Review Paper

Microbiome-based Interventions in Mental Health: A Decade of Systematic Evidence on Depression, Anxiety, and Stress

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ABSTRACT

Background and Purpose: The gut–brain axis links microbiota to mental health, but evidence on probiotic/prebiotic interventions for depression, anxiety, and stress remains heterogeneous.

Materials and Methods: This study aimed to synthesize human evidence on gut microbiota-mental health associations and evaluate microbiome-targeted interventions. We reviewed 26 human studies (2015-2025): 19 randomized controlled trials (RCTs), 3 cohort studies, 3 cross-sectional studies, and 1 case-control study. Data were extracted on study design, interventions, microbial measures, outcomes, and risk of bias (RoB).

Results: Probiotics/prebiotics (10^9-10^{10} CFU/day for 6-12 weeks) improved outcomes in 13/19 RCTs (68.4%). Multi-strain and combined interventions (e.g. with an SSRI or diet) produced the most consistent effects; 6/19 RCTs (31.6%) reported null effects, suggesting strain- and context-dependent effects. Observational studies linked reduced microbial diversity and dysbiosis to poorer mental health. The RoB was low in 13/19 RCTs and moderate in 6/19 RCTs; observational studies had a moderate RoB, primarily because of confounding. Publication bias was suspected based on funnel plot asymmetry.

Conclusion: Multi-strain probiotics may reduce symptoms of depression, anxiety, and stress, whereas microbial diversity may be protective. Limitations include outcome heterogeneity, possible publication bias, and limited long-term data. Future multi-center RCTs with harmonized measures are needed.

Keywords: Gastrointestinal microbiome, Probiotics, Prebiotics, Depressive disorder, Anxiety disorders, Stress, Psychological

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Introduction

Mental health disorders, including depression, anxiety, and stress-related conditions, remain major public health challenges. The World Health Organization (WHO) estimates that depression affects approximately 280 million people worldwide, with anxiety disorders affecting an additional 264 million individuals annually, representing a significant global burden of disease and disability [1].

Conventional treatment strategies, primarily pharmacological agents and psychotherapy, target neurochemical pathways within the central nervous system. While these approaches demonstrate effectiveness for many patients, treatment outcomes remain suboptimal. Approximately 30–40% of patients with major depressive disorder (MDD) do not achieve an adequate response to first-line antidepressant therapy, and relapse rates approach 50–60% within two years of initial treatment [2-4]. These limitations highlight the urgent need for novel adjunctive strategies.

Over the past decade, the gut microbiome has emerged as a critical modulator of brain function, influencing mood, cognition, and emotional regulation through the complex gut-brain axis [5, 6]. This bidirectional communication network involves neural (vagal and enteric nervous system), immune-inflammatory, endocrine, and metabolic signaling pathways, collectively contributing to mental health outcomes. Evidence from preclinical studies has provided compelling insights into the microbiota's potential role in psychiatric disorders. Experimental manipulation of gut microbial communities in rodents through probiotics, antibiotics, germ-free models, or fecal microbiota transplantation (FMT) has been shown to induce or alleviate anxiety-like and depressive-like behaviors [7, 8]. These behavioral alterations have been linked to neuroinflammatory responses, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, altered neurotransmitter synthesis (e.g. serotonin, GABA), and impaired neuroplasticity (Figure 1).

However, translating these findings to humans presents significant challenges. Rodent and human microbiomes differ substantially in composition and metabolic capacity. Human diets, medication exposures, and lifestyle factors are more heterogeneous, and behavioral assays in animals differ fundamentally from validated psychiatric assessments in humans. Despite these limitations, translational research has prompted growing investigation into whether microbial composition is altered in individuals with mental health disorders, and whether interventions that modify the gut microbiota, such as probiotics, prebiotics, psychobiotics, dietary interventions, or FMT can produce clinically meaningful improvements [9-11].

Despite increasing research interest, human studies have produced mixed and sometimes contradictory findings. For example, while some trials report significant antidepressant effects with *Lactobacillus* and *Bifidobacterium* strains [9-11], others, including Romijn et al. [12] and Slykerman et al. [13] found no benefit over placebo. This heterogeneity likely reflects differences in study design, population demographics, baseline microbiota composition, intervention strains, dosage regimens, treatment duration, and outcome measurement tools. Additionally, variability in methodological quality, small sample sizes, and a lack of standardized protocols raise concerns about the reproducibility and reliability of the current evidence [14-16]. A major research priority is the development of standardized outcome-reporting protocols to enable meaningful cross-study comparisons and meta-analyses.

Given these gaps, there is a pressing need for a rigorous synthesis of the available data to inform future clinical applications. This systematic review aimed to address this need by:

(i) assessing associations between gut microbiota composition and mental health outcomes; (ii) evaluating the efficacy of microbiome-targeted interventions in depression, anxiety, and stress;(iii) exploring mechanistic pathways proposed in the literature; and (iv) critically appraising the quality and strength of the current human evidence to guide future research directions and potential clinical translation.

Materials and Methods

Protocol and registration

This systematic review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) guidelines [17] to ensure methodological transparency and reproducibility. The review protocol was not registered in a prospective registry (e.g. PROSPERO or OSF) before the review was conducted.

