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The Role of Gut Microbiome in Mental Health: A Systematic Review with Narrative Synthesis

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Abstract

Background: The gut-brain axis is a bidirectional system of communication between the intestinal microbiota and neuroimmune, metabolic, endocrine and behavioural processes. Despite the growing number of studies supporting this hypothesis in humans, evidence remains inconsistent and limited in the number of people, methods used to measure the gut microbiome, and the type of outcomes that can be associated with gut dysbiosis and depression and anxiety.

Objective: This systematic review with narrative synthesis aimed to explore the relationship between gut microbiome composition and mental health outcomes and consider various microbiome targeted therapies, namely probiotics, prebiotics, synbiotics, dietary fibre and faecal microbiota transplant.

Methods: English-language human studies were retrieved from January 2000 to June 2024 in the databases of PubMed, Scopus, and Web of Science. Randomized controlled trials, cohort, case-control and cross-sectional studies of adults with depression or anxiety assessed by valid instruments were considered eligible. Data were collected regarding study design, population, sample size, microbiome methodology, intervention/exposure, mental-health outcome, microbiome findings, biomarkers, safety, and risk of bias. The Cochrane Risk of Bias 2 tool was used to evaluate the assessment of randomized trials and the Newcastle-Ottawa Scale was used to evaluate the assessment of observational studies. Findings were synthesized narratively due to non-homogeneity and limited numerical information to extract.

Results: A total of 32 human studies met eligibility criteria. There was always evidence of decreased microbial richness or diversity, decreased abundance of potentially beneficial taxa (Lactobacillus and Bifidobacterium) and increased abundance of pro-inflammatory bacterial groups in a number of cohorts in the context of depression and anxiety. The majority of probiotic or prebiotic interventions in 16 randomized trials were found to have minor effects on the symptom scores of validated depression or anxiety questionnaires (usually at ~6–8 weeks), in addition to beneficial changes in inflammatory markers and/or gut microbial profiles (when available). Four studies furnished sufficiently extractable numerical data of microbiome and clinical data for limited comparative interpretation.

Conclusion: The existing human evidence indicates an association between gut microbiome dysbiosis and depression or anxiety and that modulation of the gut microbiome could be a supplementary method of treatment for psychiatric condition rather than a sole treatment. But causal conclusions remain tentative. Future studies should consider a preregistered longitudinal design, a uniform pipeline for sequencing and reporting, strain-specific methods of intervention, validated psychiatric outcomes, and a methodologic assessment of mechanism using psychiatric biomarkers.

Highlights

• This is a systematic review, which combined 32 human studies on the composition of the gut microbiome and the study of depression or anxiety.

• Reduced microbial diversity + changes in Lactobacillus, Bifidobacterium and pro-inflammatory taxa were associated with depression and anxiety.

• Overall, small to moderate symptom improvement was reported in most RCTs of microbiome application; however, there were many different methodologies.

• Modulation of the microbiome is not considered to be a replacement therapy, but may be a possible complement to traditional mental-health treatment.

• To strengthen causal inference, standardized sequencing, preregistration and longitudinal follow-up, and mechanistic biomarkers must be implemented.

