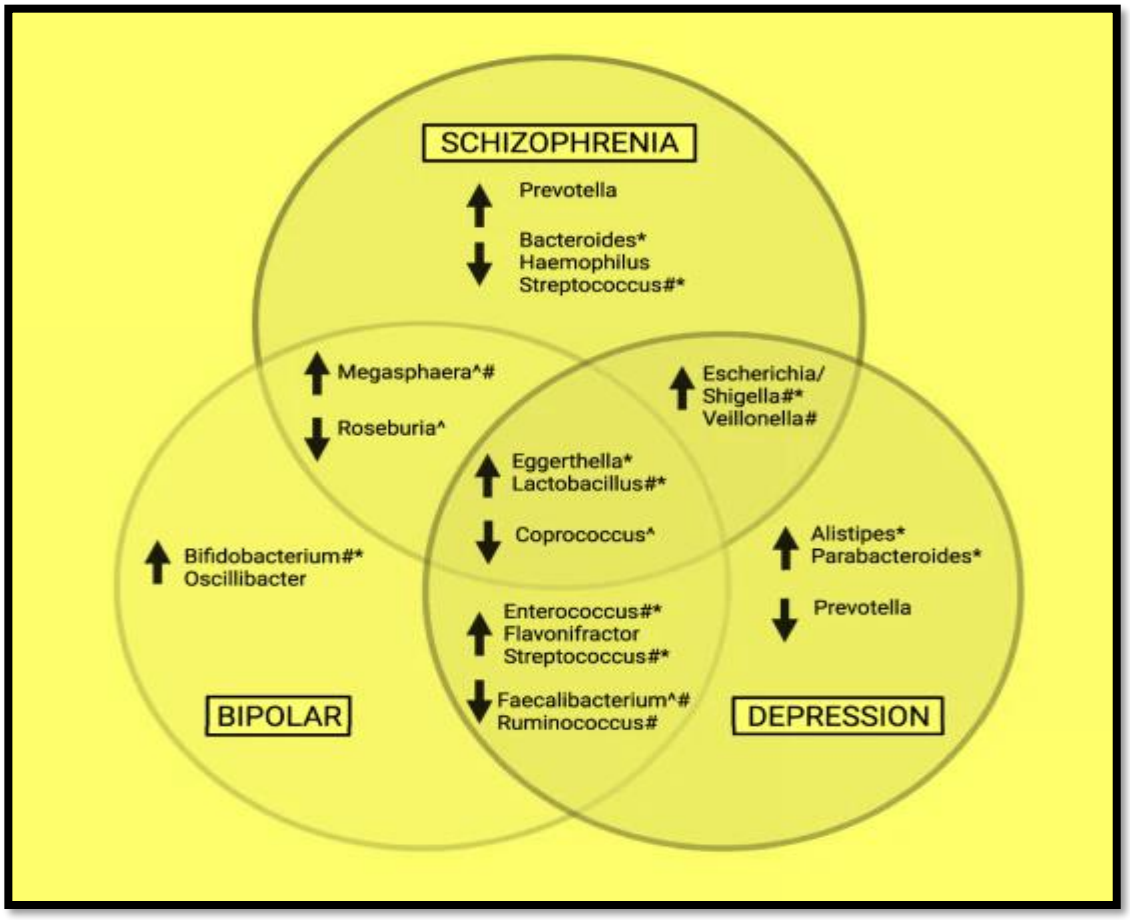

Figure 2a: Microorganisms that were frequently more or less prevalent in people with Maniac depressive illness, Depressive disorder (DD), Bipolar disorder (BD) and Schizophrenia (SZ) compared to healthy controls.