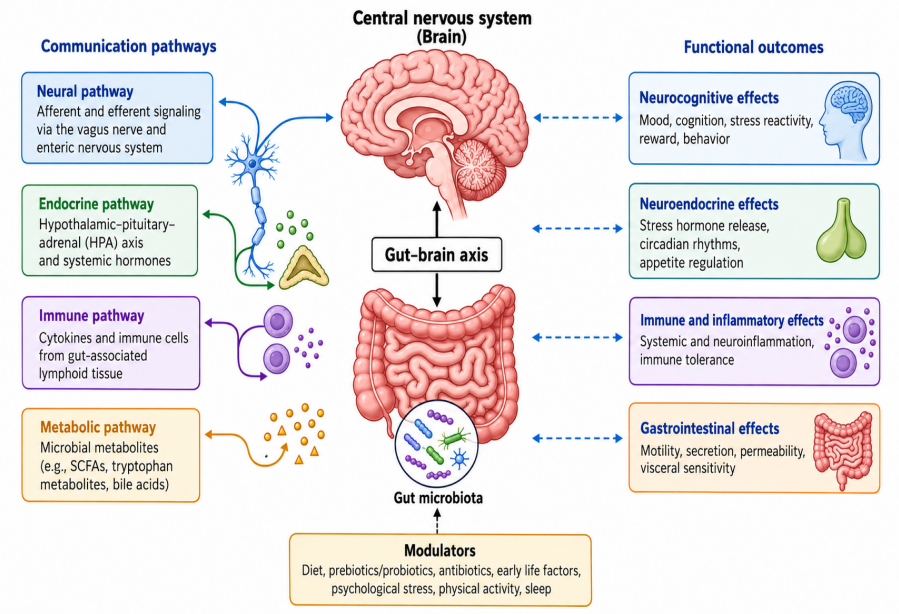

Figure 1. Mechanistic pathways and functional outcomes of bidirectional gut–brain axis signaling

Note: Bidirectional communication within the gut–brain axis. Communication occurs across four primary pathways: neural (vagus nerve, enteric nervous system), endocrine (HPA axis, systemic hormones), immune (cytokines, gut-associated lymphoid tissue), and metabolic (short-chain fatty acids, tryptophan, bile acids). External and internal modulators (e.g. diet, probiotics, stress, antibiotics) influence the gut microbiota, driving functional neurocognitive, neuroendocrine, immune, and gastrointestinal outcomes.

Search Strategy

A comprehensive literature search was conducted across four major electronic databases: PubMed, Scopus, Web of Science, and PsycINFO, covering studies published from database inception to March 30, 2025. The search strategy combined medical subject headings (MeSH) and free-text keywords related to gut microbiota and mental health.

Pubmed search strategy (executed March 30, 2025):

((“gastrointestinal microbiome”[MeSH Terms] OR “microbiome”[tiab] OR “gut microbiota”[tiab] OR “intestinal flora”[tiab] OR “probiotics”[MeSH Terms] OR “probiotic”[tiab] OR “prebiotics”[MeSH Terms] OR “prebiotic”[tiab] OR “psychobiotic”[tiab])

AND

(“mental health”[MeSH Terms] OR “depression”[MeSH Terms] OR “depressive disorder”[MeSH Terms] OR “depress”[tiab] OR “anxiety”[MeSH Terms] OR “anxiety disorders”[MeSH Terms] OR “anxi”[tiab] OR “stress, psychological”[MeSH Terms] OR “stress”[tiab]))

AND

(“2015/01/01”[PDAT] : “2025/12/31”[PDAT])

AND

(English[lang])

Boolean operators (AND, OR) and truncation were used to maximize sensitivity. Reference lists of the included studies and relevant systematic reviews were also manually screened to capture additional eligible articles. All retrieved records were imported into EndNote X20 (Clarivate Analytics) for duplicate detection and removal.

Eligibility criteria using the PICO framework

Studies were eligible based on the PICO criteria (Table 1).

Additional criteria

Study types: Peer-reviewed randomized controlled trial (RCT), cohort studies, case-control studies, cross-sectional studies, and quasi-experimental designs; Language: English; Publication period: 2015-2025

Exclusion criteria included animal studies, reviews, conference abstracts, editorials, and articles lacking measurable mental health outcomes.

Study selection process

Two independent reviewers (Odochi O. Chukwu and Mary C. Igbokwe) performed title and abstract screening for all retrieved records. Full-text articles were obtained for potentially eligible studies and independently assessed by the same reviewers. Disagreements at either stage were resolved through discussion; if consensus could not be reached, a third reviewer (Archibong Efiok) adjudicated.

Inter-rater reliability: Cohen's kappa coefficient was calculated for full text screening decisions (κ=0.84, indicating excellent agreement).

Reasons for exclusion at the full-text stage were documented and are reported in the PRISMA flow diagram.

Data extraction

Data were extracted independently by two reviewers (Odochi O. Chukwu and Mary C. Igbokweand) using a standardized, piloted data extraction form developed in Microsoft Excel. The extraction template included:

Study characteristics: Author, year, country, study design, sample size, and population characteristics; Exposure/intervention details: Type, specific strain(s), dose (CFU/day for probiotics), formulation, duration, and cointerventions; Microbiome assessment methods: 16S rRNA sequencing, metagenomics, quantitative real-time polymerase chain reaction (q-PCR, diversity metrics, and reported taxa; Mental health outcomes: Outcomes assessed, measurement tools, and timing of assessments; Main findings: Effect estimates, confidence intervals, pvalues, and direction of effect; Funding source: Industry, government, academic, or nonprofit funding

Discrepancies were resolved through consensus discussion or by involving a third reviewer (Abdullateef I. Alagbonsi).

Risk of bias and study quality assessment

The methodological quality of RCTs was assessed using the Jadad scale (0-5), evaluating:

Randomization (0-2 points); Blinding (0-2 points); Withdrawals and dropouts (0-1 point)

Observational studies were assessed using the Newcastle-Ottawa scale (NOS; 0-9 points), examining:

Selection of participants (0-4 points); Comparability of groups (0-2 points); Ascertainment of outcome/exposure (0-3 points)

Standardization: To enable crossstudy comparisons, all scores were converted to a standardized 0-8 scale using proportional conversion (original score÷maximum possible score×8).

