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SYSTEMATIC REVIEW Open Access

Gut microbiota variations in depression and anxiety: a systematic review

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Abstract

Objective The aim of this study is to investigate the characteristics of gut microbiota in depression and anxiety through a systematic review.

Methods Articles were searched in the PubMed, Embase, and PsycINFO databases from their inception to February 12th, 2023. Case-control studies on the characteristics of gut microbiota in depression and anxiety were included. Methodological quality assessment of included studies was performed using the Newcastle-Ottawa Scale (NOS). A qualitative synthesis was conducted to assess bacterial diversity (α- and β-diversity) and taxa abundance differences at the phylum, family, and genus levels.

Results A total of 24 articles were included in the systematic review, 20 studies were conducted in China. Our results showed that the findings of the α- and β-diversity assessments were inconsistent for both depression and anxiety. In gut microbiota composition, we found that depression and anxiety were characterized by an enrichment of pro-inflammatory bacteria and a depletion of anti-inflammatory SCFAs-producing bacteria. Specifically, *Actinobacteria*, *Proteobacteria*, *Rikenellaceae*, *Porphyromonadaceae* and *Bifidobacteriaceae* were more abundant in the depression group, as well as *Firmicutes*, *Prevotellacea* and *Ruminococcaceae* in lower abundance. In the anxiety group, the abundance of *Firmicutes*, *Lachnospira*, *Faecalibacterium*, *Sutterella*, and *Butyricicoccus* was lower, while the abundance of *Bacteroidetes*, *Enterobacteriaceae*, and *Fusobacterium* was increased.

Conclusions The systematic review found that depression and anxiety might be characterized by an enrichment of pro-inflammatory bacteria and the depletion of anti-inflammatory SCFAs-producing bacteria. However, there were conflicting reports on the abundance of bacteria due to confounders such as diet and psychotropic medications. Further studies are strongly suggested.

Clinical trial number Not applicable.

Keywords Depression, Anxiety, Gut microbiota, Microbiota-gut-brain axis, Systematic review

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Introduction

Depression and anxiety are common mental disorders that severely impair an individual's ability to work, study and live everyday life. According to the WHO World Report in 2023 in 2023, 5% of the world's adults are affected by depression, and 4% of the population is affected by anxiety [1, 2]. Additionally, 29.8% of patients with depression also have an anxiety disorder [3]. The comorbidity of depression and anxiety is an important factor contributing to the complexity of clinical symptoms [4].According to the Global Burden of Disease analysis, depression and anxiety are major contributors to global health burden [5]. Research indicates that anxiety and depression may share a common pathological mechanism. Current research mainly focuses on the monoamine hypothesis, brain-derived neurotrophic factor (BDNF) cascade, and inflammatory response [6–8]. However, approximately 30% of Major depressive disorder (MDD) patients do not respond to monoamine antidepressants [9, 10]. Therefore, there is an urgent need to further understand the pathophysiological changes and find effective therapeutic targets.

Patients with depression and anxiety are often accompanied by gastrointestinal symptoms. Studies have found a bidirectional connection between the gastrointestinal tract and the brain. This interaction, known as the "microbiota-gut-brain axis", suggests that the gut microbiota interacts with the nervous system. Gut microbiota may play a role in the development of depression and anxiety by influencing various physiological processes. Different gut microbiota affect cognition and emotion through neural, immune, and chemical signal networks (Fig. 1) [11, 12].Studies have found that probiotic intervention can help regulate gut microbiota imbalance and improve mood disorders through the "brain-gut axis". Therefore, exploring the gut microbial characteristics of depression and anxiety can help identify unique biomarkers, providing prospects and directions for clinical intervention.

Previous studies examining the characteristics of gut microbiota in depression and anxiety included diverse populations, such as individuals with depression and anxiety, normal individuals experiencing negative emotions, and pregnant women with mental stress [13]. This diversity increased the heterogeneity among studies.