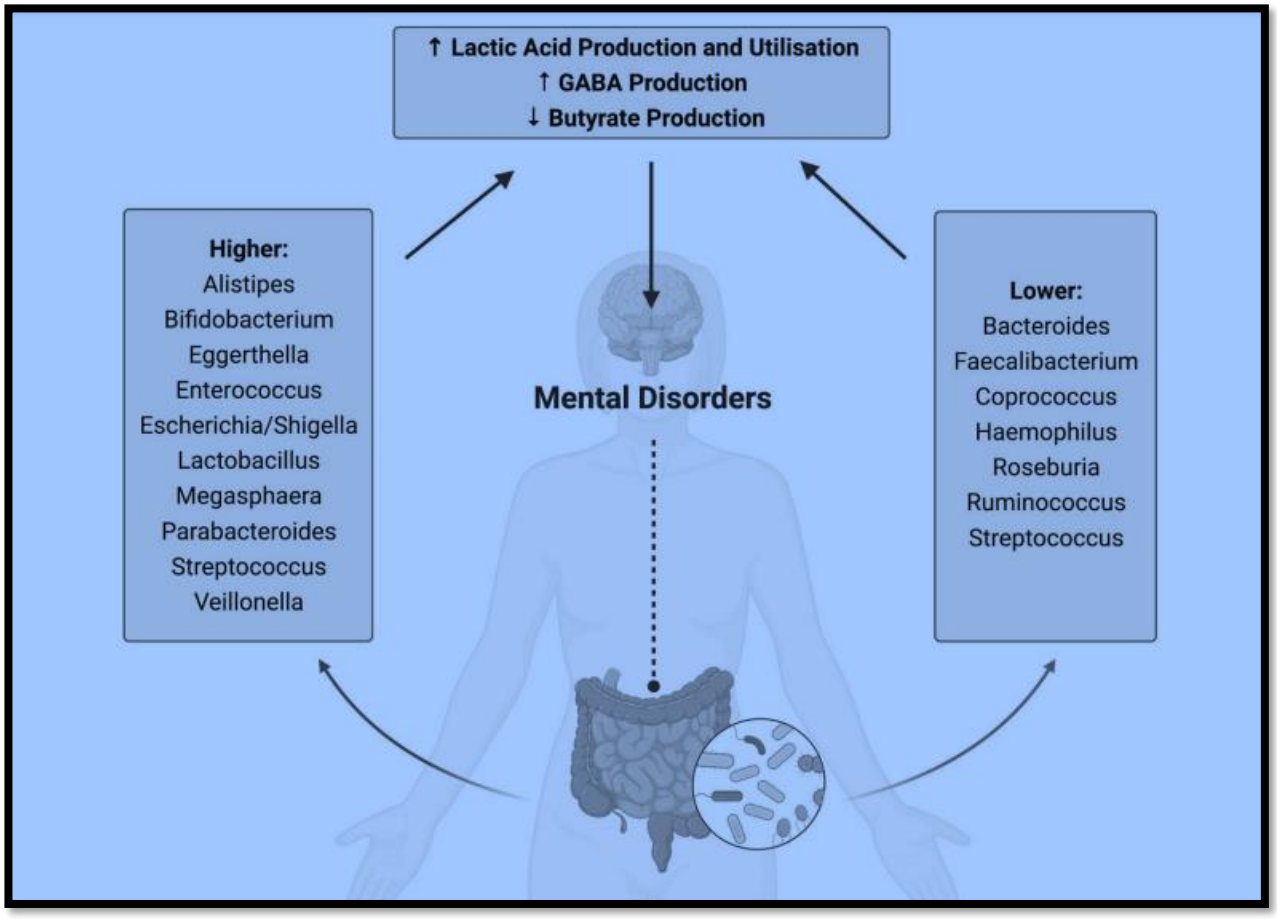

Figure 2b: Systematic diagram showing relationship between gut microbiota and mental disorders.