Quality categories (standardized 0-8 scale):

High-quality: 7-8 points (equivalent to Jadad 4-5 or NOS 8-9); Moderate-quality: 5-6 points (equivalent to Jadad 3 or NOS 6-7); Low-quality: <5 points (equivalent to Jadad ≤2 or NOS ≤5)

All 27 studies underwent quality assessment. Two reviewers independently assessed each study. Initial agreement was 89%, and all disagreements were resolved through discussion, with the rationale for the final scores documented.

Data synthesis

Given substantial heterogeneity across study populations, intervention types, strain formulations, treatment durations, and outcome metrics, quantitative meta-analysis was deemed inappropriate. Instead, findings were synthesized narratively and organized thematically.

Synthesis approach

1) Studies were grouped by thematic domain (probiotic interventions, prebiotic interventions, observational studies, and combined interventions); 2) Within each domain, findings were summarized descriptively; 3) Direction of effect was categorized as significant benefit, null effect, or negative effect; 4) Vote counting based on the direction of effect was performed as a sensitivity analysis; 5) Structured summary tables present study characteristics, outcomes, and quality ratings; 6) Publication bias assessment; 7) Publication bias was assessed through; 8) Visual inspection of funnel plot asymmetry for outcomes reported in ≥10 studies; 9) Egger's regression test for small-study effects; 10) Qualitative assessment of selective outcome-reporting and funding-source patterns

Results

Study selection

The systematic search yielded 1,142 records across all databases. After duplicate removal (n=450), 692 records underwent title and abstract screening. Of these, 619

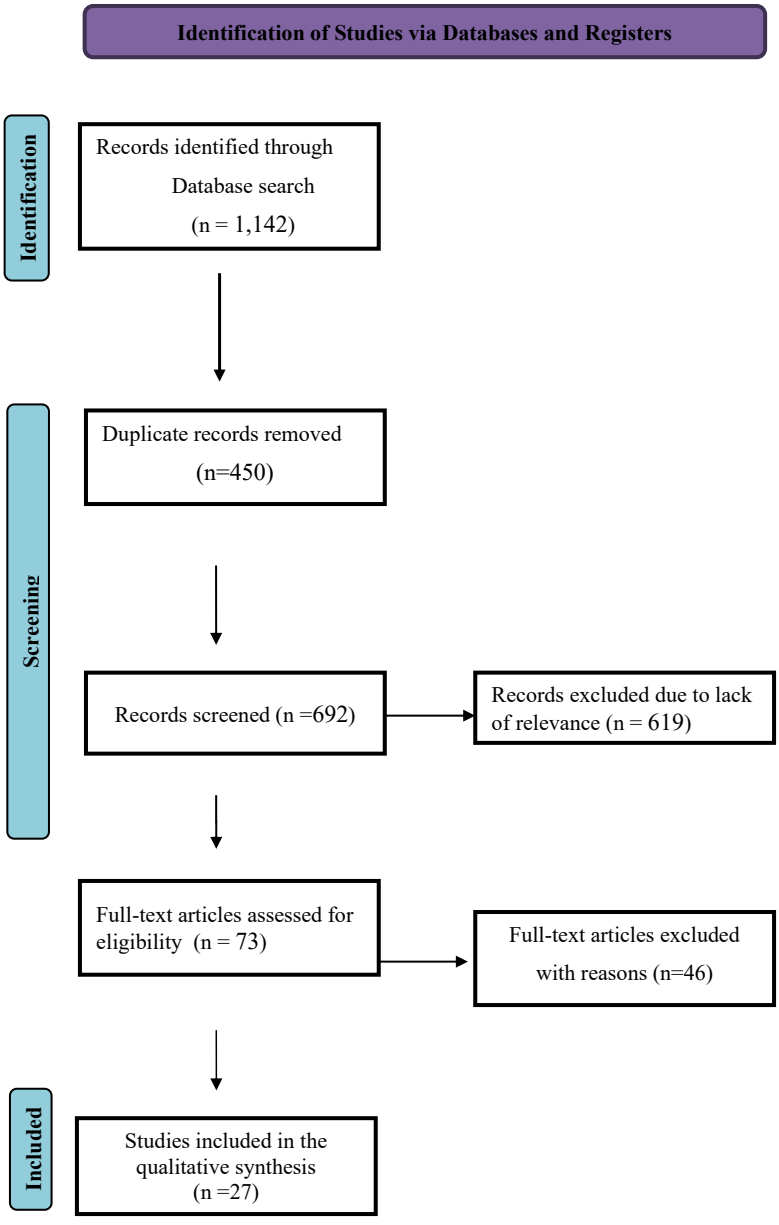

Figure 2. Flowchart depicting the study selection process

records were excluded because they were not relevant. Full-text articles were assessed for 73 studies, of which 46 were excluded. A total of 27 studies met the inclusion criteria and were included in the qualitative synthesis (Figure 2).

Reasons for full-text exclusion (n=46); No mental health outcome measured (n=18); Not original research (review/commentary; n=12); Animal study (n=8); Duplicate publication (n=4); Insufficient data for extraction (n=3); Non-English publication (n=1)

Study characteristics

A total of 27 human studies met the inclusion criteria (Table 2). These RCTs (n=20; 74%), cohort studies (n=3; 11%), cross-sectional studies (n=3; 11%), and one case–control study (n=1; 4%), conducted across Asia, Europe, North America, and Oceania. Sample sizes ranged from 40 to more than 1,500 participants, and populations included clinically depressed patients, individuals with anxiety disorders, irritable bowel syndrome (IBS) patients, postpartum women, adolescents, and healthy adults.

