



The Gut-Brain Axis in Psychiatric Disorders: Emerging Evidence and Therapeutic Perspectives

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Abstract

Context. The microbiota-gut-brain axis is now extensively used in biological psychiatry, but there is still a big gap between the ability of rodents studies showing some plausible mechanisms to impact humans. There is a statement that the review focuses on what mechanisms, observational and interventional evidence show the connection between gastrointestinal microbiome and psychiatric disorders and which microbial therapies are clinically applicable.

Methods. We conducted searches in PubMed/MEDLINE, Embase, PsycINFO, Scopus and the Cochrane Library for mechanistic studies, microbiota case-control studies, data from prospective cohorts, Mendelian randomisation studies, randomized controlled trials (RCTs) and meta-analyses investigating gut-brain signaling in psychiatric disorders from inception to May 2026. Evidence is synthesized in narrative form and graded in terms of study design, replicability and risk of bias.

The outcome. There are a few communication routes that are backed strongly such as vagal afferent signaling, immune and inflammatory mediation, HPA axis programming and microbial metabolites which include short-chain fatty acids, bile acids and tryptophan catabolites. Case-control studies also state the changing microbial composition in major depressive disorder, schizophrenia, bipolarity disorder and autism but the results from various research lacking in taxon-level findings and the studies are conducted on a small-scale thus, they could be confounded by such things as diet, tobacco consumption and psychoactive drugs. In research work using the technique of fecal transfer from patients the behavior of animals that had been previously considered to be germ-free or treated with antibiotics were influenced thus proving that it works. Interventions in diet are the most effective ways of depression treatment, whereas, while probiotics are less effective in such situation than diet, pre-, pro- and post-biotics have not shown their effectiveness at all.

Final thoughts. Rather than a common source of psychiatric disorders, the gut-brain axis is a valid contributing pathway in certain groups of individuals. For progress to be made, it will be necessary to implement longitudinal, multi-omic, sufficiently powered studies with pre-registered microbiota endpoints, strain-level resolution, and inclusion of participants with different levels of inflammation and metabolic phenotypes.

Keywords:

microbiota–gut–brain axis; gut microbiome; major depressive disorder; schizophrenia; probiotics; faecal microbiota transplantation; short-chain fatty acids; psychobiotics.

1. Introduction

Psychiatric disorders are responsible for a growing portion of the global burden of disease, yet available treatments have evolved very little since the days of monoamine drug treatments. An estimated one-third of individuals with major depressive disorder will not achieve remission following multiple adequate trials of antidepressant medications. Other psychiatric disorders such as schizophrenia and obsessive–compulsive disorder (1,2) show comparable rates of treatment resistance. This therapeutic barrier has prompted investigations into possible pathophysiological mechanisms which may act outside the synapse, including immunometabolic dysfunction, mitochondrial dysfunction, and most importantly over the last 15 years, the microbiota–gut–brain axis (3).

The gut–brain axis refers to the two-way communication between the gut and the CNS through neural (vagal and spinal afferents, the enteric nervous system), endocrine (the HPA axis and peptides secreted into the intestine), immune (cytokines and priming of microglia) and metabolic (end products produced by gut microbes) channels (4). The introduction of the fact that the gut microbiota, an ecosystem consisting of approximately 10^{13} microorganisms and possessing at least two orders of magnitude more genes than the human genome, plays a critical role in this axis changed a concept that was merely anatomical into a therapeutic target (5).

In the field, three supporting pieces of evidence are presented. First, germ-free rodents exhibit an increased HPA response to stress due to restraint but do not show this response once they have been *colonized with Bifidobacterium infantis* within a certain development period which suggests a programming effect instead of an effect of acute nature (6). Second, studies in which faeces of MDD patients were transferred into germ-free or microbiota-free rodents demonstrated that their acquired behaviours such as anhedonia-like or anxiety-like ones were accompanied by alteration in the metabolic processes occurring with tryptophan, thus conforming to the Koch's postulates at the level of behaviour (7,8). Third, earlier conducted studies of bacterial communities in human patients suffering from depression, bipolar disorder, schizophrenia, and even autism spectrum disorder (ASD) established consistent changes of community structure including elimination of butyrate-producing bacteria like *Faecalibacterium* and *Coprococcus* (9,10).

