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Probiotic, prebiotic, synbiotic and fermented food supplementation in psychiatric disorders: A systematic review of clinical trials

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ABSTRACT

The use of probiotics, prebiotics, synbiotics or fermented foods can modulate the gut-brain axis and constitute a potentially therapeutic intervention in psychiatric disorders. This systematic review aims to identify current evidence regarding these interventions in the treatment of patients with DSM/ICD psychiatric diagnoses. Forty-seven articles from 42 studies met the inclusion criteria. Risk of bias was assessed in all included studies. Major depression was the most studied disorder (n = 19 studies). Studies frequently focused on schizophrenia (n = 11) and bipolar disorder (n = 5) and there were limited studies in anorexia nervosa (n = 4), ADHD (n = 3), Tourette (n = 1), insomnia (n = 1), PTSD (n = 1) and generalized anxiety disorder (n = 1). Except in MDD, current evidence does not clarify the role of probiotics and prebiotics in the treatment of mental illness. Several studies point to an improvement in the immune and inflammatory profile (e.g. CRP, IL6), which may be a relevant mechanism of action of the therapeutic response identified in these studies. Future research should consider lifestyle and dietary habits of patients as possible confounders that may influence inter-individual treatment response.

Abbreviations: ADHD, Attention Deficit and Hyperactivity Disorder; ASD, Autistic Spectrum Disorders; AUD, Alcohol Use Disorder; BD, Bipolar Disorder; BDI, Beck Depression Inventory; BDNF, Brain-derived neurotrophic factor; CDI, Children Depression Inventory; CNS, Central Nervous System; DSM, Diagnostic and Statistical Manual of Mental Disorders; IBD, Inflammatory Bowel Disease; ICD, International Statistical Classification of Diseases and Related Health Problems; IGF-I, Insulin-like Growth Factor I; FOS, Fructooligosaccharide; GABA, gamma-aminobutyric acid; GAD, Generalized Anxiety Disorder; GBA, Gut-brain axis; GI, Gastrointestinal; GOS, Galactooligosaccharide; HDRS, Hamilton's Depression Rating Scale; MDD, Major Depressive Disorder; LPC, Lysophosphatidylcholines; MADRS, Montgomery-Adsberg Depression Rating Scale; MGBA, Microbiota-gut-brain axis; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PTSD, Post-traumatic Stress Disorder; QIDS-SR16, Quick Inventory of Depression Symptomatology – Self Reported – 16 items; RCT, Randomized Controlled Trials; RoB 2, Risk of Bias 2; ROBINS-I, Risk Of Bias In Non-Randomized Studies - of Interventions I; SCFA, Short-chain fatty acids; SAMe, S-Adenosylmethionine; SSRI, selective serotonin-reuptake inhibitors; sVCAM-1, soluble Vascular Cell Adhesion Molecule-1; SZ, Schizophrenia; TAU, Treatment as usual.

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1. Introduction

Mental and addictive disorders comprise 7% of all burden of disease, affecting more than 1.000.000.000 people globally. They are responsible for 19% of all years lived with disability (Rehm and Shield, 2019). Moreover, total disease burden may be underestimated as major psychiatric disorders such as schizophrenia (SZ), bipolar disorder (BD) or major depressive disorder (MDD) show substantial comorbidity with several chronic somatic conditions (Sariaslan et al., 2022; Berk et al., 2023). Despite recent advances, response to standard treatments is often suboptimal in terms of achieving full symptom remission or does not always meet patient needs regarding functional outcomes and quality of life (Cipriani et al., 2018; Pinto et al., 2020). Thus, new therapeutic strategies that are effective and safe are warranted for the prevention and treatment of mental disorders.

In the past years, the relevance of the gut microbiota, the complex community of microorganisms, including bacteria, archaea, viruses, and fungi, that reside in the digestive tracts of humans and other animals (Clemente et al., 2012), in the correct functioning of the gut-brain axis (GBA) has been outlined (Bienenstock et al., 2015; Cryan et al., 2019). Through a variety of different mechanisms, such as the production and availability of neurotransmitters and their precursors or microbial metabolites such as short-chain fatty acids (SCFAs), the gut microbiota modulate the immune system as well as the integrity of epithelial cells and thereby promote the correct functioning of the peripheral and central nervous system (CNS). Translocation of bacteria and membrane lipopolysaccharides (LPS) to the systemic circulation due to increased intestinal permeability can activate the immune response and cause alterations at the level of the CNS (Severance et al., 2013; Kelly et al., 2015; Scott et al., 2017). The microbiota can modulate the concentration of some neurotransmitters or their precursors at a local, systemic and central level, such as gamma-aminobutyric acid (GABA), norepinephrine, serotonin, acetylcholine or dopamine (Lyte et al., 2011; Barrett et al., 2012; Gheorghe et al., 2019). Given the role of gut microbiota in modulating human health and disease, the GBA concept has been extended to the microbiota-gut-brain axis (MGBA) (Collins et al., 2012). Dysfunction of this axis may lead to the systemic, low-grade inflammation that appears to play a role in the etiology of several mental health disorders (Berk et al., 2013; Marx et al., 2023).