The study's authors aimed to determine if there were gender differences in the gut microbiome of people with MDD. The most notable differences in bacterial taxa between female and male MDD patients were seen in the phyla Actinobacteria and Bacteroidia. [34]

In order to establish a microbiome-based strategy for differential diagnosis, Dong Z et al,2021 et al. undertook a study to examine the variations in gut microbiota between cases of MDD and general anxiety disorders (GAD). It was found that GAD had a higher prevalence of Sutterella than MDD, but Faecalibacterium was much less common. [35]

Huang Y et al,2018 studied the impact of Firmicutes on people with MDD. The MDD samples showed reduction in the phylum Firmicutes. Depressed persons were shown to have significantly lower levels of Firmicutes. Depression may be due to low-grade inflammation, and low levels of short-chain fatty acids having their origins in faulty Firmicutes. [36]

Kelly JR e al,2016 conducted research to determine whether or not changes in the gut microbiota's composition and function are involved in pathways for MDD. Anxiety-like behaviors and alterations in tryptophan metabolism are seen when fecal microbiota from depressed people are transplanted into microbiota-depleted mice. The results of these studies point to the gut microbiota as a plausible target for the treatment and prevention of depressive symptoms. [37]

Researchers looked at the possibility that the relative abundance of Prevotella and Klebsiella in the gut microbiome might serve as a diagnostic marker for individuals with severe depressive disorder. Results revealed a decrease in Bacteroidetes, as well as an

increase in the numbers of bacteria belonging to the genera Prevotella, Klebsiella, Streptococcus, and Clostridium XI. [38]

A study found among young individuals, found that depression was linked to a decline in anti-inflammatory gut flora. The gut microbiota of those with MDD were different from those of healthy controls at many taxonomic levels. Class (Clostridia and Bacteroidia) and order (Clostridiales and Bacteroidales) levels of Firmicutes were reduced while Bacteroidetes were increased in people with MDD. The results support the idea that a lack of butyrate-producing anti-inflammatory bacteria contributes to MDD, and they point to a connection between the gut microbiota and the chronic, low-grade inflammation experienced by those with MDD. Similarly, the levels of Faecalibacterium and other members of the family Ruminococcaceae were lower in the MDD group compared to the healthy control group. [39]

Clinical and pathophysiological features of irritable bowel syndrome (IBS), major depressive disorder (MDD), and IBS/MDD co-occurrence were analyzed in relation to fecal microbiota profiles using immunohistochemical analyses of sigmoid tissue biopsy specimens to assess colonic mucosal inflammation. The etiology of both IBS-D and depression may be linked to changes in the fecal microbiota. There was a correlation between the degree of inflammation in the colon and the intensity of IBS symptoms. The scientists identified three unique microbial profiles in humans, each of which has diagnostic potential for irritable bowel syndrome (IBS) or depression. [40]

Mason BL et al,2020 investigated the gut microbiota distributions in persons with co-existing depression and anxiety, along with those with just depression or only anxiety alone. Specifically, Bacteroides and the Clostridium leptum subgroup were found to be significantly different between clinical categories. But decreased Bacteroides may be more strongly linked to anxiety even in the absence of depression. [41]

2. Gut microbiota in Bipolar disorder patients

The gut microbiota composition was compared between 113 BD patients, 39 unaffected first-degree relatives, and 77 healthy persons by collecting stool samples from each group and profiling the microbiome using 16S rRNA gene amplicon sequencing. The bacterial genus. Flavonifractor has been linked to oxidative stress, inflammation, and host immune system dysfunction causing BD. [42]

Researchers looked into the gut microbiota of people with bipolar illness and compared them to those without the condition, as well as looked for correlations between the microbiome and disease load. They were associated with higher fractional representation of Faecalibacterium among people with bipolar disorder. This was the first research to examine the connections between the gut microbiota and a variety of mental conditions in a community of people with bipolar disorder. The findings lend credence to the theory that focusing on the microbiota might be a useful approach to treating bipolar illness. [43]