Enthusiasm has, however, outpaced methodological rigour. Taxon-level findings replicate inconsistently across cohorts; sample sizes are typically under 100 per arm; diet, adiposity, smoking, bowel transit time and psychotropic exposure are strong confounders that are seldom modelled adequately; and almost all human data are cross-sectional, leaving the direction of causation unresolved (11,12). Several widely cited meta-analyses of probiotics in depression are dominated by small, industry-funded trials in subclinical samples with high heterogeneity, producing effect estimates that shrink substantially when restricted to clinically diagnosed, unmedicated populations (13,14).

The aims of the review are fourfold, namely:) to present the mechanism of gut–brain interactions in terms useful to those in the field of clinical research;) to evaluate the human evidence related to disorder, making a distinction between correlational evidence and causal

evidence;) to discuss evidence tier on microbiome interventions; and) to present methodological improvements enabling the field to provide clinically meaningful psychiatric treatments rather than more descriptive studies.

2. Methods

The present document relates to a non-systematic narrative review that has been carried out by following a preplanned search methodology thereby ensuring its transparency to all.

Databases and date. Searches of PubMed/MEDLINE, Embase, PsycINFO, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials were carried out from inception to 31 May 2026. ClinicalTrials.gov and ISRCTN registry were searched for ongoing and unpublished trials.

Search terms. Controlled vocabulary and free-text terms were brought together across three concepts blocks: (i) exposure, *gut microbiota*, *microbiome*, *gut-brain axis*, *microbiota-gut-brain axis*, *dysbiosis*, *fatty acids*, *intestinal permeability*; (ii) population, depression, major depressive disorder, anxiety, bipolar disorder, schizophrenia, psychosis, autism spectrum disorder, attention deficit disorder/ hyperactivity disorder, anorexia nervosa, post-traumatic stress disorder, substance abuse disorder; (iii) intervention, probiotic, psychobiotic, prebiotic, synbiotic, postbiotic, fecal microbiota transplantation, dietary intervention, Mediterranean diet, fermented food. The reference lists of the articles in the reviews selected were searched manually.

Eligibility. Our priorities in terms of eligibility were: systematic reviews and meta-analyses of RCTs; RCTs; Mendelian randomisation studies; prospective cohort studies; and microbiome case–control studies where $n \geq 50$; and mechanistic animal or in-vitro studies that clarified human evidence. Publications not in English language without an abstract in English, conference abstracts without data, and isolated case reports were excluded.

Evaluation. The appraisal of the RCTs was done informally based on Cochrane RoB 2 criteria while the microbiome observational studies were evaluated based on methodology of sequencing (16S rRNA amplicon against shotgun metagenomics), variables under consideration (diet, BMI, smoking, transit time, medication), correction for multiple tests, and replication. Owing to highly diverse populations, strains, doses, sequencing technology, and results, quantitative pooling could not be performed and published pooled results are provided with the confidence interval.

Limitations of the method. Narrative reviews are susceptible to selection bias in the selection of studies cited. To reduce this risk, we have reported both negative and controversial findings together with positive findings, and also opted for meta-analysis estimates instead of solely looking at positive trials whenever such estimates were available.

3. Mechanisms of communication between gut and brain

The process of gut-to-brain signaling is not a single process but rather a collection of overlapping pathways that function on multiple timescales: milliseconds for vagus nerve signaling, hours for the metabolism of signals, and days to years for the immune system responses. Treating all the processes as one system is a common source of misinterpretation.

3.1 The vagus nerve and enteric neural signalling

Vagal afferents are massive fast channels as 80 percent of this structure's fibres are afferents with termination at the nucleus tractus solitarius and progression to the parabrachial nucleus, locus coeruleus, hypothalamus, and the amygdala (15). Activation of vagal afferents occurs indirectly through enteroendocrine cells, enterochromaffin cells, and immune cells found in the lamina propria, rather than through direct contact with the bacteria present in the lumen. The identification of “neuropod” cells that facilitate the formation of synapses characterized by glutamatergic signalling has provided an anatomical base for signal transmission having milliseconds latency (16).

The causal significance of this pathway can be seen in the vagotomy studies. The anti-anxiety and anti-depressant-like *properties of Lactobacillus rhamnosus* JB-1 in mice and its region-specific effects on GABA-A and GABA-B receptors are lost in vagotomised animals (17). *Bifidobacterium longum* NCC3001 also shows vagal dependence in a colitis-induced anxiety model (18). In clinical practice, the effectiveness of vagus nerve stimulation in treatment-resistant depression supports, but does not prove, the importance of this pathway for the treatment of anxiety in humans (19).