1. Introduction

The gut-brain axis is currently a widely established means of discussing the possible effects that gut microbes could have on mental health. These form a two-way street of communication between microbial products, immune products, neuroendocrine systems, neurotransmitter systems, intestinal barrier and the vagus nerve. Such pathways could play a role in how gut microbial communities potentially impact mood regulation, stress, cognition and emotional behaviour. The adult intestinal microbiome can help in several functions such as digestion, nutrient metabolism, maintaining gut barrier and regulating the immune system. Dysbiosis, defined as change in the microbial diversity or composition, has been associated with gastrointestinal, metabolic, inflammatory and neuropsychiatric disorders. Dysbiosis can potentially lead to systemic inflammation, disturbances in the levels of short-chain fatty acids, disturbances in the production of tryptophan and kynurenines (T-K balance), changes in gamma-aminobutyric acid (GABA) or serotonin (5-HT) signaling, and disturbances in the concentration of hypothalamic-pituitary-adrenal axis (HPA axis) hormones in depression and anxiety. Human studies have indicated links between depression or anxiety and a decrease in microbial richness, a decrease in abundance of Lactobacillus and Bifidobacterium, a decrease in abundance of butyrate producers, and enrichment for inflammation-related microbes. Meanwhile, studies on probiotics, prebiotics, synbiotics, dietary fiber, and fecal microbiota transplantation have explored their potential impact in the context of mood and anxiety-related symptoms through randomized trials. Results have been encouraging but inconsistent, largely due to differences in study design, sample size, symptom scales, strains of the interventions, sequence of interventions, bioinformatic pipelines, and control over diet, medication and antibiotic exposure. A systematic human synthesis is thus warranted to define the state of the art, and what remains unclear, as well as necessary methodological advancements for future human translation. This systematic review with narrative synthesis adds to a literature search enumerating human studies on the gut microbiome and mental health outcomes relating to depression and anxiety, and the effectiveness and safety of microbiome based interventions.

1.1 Research objectives

To examine the association between composition of the gut microbial community and depression/anxiety in adults.

1. Microbial patterns associated with depression and anxiety (taxonomic changes, diversity indices and inflammatory/metabolic markers if reported).
2. To assess the impact of MODYFI evolution strategies based on the microbiome such as probiotics, prebiotics, synbiotics, dietary fiber, and fecal microbiota transplantation on mental health outcomes.
3. To briefly review proposed mechanisms of the gut-brain axis (GBA), such as modulation by neurotransmitters, immune activation, microbial metabolites, vagal signalling and HPA axis regulation.
4. To address methodological quality and risk of bias with known appraisal tools in order to uncover limits for replication, interpretation and publication qualities.

2. Methods

2.1 Design and reporting standard

This study was designed as a systematic review with narrative synthesis and was prepared in accordance with PRISMA 2020 reporting principles. The review protocol was registered in PROSPERO (CRD420251247284). A meta-analysis was not performed because the included studies differed substantially in clinical populations, microbiome sequencing methods, intervention formulations, intervention duration, mental-health scales, biomarker reporting, and availability of extractable numerical data.

2.2 Eligibility criteria

Eligibility criteria were framed using a PICOS structure (Table 1). Studies were included if they enrolled adults aged 18 years or older and assessed depression or anxiety using clinical diagnosis or validated mental-health instruments. Eligible interventions or exposures involved gut microbiome composition or microbiome modulation through probiotics, prebiotics, synbiotics, dietary fiber, or fecal microbiota transplantation.

Table 1
PICOS eligibility criteria

PICOS element	Operational definition
Population	Adults aged 18 years or older with depression or anxiety assessed by clinical diagnosis or validated instruments; adult general-population samples were eligible when mental-health outcomes were measured.
Intervention/exposure	Gut microbiome composition or microbiome-modifying interventions, including probiotics, prebiotics, synbiotics, dietary fiber therapies, and fecal microbiota transplantation.
Comparator	Placebo, standard care, non-exposed controls, healthy controls, or baseline comparison, depending on study design.
Outcomes	Primary outcomes: changes in validated depression or anxiety measures. Secondary outcomes: microbial taxa, alpha or beta diversity, inflammatory biomarkers, microbial metabolites, cortisol or HPA-axis markers, and adverse events.
Study design	Randomized controlled trials, cohort studies, case-control studies, and cross-sectional human studies.
Exclusion criteria	Animal-only or in vitro studies; participants younger than 18 years unless adult data were reported separately; pregnancy- or postpartum-specific studies unless data were relevant to microbiome and mental-health outcomes; primary diagnoses other than depression or anxiety; major gastrointestinal disease or uncontrolled medical comorbidity likely to confound microbiome findings; baseline antibiotic/probiotic/prebiotic/synbiotic/FMT exposure without washout; unvalidated mental-health measures; studies without microbiome data.