The researchers wanted to see if they could use changes in gut microbiota caused by quetiapine treatment as a biomarker for BD diagnosis and treatment success, and they also wanted to compare the microbiota of patients with BD to that of healthy controls. The phylum Bacteroidetes predominates in the bacterial communities of patients with BD, whereas the phylum Firmicutes predominates in those with HCs. Butyrate-producing bacteria are present in lower numbers in untreated patients. The microbiota composition of persons with BD is changed by quetiapine treatment. The findings provide new light on the role of the gut microbiota in BD and are the first to evaluate microbial changes after quetiapine therapy. Biomarkers derived from the gut microbiota's composition may one day help in the diagnosis of BD and the estimation of therapeutic efficacy, however further study is required to prove this. [44]

The goal of the study by Lai WT et al 2021 was to see whether changes in the gut microbiota in people with bipolar illness might be evaluated by using shotgun

metagenomics. Changes in the microbiome have been suggested as a biomarker that might be used to distinguish BPD sufferers from HCs. [45]

Researchers conducted a study to better understand the gut microbiome of persons with bipolar illness. Participants with BD had a higher frequency of Clostridiaceae OTUs compared to HC, while participants with BD-II had a higher prevalence of Collinsella OTUs compared to BD-I subjects. According to the results of this research, the gut microbiota of people with BD may be different from that of those without the condition, namely due to a higher abundance of Clostridiaceae and Collinsella. [46]

Rong H et al, 2019 conducted a study on the gut microbiota of persons with major depressive disorder, bipolar disorder experiencing a major depressive episode, and healthy controls. The phyla Firmicutes and Actinobacteria had substantial increases in abundance in the MDD and BPD groups, whereas the phylum Bacteroidetes saw a major decrease. [47]

Zheng P et al, 2020 conducted a study on the markers of the gut microbiota to distinguish unipolar from bipolar disorder. Changes in covarying OTUs of the Bacteroidaceae family are seen in MDD when compared to HCs, while changes in the Lachnospiraceae, Prevotellaceae, and Ruminococcaceae families are observed in BD. It was discovered that MDD is distinguished from BD and HCs by its distinctive gut microbial composition, and authors provide a novel marker panel for distinguishing MDD from BD based on patterns in the gut microbiome. [48]

3. Gut microbiota in Schizophrenia patients

Scientists tried to find a link between alterations in gut flora and the manifestation of schizophrenia. Their results showed that the SZ group had a different microbiota in their digestive tract. It was found that Succinvibrio and Corynebacterium were linked to more severe symptoms, suggesting that these bacteria might serve as useful novel biomarkers in the diagnosis of SZ.[49]

Li S et al, 2021 tried to learn about the manner in which composition of one's gut microbiota might affect cognitive performance. It was found that number of Veillonella was much higher in SZ patients compared to NCs, while the number of Ruminococcus and Roseburia was much lower in SZ patients. The results suggest that the gut bacteria may play a role in SZ through influencing brain anatomy and function. This research sheds light on the neuropathology that underlies SZ. [50]

The pathophysiology of schizophrenia (SCZ) was investigated by Ma X et al,2020, who looked into possible links between the gut microbiota and SCZ. Significant changes were seen between SCZ patients and HCs for the families Christensenellaceae, Enterobacteriaceae, Pasteurellaceae, and Turicibacteraceae, and for the genus Escherichia. The results build on previous research and provide more evidence that the gut microbiome may play a role in the pathogenesis of SCZ by influencing brain anatomy. [51]

In a recent research, Manchia M et al, 2021 studied the connection between changes in the gut microbiota and the emergence of antipsychotic drug resistance in patients with schizophrenia. Research findings showed that SZ and HC had distinct gut microbiota. with some taxonomic levels of bacteria being exclusive to one group or the other. Research findings raise the possibility that composition of gut microbiota serves as a biosignature for both SZ and TRS. [52]

In a study Miao Y et al,2021 examined the relationship between gut microbiota and blood folic acid level in individuals with schizophrenia (SZ). Psychiatric symptoms in first-episode, were linked to low blood folic acid levels and a high abundance of Bifidobacterium. [53]