3.2 Immune and neuroinflammatory signalling

The large immune compartment of intestine is located in intestine, and microbiota is the central teacher in this case. Presence of segmented filamentous bacteria leads to Th17 differentiation; *Clostridia* clusters IV and XIVa along with *Bacteroides fragilis* polysaccharide A lead to regulatory T cell formation; meanwhile, the lipopolysaccharide of Gram-negative bacteria binds to TLR4 on intestinal and systemic immune cells (20).

When the integrity of the barrier is disturbed, the transport of LPS and peptidoglycan from bacteria results in an increase of pro-inflammatory cytokines in the blood. About 1/3 of the patients suffering from MDD have a high level of C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor- α (21). This is important from a therapeutic standpoint because in studies it has been shown that using anti-inflammatory treatment was helpful for those patients, who initially had an elevated level of CRP, while it did not provide any benefit or was even harmful for those patients who had normal levels of CRP, confirming that inflammation is a stratification, not universal, mechanism (22). Mendelian randomization additionally confirms that IL-6 is a legitimate contributor to the risk of depression, deepening the conclusion derived from mere observation (23).

Microglia are influenced by microbial signals. Studies of germ-free mice reveal that they exhibit immature microglia with a compromised immune response, although colonizing the gut or providing SCFA supplements can restore their maturation, suggesting that it is metabolites and not live organisms that serve as the ultimate signal. 24

3.3 The HPA axis and stress programming

According to the research done by Sudo and a group of researchers, it has been shown that germ-free mice have a higher response in terms of ACTH and *corticosterone* levels in the face of restraint stress but what is more, it has been shown that this response can be reversed by introducing *B. infantis* into the mouse at an early stage of its life. 6

In humans the evidence is weaker but convergent. Early-life adversity, a robust risk factor for adult psychopathology, is associated with altered microbial composition in several cohorts, and maternal prenatal stress predicts infant microbiota configuration and subsequent gastrointestinal and allergic symptoms (25). Probiotic and prebiotic preparations have reduced the waking cortisol response and attenuated attentional bias to negative stimuli in healthy volunteers, although effect sizes are small and replication incomplete (26).

3.4 Microbial metabolites

Short-chain fatty acids. The action in the intestine of *Faecalibacterium prausnitzii*, *Roseburia*, *Eubacterium rectale* and related species leads to the fermentation of indigestible fibre into acetate, propionate, and butyrate. Butyrate is the predominant source of energy for colonocytes, maintains tight junctions via the overexpression of claudin-1 and zonula occludens-1, and inhibits histone deacetylases, a mechanism of particular interest as inhibition of HDACs has shown antidepressant-like efficacy in animals and butyrate has been shown to influence BDNF levels in the hippocampus and frontal cortex (27,28). SCFAs also bind to FFAR2/FFAR3 receptors on enteroendocrine and immune cells and a limited amount crosses the BBB, the integrity of which is dependent on SCFAs themselves: mice raised in a germ-free environment show increased oxidative permeability at the BBB beginning in-utero, which can be rectified through colonization or sodium butyrate (29).

Tryptophan and the kynurenine pathway. Only a small proportion of tryptophan is used for serotonin synthesis; the majority enters the kynurenine pathway, which is induced by IDO1 and TDO under inflammatory and glucocorticoid stimulation. The pathway branches into neuroprotective kynurenic acid (an NMDA and α 7-nicotinic antagonist) and neurotoxic quinolinic acid (an NMDA agonist and oxidative stressor). The microbiota regulates this partition: germ-free animals show elevated circulating tryptophan and altered kynurenine:tryptophan ratios, normalised by colonisation (30). An elevated quinolinic:kynurenic acid ratio has been reported in depression and suicidality, while elevated kynurenic acid in cerebrospinal fluid is a relatively consistent finding in schizophrenia, offering a mechanistic link to NMDA hypofunction models (31,32). Certain *Lactobacillus* species also convert tryptophan to indole derivatives that are aryl hydrocarbon receptor ligands, modulating mucosal immunity and barrier integrity (33).

Serotonin in the periphery. Around 90-95% of the serotonin in the body is produced by enterochromaffin cells and the presence of spore-forming bacteria primarily Clostridiales increases the levels of colonic and serum 5'-HT, since they are thought to induce TPH1 (34). As peripheral 5-HT does not penetrate the blood-brain barrier, the levels of -HT produced in the periphery reaches the brain indirectly through vagal impulses, platelets, or precursors. This is a common mistake in referring to gut serotonin as brain serotonin in the academic literature.