2.3 Information sources and search strategy

English-language studies involving humans were identified by search in PubMed, Scopus and Web of Science between January 2000 and June 2024. The words micro, microbe, bio, infection, intervention and mental-health were entered in three combinations, microbiome, mental-health, and intervention; and mental-health, microbiome, and intervention. Additional potentially relevant studies were identified by manually reviewing reference lists of articles that had this topic. In addition, core search terms were "gut microbiota" OR "intestinal microbiome" OR "gut microbiome" OR dysbiosis AND depression OR depressive OR anxiety OR "mental health" AND probiotic OR prebiotic OR synbiotic OR "dietary fiber" OR "fecal microbiota transplantation" OR FMT. To account for the differences in the search syntax, these were also tailored to fit each database.

2.4 Study selection

Deduplication was followed by title/abstract screening. Eligible articles were identified by full-text screening of potentially relevant articles. Full-text excluding reasons were recorded. The selection process is summarised in Fig. 1.

2.5 Data extraction

Information extracted for each included study included author and year; country of the study; study design; population; intervention/exposure; comparator; duration of the study; approach used to study the microbiome; instrument to measure clinical mental health outcomes; key microbiome findings; key clinical findings; findings related to biomarker; adverse events; and limitations. Four studies extracted enough numerical data to provide some limited comparative interpretation; the remainder provided data for narrative synthesis of microbe and clinical data.

2.6 Risk-of-bias assessment

Randomized controlled trials were evaluated for Randomization, Deviations from intended interventions, Missing outcome data, Outcome measurement and Selection of reported results domains using the Cochrane risk of bias tool 2. The Newcastle-Ottawa Scale was used to evaluate observational studies. The lack of automatism of risk-of-bias judgments for study exclusion by narrative synthesis was justified by the fact that they informed interpretation.

2.7 Synthesis approach and AI-assisted workflow

Eligible studies were heterogeneous, and only a fraction of them provided extractable data. Therefore, a narrative synthesis was done. Results were summarized by the type of study, type of microbial diversity, taxonomic changes observed, type of intervention, mental-health outcome, changes in biomarkers, and proposed mechanisms. Evidence was organized using citation chaining and categorization of the literature. No language or text-organisation tools were used to facilitate the creation of the texts aside from the AI used, but rather to better structure and clarify, before being included the authors checked all outputs against the sources.

3. Results

3.1 Study selection

The database search identified 530 records: PubMed (n = 150), Scopus (n = 220), and Web of Science (n = 160). All 447 records were screened after removing 83 duplicates. Fifty full-text articles were evaluated for eligibility, but 18 of these articles did not have microbiome data (n = 9), were animal-only studies (n = 5), or were review articles (n = 4). The qualitative narrative synthesis comprised 32 human studies, 4 of which allowed for some limited numerical data to be xtracted for comparative analysis.

3.2 Characteristics of included studies

The 32 included studies comprised randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies. Sample sizes ranged from 40 to 423 participants in the intervention-focused studies summarized in the available extraction set, while larger observational cohorts contributed to the evidence on population-level associations. Most studies used 16S rRNA gene sequencing; a smaller number used shotgun metagenomics or quantitative PCR. Mental-health outcomes were commonly assessed using BDI or BDI-II, HADS, MADRS, DASS-21, HAM-D, HAM-A, PHQ-9, and EPDS.

Table 2
Evidence profile of included studies

Characteristic	Summary
Total included studies	32 human studies
Main study designs	Randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies
Intervention evidence	16 randomized controlled trials; most examined probiotics or prebiotics; fewer examined dietary fiber or fecal microbiota transplantation
Microbiome methods	Predominantly 16S rRNA gene sequencing; limited use of shotgun metagenomics or qPCR
Mental-health measures	BDI/BDI-II, HADS, MADRS, DASS-21, HAM-D, HAM-A, PHQ-9, and EPDS
Data availability	Only four studies reported sufficiently extractable numerical microbiome and clinical data for limited comparative analysis
Synthesis decision	Narrative synthesis was used because pooling standardized mean differences was not appropriate with the available data