In a research, Proteobacteria were discovered to be much lower in people with schizophrenia compared to those of healthy controls. Schizophrenia was associated with an increase in the species Anaerococcus and a reduction in the genera Haemophilus, Sutterella, and Clostridium. Ruminococcaceae overpopulation was linked with reduced negative symptom severity in people with schizophrenia. Bacteroides was linked to more severe depression, whereas more Coprococcus meant a higher chance of heart disease. These findings lend credence to the idea that patients with chronic schizophrenia have a unique gut microbiota compared to the general population and reflect need for more large-scale longitudinal studies on gut microbiome and schizophrenia. [54]

Nguyen TT et al,2021 examined the gut microbiota composition and functional capacity in 48 people with chronic schizophrenia and 48 healthy controls (NCs) who were similar to the patients in terms of sequencing plate, age, sex, body mass index (BMI), and antibiotic usage. Results suggested that Lachnospiraceae is linked to schizophrenia. Both the trimethylamine-N-oxide reductase and Kdo2-lipid A biosynthesis functional pathways were shown to be altered in people with schizophrenia. Pro-inflammatory cytokines and an elevated risk of cardiovascular disease were both connected to these metabolic pathways in patients with schizophrenia. [55]

Pan R et al,2020 undertook a research comparing the gut microbiota features in individuals with SZ. These findings demonstrate differences between SZ patients and healthy controls, and between patients in the acute phase and those in remission, highlighting the potential of the gut microbiota as a non-invasive diagnostic tool. [56]

Outcomes of Risk of bias assessment

Low risk of bias overall

Studies by Chen JJ et al ,2018 [34], Evans SJ et al, 2017 [43], Li S et al, 2020 [49], Miao Y et al,2021 [53]

High risk of bias overall

Studies by Bai S et al 2021 [31], Huang Y et al,2018 [36], Kelly JR e al,2016 [37], Lai WT et al 2021 [45], McIntyre RS et al, 2021 [46], Ma X et al,2020 [51], Manchia M et al,2021 [52], Nguyen TT et al,2021 [55], Pan R et al,2020 [56]

Moderate risk of bias overall

Studies by Chen JJ et al, 2018 [32], Chen YH et al, 2020 [33], Dong Z et al,2021 [35], Lin P et al 2017 [38], Liu RT et al, 2020 [39], Liu Y et al,2016 [40], Coello K et al, 2019 [42], Hu S et al,2019 [44], Rong H et al,2019 [47], Zheng P et al,2020 [48], Li S et al, 2021 [50], Nguyen TT et al, 2019 [54]. Details of analysis of risk of bias has been given in Table 2.

Table 2: Summary Cochrane ROB assessment for individual studies

Author year	Sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
Bai S et al 2021 [31]	+	-	+	+	+	+	+	-

Chen JJ et al, 2018 [32]	+	?	?	?	+	+	+	?
Chen YH et al, 2020 [33]	+	?	?	?	+	+	+	?
Chen JJ et al ,2018 [34]	+	+	+	+	+	+	+	+
Dong Z et al,2021 [35]	?	?	?	?	+	+	+	?
Huang Y et al,2018 [36]	+	-	+	+	+	+	+	-
Kelly JR e al,2016 [37]	+	-	+	+	+	+	+	-
Lin P et al 2017 [38]	+	?	?	?	+	+	+	?
Liu RT et al, 2020 [39]	+	?	?	?	+	+	+	?
Liu Y et al,2016 [40]	+	?	?	?	+	+	+	?
Mason BL et al,2020 [41]	+	+	+	+	+	+	+	+
Coello K et al, 2019 [42]	+	?	?	?	+	+	+	?
Evans SJ et al,	+	+	+	+	+	+	+	+