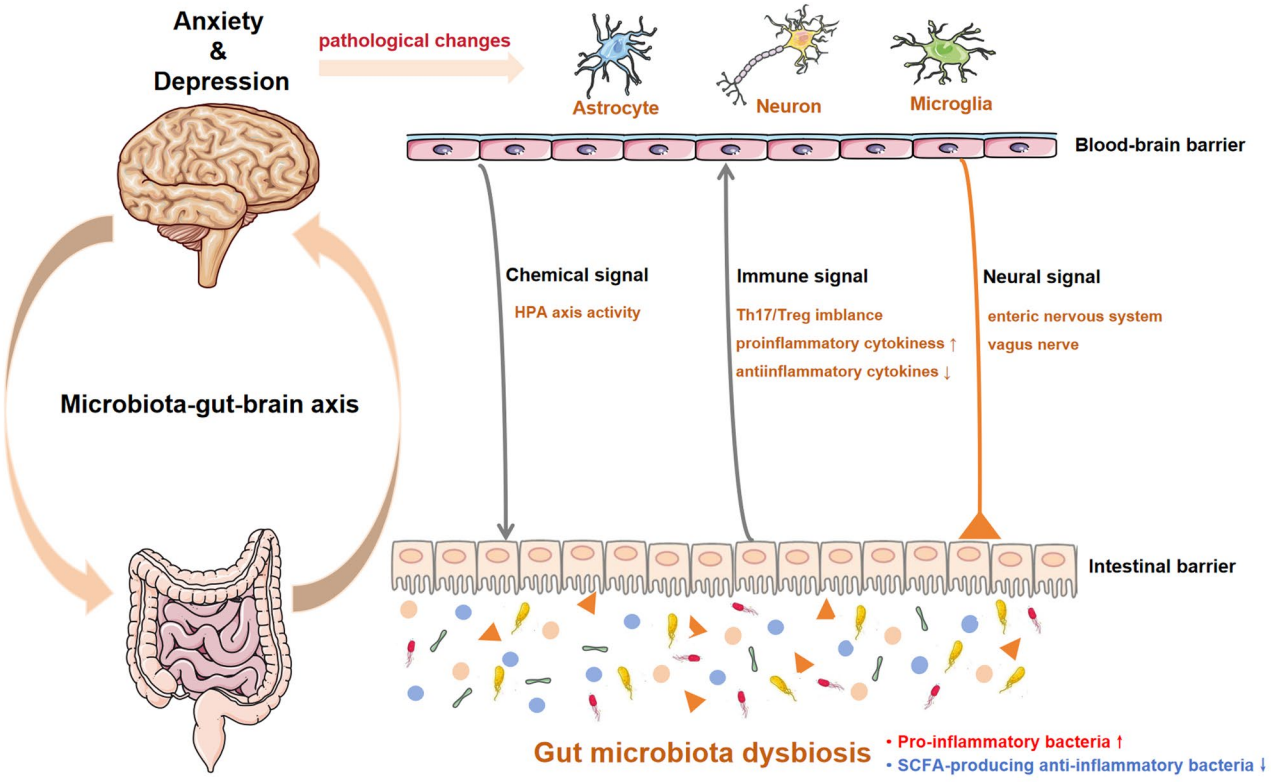

Fig. 1 The role of the microbiota-gut-brain axis in depression and anxiety. The microbiota-gut-brain axis mainly includes neural, immune and chemical signal networks. The neural signal networks include enteric nervous system (ENS), vagus nerves and so on. Abnormal ENS aggravates pathological changes of depression and anxiety. The vagus nerve is involved in transmitting microbial signals from the gut to the brain in depression. The gut microbiota and its metabolites induce neuroinflammation through Th17/Treg imbalance and the release of pro-inflammatory factors. Microbial signals and emotional disorders can activate the HPA axis, resulting in intestinal barrier impairment and inflammatory responses

Additionally, a significant amount of recent research has emerged in this field. This study not only updates a large body of recent literature but also restricts the study population to reduce heterogeneity. The aim of this study is to summarize the results of previous clinical studies through a systematic review to identify the characteristics of gut microbiota in depression and anxiety.

Methods and materials

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline. The protocol was registered with PROSPERO (Registration number: CRD42023464292).

Data sources and search strategy

We searched the PubMed, Embase, and PsycINFO databases from their inception to February 12th, 2023. The search keywords included gastrointestinal microbiome, depression, and anxiety. The detailed search strategy is provided in Table S1.

Inclusion and exclusion criteria

Studies were included if they met the following inclusion criteria: [1] The study population involved adults (≥ 18 years old); [2] They included patients with depression or anxiety, with control groups consisting of non-depressed, non-anxious, or healthy individuals; [3] Gut microbiota analysis was performed using next-generation sequencing (NGS), including 16s rRNA amplicon and shotgun metagenomic sequencing, and reported diversity (alpha or beta diversity) or taxa abundance differences; [4] The study design was a case-control study.

Studies were excluded if they met the following criteria: [1] Patients with depression or anxiety complicated with irritable bowel syndrome, inflammatory bowel disease or other diseases; [2] Data cannot be extracted; [3] Full texts were not available.

Study selection and data extraction

Two authors independently screened articles by reading the title and abstract, then reviewed the full text of potentially eligible articles for complete analysis. Two authors independently extracted data including the following items: [1] general information: title, year, country, sample size, age, proportion of female, disease, diagnostic criteria of depression or anxiety; [2] experimental methods: sequencing method and region; [3] gut microbiota composition results: α-diversity, β-diversity and taxa abundance differences at the phylum, family, and genus levels. In case of disagreement between the two authors in any aspect of study selection and data extraction, a third author was consulted.

Quality assessment

Two authors independently conducted methodological quality assessments of the included studies using the Newcastle-Ottawa Scale (NOS). Disagreements were resolved by consultation with a third author. The NOS scale consists of three domains, including selection, comparability, and exposure. The score ranges from 0 to 9 stars, and the studies were considered high quality if the score was seven or more.

Outcome measures and qualitative synthesis

The outcomes of interest were gut microbiota composition results, including the bacterial diversity (α- and β-diversity) and taxa abundance differences at the phylum, family, and genus levels. We conducted a qualitative synthesis to summarize these findings. For α-diversity, the differences in Chao, abundance-based coverage estimator (ACE), Shannon, Simpson, and phylogenetic diversity between the two groups were extracted and labeled as increasing, decreasing, or no change. For β-diversity, the method of measurement and finding were reported. For the taxa abundance differences, we summarized the findings of specific taxa which were reported significantly different in at least 2 studies and reported those increased or decreased.

Results

Search results

We searched for 7,055 articles in PubMed (2,303), Embase (4,062), and PsycINFO (690). 24 articles were finally included in the systematic review for further analysis (Fig. 2).

Study characteristics

The characteristics of the 24 studies included were shown in Table 1. There were 20 studies from China, and 4 studies from Norway [14], Ireland [15], USA [16] and Spain [17], respectively. We collected the proportion of female, age, study samples and diagnostic criteria. Among them, 19 studies were patients with depression (MDD: $n = 16$; No specific type: $n = 3$) [14–33], 3 studies were patients with GAD(Generalized anxiety disorder) [34–35, 36], and 2 studies included patients with depression and anxiety.(MDD&GAD: $n = 1$; No specific type: $n = 1$) [16, 37]. Diagnostic criteria: Sixteen studies used DSM-IV criteria for diagnosis, five used ICD-10, one used CCDCMD-3, one used HDRS-17 for diagnosis and assessment, and one study did not report the diagnostic criteria [15]. In addition, we have extracted the sequencing method of intestinal microflora. Twenty-one studies used 16s rRNA gene sequencing from different regions, and four studies used Shotgun metagenomics sequencing [22, 24, 26, 29].