Although this is an evolving area of research and findings may be preliminary, several consistent compositional alterations in the gut microbiota associated with mental illnesses have been described (Nikolova et al., 2021; McGuinness et al., 2022). Indeed, a decrease in the overall beta-diversity of the microbiota has been observed in patients with major depressive disorder (MDD) compared to healthy controls (Valles-Colomer et al., 2019; Alli et al., 2022). Additionally, altered levels of certain bacterial species have been found, such as a decrease in bacteria belonging to the *Bifidobacterium* and *Lactobacillus* genera, which are known for their anti-inflammatory properties and probiotic potential (Jiang et al., 2015; Sanada et al., 2020). Other studies have found a significantly different gut microbiota composition and function in patients with schizophrenia (SZ) compared to healthy controls (Murray et al., 2023). In addition, certain bacteria, including *Veillonellaceae* and *Lachnospiraceae*, may be associated with SZ (Shen et al., 2018; Szeligowski et al., 2020). Moreover, some studies have reported decreased diversity in the gut microbiota of individuals with bipolar disorder (BD) compared to healthy controls (Evans et al., 2017). Specific bacteria such as *Faecalibacterium* and *Bacteroides* have been found in lower quantities in the gut of individuals with BD (Painold et al., 2019). In many instances, human to rodent faecal microbiota transplantation studies have been deployed to verify a potential causal role for these disease-associated gut microbiota compositions and symptom generation (Kelly et al., 2016; Gheorghe et al., 2021).

Consistent research supports the role of the MGBA in the pathogenesis of psychiatric disorders (Cryan et al., 2019; McGuinness et al., 2023). Thus, the therapeutic modulation of the MGBA has been considered for the management of several mental disorders (Mörkl et al., 2020; Berding et al., 2021). In this vein, the use of probiotics (live strains of strictly selected microorganisms which, when administered in adequate amounts, confer a health benefit on the host (Gibson et al., 2017)), prebiotics (a substrate that is selectively utilized by host microorganisms conferring a health benefit (Gibson et al., 2017)), synbiotics (a mix of probiotics and prebiotics that beneficially affects the host (Swanson et al., 2020)) or fermented foods, e.g., foods made through desired microbial growth and enzymatic conversions of food components (Marco et al., 2021) may contribute to this modulation, as well as the intervention in dietary habits and exercise. These microbiota-orientated interventions are collectively termed 'psychobiotic', a definition that has been expanded to include any exogenous influence whose effect on the brain is bacterially mediated (Dinan et al., 2013; Sarkar et al., 2016; Cryan et al., 2019).

The most recent reviews published on this topic do not fully include or evaluate all the clinical trials published to date in a comprehensive way (Ng et al., 2023; Forth et al., 2023) and importantly, many of them do not specifically focus on clinical populations (Goh et al., 2019). Also, most of these previous reviews focused on different psychiatric diagnosis separately. Moreover, many reviews focused on specific types of psychobiotics, e.g., probiotics only. We consider that combining a clinical approach and a comprehensive perspective of all mental disorders may help to gain a clearer understanding of the potential therapeutic role of these MGBA-modulating strategies. In addition, many prior reviews on this topic largely focused on clinical effectiveness with less emphasis on the underlying mechanisms of psychobiotic action (Ng et al., 2023). Therefore, the present review aims to identify the current evidence regarding the efficacy of probiotic, prebiotic or synbiotic supplementation and fermented foods in several relevant outcomes among individuals with a clinically defined psychiatric diagnosis.

2. Methods

The identification of the articles was made through a systematic review, conducted in compliance with the latest version of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) (Page et al., 2021). The protocol was registered in the International Prospective Register of Systematic Reviews PROSPERO (CRD 42022299512).

2.1. Search strategy

Five databases (Medline/PubMed, EMBASE, Scopus, Web of Science and PsycINFO/ ProQuest) were searched using the following search terms from inception to March 31st, 2023: *"psychotic disorder" OR schizophrenia OR "first episode" OR "bipolar disorder" OR "depressive disorder" OR "major depression" OR "mood disorder" OR "anorexia" OR bulimia OR "binge eating" OR "eating disorder" OR "sleep disorder" OR "insomnia" OR "neurodevelopmental disorder" OR "attention deficit hyperactivity disorder" OR "attention deficit disorder" OR ADHD OR ADD OR "anxiety disorder" OR PTSD OR OCD OR phobi* OR "obsessive compulsive" OR "panic disorder" OR "personality disorder" OR impulsive* OR "dual diagnosis" OR "substance use" OR "alcohol use" OR "alcohol misuse" OR "alcohol abuse" OR "alcohol addiction" OR "alcohol dependence" OR "substance misuse" OR "substance abuse" OR "substance addiction" OR "substance dependence" OR "gambling disorder" OR "behavioural addiction" OR "behavioral addiction" cross-referenced with prebiotic* OR probiotic* OR synbiotic OR postbiotic OR "fermented food" OR yogurt OR kefir OR sauerkraut OR lactobacillus OR Bifidobacterium OR dietary fibre* OR dietary fiber* OR inulin OR fructan* OR fructo-oligosaccharide* OR oligofructose OR galactooligosaccharide* OR oligosaccharide**.

The search was restricted to human studies. Moreover, manual searches were carried out in ClinicalTrials.gov and in the references of the retrieved studies and other review articles to ensure no study was lost in the search process.

2.2. Inclusion and exclusion criteria

Clinical studies (placebo-controlled randomized clinical trials (RCT), placebo-controlled open clinical trials, single-arm clinical trials) conducted in humans were eligible for *inclusion*. The target population was people diagnosed with a confirmed clinical diagnosis of mental disorder. Studies examining the use of prebiotics, probiotics, synbiotics or fermented foods were included. Studies including clinical outcomes such as psychiatric symptom improvement, differences in hospitalization or other mental healthcare resources use were considered, as well as those measuring effects on cognition. Moreover, studies measuring biochemical and immunomodulatory parameters were also included.