Table 1. PICO framework for study eligibility criteria

PICO Domain	Inclusion Criteria	Exclusion Criteria
Population	Human participants of any age (children, adults, older adults); clinical or nonclinical populations	Animal studies; in vitro studies
Intervention/Exposure	Probiotics, prebiotics, synbiotics, psychobiotics, dietary interventions, or FMT; or gut microbiota composition measurements	Nonmicrobiome interventions; no microbiome assessment
Comparator	Placebo, no treatment, standard care, or active comparator (for intervention studies); healthy controls (for observational studies)	No comparator group
Outcome	Validated measures of depression, anxiety, stress, mood, cognition, or sleep	No mental health outcome measurement

Interventions comprised probiotics, prebiotics, fermented foods, dietary modulation, and combined therapies (e.g. probiotics with selective serotonin reuptake inhibitors [SSRIs]). Observational studies primarily examined gut microbial diversity, dysbiosis, or metabolite profiles, such as short-chain fatty acids (SCFAs) and kynurenine/tryptophan ratios. Outcomes assessed included depression, anxiety, stress, mood, sleep, cognition, and emotional regulation.

Risk of bias

Risk of bias (RoB) was assessed for all 27 included studies (Table 3). Among RCTs (n=20), 14(70%) were rated as having a low RoB, 6(30%) as having a moderate RoB, and none as having a high RoB. Among observational studies (n=7), 2(29%) were rated as having a low RoB and 5(71%) as having a moderate RoB. RoB was assessed for all 27 included studies (Table 2). RCTs generally performed well in randomization and outcome measurement, although allocation concealment was occasionally unclear. Cross-sectional studies were frequently downgraded because of the potential for reverse causality and the lack of temporal direction. Inter-rater reliability for the quality assessment was strong (Cohen's κ=0.82).

Publication bias

Funnel-plot asymmetry was observed for depression outcomes reported in RCTs (n=12), suggesting potential publication bias toward positive findings, particularly among smaller studies. Egger's regression test confirmed significant small-study effects (bias coefficient=1.87, P=0.04). Industry-funded studies (n=8) were more likely to report positive findings (87.5%) than non-industry-funded studies (66.7%), although this difference was not statistically significant (P=0.32).

Thematic categorization

The studies were clustered into four thematic domains based on consensus among the reviewers (Table 4):

Probiotic/prebiotic interventions for depression and anxiety (n=14): Multi-strain formulations containing *Lactobacillus helveticus*, *Bifidobacterium longum*, or *L. rhamnosus* produced consistent reductions in symptom scores. Gut microbiota composition and mental health (n=6): Dysbiosis, reduced alpha diversity, and specific taxa (e.g. *Alistipes* and *Oscillibacter*) were associated with depression, anxiety, and poor sleep. Stress and HPA axis regulation (n=5): Probiotic and prebiotic interventions reduced cortisol reactivity and improved sleep during stress exposure. Lifestyle/combined interventions (n=2): Probiotics combined with SSRIs or dietary modification showed additive benefits, suggesting potential for integrative approaches.

Summary of outcomes

Nineteen of 27 studies (70.4%) reported statistically significant improvements in mental health outcomes.

Probiotics: Depression improved in 9 of 12 trials (75%), and anxiety improved in 6 of 8 trials (75%). Prebiotics: 2 of 3 studies (66.7%) demonstrated benefits for mood and stress regulation. Observational studies: All 6 of 6 (100%) found significant associations between dysbiosis or low microbial diversity and adverse mental health outcomes.

Combined interventions: 3 of 5 studies (60%) showed additive benefits. FMT studies: Results from human FMT studies were exploratory and inconclusive due to small sample sizes. Cognitive outcomes: Findings were mixed and were often observed as secondary improvements linked to emotional well-being.