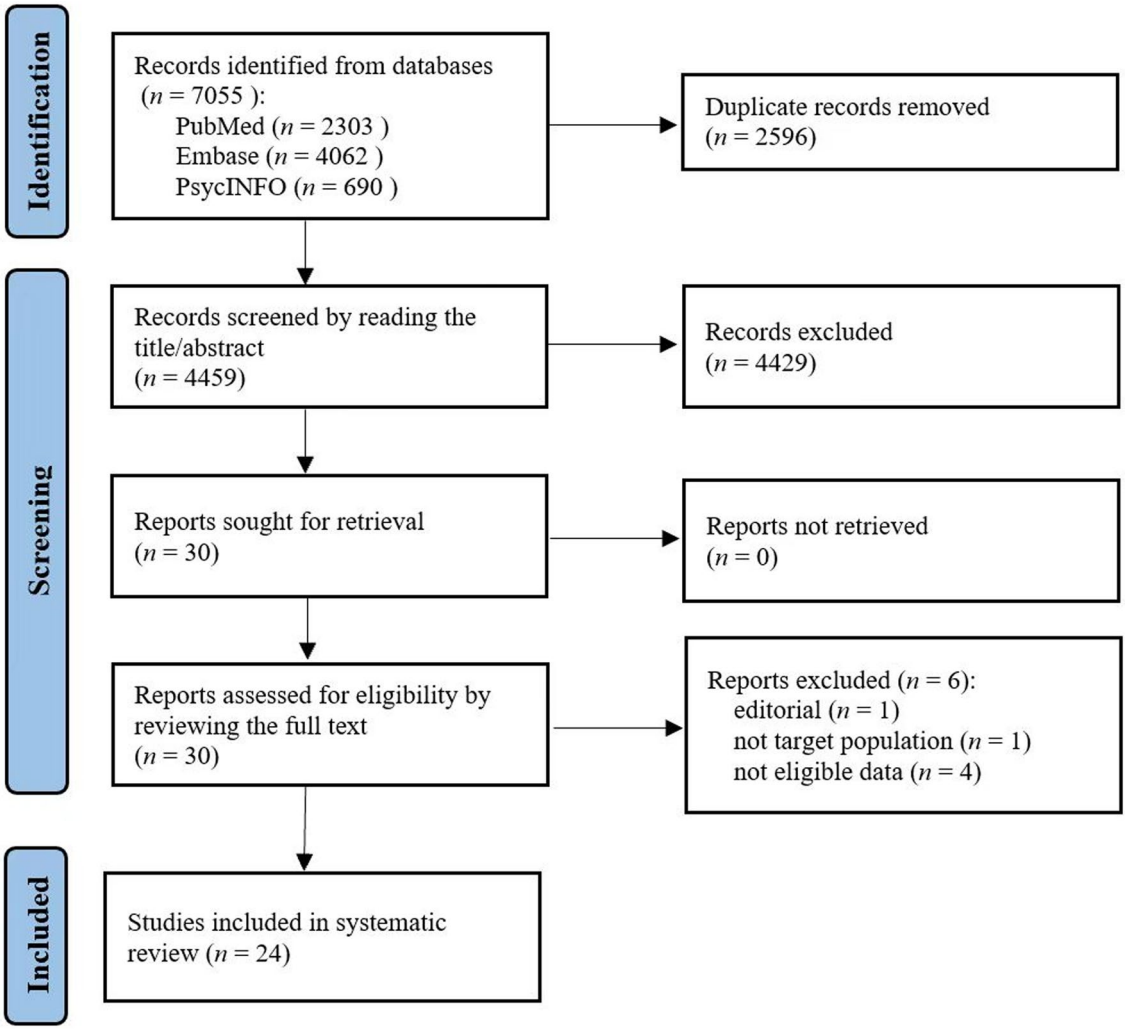

Fig. 2 PRISMA flow diagram of study selection

Quality assessment

In Table 2, the quality assessment of the studies showed that most of the studies were of high quality, with 22 studies scoring 7 or more stars. Two [15, 17] studies were of low quality (6 points). All studies were scored in "Definition of controls", "Comparability of cases and controls", "Ascertainment of exposure" and "Same method of ascertainment for cases and controls", but none of which was reported "Non-response rate".

α-diversity and β-diversity

The difference of α-diversity and β-diversity index between the patients and the control group is shown in Table 3.

α-diversity

α-diversity is used to reflect the diversity of microbial community. Five indicators were used to evaluate α diversity, including Chao, ACE, Shannon, Simpson, and phylogenetic diversity in the included studies. The most widely adopted index in depression is the Shannon index, which was examined in every study except two [14, 34]. There was no significant difference in alpha diversity between patients with depression and healthy participants in 16 of 21 studies [14–30, 34, 37]. However, four studies showed that α-diversity was lower in the depression patients groups compared with control groups [15, 19, 29, 31]. One study found an increased Shannon index in depressive disorders [33].

In the studies by Mason et al. [16] and Jiang H et at [36], there was no significant difference in alpha diversity between the anxiety disorders and the control group. Three studies found lower alpha diversity in the GAD compared with control groups [34, 35, 37].

β-diversity

β-diversity is a measure of inter-individual diversity that examines similarity of communities compared with the