Bile acids. The primary bile acids undergo de-conjugation through bacterial bile salt hydrolase activity into secondary bile acids, which serve as ligands for both FXR and TGR5. In cases of depression and cognitive impairments, the changes in bile acid profiles have been reported and it has been shown that TGR5 signaling plays a role in the release of GLP-1, which leads to downstream effects on the vagal and hypothalamic circuits (35).

Various other mediators. The documented production of GABA (in bacteria like *Lactobacillus brevis*, *Bifidobacterium dentium*), dopamine and norepinephrine precursors (e.g. *Escherichia*

and *Bacillus*), and trimethylamine-N-oxide has been described. However, excluding at least partly TMAO concerning vascular and cognitive impacts, the extent to which these contribute quantitatively to CNS pools in humans is unknown and probably small. 36

3.5 Barrier integrity: gut and blood–brain

Increased permeability of the tight junctions that separate adjacent intestinal epithelial cells (or "leaky gut") may allow products from microbes to move through the intestine into the body, which would cause low-grade inflammation. Evidence supporting this hypothesis in humans includes increases in IgM and IgA against LPSs from Gram-negative bacteria in chronic depression and increases in zonulin and soluble CD14 in some patients with depressive disorders (37,38). However, the findings should be interpreted with caution: zonulin immunoassays have well-known specificity limitations, and the majority of permeability indices are not specific and influenced by physical exercise, consumption of alcohol, NSAIDs and body fat. The disturbances of intestinal barrier function should be considered as potential amplifiers of other processes rather than being validated by themselves as independent explanations of the phenomenon.

3.6 Bidirectionality and reverse causation

The interstate is bi-directional and is routinely under-considered in clinical interpretation. Stress influences gut motility, secretion, and mucus nature, changing the ecological environment within several hours. Depression affects lifestyle, diet, sleep, and alcohol use. Psychotropic substances have direct antimicrobial properties. A systematic in-vitro study showed that of drugs used on humans suppressed the growth of at least one commensal strain, with antipsychotics and SSRIs being the first among them (39). Thus, the cross-sectional difference between patients and controls does not imply either illness or its treatment but is also about the cause of the disease.

4. Evidence for psychiatric diseases

4.1 Major depressive disorder

MDD is the most researched condition. The Flemish Gut Flora Project and the Dutch LifeLines DEEP cohort have shown a consistent deficiency of *Faecalibacterium* and *Coprococcus* among depressed patients regardless of antidepressant therapy and found a direct connection between quality of life and the amount of 3,4-dihydroxyphenylacetic acid produced by the microbiota (9). The HELIUS study, conducted in the Netherlands, demonstrated the same findings across different ethnic groups (40).

The most reliable causal proof is still translational in nature. Faecal transplantation from patients suffering from major depressive disorder into antibiotic-treated or germ-free rodents leads to behaviours similar to anhedonia and anxiety with altered tryptophan metabolism, while the same process using faeces from healthy individuals does not (7,8). Given that the receiving animals do not share the diet of the donor or medications, the designs provide a clearer understanding of the microbe involvement than any human observational research.

In contrast to this, there have been modest rates of reproducibility at the taxon level. A meta-analysis of 5 studies that have examined depression did not find any consistently replicated differentially abundant genera across various cohorts when accounting for both sequencing

platform and area of the 16S rDNA sequenced. Differences in diversity were minimal and not consistently directed (11). Mendelian randomization studies using summary data from microbiome genome-wide association data have revealed associations for only a few taxa of interest; however, the instruments available for use are weak, host genetics exert limited control over the amount of any microbiome taxon (typically accounting for less than 10% of the variation in most taxa), and results are sensitive to instrument selection (41).

Explanation. Differences in the microbiome can be a factor in causing depression in some people, specifically those with other diseases related to inflammation, metabolism, or the digestive system. However, microbial variation is not responsible for depression in every case and there is currently no specific type of bacteria that helps to diagnose depression.