Studies including non-clinical population without a DSM or ICD diagnosis as study participants were *excluded*, as well as case reports, case series and studies with less than 10 participants were excluded. Autism and autistic spectrum disorders (ASD) were excluded given the amount of systematic reviews recently published (Yang et al., 2020; Davies et al., 2021; Tan et al., 2021). Dementia and other neurodegenerative disorders were also excluded due to the variability in definitions and inclusion of different diseases under the umbrella-term "dementia". Finally, studies in languages other than English were excluded.

2.3. Study selection and data extraction

The articles identified in the five databases were imported into Rayyan (www.rayyan.ai) (Ouzzani et al., 2016). Two researchers (CR and VB-M) independently and masked examined the titles and abstracts of the retrieved studies to identify those fulfilling selection criteria. Subsequently, the selected articles where examined in full text. Discrepancies were solved by discussion.

The following data were extracted from each article: author, country, diagnosis (and the criteria used in every diagnosis), sample and population characteristics including age and gender, duration of the intervention, type of intervention (e.g., probiotic) and dosage, outcomes including clinical variables (and the corresponding measurement instruments), biochemical, immunomodulatory and inflammation parameters, and the main results for each outcome.

2.4. Risk of bias and quality assessment

The risk of bias was assessed by two of the authors (CR and JS) using Cochrane's Risk of Bias 2 (Rob 2) tool for randomized clinical trials (Sterne et al., 2019) and Cochrane's Risk Of Bias In Non-Randomized Studies - of Interventions I (ROBINS-I) tool for non-randomized studies (Sterne et al., 2016a, 2016b).

The quality of the RCTs was assessed by two of the authors (CR and JS) using the PEDro Scale (Verhagen et al., 1998).

3. Results

A total of 3809 hits were retrieved from databases (449 in Pubmed, 236 in PsycINFO/ProQuest, 1678 in Scopus, 904 in EMBASE and 542 in Web of Science) as potential papers for inclusion. The flow diagram of the literature research process and study selection is described in Fig. 1.

A total of 47 articles from 42 studies met the selection criteria of the present systematic review and 34 of them were RCTs. Characteristics of the studies based on PICOS (population, intervention, comparison, outcome and study design) are shown in Table 1.

Significant patient population heterogeneity existed among the studies included in the review with 19 focused on MDD, 11 in schizophrenia (SZ), five in bipolar disorder (BD), four in anorexia nervosa, three in Attention Deficit and Hyperactivity Disorder (ADHD), and one in Generalized Anxiety Disorder (GAD), Post-traumatic Stress Disorder (PTSD), insomnia, Tourette Syndrome, and Alcohol Use Disorder (AUD) each.

The total sample of this systematic review comprised 2089 individuals with a DSM/ICD-defined psychiatric disorder. The median intervention period with a prebiotic, probiotic or synbiotic was eight weeks. Regarding the type of psychobiotic, 34 of the 42 studies used probiotics, of which 13 used a single strain, 16 a multi-strain probiotic

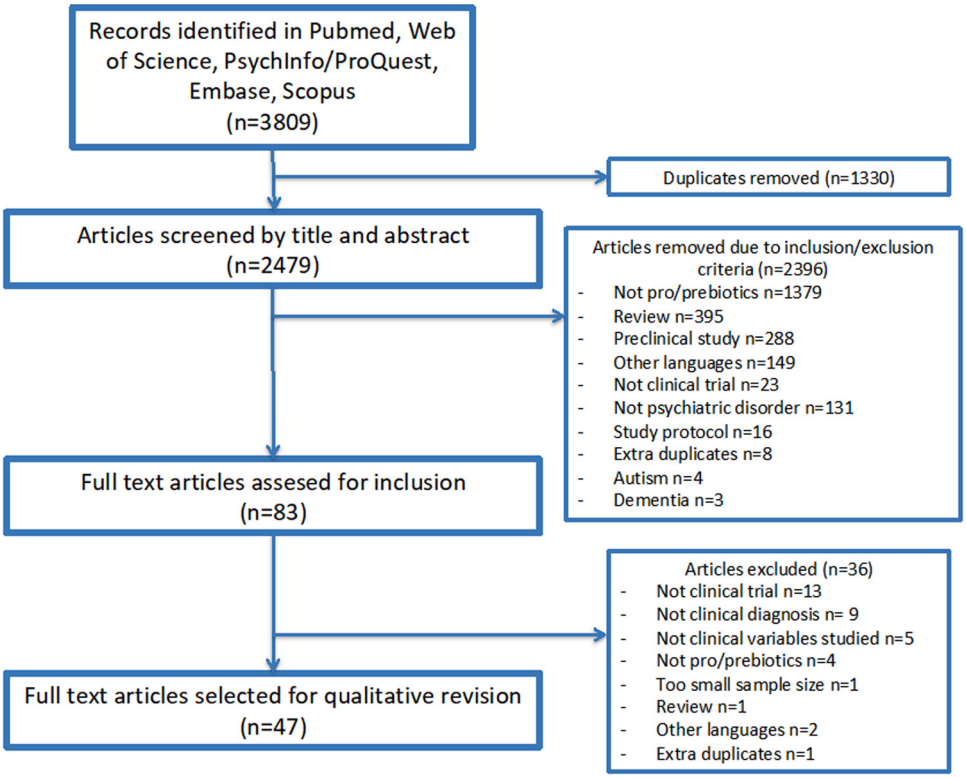

Fig. 1. Flow diagram of literature research.