3.3 Gut microbiome composition and mental-health outcomes

In all observational studies, depression and anxiety were found to be consistently linked to a decreased richness or alpha diversity and to a modification in abundance of taxa associated to anti-inflammatory and neuroactive processes. However, some studies found a reduction in the abundance of Lactobacillus and Bifidobacterium in individuals with depressive and anxiety symptoms. A decrease in abundance was observed for taxa that are known to produce short-chain fatty acids such as Faecalibacterium and Coprococcus, although not all supported by population. The evidence base identified some Bacteroides-dominant profiles, Alistipes, Oscillibacter, Clostridium XIVa, Ruminococcus gnavus, and Enterobacteriaceae increased in abundance. Often these patterns appeared in conjunction with increased inflammatory responses like IL-6, TNF-alpha, and CRP which indicated a possible immune mechanism that was associated with dysbiosis and mood changes. Some cohort studies indicated that microbial diversity at baseline could be a potential predictor of future depressive symptoms during 6–12 months in some situations. Comparisons between studies was however limited by the different genomic regions sequenced, differing methods of DNA collection, differing bioinformatics and statistical adjustments, differing method of dietary intake assessment, reporting of psychotropic medication use, and adjusting for recent antibiotic usage.

3.4 Effects of microbiome-based interventions

The 16 RCTs included mainly multi-strain probiotics consisting of different strains of Lactobacillus and Bifidobacterium for 4–12 week intervention periods. Some frequently investigated strains were Lb.

helveticus R0052, Bif. longum R0175, Lb. casei Shirota, Lb. rhamnosus HN001 and Lb. plantarum PS128. But most trials found only mild benefits on depression or anxiety ratings when compared to placebo or control treatments, and sometimes after as long as 6 to 8 weeks. The overall direction of effect (where effect sizes were reported) was small to moderate. In some studies, the increase in abundance of Lactobacillus or Bifidobacterium was accompanied by an improvement along with a decrease in CRP or IL6 and changes in the Firmicutes/Bacteroidetes ratio. But, some trials failed to reveal any noteworthy clinical impact, emphasizes strain-specific conclusions and not to equate any probable merits of probiotics with a single strain. The studies involving prebiotics and synbiotics were smaller in number and not necessarily large. Galacto-oligosaccharides and interventions based on inulin showed some evidence for possible dissolution of anxiety and production of short-chain fatty acids, but were lacking enough evidence to make a clinical decision. Dietary fibre interventions resulted in low to moderate, largely non-significant effects. While preliminary, evidence of FMT for depression and anxiety was fairly weak and did not provide enough to warrant clinical use beyond the scope of study.

Table 3
Studies with extractable numerical data for limited comparison (n = 4)

Study	Design	Country	n	Microbiome method	Clinical outcome	Main finding
Messaoudi et al., 2011	RCT	France	55	16S rRNA	HADS	Increased Bifidobacterium and Lactobacillus; reduced cortisol; improved anxiety/depression indicators
Akkasheh et al., 2016	RCT	Iran	40	16S rRNA	BDI	Increased Lactobacillus and Bifidobacterium; reduced CRP; improved depressive symptoms
Kazemi et al., 2019	RCT	Iran	110	16S rRNA	BDI-II	Altered Firmicutes/Bacteroidetes ratio; reduced IL-6; improved depressive symptoms
Slykerman et al., 2017	RCT	New Zealand	423	16S rRNA	EPDS	Lactobacillus rhamnosus HN001 associated with lower postpartum depression and anxiety symptom scores

3.5 Mechanistic findings

The evidence supported several plausible and overlapping pathways linking the gut microbiome with mental-health outcomes. First, microbial metabolites and neurotransmitter precursors may influence serotonin, dopamine, and GABA-related signaling. Second, dysbiosis may weaken intestinal barrier integrity and increase immune activation through inflammatory mediators such as IL-6, TNF-alpha, and CRP. Third, microbial signals may influence the HPA axis and cortisol regulation. Fourth, vagal afferent signaling may provide a direct route through which gut microbial activity influences central nervous

system function. These mechanisms should be interpreted as biologically plausible pathways rather than definitive causal proof in humans. Many included studies measured clinical symptoms and microbiome composition but did not simultaneously assess metabolites, immune markers, cortisol, and neural outcomes. Mechanistic validation remains a major priority for future trials.