Table 1 Characteristics of included studies

No.	Study	Country	Sample size	Range age or mean	Female (%)	Disease	Diagnostic criteria	Sequencing method
1	Cheng Y 2022	China	case: n=57 control: n=48	case: 41.24±3.82 control: 40.91±4.4	case: 58.3% control: 57.9%	GAD	CCDCMD-3	16S rRNA (not specified)
2	Dong Z 2022	China	case: n=63 control: n=30	case: 28.34±8.63 control: 29.23±6.59	case: 68.3% control: 66.7%	MDD	DSM-IV	16S rRNA (V3-V4)
3	Li X 2022	China	case: n= 40 control: n=22	case: 37:9±1 control: 44:0±1	case: 62.5% control: 40.9%	MDD	ICD-10	16S rRNA (V3-V4)
4	Zhong Q 2022	China	case: n= 130 control: n=131	case: 36.61±14.57 control: 37.07±14.22	case: 67.7% control: 67.9%	MDD	DSM-IV	16S rRNA (not specified)
5	Zheng S 2021	China	case: n= 30 control: n=30	case: 30.80±10.85 control: 33.37±7.02	case: 60.0% control: 56.67%	Depression	ICD- 10	16S rRNA (not specified)
6	Lai W 2021	China	case: n=26 control: n=29	case:43.73±11.46 control: 39.41±10.96	case: 69.2 % control: 55.2%	MDD	DSM-IV	Shotgun metagenomics
7	Bai S 2021	China	case: n= 60 control: n=60	case: 35.62±17.10 control: 35.13±15.79	case: 65.0% control: 60.0%	MDD	DSM-IV	16S rRNA (not specified)
8	Caso 2021	Spain	case: n=68 control: n=45	case: 43.98 control: 44.72	case: 77.9% control: 75.5%	MDD	DSM-IV	16S rRNA (V3-V4)
9	Chen Y 2021	China	case: n= 62 control: n=46	case: 39.58±12.66 control: 36.93±8.58	case: 100% control: 100%	MDD	DSM-IV	16S rRNA (V3-V4) Shotgun metagenomics
10	Dong Z 2021	China	case: n=23(MDD) n=21(GAD) control: n=10	case: 30.04±5.90(MDD) 30.43±7.95(GAD) control: 30.22±6.50	case: 9.6%(MDD) 66.7%(GAD) control:60.0%	MDD&GAD	DSM-IV	16S rRNA (V3-V4)
11	Zhang Q 2021	China	case: n=36 control: n=45	case: 36.81±13.52 control: 39.29±11.44	case: 41.7 % control: 57.8%	MDD	ICD-10	16S rRNA (V4-V5)
12	Mason 2020	USA	case: n=8(anxiety) n=14(depression) control: n=10	case: 40.0±13.7(anxiety) 41.9±12(depression) control: 33±8.4	case: 100%(anxiety) 79.0%(depression) control: 60.0%	Depression& Anxiety	DSM-IV	16S rRNA (V4)
13	Yang J 2020	China	case: n= 155 control: n=156	case: 18-65 control: 18-65	NA	MDD	DSM-IV	Shotgun metagenomics
14	Zheng P 2020	China	case: n=165 control: n=217	NA	NA	MDD	DSM-IV	16S rRNA (V3-V4)
15	Chen Y 2019	China	case: n=36 control: n=24	case: 46.08±12.09 control: 41.83±13.93	case: 55.6% control: 58.3%	GAD	DSM-IV	16S rRNA (V3-V4)
16	Chung 2019	China	case: n=36 control: n=37	case: 45.83±14.08 control: 41.19±12.73	case: 82.4% control: 62.2%	MDD	DSM-IV	16S rRNA (V3-V4)
17	Rong H 2019	China	case: n=31 control: n=30	case: 41.58±10.40 control: 39.47±10.22	case: 71.0% control: 53.3%	MDD	DSM-IV	Shotgun metagenomics
18	Chen J 2018	China	case: n=44 control: n=44	case: 41.5±11.53(female) 40.35±11.05(male) control: 43.95±12.11(female) 42.80±12.13(male)	case: 54.5% control: 54.5%	MDD	HDRS-17	16S rRNA (V3-V5)
19	Huang Y 2018	China	case: n=27 control: n=27	case: 48.7±12.8 control: 42.3±14.1	case: 74.1% control: 74.1%	MDD	ICD-10	16S rRNA (V3-V4)
20	Jiang H 2018	China	case: n=40 control: n=36	case:33.4±3.58 control: 35.6±6.98	case: 75.0% control: 64.0%	GAD	DSM-IV	16S rRNA (V3-V4)
21	Lin P 2017	China	case: n= 10 control: n=10	case: 36.2±10.1 control: 38.1±2.9	case: 40.0% control: 40.0%	MDD	DSM-IV	16S rRNA (V3-V4)
22	Kelly 2016	Ireland	case: n= 34 control: n=33	case:45.8±11.5 control: 45.8±11.9	case: 32.8% control: 42.4%	Depression	NA	16S rRNA (not specified)
23	Jiang H 2015	China	case: n=46 control: n=30	case:18-40 control: 18-38	case: 41.3% control: 50.0%	MDD	DSM-IV	16S rRNA (V1-V3)
24	Naseribafrouei 2014	Norway	case: n= 37 control: n=18	case: 49.2 ± 13.9 control: 46.1± 13.9	case: 54.1% control: 61.1%	Depression	ICD-10	16S rRNA (not specified)

Notes CCDCMD-3: Chinese Classification and Diagnostic Criteria for Mental Disorders, third edition; DSM-IV: the Diagnostic and Statistical Manual of Mental Disorders; ICD-10: the International Statistical Classification of Diseases and Related Health Problems 10th Revision; NA: not reported; MDD: Major depressive disorder; GAD: Generalized anxiety disorder

Table 2 Methodological quality of included studies

No.	Study	Selection				Comparability	Exposure			Sum
		Is the case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
1	Cheng Y 2022	*	*		*	**	*	*		7
2	Dong Z 2022	*	*	*	*	**	*	*		8
3	Li X 2022	*	*		*	**	*	*		7
4	Zhong Q 2022	*	*		*	**	*	*		7
5	Zheng S 2021	*	*		*	**	*	*		7
6	Lai W 2021	*	*	*	*	**	*	*		8
7	Bai S 2021	*	*		*	**	*	*		7
8	Caso 2021	*			*	**	*	*		6
9	Chen Y 2021	*	*		*	**	*	*		7
10	Dong Z 2021	*	*	*	*	**	*	*		8
11	Zhang Q 2021	*	*	*	*	**	*	*		8
12	Mason 2020	*	*	*	*	**	*	*		8
13	Yang J 2020	*	*		*	**	*	*		7
14	Zheng P 2020	*	*		*	**	*	*		7
15	Chen Y 2019	*	*		*	**	*	*		7
16	Chung 2019	*	*	*	*	**	*	*		8
17	Rong H 2019		*	*	*	**	*	*		7
18	Chen J 2018	*	*		*	**	*	*		7
19	Huang Y 2018	*	*		*	**	*	*		7
20	Jiang H 2018	*	*		*	**	*	*		7
21	Lin P 2017	*	*		*	**	*	*		7
22	Kelly 2016		*		*	**	*	*		6
23	Jiang H 2015	*	*		*	**	*	*		7
24	Naseribafrouei 2014	*	*		*	**	*	*		7

other samples analysed. The distance between samples can be calculated by weighted (Bray-Curtis and Weighted Unifrac) and unweighted (Jaccard and Unweighted Unifrac) algorithms to obtain the β value between sample. The Beta diversity analysis is performed based on the distance matrix, such as PCA and PCoA. Moreover, combined with other multivariate statistical analysis methods (OPLS-DA, PLS-DA, PERMANOVA, ANOSIM) to detect the variability between samples.

Findings in depressive disorders β-diversity between participants with depressive disorders and controls was reported in 20 studies, with a variety of measures. Only one study did not perform β-diversity. Seven studies found no difference between depression and controls. Four studies [17, 18, 29, 37] used metric methods based on Bray-Curtis. Two [16, 33] used weighted or unweighted UniFrac. 13 studies [14, 15, 20, 22–28, 30–32] found significant differences in participants with a depressive disorder relative to controls, and most studies used PCoA analysis (10 of 13) [15, 20, 22–26, 30–32].

Findings in anxiety disorders Five studies comparing anxiety disorders with healthy controls, four studies analysed β-diversity. Three studies reported that there were differences between two groups [35–37], and one study found no significant difference [16].