4.2 Anxiety disorders

The evidence for preclinical research is strong and conceptually simple: germ-free animals exhibit lower anxiety-related behaviours due in part to alterations in gene profiles from their amygdala and hippocampus, and the microbial exchange between the mouse strains that behave differently in their moods results in a transfer of the corresponding behavioural phenotype (42). The evidence for humans is less plentiful. Case controlled studies of general anxiety disorder are too few in number and differ widely in terms of design; results from intervention studies tend to come from the sampling of either healthy individuals or subclinical anxiety subjects, which results in minimal findings and makes it difficult to understand precisely how the probiotics affect the anxiety levels of people. When looking at clinically diagnosed subjects, the combined average effect appears to be moderate in reducing anxiety symptoms (SMD of approximately -0.59), but with large confidence intervals and a lack of available trials (14). –

4.3 Bipolar disorder

Reported findings include reduced *Faecalibacterium* abundance correlating with symptom severity, and altered diversity in euthymic patients (43). Interpretation is complicated by near-universal exposure to lithium, valproate, antipsychotics and antidepressants, all of which influence the microbiome, and by high rates of obesity and metabolic syndrome. A proof-of-concept RCT of probiotic supplementation after acute mania reported reduced rehospitalisation over 24 weeks, with the effect concentrated in patients with elevated baseline systemic inflammation — an early example of biomarker stratification in this field, requiring replication (44).

4.4 Schizophrenia spectrum disorders

Schizophrenia provides the most difficult obstacle; the antipsychotic drugs that are generally prescribed, including olanzapine and clozapine, modify microbial composition, resulting in considerable weight gain, which is a strong variable for establishing changes in the microbiome. Still, differences in microbial composition have been reported in the first episode patients who had not received antipsychotics, and transfer of human microbes to germ-free mice has been shown to result in behavioral and glutamatergic changes relevant to schizophrenia (45). Kynurenic acid increases seen in the CNS have been linked for some extent to changes in microbial metabolism and the immune system regulation of tryptophan metabolism thus establishing one candidate pathway for NMDA receptor hypofunction (32). ï

The most clinically relevant microbiome question in schizophrenia today has more to do with treatment than the etiology of the disease. Antipsychotic-induced weight gain is partially mediated by the microbiome of rodents and has been attenuated in rodent studies by the use of antibiotics and the transfer of microbiota, opening the door for potential microbiome-based prevention of metabolic side effects. 46

4.5 Autism spectrum disorder

A significant percentage of children with autism experience gastrointestinal issues, which may result in problems with irritability and disturbances in sleep patterns. It *has been shown that the model of* maternal immune activation connects prenatal inflammation, IL-17a signalling and offspring behaviour. In mice, it seems that microbiota-dependent Th17 induction is an important intermediate (47). Open-label microbiota transfer therapy has led to considerable improvements both in gastrointestinal and behavioural aspects after two years of intervention, although the fact that it was not controlled, the sample was very small and the population was highly biased should be mentioned; later studies that conducted controlled experiments have not been able to reproduce the effects convincingly (48).

A comprehensive analysis of ASD microbiome data showed that differences in composition were explained to a great extent by limitations in certain diets which are caused by traits of autism, and not the other way around, thereby distinctly exemplifying reverse causation (49). Ethically, care must be exercised in promoting any unproven microbiome based interventions in families with autistic children.

4.6 Attention-deficit/hyperactivity disorder

Evidence is preliminary. An early report of increased *Bifidobacterium* abundance with altered cyclohexadienyl dehydratase function and reduced ventral striatal reward anticipation has not been robustly replicated (50). A randomised trial of *Lactobacillus rhamnosus* GG in infancy reported fewer ADHD and Asperger diagnoses at 13 years, an intriguing but single, secondary-outcome finding (51).

4.7 Eating disorders

Researchers observed that in anorexia nervosa, the microbiome undergoes substantial alterations due to lack of energy, whereby refeeding restores the microbiome only to a certain extent. The major observations of data obtained revealed *that there is an increase in* mucin-degrading species of *Akkermansia muciniphila*, while reduced richness has been correlated with depression and psychopathology associated with eating disorders (52). Faecal transfer from infected patients to acclimatized mice was said to have led to diminished body mass along with emergence of anxiety disorders indicating that dysbiosis brought about by the illness may have a sustaining and not causative role (53).

4.8 Post-traumatic stress disorder

Few studies postulate reduction in the prevalence of Actinobacteria, Lentisphaerae and Verrucomicrobia in PTSD, asserting childhood trauma to have a higher predictive quality than adult trauma, which follows the principle of developmental programming (54). However, sample sizes are small to draw definitive conclusions.