2017 [43]								
Hu S et al,2019 [44]	?	?	?	?	+	+	+	?
Lai WT et al 2021 [45]	+	-	+	+	+	+	+	-
McIntyre RS et al, 2021 [46]	+	-	+	+	+	+	+	-
Rong H et al,2019 [47]	+	?	?	?	+	+	+	?
Zheng P et al,2020 [48]	+	?	?	?	+	+	+	?
Li S et al, 2020 [49]	+	+	+	+	+	+	+	+
Li S et al, 2021 [50]	?	?	?	?	+	+	+	?
Ma X et al,2020 [51]	+	-	+	+	+	+	+	-
Manchia M et al,2021 [52]	+	-	+	+	+	+	+	-
Miao Y et al,2021 [53]	+	+	+	+	+	+	+	+
Nguyen TT et al, 2019 [54]	?	?	?	?	+	+	+	?
Nguye	+	-	+	+	+	+	+	-

n TT et al,2021 [55]								
Pan R et al,2020 [56]	+	-	+	+	+	+	+	-

Minimum Risk of Bias represented by +

Moderate Risk of Bias represented by?

Maximum Risk of Bias -

Discussion

As far as we are aware, this is the first systematic review of the research on the issue of gut microbiota composition and major psychiatric disorders such as MDD, BD, and SZ. We did discover widespread differences in the gut microbiota makeup of patients and controls under each category of personal disorder. We also found that there are distinct bacterial taxa that had differing abundances in patients with these three psychiatric illnesses compared to healthy controls. We found a great deal of variation in study designs and reporting, such as in the inclusion and exclusion of study populations, sampling feces for study of gut microbiota; considering or adjusting for important factors known to impact gut microbiota composition; storing feces; processing feces; analyzing feces. Last but not least, we conducted a quality assessment of the included research; the results lend credence to the creation of norms for the execution and reporting of microbiome-related studies.

Our analysis showed that patients with all three psychiatric disorders (MDD, BD, SZ) had higher levels of Eggerthella and Lactobacillus and lower levels of Coprococcus compared to controls. Multiple diseases also shared several bacterial genera. Additionally, MDD and SZ were shown to have an increase in Escherichia coli, Shigella, and Veillonella whereas SZ and BD shared an increase in Megasphaera and a reduction in Roseburia. Enterococcus faecium, Flavonifractor, and Streptococcus were associated with MDD and BD, whereas decreased Faecalibacterium and Ruminococcus were associated with BD.

While there were certain taxa that were differently abundant between patients and controls for all three psychological disorders, there were also some taxa that were differentially abundant just for one condition. Patients with MDD typically had higher levels of Alistipes and Parabacteroides and lower levels of Prevotella, whereas patients with BD typically had higher levels of Bifidobacterium and Oscillibacter, and patients with SZ typically had higher levels of Prevotella and lower levels of Bacteroides, Haemophilus, and Streptococcus.

Our analysis showed an increase in lactic acid-producing bacteria in all three psychological disorders (MDD, BD, and SZ). Cases of the three psychological disorders had a greater prevalence of the genus Lactobacillus. Other lactic acid manufacturers, such as Enterococcus and Streptococcus and Bifidobacterium were also observed to be more abundant in patients with MDD, BD, SZ respectively. Metabolic regulation, pathogen protection, and immunomodulatory actions are only some of the host-beneficial effects attributed to these bacteria [24-28]. Cross-feeding occurs when bacteria that make lactate also offer it to bacteria that utilize lactate as a substrate to produce metabolites such the SCFA butyrate [29]. However, there are situations when host health is compromised by lactate generation and use. Lactic acid buildup in the intestines has been linked to acidosis, cardiac arrhythmias, and neurotoxicity [29, 30]. Improving results in moderate to severe MDD [32] also raise butyrate-producing bacteria [33], suggesting that

mitochondrial dysfunction may be at the root of many psychological disorders. There is proof that enriched bacteria may affect GABA metabolism [32,33].