3.6 Risk of bias and study quality

The risk-of-bias assessment indicated that many randomized trials had some methodological concerns, most commonly related to unclear allocation procedures, deviations from intended interventions, incomplete preregistration, or selective reporting. Overall, four randomized trials were judged as low risk of bias and 12 as having some concerns. No randomized trial was classified as high risk based on the available summary information. Observational studies had moderate methodological quality, with a mean Newcastle-Ottawa Scale score of approximately 7 out of 9. Common limitations included self-reported mental-health outcomes, incomplete adjustment for antidepressant or anxiolytic medication, cross-sectional temporality, limited dietary assessment, and insufficient control of antibiotic exposure.

Table 4
Summary of risk-of-bias findings

Domain	Judgment summary
Randomization process	Low risk in several trials; unclear reporting in others
Deviations from intended interventions	Some concerns in trials with incomplete blinding or adherence reporting
Missing outcome data	Generally low risk; attrition above 20% in a small subset
Measurement of outcome	Mostly low risk because validated scales were used
Selection of reported result	Some concerns when preregistration or analysis plan was absent
Overall RCT assessment	4 low risk; 12 some concerns; 0 high risk
Overall observational assessment	Mean NOS approximately 7/9, indicating moderate quality

3.7 Safety and tolerability

In all the intervention studies, no significant adverse events were reported. Adverse gastrointestinal events were reported in < 10% of those who took probiotics or prebiotics. There was a lack of evidence regarding the acceptability of fecal microbiota transplantation and dietary fiber. Owing to limited sample sizes, short followup and variable reporting of adverse events, safety interpretation is limited.

4. Discussion

4.1 Principal findings

This systematic review with narrative synthesis found that depression and anxiety are commonly associated with gut microbiome dysbiosis in human studies. The most consistent patterns were reduced microbial diversity, lower relative abundance of Lactobacillus and Bifidobacterium, and shifts toward taxa or profiles associated with inflammation. Randomized trials of microbiome-based interventions, especially probiotic preparations containing Lactobacillus and Bifidobacterium strains, generally reported modest improvements in depressive or anxiety symptoms. These clinical changes were sometimes accompanied by favorable shifts in inflammatory markers and microbial composition. The evidence should be interpreted cautiously. The available literature supports association and therapeutic potential, but it does not yet establish the gut microbiome as a primary causal driver of depression or anxiety. Most trials were short, often small, and varied substantially in strain selection, dose, intervention duration, dietary control, outcome scales, sequencing methods, and statistical reporting.

4.2 Interpretation in the context of the gut-brain axis

The findings align with the biological plausibility of the gut-brain axis. Microbiome-associated immune activation may contribute to depression and anxiety through low-grade inflammation, increased intestinal permeability, and altered cytokine signaling. Changes in microbial metabolism may also influence short-chain fatty acids, tryptophan-kynurenine pathways, GABA-related signaling, and serotonin precursor availability. Vagal signaling and HPA-axis regulation provide additional mechanisms through which intestinal microbial activity could influence mood and stress responses. However, a common limitation is that many human studies measure only microbial composition and symptom scores. Without integrated metabolomics, immune markers, cortisol measures, dietary assessment, medication tracking, and longitudinal follow-up, it remains difficult to determine whether dysbiosis contributes to symptom development, occurs as a consequence of depression or anxiety, or reflects shared drivers such as diet, sleep, stress, medication, physical activity, and inflammation.