Taxonomic findings

Findings in depressive disorders

We summarized the representative taxa findings of depression patients versus controls at three levels (phylum, family, and genus levels) (Fig. 3). The relative abundance of bacteria was found significant differences between the two groups involving in 4 phyla, 8 families and 21 genera. The tree gram was used to illustrate the relationships between the shown genera, families, and phyla. As shown in Fig. 4, there were four phyla including

Table 3 Summary of bacterial diversity assessments of the included studies

No.	Study	α diversity					β diversity		
		Chao	ACE	Shannon	Simpson	phylogenetic diversity	Metric	Analysis	Finding
Depression									
1	Dong Z 2022	=		=			Bray–Curtis	PCoA ANOSIM	no sig.different
2	Li X 2022	↓	↓	↓	↑		/	PCA	no sig.different
3	Zhong Q 2022			=	=		/	PCoA	sig.different
4	Zheng S 2021	=	=	=	=		/	/	/
5	Lai W 2021			=			Bray - Curtis	PCoA PERMANOVA	sig.different
6	Bai S 2021	=		=	=	=	/	PCoA OPLS-DA	sig.different
7	Caso 2021			=			Bray-Curtis Jaccard	PCoA PERMANOVA	no sig.different
8	Chen Y 2021	=	=	=	=		Unweighted UniFrac Weighted UniFrac	PCoA	sig.different
9	Dong Z 2021	=	=	=	=		Bray-Curtis	PCA	no sig.different
10	Zhang Q 2021	=	=	=	=		Weighted UniFrac Unweighted UniFrac Bray - Curtis Jaccard	PCoA ANOSIM	sig.different
11	Mason 2020			=			Weighted UniFrac	PERMANOVA	no sig.different
12	Yang J 2020	=		=	=		Bray-Curtis distance	PCoA PERMANOVA	sig.different
13	Zheng P 2020	=	=	=	=		/	PERMANOVA PLS-DA	sig.different
14	Chung 2019	=		=		=	Unweighted UniFrac Weighted UniFrac	PERMANOVA	sig.different
15	Rong H 2019	↓		=	=		Bray-Curtis	PCoA	no sig.different
16	Chen J 2018			=	=	=	/	PCoA PLS-DA	sig.different
17	Huang Y 2018	↓	↓	↓		↓	Unweighted Unifrac Weighted Unifrac	PCoA	sig.different
18	Lin P 2017	/	/	/	/	/	Weighted UniFrac	PCoA	sig.different
19	Kelly 2016	↓		=		↓	Bray-Curtis Unweighted Unifrac Weighted Unifrac	PCoA	sig.different
20	Jiang H 2015	=	=	↑	=		Unweighted UniFrac	PCoA	no sig.different
21	Naseribafrouei 2014				=		/	PCA PLS-DA	sig.different
Total	↑			**1**	**1**		**sig.different: 13** **no sig.different: 7**		
	↓	**4**	**2**	**2**		**2**			
	=	**10**	**6**	**16**	**12**	**3**			
Anxiety									
1 2	Cheng Y 2022 Dong Z 2021	↓ ↓	↓	↓	↑		/ Bray-Curtis	/ PCA	/ sig.different
3	Mason 2020			=			Weighted UniFrac	PERMANOVA	no sig.different
4	Chen Y 2019	=	↓	=	=		Unweighted UniFracs Weighted UniFracs	PCoA PERMANOVA	sig.different
5	Jiang H 2018	=		=	=		UnweightedUniFrac	PCoA PERMANOVA	sig.different
Total	↑				**1**		**sig.different: 3** **no sig.different: 1**		
	↓	**2**	**2**	**1**					
	=	**2**		**3**	**2**				

Bacteroidetes, *Firmicutes*, *Actinobacteria* and *Proteobacteria*. *Bacteroidetes* involved in 5 families and 4 genera. *Firmicutes* involved in 8 families and 12 genera. *Actinobacteria* involved in 3 families and 4 genera. *Proteobacteria* involved in 2 families and 1 genus.

At the phylum level, eleven studies showed significant differences of relative abundance. The differential gut microbiota mainly included *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria*. The most consistent changes were the enrichment of *Actinobacteria* (4 of 5 studies) [18, 22, 28, 29]and *Proteobacteria* (3 of 4 studies) [29, 31, 33] in depression disorders. The results of the study reported that relative abundance differences in *Bacteroidetes* and *Firmicutes* were contradictory. A