Our analysis also revealed that all three psychological disorders shared an increase in the abundance of bacteria involved in the metabolism of glutamate and -aminobutyric acid (GABA). Again, there was less evidence to imply that this pattern was linked to any one ailment in particular; rather, elevated Lactobacillus was a trait shared by a wide range of conditions. MDD was characterized by increased abundances of bacteria involved in glutamate and GABA metabolism, including Alistipes and Parabacteroides, whereas BD was characterized by increased abundances of Bifidobacterium and Enterococcus and both MDD and BD were characterized by increased abundances of Bacteroides and Streptococcus. Genes encoding glutamate decarboxylase (GAD) enzymes, which catalyze the conversion of L-glutamate to GABA, are found in the lactic acid bacteria Lactobacillus, Bifidobacterium, and Enterococcus [33, 34].

Despite getting less attention from researchers, it seems that Eggerthella may alter glutamate metabolism, since elevated levels of this bacteria have been linked to abnormalities in glutamate metabolism in children with autism spectrum disorder [35]. GABA production has also been associated with the bacterial species Bacteroides, Escherichia, and Parabacteroides [36]. Increased numbers of these gut bacteria have been linked to an array of mental health conditions, suggesting that they may promote glutamate depletion and GABA production. Various bacterial abundances may have various pathophysiological effects, although this has yet to be proved. The complexity of the role played by the human gut microbiota in health and disease necessitates the use of advance research methods. More study is needed to determine whether or not alterations in the gut microbiota are primarily driven by pathophysiology or by common risk factors like nutrition, or whether or not they are driven by both. Changes in gut microbiota and their possible influence on disease development may be recorded in future longitudinal cohort studies. The biochemical and molecular impact that certain bacterial taxa have on host health and sickness may be elucidated via intervention studies. There is a significant lack of repeatability and heterogeneity in study methodologies. This literature review sheds insight on the wide discrepancy between how human microbiome data is collected and reported.

Consensus on best-practice methods is always shifting or being updated, which makes establishing or identifying 'gold-standards' difficult due to the quick rate at which this sector is expanding. Limited resources often force researchers to use suboptimal research designs and settle for limited sample sizes. Since there are no well-established methods for calculating power, it is not always clear whether microbiome research have adequate power to identify differences. There is an urgent need for clarity in reporting of microbiome research and for the consideration of these restrictions within individual investigations because of the impact of different microbiome-related study procedures on study outcomes [37-39]. Mutations in the gut microbiota have been linked to a wide range of factors, not all of which are within the control of the person. It is crucial to collect information on these factors in order to assess and interpret findings correctly. The fact that gut microbiota composition is often a secondary research outcome may account for the lack of collection and consideration of factors in study design. Possibly improving methodological consistency and repeatability [40-43] is the 'Strengthening the Organizing and Reporting of Microbiome studies' (STORMS) tool [44-52], a newly created checklist for the reporting of human microbiome research. [53-56],

Limitations and strengths

Several aspects of our present review's methodology affect how these findings should be interpreted. One problem is that the included studies were cross-sectional, thus no causation can be inferred and no time-dependent changes in the gut microbiota can be accounted for. Second, when broken down by country of origin, Chinese studies are noticeably overrepresented. This imbalance in sample area may have affected the findings of our synthesis since various geographical locations are linked to diverse microbial compositions. This study focused only on characterizing gut bacteria, despite mounting evidence that these organisms have an impact on host psychology and behavior. The GI tract is home to a wide variety of microorganisms, including archaea, viruses, bacteriophages, and fungus; research into the effect these microbes may have on host mental health is only beginning. Fourth, it is well acknowledged that using just compositional data in studies of the gut microbiome (mostly using 16S) has significant drawbacks, including decreased sensitivity and resolution.

Despite these caveats, the information presented here lays a crucial groundwork for future research into the role of the gut microbiota in psychiatry. As additional studies are conducted and published utilizing recent methodologies (such as metagenomics, metabolomics, and meta-transcriptomics), we will be able to get a deeper understanding of the gut microbiome beyond what is now known about its makeup. Psychiatry is currently lacking in biomarkers for diagnosis and prognosis as well as a strong understanding of the etiology of disease. may gain greatly from this. Fifth, there is the possibility of unmeasured confounding skewing our syntheses. Few researches even attempted to account for possible confounding by collecting covariate data consistently across trials.