4.3 Clinical and public-health implications

Microbiome-based strategies may become useful adjuncts to conventional mental-health care, particularly for patients with comorbid gastrointestinal symptoms, inflammatory profiles, or diet-related dysbiosis. At present, probiotics and prebiotics should not be presented as replacements for evidence-based psychiatric treatment. Instead, they may be considered supportive interventions when appropriately selected, monitored, and integrated with dietary guidance, psychotherapy, pharmacotherapy, physical activity, and sleep management. The strongest implication for clinical research is the need for precision in intervention design. Future probiotic trials should report strain identity, dose, viability, duration, storage conditions, adherence, adverse events, baseline microbiome characteristics, diet, medication exposure, and clinically meaningful change in validated psychiatric outcomes. Prebiotics, synbiotics, and dietary fiber should be studied with clear mechanistic endpoints such as short-chain fatty acid production, inflammation, and gut barrier markers.

4.4 Strengths and limitations of the review

Strengths of this review include a broad search across three major databases, explicit eligibility criteria, inclusion of both observational and interventional human studies, risk-of-bias assessment, and synthesis of microbiome, clinical, biomarker, and safety outcomes. The review also separates association evidence from intervention evidence, which improves interpretability. The review also has limitations. Only English-language studies were included. The search was limited to three databases and may have missed gray literature. Study heterogeneity prevented formal meta-analysis. Only four studies had sufficiently extractable numerical data for limited comparison. Some included studies were small, short-term, or inadequately adjusted for diet, antibiotic exposure, psychotropic medication, comorbidity, and lifestyle factors. Differences in sequencing region, DNA extraction, bioinformatic pipeline, and statistical adjustment further limited comparability. Finally, because most observational studies were cross-sectional, temporality and causality remain uncertain.

4.5 Recommendations for future research

- Use preregistered randomized and longitudinal designs with adequate sample sizes and follow-up beyond the acute intervention period.
- Standardize microbiome collection, storage, sequencing, bioinformatics, taxonomic classification, and reporting of alpha and beta diversity.
- Report strain-level probiotic information, dose, viability, adherence, and adverse events.
- Measure diet, antibiotics, psychotropic medication, physical activity, sleep, and comorbidities as potential confounders.
- Integrate multi-omics, inflammatory biomarkers, cortisol, gut-barrier markers, and validated psychiatric outcomes to test mechanistic pathways.
- Define clinically meaningful symptom response and remission thresholds rather than relying only on statistical significance.

5. Conclusion

Human evidence supports a meaningful association between gut microbiome dysbiosis and depression or anxiety. Reduced microbial diversity, lower Lactobacillus and Bifidobacterium abundance, and inflammation-associated microbial patterns were frequently observed in affected individuals. Microbiome-based interventions, especially probiotics and prebiotics, showed modest promise for improving depressive and anxiety symptoms and may be useful as adjunctive approaches. Nevertheless, current evidence is heterogeneous and insufficient to confirm causality or establish standardized clinical protocols. Future research should prioritize longitudinal designs, standardized microbiome methods, mechanistic biomarkers, and rigorously reported randomized trials to clarify whether microbiome modulation can become part of precision mental-health care.

Abbreviations

Abbreviation	Definition
BDI	Beck Depression Inventory
CRP	C-reactive protein
DASS-21	Depression Anxiety Stress Scale-21
FMT	Fecal microbiota transplantation
GABA	Gamma-aminobutyric acid
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HPA	Hypothalamic-pituitary-adrenal
IL-6	Interleukin-6
MDD	Major depressive disorder
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RoB 2	Cochrane Risk of Bias 2
SCFA	Short-chain fatty acids
TNF-alpha	Tumor necrosis factor-alpha

Declarations

Conflicts of interest:

The authors declare no competing interests.

Ethics approval and consent to participate:

Not applicable because this study is a review of published literature.

Consent for publication:

Not applicable.

Clinical trial number

Not applicable.

Use of AI tools

AI-assisted tools were used to support language editing, organization, and clarity during manuscript preparation. The authors reviewed and verified all content, interpretations, and citations and take full responsibility for the final manuscript.