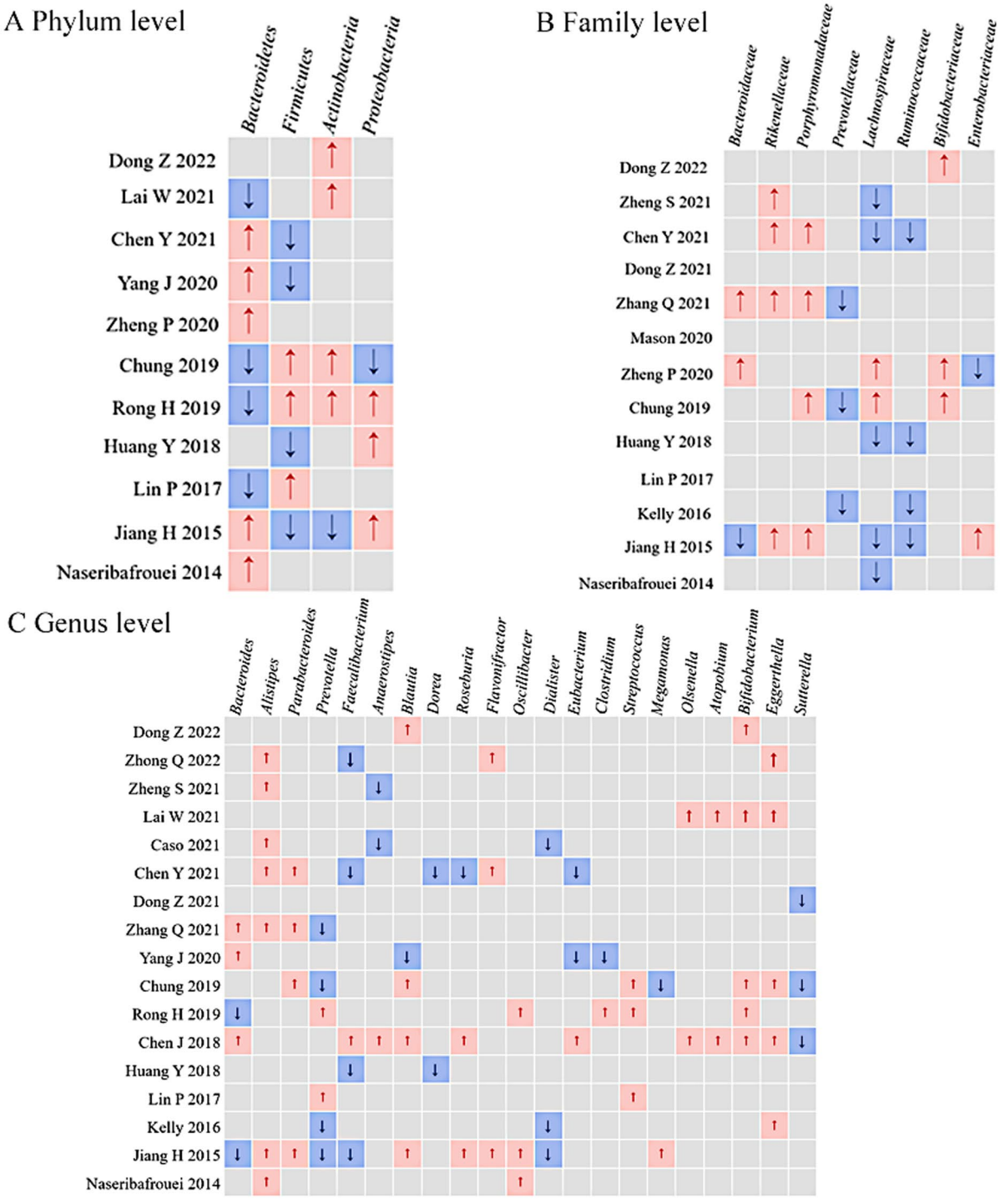

Fig. 3 Summary of taxa abundance differences in depression patients compared to control groups. (**A**) phylum level; (**B**) family level; (**C**) genus level

lower abundance of *Bacteroidetes* (4 of 9 studies) [22, 28, 29, 32] and *Firmicutes* (4 of 7 studies) in depression was observed.

At the family level, five gut microbiota showed consistent results, including *Rikenellaceae* (4 studies) [21, 24, 25, 33], *Porphyromonadaceae* (4 studies) [24, 25, 28, 33], *Prevotellaceae* (3 studies) [15, 25, 28], *Ruminococcaceae* (4 studies) [15, 24, 31, 33] and *Bifidobacteriaceae* (3 studies) [18, 27, 28]. Among them, the relative abundance of *Rikenellaceae* [21, 24, 25, 33], *Porphyromonadaceae* [24, 25, 28, 33]and *Bifidobacteriaceae* [18, 27, 28] was observed enrichment in the depression groups. The abundance of *Prevotellaceae* [15, 25, 28] and *Ruminococcaceae* [15, 18, 24, 31, 33] was lower in depression

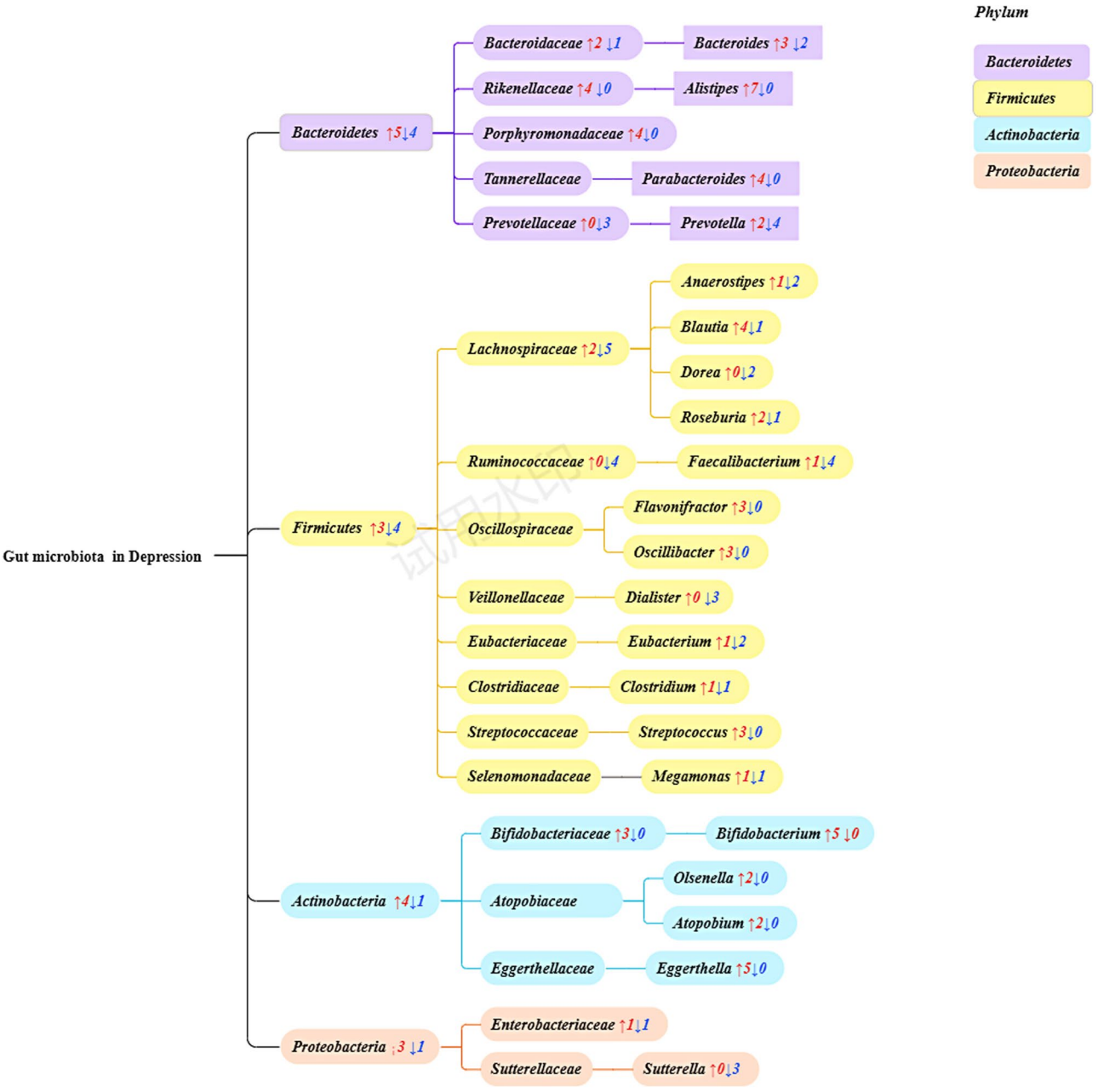

Fig. 4 Tree gram of the gut microbiota in depressive disorders

disorders. The more consistent changes were the enrichment of *Bacteroidaceae* (2 of 3 studies) [25, 27] and depletion of *Lachnospiraceae* (5 of 7 studies) [14, 21, 24, 31, 33] in depression. The relative abundance of *Enterobacteriaceae* showed conflicting results in two studies [27, 33].