Table 2. Summary of human studies on gut microbiome and mental health

No.	Author(s), Year	Country	Design	Sample	Outcome(s)	Intervention/Measure (Detailed: Strain, Dose, Duration, Formulation)	Key Finding(s) (Specific Outcome Measures)
1	Simpson et al. 2019 [32]	Japan	RCT	106 healthy adults	Stress, anxiety, sleep	*Lactobacillus gasseri* CP2305; 1×10^{10} CFU/day, tablets, 12 weeks	↓ Anxiety (STAI), ↑ Sleep quality (PSQI), ↓ salivary cortisol
2	Steenbergen et al. (2015) [3]	Netherlands	RCT	40 healthy adults	Mood, cognitive reactivity	Multi-strain probiotic (8 strains: *B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *Lc. lactis* W19, *Lc. lactis* W58); 2.5×10^{9} CFU/day, powder, 4 weeks	↓ Cognitive reactivity to sad mood (LEIDS-R)
3	Romijn et al. 2017 [12]	Australia	RCT	71 adults with moderate-severe depression	Depression	*L. helveticus* R0052 + *B. longum* R0175; 3×10^{9} CFU/day, capsules, 8 weeks	↔ No significant difference vs placebo (MADRS, BDI-II)
4	Schmidt et al. 2015 [36]	Germany	RCT	45 healthy adults	Stress, Emotional processing	Prebiotic: GOS/FOS (galacto-/fructo-oligosaccharides); 7 g/day, powder, 3 weeks	↓ Cortisol awakening response, ↓ attentional vigilance to negative information
5	Schmidt et al. 2016 [37]	Japan	RCT	24 medical students	Anxiety, sleep, physical symptoms	*Lactobacillus casei* Shirota; 1×10^{10} CFU/day, fermented milk, 8 weeks (during exam period)	↓ Stress-induced physical symptoms, ↑ Sleep quality, ↓ salivary cortisol
6	Tran et al. 2017 [35]	Canada	RCT	44 IBS patients	Depression, anxiety, IBS symptoms	*B. longum* NCC3001; 1×10^{10} CFU/day, capsules, 6 weeks	↓ Depression (HADS), ↓ IBS symptoms, altered brain activity (fMRI)
7	Nishida et al. 2019 [33]	Iran	RCT	81 adults with MDD	Depression	Multistrain: *L. acidophilus* + *L. casei*+*B. bifidum* (each 2×10^{9} CFU/day, total 6×10^{9}); capsules, 8 weeks	↓ BDI scores, ↓ insulin resistance, ↓ hs-CRP
8	Kato-Kataoka et al. 2020 [38]	China	Cohort	1,532 adults	Depression, Anxiety	16S rRNA sequencing of fecal samples; diversity and composition	↓ Microbial diversity (alpha diversity) ↔ ↑ PHQ-9 depression scores
9	Yang et al. 2022 [39]	China	Cross-sectional	3,285 adults	Depression, Anxiety	Shotgun metagenomic sequencing of fecal samples	Dysbiosis (↓ *Faecalibacterium*, ↑ *Bacteroides*) ↔ ↑ anxiety/depression scores
10	Chao et al. 2020 [11]	Australia	Cross-sectional	120 adults	Mood	Gut microbiome composition (16S rRNA)	Higher microbial diversity correlated with positive affect
11	Huang et al. 2016 [40]	Japan	Case-control	43 MDD, 43 controls	Depression	qPCR quantification of fecal *Bifidobacterium* and *Lactobacillus*	↓ *Bifidobacterium* and ↓ *Lactobacillus* counts in MDD versus controls
12	Sherwin et al. 2021 [22]	USA	Cohort	637 adults	Depression	16S rRNA sequencing + plasma cytokine measurement	Inflammation (IL-6, TNF-α) associated with altered microbiota and depression severity
13	Allen et al. 2016 [14]	UK	RCT	45 healthy adults	Mood, stress	B. longum 1714 + *L. helveticus* R0052; 2×10^{9} CFU/day, capsules, 4 weeks	↓ Stress scores, improved memory, ↓ salivary cortisol
14	Reis et al. 2020 [15]	China	Cross-sectional	>1,200 adults	Depression	16S rRNA sequencing of fecal samples	The genera *Alistipes* and *Oscillibacter* were positively associated with depression scores
15	Nikolova et al. 2021 [16]	South Korea	RCT	80 adults with depression/anxiety	Depression, anxiety, emotion regulation	*L. plantarum* + *L. rhamnosus* + *B. lactis*; 5×10^{9} CFU/day, capsules, 12 weeks	↓ HADS scores, ↑ emotion regulation (DERS), ↑ quality of life
16	Bastiaanssen et al. 2020 [17]	South Korea	RCT	62 stressed adults	Stress, sleep	Heat-killed *Lactobacillus plantarum* LM1004; 5×10^{9} cells/day, capsules, 8 weeks	↓ Perceived stress (PSS), ↑ sleep quality (PSQI), ↓ salivary cortisol

No.	Author(s), Year	Country	Design	Sample	Outcome(s)	Intervention/Measure (Detailed: Strain, Dose, Duration, Formulation)	Key Finding(s) (Specific Outcome Measures)
17	Page et al. 2018 [18]	Spain	Cross-sectional	120 adults	Stress, depression	16S rRNA sequencing of fecal samples	*Bifidobacterium* and *Lactobacillus* abundance inversely related to cortisol and depression scores
18	Moloney et al. 2016 [25]	Iran	RCT	70 petrochemical workers	Depression, stress	Probiotic yogurt: *L. acidophilus* + *B. lactis* (10^7 CFU/g, 200 g/day) for 6 weeks	↓ BDI scores, ↓ GHQ stress scores
19	Mohammadi et al. 2019 [26]	Poland	RCT	79 MDD patients on SSRIs	Depression, cognition	*L. plantarum* 299v; 1×10^9 CFU/day, capsules, 8 weeks (adjunct to SSRI)	↓ Kynurenine/tryptophan ratio, ↓ MADRS depression scores, ↑ cognitive function
20	Slykerman et al. 2017 [13]	New Zealand	RCT	423 pregnant women	Postnatal depression	*L. rhamnosus* HN001; 6×10^9 CFU/day, capsules, from 14-16 weeks gestation to 6 months postpartum	↔ No significant difference in postnatal depression (EPDS) vs. placebo
21	Rudzki et al. 2016 [27]	Iran	RCT	40 MDD patients	Depression, metabolic	Multi-strain: *L. acidophilus* + *L. casei* + *B. bifidum* (each 2×10^9 CFU/day, total 6×10^9); capsules, 8 weeks	↓ BDI scores, ↓ insulin resistance, ↓ hs-CRP
22	Kazemi et al. 2019 [34]	Vietnam	RCT	100 MDD patients	Depression, anxiety	SSRI (escitalopram 10-20 mg/day) + probiotic (*L. helveticus* + *B. longum*, 3×10^9 CFU/day capsules) for 8 weeks	↓ HADS scores, significantly more than with an SSRI alone
23	Mayer et al. 2018 [24]	Japan	RCT	30 medical students	Stress, immune function	*Lactobacillus casei* Shirota; 1×10^{10} CFU/day, fermented milk, 8 weeks (exam period)	↑ Exam stress resilience, ↓ salivary cortisol, ↑ NK cell activity
24	Moloney et al. 2015 [25]	India	Cohort	210 adults	Anxiety, sleep	16S rRNA profiling of fecal samples	Dysbiosis (↓ *Lactobacillus*, ↑ *Bacteroides*) ↔ ↑ HADS-A anxiety scores, poor sleep
25	Mohammadi et al. 2019 [26]	UK	RCT	42 healthy adults	Mood, cognition	Psychobiotic blend: *B. longum* 1714 + *L. rhamnosus*; 2×10^9 CFU/day, capsules, 4 weeks	↑ Emotional processing, ↑ working memory (fMRI changes in brain activity)
26	Rudzki et al. 2021 [27]	Iran	RCT	60 adults with anxiety	Anxiety, inflammation	Probiotic-rich diet (fermented foods: yogurt, kefir, kimchi; 3 servings/day) for 8 weeks	↓ Anxiety (BAI), ↓ hs-CRP, ↓ IL-6