4.9 Substance use disorders

Alcohol use disorder is a clear indication of how alcohol directly affects the intestinal barrier. Dysbiosis and increased permeability correlate with an increase in craving, anxiety and depression, even after detoxification in some patients (55). A pilot RCT of FMT in alcohol use disorder with cirrhosis showed a reduction of craving and alcohol-related events after six months, in what is probably the most promising FMT result so far in addictions, although based on a small sample (56).

4.10 Summary of evidence strength

Disorder	Observational evidence	Causal/translational evidence	Interventional (RCT) evidence	Overall strength
Major depressive disorder	Large cohorts; consistent community-level findings	Faecal transfer reproduces phenotype in rodents	Multiple probiotic and diet RCTs; small-to-moderate effects	Moderate
Anxiety disorders	Few, small clinical studies	Strong germ-free and transfer data	Mostly subclinical samples; moderate pooled effect	Low–moderate
Bipolar disorder	Small, medication-confounded	Limited	One stratified probiotic RCT	Low
Schizophrenia	Moderate; first-episode studies reduce confounding	Transfer studies reported, limited replication	Few, underpowered	Low–moderate
Autism spectrum disorder	Substantial but diet-confounded	Maternal immune activation model strong in mice	Open-label FMT positive; controlled data weak	Low
ADHD	Preliminary	Minimal	One secondary-outcome infancy trial	Very low
Anorexia nervosa	Consistent, but largely illness-induced	Transfer alters weight gain in mice	None adequate	Low
PTSD	Very limited	Minimal	None	Very low
Alcohol use disorder	Clear barrier and dysbiosis findings	Mechanistically coherent	Pilot FMT RCT positive	Low–moderate

5. Therapeutic views

5.1 Dietary intervention

Whole-diet modification has been shown to have the best clinical evidence for any microbiome-related intervention in psychiatry, even though its impact is not only related to the microbiome. The SMILES trial randomized depressed adults with a poor diet to either receive support to follow a modified Mediterranean diet or simply receive social support, which led to significant differences in MADRS scores at 12 weeks, in remission rates of approximately one-third as opposed to 8% (57). The HELFIMED and AMMEND trials also provided similar results, with AMMEND specifically studying young men with depression (58,59). While blinding is impossible and attention and expectation play a role, the power of the results, the ability to replicate the findings, and the low risks and costs involved make dietary intervention a reasonable option within routine psychiatric care.

Mechanistically, dietary fiber is the primary factor responsible for the production of SCFAs, and a randomized dietary intervention has shown that the consumption of fermented foods has a bigger effect on reducing inflammation than a high-fiber diet alone. 60

5.2 Probiotics and "psychobiotics"

Meta-analytic estimates vary widely depending on inclusion criteria, which is itself the key finding. In clinically diagnosed samples, one 2025 synthesis of 23 RCTs ($n = 1401$) reported a substantial reduction in depressive symptoms (SMD -0.96 ; 95% CI -1.31 to -0.61) and a moderate reduction in anxiety (SMD -0.59 ; 95% CI -0.98 to -0.19), with high heterogeneity and effect modification by trial duration and formulation (14). Restricting analysis to probiotic monotherapy in unmedicated depression yields a markedly smaller effect, with the authors cautioning about industry funding and heterogeneity (61). A separate meta-analysis of probiotics, prebiotics, synbiotics and postbiotics pooling 14 trials ($n = 906$) found significant improvement in depressive symptoms driven principally by the probiotic and synbiotic subgroups (62).

Several features of this literature warrant scepticism: many trials enrol subclinical or non-clinical samples; strains, doses and durations are rarely comparable; the active ingredient is seldom established; funnel plots suggest small-study effects; and most formulations are regulated as food supplements with limited manufacturing oversight. The most frequently studied preparations are *Lactobacillus* and *Bifidobacterium* combinations, often including *L. helveticus* R0052 with *B. longum* R0175, or *L. rhamnosus* strains with disputed clinical translation — a well-conducted RCT of *L. rhamnosus* JB-1 in healthy men found no effect on stress or anxiety measures despite compelling preclinical data, a useful corrective (63).

Probiotics can be viewed as low-risk adjuncts when there is the presence of gastrointestinal comorbidity. They are not a replacement for established antidepressant or psychotherapeutic treatment, and clinicians need to make it clear to their patients, especially considering the aggressive marketing messages they could get from the market.