Conclusion

Our systematic review did find that psychological disorders MDD, BD and SZ appeared to exhibit different overall compositional differences in gut microbiome compared to controls. There was a general trend toward the finding of increased abundances of bacteria involved in glutamate and GABA metabolism, and lower abundances of butyrate-producing bacteria in these psychological disorders. Future research using multi-omics methodologies is required to elucidate the implications of compositional and taxonomic changes for psychological disorder pathophysiology and etiology. Our results suggest that certain bacterial genera may one day be useful for diagnosis and prognosis; additional study is needed to validate this. Furthermore, these results may lend credence to alternative therapeutic approaches, include diet plans that aim to correct an imbalance in the gut microbiome. The study of the human microbiome has a clear and urgent need for standardized reporting and techniques.

Ethical Declaration:

1. Adherence to Guidelines: This systematic review has been conducted in accordance with established guidelines and standards, including the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Literature Search and Selection: The literature search and selection process followed in this systematic review aimed to be comprehensive, unbiased, and transparent. Efforts were made to include all relevant studies and to minimize selection bias.

3. Data Extraction and Synthesis: Data extraction and synthesis were performed with rigor and transparency. The methods used for data extraction and synthesis are clearly outlined in the methodology section of this systematic review.

4. Ethical Approval: As a review of existing literature, this systematic review did not involve the collection of new data from human subjects. Therefore, ethical approval was

not required. However, ethical considerations related to the original studies included in the review were examined to ensure that they adhered to ethical standards.

5. Inclusion and Exclusion Criteria: The inclusion and exclusion criteria for study selection were defined a priori and are detailed in the methodology section. Studies were included based on relevance to the research question, and the exclusion criteria were applied consistently.

6. Conflict of Interest: The author(s) declare no conflict of interest that could influence the objectivity or validity of the systematic review. Any financial, personal, or professional affiliations that might be perceived as a conflict of interest are disclosed.

7. Reporting Biases: Efforts were made to identify and minimize reporting biases throughout the systematic review process. Any challenges or limitations related to reporting biases are acknowledged and discussed in the results or discussion section.

8. Transparency and Reproducibility: This systematic review is transparent in its methodology, and all data extraction forms, search strategies, and other relevant documents are available upon request to ensure the reproducibility of the review.

9. Funding and Support: This systematic review received no external funding. The author(s) have not received any financial or material support that could influence the outcome or interpretation of the review.

10. Compliance with Applicable Laws and Regulations: The systematic review complies with all relevant national and international laws and regulations governing research, including ethical considerations related to the review process.

Data Access Statement

The data used in this systematic review were derived from previously published studies and are available in the public domain. The full list of included studies, search strategies, and detailed inclusion/exclusion criteria can be found in the supplementary materials accompanying this publication.

Access to Included Studies: The references for all included studies, along with relevant publication details, are provided in the references section of this article. Readers are encouraged to refer to the original publications for detailed information on each study.

Search Strategy: The search strategy employed in this systematic review, including the databases searched, search terms, and any additional filters applied, is available in the supplementary materials. Researchers interested in replicating or extending this review are encouraged to use the provided search strategy as a starting point for their own investigations.

Inclusion/Exclusion Criteria: Detailed inclusion and exclusion criteria used in the selection of studies for this systematic review are outlined in the methodology section. These criteria provide transparency regarding the study selection process and can be used as a reference for researchers conducting similar reviews.

Supplementary Materials: Additional supplementary materials, including data extraction forms, quality assessment tools, and any other relevant documents used in the review process, are available upon request. These materials aim to enhance the transparency and reproducibility of the systematic review.

Contact Information: For inquiries regarding the supplementary materials or any additional information related to this systematic review, please contact Dr. Imran Rangraze at dr.imranr@gmail.com.

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