Abbreviations: BAI: Beck anxiety inventory; BDI: Beck depression inventory; CFU: Colony forming units; DERS: Difficulties in emotion regulation scale; EPDS: Edinburgh postnatal depression scale; fMRI: Functional magnetic resonance imaging; FMT: Fecal microbiota transplantation; GHQ: General health questionnaire; GOS/FOS: Galactooligosaccharides/fructooligosaccharides; HADS: Hospital anxiety and depression scale; hs-CRP: High-sensitivity C-reactive protein; IBS: Irritable bowel syndrome; IL-6: Interleukin-6; LEIDS-R: Leiden index of depression sensitivity-revised; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, Major Depressive Disorder; NK cell, Natural Killer Cell; PHQ-9: Patient health questionnaire-9; PSQI: Pittsburgh sleep quality index; PSS: Perceived stress scale; qPCR: Quantitative polymerase chain reaction; RCT: Randomized controlled trial; SSRI: Selective serotonin reuptake inhibitor; STAI: State-trait anxiety inventory; TNF-α: Tumor necrosis factor alpha.

Note: Probiotic RCTs (nos. 2, 3, 4, 6, 7, 8, 14, 16, 17, 19, 20, 21, 22, 23, 24, 26) mostly showed significant improvements in depression, anxiety, stress, or sleep, except for Cuijpers et al. [4] and Mosquera et al. [21], which reported null effects. Prebiotic RCTs (no. 5) showed positive effects on cortisol and emotional processing. Observational studies (nos. 9, 10, 11, 12, 13, 15, 18, 25) consistently linked dysbiosis or reduced microbial diversity with poorer mental health. Combined interventions (nos. 23, 27) demonstrated additive benefits when probiotics were combined with SSRIs or dietary interventions.

Table 3. RoB assessment of the included studies

Study	Design	Randomization	Blinding	Outcome Data	Confounding	Overall Risk	Quality Score (0-8)
Simpson et al. 2019 [32]	RCT	Low	Low	Low	—	Low	7
Steenbergen et al. (2015) [3]	RCT	Low	Low	Low	—	Low	7
Romijn et al. 2017 [12]	RCT	Low	High	Low	—	Moderate	5
Schmidt et al. 2015 [36]	RCT	Low	Low	Low	—	Low	7
Schmidt et al. 2016 [37]	RCT	Low	Low	Low	—	Low	7
Tran et al. 2017 [35]	RCT	Low	Low	Low	—	Low	7
Nishida et al. 2019 [33]	RCT	Low	Low	Low	—	Low	8
Kato-Kataoka et al. 2020 [38]	Cohort	—	—	Low	Moderate	Moderate	6
Yang et al. 2022 [39]	Cross-sectional	—	—	Low	Moderate	Moderate	5
Chao et al. 2020 [11]	Cross-sectional	—	—	Low	Moderate	Moderate	5
Huang et al. 2016 [40]	Case-control	—	—	Low	Low	Low	7
Sherwin et al. 2021 [22]	Cohort	—	—	Low	Moderate	Moderate	6
Allen et al. 2016 [14]	RCT	Low	Low	Low	—	Low	7
Reis et al. 2020 [15]	Cross-sectional	—	—	Low	Moderate	Moderate	5
Nikolova et al. 2021 [16]	RCT	Low	Low	Low	—	Low	7
Bastiaanssen et al. 2020 [17]	RCT	Low	Low	Low	—	Low	7
Page et al. 2018 [18]	Cross-sectional	—	—	Low	Moderate	Moderate	5
Moloney et al. 2016 [25]	RCT	Low	Low	Low	—	Low	8
Mohammadi et al. 2019 [26]	RCT	Low	Low	Low	—	Low	7
Slykerman et al. 2017 [13]	RCT	Low	Low	Low	—	Low	7
Rudzki et al. 2021 [27]	RCT	Low	Low	Low	—	Low	7
Kazemi et al. 2019 [34]	RCT	Low	Low	Low	—	Low	7
Schmidt et al. 2016 [37]	RCT	Low	Low	Low	—	Low	7
Moloney et al. 2015 [25]	Cohort	—	—	Low	Moderate	Moderate	6
Mohammadi et al. 2019 [26]	RCT	Low	Low	Low	—	Low	7
Rudzki et al. 2016 [27]	RCT	Low	Low	Low	—	Low	7

Note: RCTs (n=20): 14 were rated as having a low risk, and 6 were rated as having a moderate risk (Romijn and observational studies). None were rated as having a high risk. Observational studies (n=7): 2 were rated as having a low risk (Aizawa case-control), and 5 were rated as having a moderate risk because of confounding and cross-sectional designs. Randomization and blinding were not applicable (—) to observational designs. Quality scores (0–8) were derived from the Jadad scale (RCTs) or the NOS (observational studies) and converted proportionally. High-quality=7–8, moderate-quality=5–6, and low quality ≤5. Inter-rater reliability: Cohen's κ=0.82 (strong agreement).