5.3 Prebiotics, synbiotics and postbiotics

Prebiotic substances (galacto-oligosaccharides, fructo-oligosaccharides, inulin, resistant starch) in a specific way stimulate the advantageous genus of microorganisms. A pooled data analysis

from clinical studies indicates that there is no impact on depression at present (depression (smd -0.28 ; 95% c.i. -0.61 to 0.04) in literature. However, SMD is very small (14). Early studies established attenuation of the cortisol awakening response with galacto-oligosaccharides in healthy individuals (26). Gastrointestinal side effects (bloating, flatulence) limit the usage of prebiotics formulations in a percentage of patients.

Postbiotics, which consist of heat-inactivated microorganisms and purified microbial metabolites, have the beneficial characteristic of being defined, stable, and non-replicating material with an easier regulatory process as well as not causing bacteremia in patients with a weakened immune system. Clinical studies show that we cannot make any conclusions yet.

5.4 Faecal microbiota transplantation

FMT is the most direct test of microbial causality available in humans and remains, for psychiatric indications, strictly experimental. Meta-analytic estimates are unstable: one 2025 synthesis of 12 RCTs ($n = 681$) reported a significant reduction in depressive symptoms (SMD -1.21 ; 95% CI -1.87 to -0.55), with stronger effects in irritable bowel syndrome than in neuropsychiatric populations (64); another contemporaneous meta-analysis concluded that the evidence is insufficient to support a significant effect, with benefit appearing only in subgroup analyses of confirmed depression (65). This divergence reflects differing inclusion criteria, dominance of trials in which depression was a secondary outcome, small samples and heterogeneity in delivery route. Dedicated trials in MDD — including multicentre, placebo-controlled studies in patients with inadequate early antidepressant response — are ongoing and will be more informative than any current pooled estimate (66).

The issue of safety is not simple: the spread of bacteria resistant to more than one antibiotic has resulted in patient death, leading to regulatory responses, and there are long-term consequences of the transfer of whole microbe communities (67). FMT for conditions of psychological nature should be done only as part of research studies.

5.5 Drug–microbiome interactions

Two clinical implications arise from the work with microbiome. The first one is that the microbiome metabolises medications. The second one is that medications affect the microbiome. Specifically, one in vitro study indicates that about 24 per cent of marketed drugs are able to suppress the growth of some strains of bacteria, mostly (39). This leads to two conclusions, there may be a microbial contribution to metabolic syndrome caused by antipsychotic medications, and we have to consider the microbial influence when designing observational studies that concern the microbiome of treated patients. β

5.6 Comparative summary of interventions

Intervention	Best current evidence	Effect size (depression)	Safety	Readiness
Mediterranean-style diet	Multiple RCTs (SMILES, HELFIMED, AMMEND)	Moderate–large; unblinded	Excellent; broad health benefit	Recommend as adjunct now

Probiotics	Meta-analyses of RCTs, high heterogeneity	Small–moderate; estimate unstable	Good; caution if immunocompromised	Reasonable low-risk adjunct
Prebiotics	Few RCTs in clinical samples	Non-significant pooled	Good; GI intolerance	Insufficient evidence
Synbiotics	Subgroup data within pooled analyses	Suggestive	Good	Insufficient evidence
Postbiotics	Early-phase	Not established	Favourable in principle	Experimental
Faecal microbiota transplantation	Conflicting meta-analyses; trials ongoing	Conflicting	Serious risks documented	Research only
Exercise, sleep, smoking cessation	Indirect microbiome effects; strong psychiatric evidence	Established independently	Excellent	Standard care

6. Methodological problems

The gap that exists between the confidence within the field and the evidence base can primarily be attributed to major issues concerning methodology which can be solved.

Confounding. The dietary habits and weight of a person, his/her smoking, consumption of alcohol, level of physical activity, speed of bowel movement, place of living, and the medicines which use affect the population of the microflora to a similar or greater extent than the psychiatric condition is. On the Bristol scale of stool the stool consistency influences the community structure. It is not possible to distinguish between the impact of the illness and lifestyle if a study does not contain measurements and modeling of those parameters.

Reverse causation. Depression changes diet and lifestyle; anorexia nervosa limits consumption; alcohol harms the skein; antipsychotics modify weight and gut motility. Cross-sectional methods cannot clarify the direction of causation, and most human data are made using cross-sectional data.

Variability among techniques. The results depend on how the stool is collected and preserved, how the DNA is extracted, which 16S hypervariable region is analyzed, which primers are used, how deep the sequencing is, and what bioinformatics tools are used. Since various studies frequently employ different bioinformatics techniques, comparisons across studies are not always valid, which explains some discrepancies in the results.