At the genus level, 17 studies found significant differences of microbiota between depression patients and controls, with changes in abundance mainly observed for 21 genera. The consistent results were the enrichment of *Alistipes* (7 studies) [14, 17, 20, 21, 24, 25, 33], *Parabacteroides* (4 studies) [24, 25, 28, 33], *Flavonifractor* (3 studies) [20, 24, 33], *Oscillibacter* (3 studies) [14, 29, 33], *Streptococcus* (3 studies) [28, 29, 32], *Olsenella* (2 studies) [22, 30], *Atopobium* (2 studies) [22, 30], *Bifidobacterium* (5 studies) [18, 22, 28, 29, 30] and *Eggerthella* (5 studies) [15, 20, 22, 28, 30] and the depletion of *Dorea* (2 studies) [24, 31], *Dialister* (3 studies) [15, 17, 33], and *Sutterella* (3 studies) [28, 30, 37] in the depression groups. In addition, a higher abundance of *Bacteroides* (3 of 5 studies) [25, 26, 30], *Blautia* (4 of 5 studies) [18, 28, 30, 33] and *Roseburia* (2 of 3 studies) [30, 33] were observed in depression. The more consistent changes were a lower abundance of *Prevotella* (4 of 6 studies) [15, 25, 28, 33], *Faecalibacterium*

(4 of 5 studies) [20, 24, 31, 33], *Anaerostipes* (2 of 3 studies) [17, 21], and *Eubacterium* (2 of 3 studies) [24, 26]. *Megamonas* and *Clostridium* showed opposite results in two studies respectively. The number of literature of the representative taxa findings of depression patients was summarized at phylum, family, and genus levels.

Findings in anxiety disorders

We summarized the representative taxa of anxious patients versus controls from observational studies at three levels (phylum, family, and genus levels). A total of 5 studies were involved [16, 34–37]. At the phylum level, the most consistent changes were the enrichment of *Bacteroidetes* (2 of 2 studies) [36, 37] and the depletion of *Firmicutes* (3 of 3 studies) [35–37] in GAD. However, at the family and genus levels, the number of studies which reported the changes of specific taxa were less than two. At the family level, Chen Yi-Huan et al. found that *Enterobacteriaceae* increased and *Prevotellaceae* reduced in anxiety disorders [35]. Yuanyuan Cheng et al. found that the abundance of *Porphyromonadaceae* increased in anxiety patients [34]. At the genus level, *Lachnospiraceae* and *Ruminococcaceae* were less abundant in anxiety patients [35]. In addition, Hai-yin Jiang et al. found that *Fusobacterium* was increased in GAD patients compared with healthy people. Meanwhile, *Faecalibacterium*, *Eubacterium rectale*, *Sutterella*, *Lachnospira*, and *Butyricicoccus* decreased in GAD patients [36].

Discussion

The systematic review provided a summary focused on the characteristics of gut microbiota in patients with depression or anxiety. Our results showed that the findings of the α and β diversity assessments were inconsistent whether in depression or anxiety. In gut microbiota composition, we found the differences between case groups and control groups might be localised to specific microbial taxa. We will discuss these findings in detail in the following sections.

Compared with the previous study [13], this was not just an update of gut microbiota research in patients with depression or anxiety. There were several strengths in our study as follows. First, we searched and included a large number of studies published in recent years [17–26, 34, 37]. Second, in order to reduce inter-study heterogeneity, for the selection of patients, depression and anxiety co-existing with other diseases were excluded from the study. For the sequencing methods, the studies using the NGS were only included Third, we made the characteristics of gut microbiota more intuitive and visual by using tables and figures to present the data.

α diversity and β diversity were performed a qualitative synthesis. The results of the included studies showed that the microbial diversity in patients with depression or anxiety are inconsistent compared with healthy people. For α diversity, except for a few studies that found lower α diversity in patients with depression or anxiety, most studies found no significant difference in α diversity between the two groups. Similarly, significant differences of β diversity were observed between depressed or anxious patients and healthy controls in approximately half of the studies. The inconsistencies in diversity results may be related to confounding factors such as sequencing depth, diet, and psychotropic medications [13, 38]. It suggested that the applicability of diversity indexes as an assessment of host health should be questioned. We should reflect on the limitations of the extant study and provide direction for future research.

The results showed that significant differences of microbiota were mainly focused on *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria* at the phylum level. Consistent with previous studies [13, 39], the higher abundance of *Parabacteroides*, *Oscillibacter*, *Streptococcus*, *Bifidobacterium* and *Eggerthella*, and the lower abundance of *Prevotellaceae*, *Ruminococcaceae* and *Faecalibacterium* has been reported to be associated with depression in our study. Inflammation has been widely recognized as a mechanism in the pathogenesis of depression and anxiety. Microbes and their metabolites and lipopolysaccharide (LPS) interact with macrophages and can stimulate immune responses by releasing proinflammatory factors, resulting in changes in inflammatory markers and depressive symptoms [11, 12, 38]. At the same time, microorganisms can also mediate neuroinflammation by Th17/ regulatory T cell (Treg) imbalance. In addition, microbial signals and emotional disorders can activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in intestinal barrier impairment and inflammatory responses. *Parabacteroides* and *Oscillibacter* are Gram-negative bacteria, which contain LPS in the outer cell membrane leaflet. LPS interacts with macrophages to stimulate the immune response by releasing proinflammatory cytokines [40]. Studies have found that *Eggerthella* induces intestinal inflammation by activating Th17 cells [41]. *Prevotellaceae*, *Faecalibacterium and Ruminococcaceae* can produce short-chain fatty acids (SCFA) such as acetic acid and butyric acid [42–44]. Short-chain fatty acids are involved in protecting gastrointestinal mucosa, reducing pro-inflammatory factors and increasing anti-inflammatory mediators [45, 46]. The increase in these pro-inflammatory bacteria and the decrease in anti-inflammatory bacteria further support the idea that depression is associated with an inflammatory state.

Bifidobacterium is generally considered to be anti-inflammatory and regulate intestinal homeostasis. Interestingly, consistent with previous studies, we found that *Bifidobacterium* was enriched in depression.

Bifidobacterium can form different ecological relationships with its host, ranging from opportunistic pathogenic interactions to symbiotic and even health-promoting relationships [47]. Thus, there is no clear demarcation between beneficial and pathogenic bacteria, and attention to microbiota balance may be more important than a single class of bacterial regulation.