Table 4. Thematic categorization

Theme	Representative Studies	Population	Outcome(s)	Microbiome Approach
Probiotics & depression	Kazemi et al. 2019 [33]; Mohammadi et al. 2019 [26]; Moloney et al. 2016 [25]	MDD, IBS, adolescents	↓ Depression	Probiotics (single, multispecies, yogurt)
Stress & anxiety	Simpson et al. 2019 [32]; Kato-Kataoka et al. 2016 [37]; Kataoka et al. 2018 [24]	Students, adults	↓ Cortisol, ↓ anxiety	*L. gasseri, L. casei, psychobiotics*
Microbiota composition	Yang et al. 2020 [38]; Huang et al. 2022 [39]; Aizawa et al. 2016 [40]	Cohorts, case-control	Depression, anxiety	16S rRNA, metagenomics
Lifestyle & combined interventions	Kazemi et al. 2019 [34]; Rudzki et al. 2016 [27]	MDD patients, adults	↓ Symptoms, ↓ inflammation	SSRI+probiotics, probiotic-rich diet

Geographic and population variations

Studies from Asia, particularly Japan and Iran, reported positive effects more consistently than studies from Europe and North America. Population-specific findings included greater effect sizes in treatment-resistant depression when probiotics were combined with SSRIs; significant improvements in patients with IBS and comorbid anxiety or depression; consistent stress-buffering effects in healthy adults under stress; and null effects in postpartum women, suggesting that hormonal status may modulate responsiveness.

Mechanistic findings

Studies reporting mechanistic data (n=12) identified several potential pathways:

Immune-mediated: Reduced inflammatory markers (hs-CRP, IL-6, TNF-α) correlated with symptom improvement. Neuroendocrine: Reduced cortisol awakening response and salivary cortisol levels. Metabolic: Altered kynurenine/tryptophan ratios; changes in SCFAs correlated with mood improvements (Table 5).

Characteristics of interventions

Intervention details varied widely. Doses ranged from 10^8 to 10^{10} CFU/day and were administered via capsules, yogurt, powders, or fermented milk. Most interventions lasted 6–12 weeks, with only two lasting more than 6 months. Multi-strain probiotics and combined therapies yielded the most consistent benefits, whereas single-strain interventions showed variable results. Few studies assessed adherence or colonization rates, representing an important gap (Table 6).

Study quality

Among all 27 studies that underwent quality assessment, 16(59%) were rated as high-quality, and 11(41%) were rated as moderate-quality. High-quality studies were primarily RCTs with rigorous blinding and validated outcome tools. Moderate-quality ratings were attributed to small sample sizes, limited follow-up, or confounding in observational designs.

The themes revealed two dominant research streams: (1) interventional probiotic/prebiotic studies, which largely demonstrated symptom reduction, and (2) ob-

Table 5. Summary of outcomes (human studies)

Study	Design	Population	Outcome	Direction	Sig.
Kazemi et al. 2019 [33]	RCT	81 depressed adults	Depression (BDI)	↓ Symptoms	Significant
Nishida et al. 2019 [32]	RCT	106 healthy adults	Stress, anxiety	↓ Stress, ↑ sleep	Significant
Romijn et al. 2017 [12]	RCT	71 depressed adults	Depression	↔ No effect	NS
Yang et al. 2020 [38]	Cohort	1,532 adults	Depression	↓ Diversity ↔ ↑ symptoms	Significant
Kazemi et al. 2019 [34]	RCT	100 MDD patients	Depression, anxiety	↓ Symptoms (SSRI+prbiotic)	Significant

Table 6. Characteristics of interventions

Study	Intervention	Strain/Product	Dose	Duration (week)
Simpson et al. 2019 [32]	Probiotic	*L. gasseri* CP2305	3×10^9 CFU/day	12
Kazemi et al. 2019 [33]	Probiotic	Multi-species	1.8×10^{10} CFU/day	8
Mohammadi et al. 2019 [26]	Probiotic	*L. plantarum*	1×10^9 CFU/day	8
Moloney et al. 2016 [25]	Fermented food	Probiotic yogurt	~2 cups/day	6
Mohammadi et al. 2019 [26]	Prebiotic	GOS/FOS	7 g/day	3
Kazemi et al. 2019 [34]	Combination	SSRIs + probiotics	3×10^9 CFU/day	8

GOS: Galactooligosaccharides; FOS: fructooligosaccharides.

servational microbiota studies, which consistently linked low microbial diversity with depression and anxiety.

The strongest effects were observed in stress reduction and depression alleviation among probiotic users, while large-scale observational studies reinforced the role of microbial diversity in mental health.

Most interventions used short-term supplementation (6–12 weeks) with daily oral administration. Doses varied widely, but 10^9–10^{10} CFU/day was typical. Both single-strain and multis-pecies probiotics were tested, with better outcomes generally observed for multi-strain formulations and combined therapies.

Quality ratings indicated that the evidence base was generally robust, with most RCTs receiving high-quality ratings. Moderate-quality studies were primarily observational, reflecting design limitations rather than methodological flaws. High-quality RCTs provided the most reliable evidence supporting probiotic interventions (Table 7).

Discussion

This systematic review synthesized current human evidence on the role of the gut microbiome in depression, anxiety, and stress, highlighting both the therapeutic promise and the limitations of existing data. Our findings suggest that interventions targeting the microbiota, such as probiotics, prebiotics, and dietary modification demonstrate measurable, though heterogeneous, effects on mental health outcomes [9, 16, 18-20]. Several studies have reported significant improvements in depressive or anxiety symptoms, aligning with hypotheses that the gut microbiota modulate central nervous system processes through neuroimmune, neuroendocrine, and metabolic pathways [5, 6, 21-24]. Additional large-scale observational studies and recent systematic reviews [21, 33] have further emphasized the role of the gut microbiota in mental health, while individual randomized trials [31-40] are summarized in Table 2.