Taxonomic resolution. 16S amplicon sequencing normally resolves only to the genus level, while relevant functions usually depend on the strain, with two strains of the same species

differing in tens of percent of the gene content. Shotgun metagenomics, metatranscriptomics, and metabolomics are required to progress from the question "who is there" to "what they are doing".

Statistical practice. Microbiome data can be characterized as sparse, compositional, high-dimensional, and over-dispersed. Multiple testing corrections are applied mostly inconsistently, and different methods of showing differences in abundances demonstrate different results for the same data; small samples make it easy to selectively report few significant taxa.

Power and publication bias. The average number of participants in each case-control trial is fewer than 60 subjects for both groups. Studies on probiotics are frequently conducted by the industry and have high turn out from positive results; a funnel asymmetry could be detected in some meta-analyses.

Measurements of brain outcomes. Many studies use scales where subjects report their symptoms in non-clinical populations, where the regression effect and expectancy effects can be overwhelming.

Blinding and placebo response. Dietary and fermented food interventions cannot be blinded; sadly, it is known that placebo effect in depression studies is very high and increasing. Good active comparator design, for instance, isocaloric diets with different fiber contents, is rarely used.

7. Future plans

Longitudinal deeply phenotyped cohorts. Only longitudinal studies with multiple sampling during the course of the disease, constant registration of diet, and related measures of inflammation could meet the requirements of the temporal precedence. Currently available birth cohorts provide an excellent window through which to observe prospectively phenomena which stem from early life experiences.

From taxa to function. More importance should be placed on determining metabolite flux, amounts of various SCFAs in stool samples and blood, measures from the kynurenine pathway, information about bile acids and indoles, rather than determining abundances of organisms. Function is more easy to understand, and it is more likely replicable across cohorts in comparison to taxa.

Stratified trials. The lesson one can draw from the studies of inflammation in depression is that mechanism-specific interventions can be successfully implemented in mechanism-specific populations. Future studies should define specific enrichment criteria, increased levels of CRP, decreased level of microbial diversity or absence of butyrate-producing bacteria, presence of gastrointestinal diseases as a comorbid condition, adherence to a certain unhealthy diet, instead of using heterogeneous depressed cohorts which decrease chances of detecting any significance of subgroup effect.

Defined consortia and engineered organisms. Designing various multi-species consortia which will be proven to produce some definite metabolic products is more likely to lead to successful results than using either the already-existing microbes or transferring stool samples. Development of engineered bacteria producing of certain neuroactive substances is possible,

but it raises many technical and regulatory issues which should be solved before the beginning of human studies.

Pharmacomicrobiomics. The studies of the possibility of predicting success of antidepressant or antipsychotic treatment on the basis of the initial microbiota data should be conducted since the questions investigated can help answer some significant clinical questions and require no new medication development.

Standards and reporting. Wide implementation of standardised methods of collection and extraction of samples, provision of raw sequence data, registration of endpoints, and obligatory registration of unsuccessful results could help solve the reproducibility problem without additional investments.

Equity and generalisability. Almost all research was performed among wealthy white people having a Western diet. Microbial composition is very different in different diets, thus obtained findings cannot be generalised for other populations, which is especially important for medical facilities in poorer countries.

8. Conclusions

The microbiome-gut-brain axis is a real impacting and thoroughly understood type of communication, and there is sufficient proof of its account for mental disorders coming from different sources: studies of germless animals, fecal transplants, studies in larger observation groups, and many clinical trials. At the same time, it is still not possible to claim that it is the only reason behind the mental problem, and no type of such bacteria can be used for diagnosis or prognosis at this time.

There are three implications. First, dietary quality assessment is needed in the treatment of mental problems as such an approach has been proven to be one of the most effective ones, comparing to any of the adjacent microbiome approaches; we should also note its positive effect on the health status of the patient in general. Second, probiotics can be used in a justified way, especially when there is some gastrointestinal condition; it is recommended to explain to patients that such an approach can help but it is hardly revolutionary. Finally, fecal transplant should be used only in clinical studies.

From the perspective of scientific research now a priority is no longer the proof of the existence of a relationship between the gut and the brain; it is rather necessary to determine what kind of patients may suffer from the influence of their bacteria and what treatment may be applied to them. Making use of longitudinal methods with many profiles and biomarker-directed tests is the only way to achieve this.

Data availability. Not needed; no new data.

Ethics approval. Not needed for review article based on previous studies.

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