In our study, other findings that have previously not been reported were association with the enrichment of *Alistipes* and *Flavonifractor* in depression. It was shown that *Alistipes* abundance significantly increased when mice were exposed to stress [48]. *Alistipes* is an indole-positive organism that reduces the availability of serotonin and disrupts the gut-brain axis when it increases. Tryptophan is a precursor of serotonin, a decrease of which has been linked to depression [33]. Studies have found that *Flavonifractor* is highly abundant in affective disorders, which may be related to its enhancement of oxidative stress and low grade inflammation [49].

In the anxiety group, we found *Firmicutes* and their subphylum such as *Lactobacillus*, *Vagococcus*, *Fusicatenibacter*, *Ruminococcaceae*, *Faecalibacterium*, *Lachnospira*, *Butyricicoccus* were decreased [34, 36, 37]. Consistent with our results, an animal experiment showed that *Firmicutes* levels were significantly reduced in mice with higher level of anxiety [50]. We also found that the abundance of *Enterobacteriaceae* increased in anxiety patients. The elevated levels of *Enterobacteriaceae* could induce inflammation and increase intestinal permeability [51]. Reduced *Lachnospiraceae* and *Ruminococcaceae* taxa in anxious patients could reduce the oxidative and inflammatory damage of mouse epithelium [52]. As a SCFA, butyrate is the main energy source of intestinal cells, mainly produced by *Ruminococcaceae* and *Lachnospiraceae* [53–55], and enhances the integrity of the intestinal barrier by inhibiting inflammation [56]. In the study by Hai-yin Jiang et al., *Fusobacterium*, as Gram-negative anaerobic bacteria, showed invasive and pro-inflammatory properties related to immune activation [57, 58]. Meanwhile, the reduction of *Faecalibacterium*, *Lachnospira* and other five taxon can reduce the production of short-chain fatty acids (SCFA) in the intestine, leading to intestinal barrier dysfunction [55].Therefore, even though the two studies didn't find the same bacteria, we found that taxa decreased in anxious patients such as *Lachnospiraceae*, *Ruminococcacea*, *Faecalibacterium*, *Eubacterium rectale*, *Sutterella*, *Lachnospira*, and *Butyricicoccus* had anti-inflammatory properties, the enriched taxa such as *Enterobacteriaceae* and *Fusobacterium* had pro-inflammatory properties. However, due to the limited number of anxiety-related studies, the evidence of microbiota characteristics in anxiety disorders was insufficient, and future research is required to focused on this field. The above evidence suggests that there might be a common gut microbiota mechanism for anxiety and depression.

First, in both anxiety and depression, the bacterial communities with reduced abundance were *Ruminococcaceae*, *Faecalibacterium*, and *Prevotellaceae*. The reduced abundance of *Ruminococcaceae* and *Faecalibacterium* was associated with weakened anti-inflammatory effects, often accompanied by decreased butyrate production, suppressed Treg cell differentiation, and impaired intestinal barrier integrity [33, 38, 59]. Similarly, the reduced abundance of *Prevotellaceae* was linked to abnormal neurotransmitter metabolism, including reduced GABA synthesis, altered tryptophan metabolic pathways, and heightened neuroinflammatory responses [60]. Conversely, the bacterial family that showed increased abundance in both anxiety and depression was *Porphyromonadaceae*. This elevation was linked to enhanced oxidative stress, which promotes LPS production, increases inflammatory factor expression, and negatively impacts neuroplasticity [61, 62]. Secondly, distinct gut microbiota characteristics were observed between anxiety and depression. Anxiety was marked by a significant increase in the abundance of *Enterobacteriaceae*, while depression was characterized by elevated levels of *Parabacteroides*, *Oscillibacter*, *Streptococcus*, and *Eggerthella*. Anxiety typically manifests as an acute stress response, involving rapid activation of the sympathetic nervous system, acute HPA axis stimulation, and acute inflammatory responses [63, 64]. In contrast, depression is mainly associated with chronic low-grade inflammation. The significant increase in *Enterobacteriaceae* is positively associated with acute stress response [65]. The increased abundance of *Parabacteroides*, *Oscillibacter*, and *Eggerthella* has been correlated with persistent chronic stress responses, whereas elevated *Streptococcus* levels are associated with sustained neuroinflammation and increased oxidative stress [14, 15, 32, 33, 38, 66, 67, 68]. In summary, the mechanisms of gut microbiota changes in anxiety and depression involve stress response pathways, immune-inflammatory regulation, metabolic responses, and neurotransmitter alterations, while also impacting intestinal barrier function [13, 64, 69, 70, 71]. Anxiety primarily represents an acute stress response, whereas depression is characterized by a chronic stress response, which explains the distinct differences in gut microbial composition between these two conditions.

There were some limitations in our study. First, geographic region and diet could affect the composition of the microbiome [72, 73]. Most of the included studies were from Asia, and did not consider the effects of diet and psychiatric medication. Second, the differences of analytical methods may affect the results. For example, the sequencing method involved various regions (V1–V5), and the diagnostic criteria used different scales for

depression and anxiety. Third, the sample sizes of the included studies ranged from 30 to 70 cases, with only three studies exceeding 100 participants [20, 26, 27]. As 16 S rRNA sequencing is well-suited for large-scale studies, the results from studies with small sample sizes need to be interpreted with caution [74]. In addition, only four studies out of 20 performed shotgun metagenomics. 16sRNA technology may have biased the results being that this technology is more limited to find a wider range of bacterial taxa. Future research should prioritize larger sample sizes and utilize metagenomic sequencing approaches [75].

Conclusion

The reported differences in composition of gut microbiota indicated that depression and anxiety may be characterized by an enrichment of pro-inflammatory bacteria and the depletion of anti-inflammatory SCFAs-producing bacteria. However, our results showed that the abundance of gut microbiota in patients with depression or anxiety are conflicting. The inconsistency suggests that there may be confounders such as diet and psychotropic medications. Therefore, further studies considering confounders should be strongly suggested.

Abbreviations

ACE	Abundance-based coverage estimator
BDNF	Brain-derived neurotrophic factor
ENS	Enteric nervous system
GAD	Generalized anxiety disorder
HPA	Hypothalamic-pituitary-adrenal
LPS	Lipopolysaccharide
MDD	Major depressive disorder
NGS	Next-generation sequencing
NOS	Newcastle-Ottawa Scale
Treg	Regulatory T cell
SCFA	Short-chain fatty acids

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

YYC analyzed the data, and wrote the manuscript. YRC and WCP involved in the literature search and collection of data. YYC and JWD evaluated the literature quality. LZS took part in the overall checking. MMM conceived the study design, validated the data, and modified the manuscript. All authors approved the final manuscript.

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Data availability

The datasets supporting the conclusions of this article are included within the article (and its additional file).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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