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Data availability:

All data supporting the conclusions of this review are included in the article. Detailed extraction forms may be made available by the corresponding author upon reasonable request.

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Figures

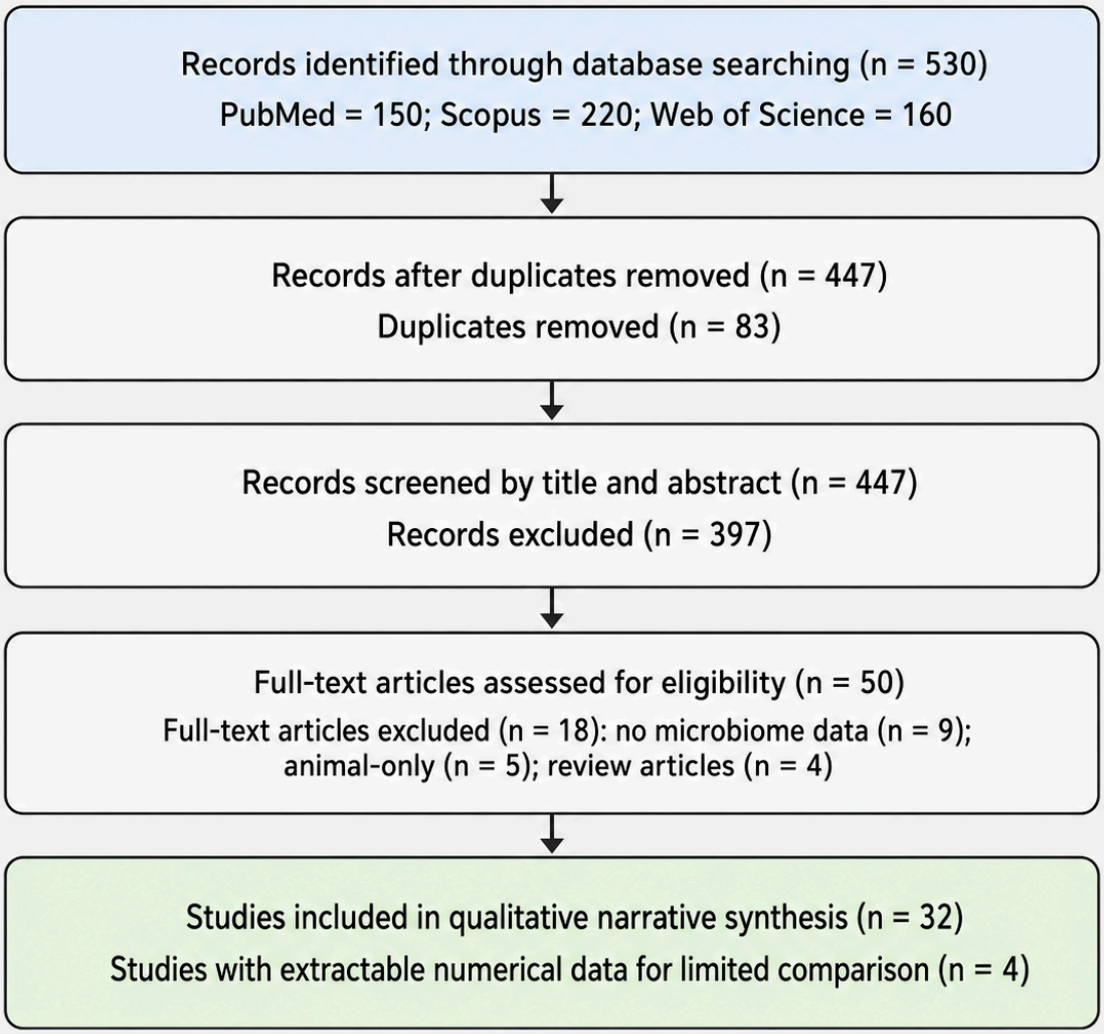


Figure 1

PRISMA flow diagram for the selection of studies included in the review.