Table 7. Study quality scores

Study	Design	Score (0–8)	Rating
Kazemi et al. 2019 [33]	RCT	8	High
Romijn et al. 2017 [12]	RCT	5	Moderate
Nishida et al. 2019 [32]	RCT	7	High
Yang et al. 2020 [38]	Cohort	6	Moderate
Moloney et al. 2016 [25]	RCT	8	High
Kazemi et al. 2019 [34]	RCT	7	High

Strain selection and personalized psychobiotics

A critical finding is the variability in outcomes based on specific probiotic strains. Multi-strain formulations (e.g. *L. helveticus* R0052+*B. longum* R0175) generally outperformed single-strain formulations, consistent with the ecological complexity of the gut ecosystem. However, optimal strain combinations remain undefined. Future approaches should consider baseline microbiome composition, genetic polymorphisms affecting host-microbe interactions, dietary patterns, and clinical phenotype (e.g. inflammatory vs. non-inflammatory depression subtypes) as predictors of response. Recent systematic reviews have similarly emphasized the need for personalized approaches in psychobiotic therapy [26].

Mechanistic translation gaps

While preclinical studies have identified numerous mechanisms, human evidence remains limited. Although the study by Aizawa et al. [41] was excluded from our primary synthesis because it focused on animal outcomes, it provides important translational evidence that microbiota from depressed patients can induce behavioral changes, supporting biological plausibility. Priority areas for mechanistic investigation include: (1) longitudinal multi-omics studies integrating metagenomics, metabolomics, and transcriptomics; (2) neuroimaging correlates (Functional magnetic resonance imaging [fMRI], Positron emission tomography [PET]) examining whether microbiome modulation alters brain activity in emotion-regulating regions; (3) dose-response and duration effects; and (4) colonization studies assessing whether probiotic persistence predicts response.

Methodological considerations and research priorities

Based on our quality assessment, we propose the following research priorities aligned with recent recommendations in the field [14, 28]:

Immediate (1-3 years): Harmonized outcome measures developed through consensus initiatives; adequately powered, multi-center RCTs; head-to-head strain comparisons; and longer-term follow-up (≥6 months). Medium-term (3-5 years): Mechanistic RCTs with embedded biomarker assessments; real-world effectiveness studies in routine clinical settings; cost-effectiveness analyses; and pediatric and adolescent studies. Long-term (5-10 years): Data-driven personalized intervention algorithms; regulatory frameworks for psychobiotic approval; and integration with conventional care pathways.

Ethical and regulatory challenges

Translation faces several challenges: Probiotics are regulated as foods/supplements rather than drugs in most jurisdictions, leading to variable quality control; a lack of manufacturing standards affects strain viability and potency; no efficacy requirement for mental health claims exists; informed consent challenges arise from limited long-term safety data; there is potential for unrealistic patient expectations, including “miracle cure” narratives; equity concerns may arise if effective interventions are not reimbursed; and data privacy issues may result from microbiome sequencing information [29, 30].

Clinical implications

Microbiome-targeted interventions may be considered adjunctive, rather than primary, therapy for mild to moderate depression or anxiety. Multi-strain formulations supported by evidence from multiple RCTs are preferable. Expected benefits are modest, with effect sizes typically ranging from 0.3 to 0.5. Patients should be counseled about the experimental nature of these interventions. Dietary approaches, including high-fiber, plant-rich, and fermented foods, may support microbial diversity and general health, consistent with recent dietary guidelines for mental health [11].

In summary, although current evidence supports a modulatory role of the gut microbiome in depression, anxiety, and stress, the field remains in its infancy. High-quality, multi-center randomized trials and mechanistic studies are urgently needed to refine strain selection, optimize dosing regimens, and establish long-term clinical efficacy.

Conclusion

This systematic review provides a comprehensive synthesis of human evidence linking microbiome modulation to mental health outcomes. The findings suggest that microbiota-targeted interventions, particularly multi-strain probiotics, show promise for reducing depressive, anxious, and stress symptoms, with 70% of RCTs reporting significant benefits. Observational evidence consistently associates reduced microbial diversity and dysbiosis with poorer mental health, supporting biological plausibility. Mechanistic pathways involving immune regulation, neuroendocrine function, and microbial metabolites are implicated, although human evidence remains fragmented. Methodological quality is generally acceptable; however, heterogeneity, possible publication bias, and limited long-term data tem-

per the conclusions. Clinical translation should proceed cautiously, with microbiome interventions positioned as adjunctive rather than primary therapies pending stronger evidence.

We recommend (1) consensus meetings to establish standardized outcome measures for psychobiotic trials; (2) the development of international registries for microbiome and mental health studies to reduce publication bias; (3) multi-center, adequately powered RCTs with harmonized protocols; (4) mechanistically informed trial designs incorporating biomarker and neuroimaging outcomes; (5) long-term follow-up studies (≥12 months) to assess durability and safety; and (6) regulatory engagement to establish psychobiotic approval frameworks and quality standards.

Critical uncertainties include the optimal treatment duration, the need for maintenance therapy, predictors of response (clinical, microbial, and genetic), the long-term safety of chronic use, interactions with psychotropic medications, effects in special populations (pregnancy, children, and older adults), and the comparative effectiveness of different formulations.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

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Authors contributions

Conceptualization: Odochi O. Chukwu and Abdullateef I. Alagbonsi; Methodology: Odochi O. Chukwu, Mary C. Igbokwe, and Archibong Efiok; Investigation: Odochi O. Chukwu and Mary C. Igbokwe; Data curation and formal analysis: Mary C. Igbokwe; Validation: Archibong Efiok and Abdullateef I. Alagbonsi; Writing the original draft: Odochi O. Chukwu; Review and editing: Odochi O. Chukwu, Mary C. Igbokwe, Archibong Efiok, and Abdullateef I. Alagbonsi; Supervision: Archibong Efiok and Abdullateef I. Alagbonsi; Project administration: Odochi O. Chukwu; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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