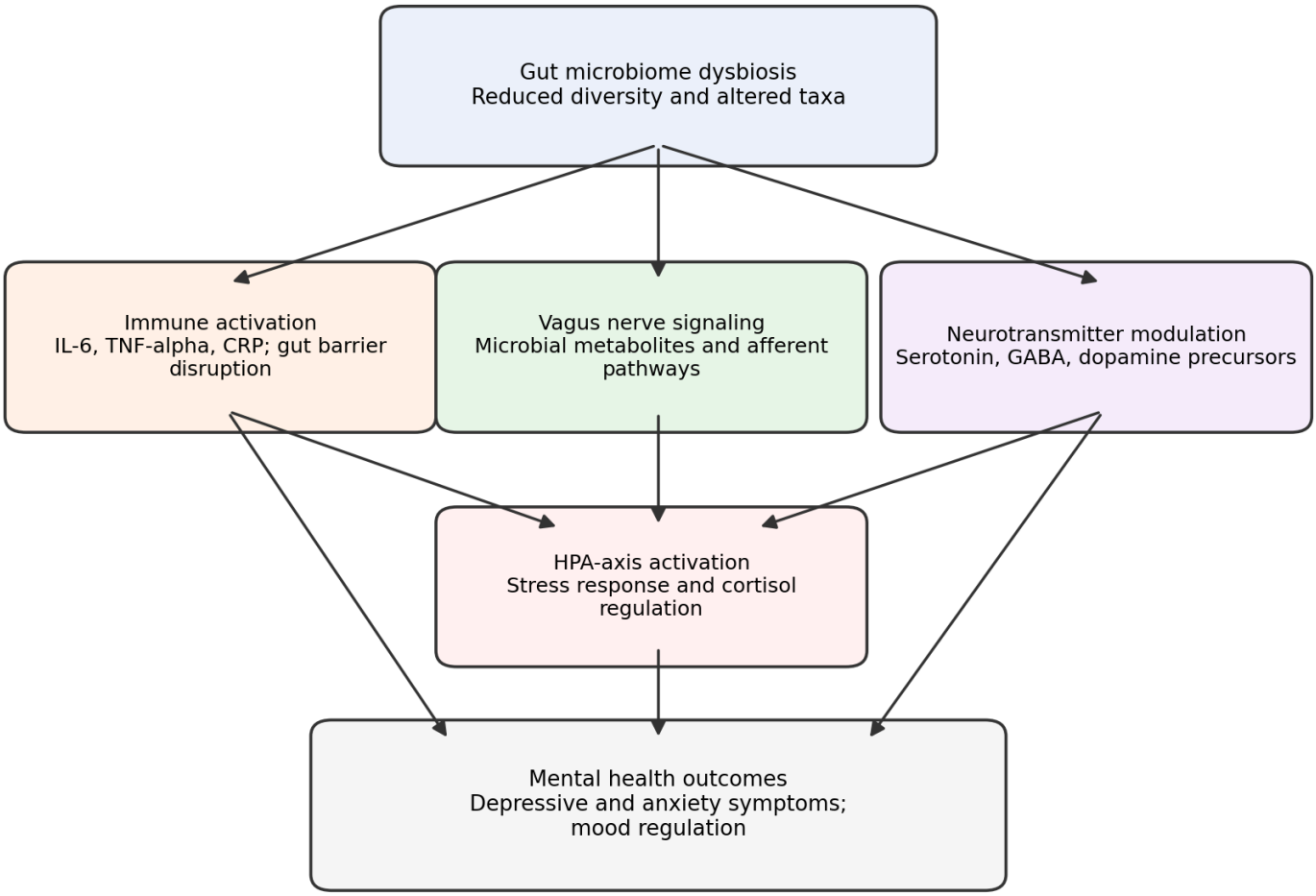


Figure 2

Proposed gut-brain axis pathways linking gut microbiome dysbiosis with depression and anxiety outcomes.