Table 1
Characteristics of the studies included in the systematic review following PICOS (Population, Intervention, Comparison, Outcome and Study type) criteria.

Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
Reiter et al. (2020) (Austria)	DB PC RCT	MDD (MINI)	MDD inpatients (n = 61) *Age (y):* - Probiotic: 43 ± 14.31 - Placebo: 40.11 ± 11.45 *Females (%):* - Probiotic: 71.4 - Placebo: 81.8	4	Probiotic: *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51 and W52, *Lactobacillus acidophilus* W22, *Lactobacillus casei* W56, *Lactobacillus paracasei* W20, *Lactobacillus plantarum* W62, *Lactobacillus Salivarius* W24, *Lactococcus lactis* W19 (7.5×10^9 CFUs total) + Biotin	Depressive symptoms (HDRS; BDI) Inflammatory parameters gene expression (IL-6, TNF-α, NFBK1)	No significant change in depressive symptoms between groups (BDI; HDRS) IL-6 gene expression was increased in the probiotic group only. No significant changes in TNF-α or NFKB1 gene expression
Reininghaus et al. (2020a) (Austria)	DB PC RCT	MDD (MINI)	(*Same as*Reiter et al., 2020)	4	(*Same as*Reiter et al., 2020)	Psychiatric symptoms (HDRS; BDI; SCL-90; MSS; Likert scale) GI Symptoms (GLQI) Zonulin concentrations	No significant changes in any measure
Arifdjanova et al. (2021) (Russia)	DB PC RCT	MDD (ICD-10)	Mild or moderate depressive disorder and HC (n = 149) *Age:* N/A *Gender*: N/A	6	Probioctic: *Bifidobacterium*, *Lactobacillus* and *Streptococcus* strains (3 capsules) + Escitalopram 10 mg	Depressive symptoms (HDRS) Biochemical and inflammatory parameters (IL-1B, IL-6, TNF-α, NO, cortisol, catecholamines)	No significant differences in depressive symptoms (HDRS). Significant reduction in levels of IL-6, TNF-α and NO in the probiotic group. No significant changes in IL-1, cortisol and catecholamine blood levels
Rudzki et al. (2019) (Poland)	DB PC RCT	MDD (DSM-IV-R)	MDD outpatients treated with SSRI (n = 60) *Age (y):* - Probiotic: 39.9 ± 9.96 - Placebo: 38.9 ± 12.0 *Females (%):* - Probiotic: 76.7% - Placebo: 66.7%	8	Probiotic: *Lactobacillus plantarum* 299 v (2×10^{10} CFUs)	Psychiatric symptoms (HDRS; SCL-90) Neurocognitive performance: - Attention and processing speed (APT; Stroop test) - Verbal and learning memory (CVLT) - Attention and executive functioning (TMT-A, TMT-B) - Executive functions (RFFT) Biochemical parameters (tryptophan metabolism, cytokines, hs-CRP, TSH, cortisol)	Improvement in attention, processing speed and verbal/learning memory (APT and CVLT) in the intervention group after 8 weeks of intervention. No significant changes in other test of processing speed, or executive functions (Stroop Test parts A and B, RFFT, TMT-A and TMT-B) Significant decrease in KYN concentration in the probiotic group. Significant increase in 3HKYN:KYN ratio in the probiotic group. No changes in KYNA, 3HAA, AA. No significant changes in TNF-alfa, IL-6, IL-1, TSH, hs-CRP or cortisol concentrations
Akkasheh et al. (2016) (Iran)	DB PC RCT	MDD (DSM-IV)	MDD patients (n = 40) *Age (y):* - Probiotic: 38.3 ± 12.1 - Placebo: 36.2 ± 8.2 *Gender (% fem):* N/A	8	Probiotic: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum* (2×10^9 CFUs each)	*Primary:* Depressive symptoms (BDI) *Secondary:* Biochemical (HOMA-IR, QUICKI, FPG, insulin, lipids) inflammatory (hs-CRP) and oxidative stress biomarkers (TAC, GSH)	Significant improvement in depressive symptoms (BDI) in the probiotic group. Significant decreases in insulin, HOMA-IR and hs-CRP in the probiotic group No significant differences in FPG, QUICKI, lipid concentrations, TAC or GSH
Saccarello et al. (2020) (Italy)	DB PC RCT	MDD (ICD-10)	Mild to moderate depression outpatients (n = 89) *Age (y):* - Probiotic: 48.6 ± 10.67 - Placebo: 47.5 ± 11.9 *Females (%):* - Probiotic: 84.4 - Placebo: 79.5	6	Probioctic + Nutraceutical: *Lactobacillus Plantarum* HEAL9 © (1×10^9CFUs) + SAMe (200 mg)	Depressive symptoms (Z-SDS)	Significant reduction in depressive symptoms including anxiety and somatic components (Z-SDS total score, the cognitive and anxiety subdomains and the anxiety questionnaire)

(*continued on next page*)

Table 1 (*continued*)

Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
Tian et al. (2023) (China)	DB PC RCT	MDD (DSM-IV)	Mild to moderate depression patients (n = 28) *Age (y):* - Probiotic: 38.87 ± 17.62 - Placebo: 48.08 ± 18.61 *Females (%):* - Probiotic: 73.33 - Placebo: 76.92	4	Probiotic: *Bifidobacterium breve*, *Bifidobacterium longum, Pediococcus acidilactici* (4×10^9 CFUs/g; 4 g)	General psychiatric (BPRS) and depressive symptoms (HDRS; MADRAS) GI symptoms (GSRS)	Significant improvement in depressive and psychiatric symptoms in the probiotic group (HDRS, BPRS, MADRS). Significant improvement in GI symptoms (GSRS)
Ghorbani et al. (2018) (Iran)	DB PC RCT	MDD (DSM-V)	MMD outpatients treated with Fluoxetine (n = 40) *Age (y):* - Synbiotic: 34.45 ± 3.95 - Placebo: 35.50 ± 5.27 *Females (%):* - Probiotic: 70 - Placebo: 70	6	Synbiotic: (Familact H © 500 mg): *Lactobacillus casaei* (3×10^8 CFU/g), *Lactobacillus acidophilus* (2×10^8 CFUs/g), *Lactobacillus bulgarigus* (2×10^9 CFUs/g), *Lactobacillus rhamnosus* (3×10^8 CFUs/g), *Bifidobacterium breve* (2×10^8 CFU/g), *Bifidobacterium longum* (10^9 CFUs/g), *Streptococus thermophilus* (3×10^9 CFUs/g) and FOS (100 mg)	Depressive symptoms (HDRS)	Significant improvement in depressive symptoms (HDRS)
Schaub et al. (2022) (Switzerland)	PC RCT	MDD (ICD-10)	MDD inpatients (n = 47) *Age (y):* - Probiotic: 39.43 ± 11.45 - Placebo: 38.77 ± 10.32 *Females (%):* - Probiotic: 67 - Placebo: 50	4	Probiotic: *Streptococcus thermophiles, Bifidobacterium breve, Bifidobacterium longus, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii* (9×10^{11} CFUs total)	*Primary:* Depressive symptoms (HDRS) *Secondary:* Depressive and anxiety symptoms (BDI, STAI) and GI symptoms (GSRS) Functional imaging	Significant improvement in depressive symptoms (HDRS) in the probiotic group. No changes in secondary psychiatric outcomes (BDI, STAI) and GI symptoms. Significant increased gray matter volume in the calcarin sulcus and activation decrease in the right and left putamen in the probiotic group.
Schneider et al. (2023) (Switzerland)	PC RCT	MDD (ICD-10)	(*Same as* Schaub et al., 2023)	4	(*Same as* Schaub et al., 2023)	Neurocognitive performance -Verbal learning and memory (VLMT) - Visual memory and working memory (Corsi Block-tapping test, 2-back task) - Attention and executive functioning (TMT-A, TMT-B) BDNF levels	Significant improvement in verbal learning and memory (VLMT) but not in the remaining tests, in the probiotic group. No differences in BDNF levels between groups.
Bambling et al. (2017) (Australia)	Single group intervention	MDD (MINI)	Treatment Resistant MDD (n = 12) *Age (y):* 49.3 ± 10.9 *Females (%):* 66.66	8 + 8 folllow-up	Probiotic + Nutraceutical: *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Streptoccocus thermophiles* (2×10^{10}CFUs total) + Magnesium orotate (1600 mg)	Depressive symptoms (BDI, OQ45) Quality of life (QoL)	Significant improvement in depressive symptoms (BDI, OQ45) at the end of intervention but not at follow-up. A trend to improvement in QoL both at the end of intervention and follow-up
Otaka et al. (2021) (Japan)	Single arm clinical trial	BD + MDD (DSM-V)	BD + MDD patients (n = 18) *Age (y):* 46.6 ± 11.4 *Females (%):* 77.77	12	Probiotic: *Lactobacillus paracasei* Shirota (8×10^{10} CFUs)	Depressive (HDRS, BDI), anxiety (STAI) and sleep (PSQI) symptoms. GI symptoms (GSRS)	Significant improvement in depressive (HDRS, but not in BDI) and sleep symptoms (PSQI). No significant changes in anxiety (STAI) or GI symptoms (GSRS). A subanalysis revealed a relationship between the amount of *Bifidobacterium* and *Atopobium* clusters and the intervention-

(*continued on next page*)

Table 1 (*continued*)

Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
							associated improvement in depressive symptoms
Miyaoka et al. (2018) (Japan)	Open clinical trial	MDD (DSM-IV-TR)	Treatment-resistant MDD (n = 40) *Age (y):* - Probiotic: 42.4 ± 15.6 - Placebo: 41.9 ± 14.2 *Females (%):* - Probiotic: 52 - Placebo: 52	8	Probiotic: *Clostridium Butiricum* MIYAIRI 588 © (60 mg)	*Primary:* Depressive symptoms (HDRS) *Secondary:* Depressive (BDI) and anxiety symptoms (BAI)	Significant improvement in depressive and anxiety symptoms (HDRS, BDI and BAI) in the probiotic group
Wallace et al. (2021) (Canada)	Open single-arm trial	MDD (DSM-IV)	Drug-naïve MDD episode (n = 10) *Age (y):* 22.5 ± 7 *Gender (% fem):* 70%	8	Probiotic: *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 (10% and 90% of the composition respectively, 3 $\times 10^9$ CFUs total)	*Primary:* Depressive symptoms (MADRS) *Secondary:* Psychiatric symptoms (QIDS-SR16; SHAPS; GAD-7; STAI; PSQI)	Significant improvement in depressive and anxiety symptoms until week 4 of intervention but not at week 8 (MADRS, QIDS-SR16, GAD-7, but not in SHAPS and STAI) Significant sleep quality improvement at the end of intervention (PSQI)
Chen et al. (2021) (Taiwan)	Open single-arm trial	MDD (DSM-V)	MDD (n = 11) *Age (y):* 39.4 ± 12 *Gender (% fem):* 72.72%	8	Probiotic: *Lactobacillus plantarum* PS128 (6×10^{10} CFUs)	Depressive symptoms (HDRS; DSSS) Inflammation biomarkers (hs-CRP, IL-6, TNF-α)	Significant improvement in depressive and somatic symptoms (HDRS, DSSS) No significant changes in inflammation biomarkers (hs-CRP, TNF-α, IL-6)
Majeed et al. (2018) (India)	DB PC RCT	MDD (DSM-IV)	MDD + IBD patients (n = 40) *Age (y):* - Probiotic: 40.36 ± 10.28 - Placebo: 43.88 ± 9.85 *Gender (% fem):* - Probiotic: 85% - Placebo: 85%	13	Probiotic: *Bacillus coagulans* MTCC 5856 (2×10^9 CFUs)	*Primary:* Depressive symptoms (HDRS; MADRS; CES-D) and IBS symptoms (IBS-QOL) *Secondary:* Other efficacy assessments (CGI-I; CGI-S; RMBPC; GI-DQ and mESS)	Significant improvement in depressive and GI symptoms (HDRS, MADRS, CES-D, CGI and IBS-QOL) at day-60 and at the end of follow-up in the probiotic group. Significant decrease of serum myeloperoxidase levels in the probiotic group
Zhang et al. (2021) (China)	DB PC RCT	MDD (DSM-V)	MDD with constipation (n = 69) *Age (y):* - Probiotic: 45.8 ± 12.3 - Placebo: 49.7 ± 9.6 *Gender (% fem):* - Probiotic: 63.15% - Placebo: 64.51%	9	Probiotic: *Lacticaseibacillus paracasei* strain Shirota (100 mL beverage; 10^8 CFUs/mL)	*Primary:* Constipation symptoms (PAC-SYM) *Secondary:* Depressive symptoms (BDI; HDRS) Inflammatory biomarkers (IL-1, IL-6, TNF-α)	No significant differences in in general constipation symptoms (PAC-SYM total scores) between groups, but significant differences in rectal tearing after a bowel movement and stool symptoms (PAC-SYM items 7-12) in the probiotic group No significant differences in depressive symptoms (BDI; HDRS) Significant reduction in IL-6, but not in TNF-α and IL-1, in the probiotic group.
Vaghef-Mehrabany et al. (2021) (Iran)	DB PC RCT	MDD (DSM-V)	MDD and obesity women (n = 45) *Age (y):* - Prebiotic: 37.45 ± 6.77 - Placebo: 40.0 ± 8.66 *Gender (% fem):* - Probiotic: 100% - Placebo: 100%	8	Prebiotic: Inulin (10 g) + Caloric restriction	*Primary:* Depressive symptoms (HDRS; BDI) *Secondary:* Anthropometric measures, resting metabolic rate and biochemical parameters (HOMA-IR, FPG, lipid profile)	No significant beneficial effect on depressive symptoms in the prebiotic group (HDRS, BDI), but patients with a weight loss of a minimum 1.9 kg showed an improvement in depressive symptoms (HDRS, only a trend in BDI) No significant between-group differences in any secondary outcome
Vaghef-Mehrabany et al. (2023) (Iran)	DB PC RCT	MDD (DSM-V)	(*Same as* Vaghef-Mehrabany et al., 2021)	8	(*Same as*Vaghef-Mehrabany et al., 2021)	*Primary:* Depressive symptoms (HDRS) *Secondary:* Depressive and anxiety symptoms (BDI, STAI), anthropometric measures, resting	No significant beneficial effect on depressive and anxiety symptoms in the prebiotic group (HDRS, BDI; STAI) No significant differences in anthropometric measures, resting

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Table 1 (*continued*)

Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
						metabolic rate and oxidative stress/ inflammatory biomarkers (Zonulin, BDNF, hs-CRP, IL-10, TNF-α)	metabolic rate or any biomarker measured compared to placebo (Zonulin, BDNF, hs-CRP, IL-10, TNF-α)
Ghaderi et al. (2019) (Iran)	DB PC RCT	SZ (DSM-IV-TR)	SZ inpatients (n = 60) - Probiotic: 44.8 ± 8.3 - Placebo: 43.2 ± 6 *Females (%):* - Probiotic: 6.7 - Placebo: 6.7	12	Probiotic + nutraceutical: *Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus fermentum* and *Bifidobacterium bifidum* (2×10^9 CFUs each) + Vitamin D3 (50000 IU/2 weeks)	Psychiatric Symptoms (PANSS; BPRS) Oxidative stress and cardiometabolic risk biomarkers (TAC, GSH, MDA, hs-CRP, NO, HOMA-R, QUICKI, FPG, insulin, lipid profile)	Significant improvement in PANSS general and total scores in the probiotic group but not in BPRS o PANSS positive subscale. Significant increase of 25-OH-Vitamin D levels, TAC and QUICKI. Significant decrease in MDA, insulin, HOMA-IR, hs-CPR, triglycerides, total/ HDL cholesterol ratio and FPG.
Jamilian et al. (2021) (Iran)	DB PC RCT	SZ (DSM-IV-TR)	SZ inpatients (n = 51) *Age (y):* - Probiotic: 46.4 ± 10.5 - Placebo: 43.9 ± 6.9 *Females (%):* N/A	12	Probiotic + nutraceutical: *Lactobacillus acidophilus, Bifidobacterium lactis, Bifidobacterium bifidum*, and *Bifidobacterium longum* (2×10^9 CFU each) + selenium yeast (200 mcg)	(*Same as*Ghaderi et al., 2019)	Significant improvement in PANSS general scores in the probiotic group. Significant increase in total TAC, GSH and QUICKI. Significant decrease in hs-CRP, FPG, insulin and HOMA-IR.
Dickerson et al. (2014) (USA)	DB PC RCT	SZ (DSM-IV)	SZ outpatients (n = 58) *Age (y):* - Probiotic: 44.8 ± 11.2 - Placebo: 48.1 ± 9.4 *Females (%):* - Probiotic: 29.03% - Placebo: 40.74%	14	Probiotic: *Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis* Bb12 (10^9 CFUs each)	*Primary:* Psychiatric symptoms (PANSS) *Secondary:* Bowel movement difficulty (4-point scale from "no" to "severe" difficulty)	No significant differences in PANSS total score between groups. Patients in the probiotic group were less likely to develop "severe" bowel difficulty throughout the trial.
Tomasik et al. (2015) (USA)	DB PC RCT	SZ (DSM-IV)	SZ outpatients (n = 58) (*Same as*Dickerson et al., 2014)	14	(*Same as*Dickerson et al., 2014)	Psychiatric symptoms (PANSS). Inflammatory biomarkers (47 different biomarkers including cytokines, chemokines and acute-phase reactants)	No significant differences in PANSS scores between groups. Significant reduction in the vWf and trend increase ($p < 0.08$) in MCP-1, BDNF, T Cell Specific Protein RANTES and MIP-1b.
Severance et al. (2017) (USA)	DB PC RCT	SZ (DSM-IV)	SZ outpatients (n = 56) *Age (y):* - Probiotic: 44.66 ± 11.4 - Placebo: 48.11 ± 9.6 *Females (%):* - Probiotic: 27 - Placebo: 42	14	(*Same as*Dickerson et al., 2014)	*Candida albicans* seropositivity (Anti-*C. albicans* IgG levels) Psychiatric symptoms (PANSS) Bowel movement difficulty (4-point scale from "no" to "severe" difficulty)	No significant differences in PANSS total score between groups. Significant reduction of Anti-*C. albicans* IgG levels only in males, (in both males and females when stratified by baseline GI problems)
Mujahid et al. (2022) (Indonesia)	RCT	SZ (DSM-V)	SZ inpatients (n = 42) *Age (y):* - Probiotic: 33.57 ± 8.07 - Placebo: 35.71 ± 6.41 *Females (%):* - Probiotic: 23.8 - Placebo: 23.8	6	Probiotic: no strain/dosage information available	Psychotic Symptoms (PANSS) IL-6 serum levels	Significant reduction in psychotic symptoms in the probiotic group Significantly higher IL-6 decrease in the probiotic group. No correlation between IL-6 and PANSS reduction
Okubo et al. (2019) (Japan)	Open-label, single-arm clinical trial	SZ (DSM-V)	SZ outpatients w/ anxiety and depressive symptoms (n = 29) *Age (y):* N/A (median=45) *Females (%):* 58.62	4 + 4 follow-up	Probiotic: *Bifidobacterium breve* A-1 (10×10^{10} CFUs)	*Primary:* Subjective (HADS) and objective (PANSS) anxiety and depressive symptoms *Secondary:* Inflammatory biomarkers (34 cytokines and related molecules)	Significantly improvement in anxiety/ depression (HADS) after treatment but not after follow-up. Significant improvement in PANSS depression/anxiety score after follow-up. Significant increase in IFN-γ, IL1-R1, IL-10, IL-22, TNF-β and TRANCE, and a decrease in TNF-α. No significant changes in other cytokines.

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Table 1 (*continued*)

Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
Yang et al. (2021) (China)	Open-label clinical trial	SZ (DSM-V)	FEP inpatients (n = 67) *Age (y):* - Probiotic: 24.12 ± 5.49 - No probiotic: 23.64 ± 4.99 *Females (%):* - Probiotic: 72.72 - No probiotic: 64.7	12	Probiotic: *Bifidobacterium*, *Lactobacillus* and *Enterococcus* (3 $\times 10^7$ CFUs each) + Olanzapine vs. Olanzapine alone	*Primary:* Olanzapine-induced weight gain and appetite (self-administered, 3-level, appetite scale) *Secondary:* Psychotic symptoms (PANSS)	Significantly reduced weight gain and BMI change until week 4, which was not maintained afterwards. No significant changes in appetite. No significant changes in psychotic symptoms (PANSS)
Huang et al. (2022a) (China)	2 RCTs	SZ (DSM-V)	FEP drug-naïve patiens Study 1 (n = 76) *Age (y):* - Probiotic: 24.82 ± 5.64 - No probiotic: 23.43 ± 4.89 *Females (%):* - Probiotic: 28 - No probiotic: 35 Study 2 (n = 58) *Age (y):* - Probiotic: 24.60 ± 8.65 - No probiotic: 24.21 ± 4.65 *Females (%):* - Probiotic: 76.7 - No probiotic: 75	12	Study 1: Probiotic: Bifico © (1680 mg) + Olanzapine 15-2 (1680 mg) + Olanzapine 15-20 mg vs. Olanzapine alone Study 2: Probiotic: Bifico © (1680 mg) + Olanzapine 15-2 (1680 mg) + Olanzapine 15-20 mg + dietary fiber (60 mg) vs. Olanzapine alone	*Primary:* Olanzapine-induced weight gain and BMI *Secondary:* Biochemical biomarkers (insulin, FPG, HOMA-IR, lipid metabolism)	Study 1: no differences in weight gain or BMI. Significant increased HOMA-IR in the olanzapine alone group. No significant changes in other biomarkers. Study 2: significantly increased weight gain, BMI and HOMA-IR in the Olanzapine alone group. Significant differences in HDL-c but not in LDL-c, triglycerides, total cholesterol or other parameters.
Huang et al. (2022b) (China)	2 × 2 factorial design DB PC RCT	SZ (DSM-V)	SZ patients treated with Olanzapine (n = 118) *Age (y):* - Probiotic + fiber: 24.88 ± 2.28 - Probiotic + placebo: 24.03 ± 2.05 - Fiber + placebo: 26.76 ± 2.03 - Double placebo: 26.53 ± 2.42 *Gender (% fem):* N/A	12	Probiotic: Bifico ©(1680 mg) + Olanzapine 15-2 (*Bifidobacterium*, *Lactobacillus* and *Enterococcus* 1.7 $\times 10^9$, 3.8 $\times 10^8$, 7.8 $\times 10^8$ CFU respectively; 1680 mg) + dietary fiber (60 mg) vs. Bifico (1680 mg) + fiber placebo vs. probiotics placebo + dietary fiber (60 mg) vs. probiotics placebo + fiber placebo	*(Same as* Huang et al., 2022a*)*	Weight and BMI significantly decreased in the probiotic + fiber group and increased in the placebo group. No significant changes in probiotics or fiber alone group. Insulin and IRI increased and HDL-C decreased in the placebo group. Probiotic and dietary fiber was superior to placebo in insulin, IRI, cholesterol and HDL-C and superior to probiotic alone in cholesterol levels. Probiotics alone were superior to placebo on IRI and HDL-C Fiber alone was superior to placebo on insulin and IRI. No significant changes were observed between biochemical parameters among probiotics alone and fiber alone.
Kao et al. (2019) (United Kingdom)	RCT	SZ	SZ outpatients (n = 27) *Age (y):* - Prebiotic: 34.45 ± 2.42 - Placebo: 38.8 ± 2.27 *Females (%):* - Prebiotic: 38 - Placebo: 40	24	Prebiotic: B-GOS (Galactooligosacharide)	Neurocognitive performance (BACS) Weight gain Inflammation biomarkers (hs-CRP, IL-6, acetate)	Improvement in composite T-Scores of BACS. Subtest data show improvement was driven by the subtest of executive function. No significant changes in weight gain, hs-CRP, IL-6 or acetate
Dickerson et al. (2018) (USA)	DB PC RCT	BD (DSM-IV-TR)	BD-I and SAD inpatients with mania (n = 56) *Age (y):*	24	Probiotic: *Lactobacillus* GG and *Bfidobacterium Lactis* Bb12 (>10^8 CFUs total)	*Primary:* Time to rehospitalization *Secondary:* General psychiatric	Significant improvement in time to all psychiatric rehospitalizations and fewer days hospitalized in the probiotic group.

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Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
			- Probiotic: 37.9 ± 11.7 - Placebo: 33.3 ± 13.3 *Females (%):* - Probiotic: 73 - Placebo: 55			(BPRS), manic (YMRS) and depressive (MADRAS) symptoms.	When stratified by level of systemic inflammation, the probiotic was significantly associated with a 90% reduction in the risk of hospitalization among those with higher (above percentile 50) levels. No significant differences in psychiatric symptoms.
Eslami Shahrbabaki et al. (2020) (Iran)	DB PC RCT	BD (DSM-V)	Drug-free BD-I inpatients with mania (n = 38) *Age (y):* - Probiotic: 38.9 ± 9.83 - Placebo: 35 ± 8.18 *Gender:* N/A	8	Probiotic: *Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium langum* and *Bifidobacterium acidophilus* (1,8 $\times 10^9$ CFUs total)	Depressive (HDRS) and manic (YMRS) symptoms	No significant differences in manic (YMRS) and depressive (HDRS) symptoms.
Zeng et al. (2022) (China)	DB PC RCT	BD (DSM-V)	First episode BD (n = 42) *Age (y):* - Probiotic: 22.29 ± 5.13 - Placebo: 20.86 ± 2.90 *Gender:* N/A	13	Probiotic: *Bifidobacterium, Lactobacillus* and *Enterococcus* (at least 1 $\times 10^7$ CFU total)	Mood (HDRS; YMRS) and anxiety (HAMA) symptoms and its relationship with plasma oxidative stress and purine metabolism biomarkers (creatine, inosine, hypoxanthine, choline, uric acid, allantoic acid and LPCs)	Significantly higher improvement in manic (YMRS), but not other symptoms (HDRS; HAMA). No significant differences with placebo in changes in oxidative stress biomarkers, but changes in YMRS scores and LPCs positively correlated in the probiotic group, but not any other biomarker.
Reininghaus et al. (2020b) (Austria)	Single Arm Open Clinical Trial	BD (DSM-IV)	Euthymic BD (n = 27) *Age (y):* 50.7 ± 12.2 *Females (%):* 40.7	13	Probiotic (OMNi-BiOTic Stress Repair ©): *Bifidobacterium bifidum* W23, *Bifidobacterium* lactis W51 and W52, Lactobacillus *acidophilus* W22, *Lactobacillus casei* W56, *Lactobacillus paracasei* W20, *Lactobacillus plantarum* W62, *Lactobacillus Salivarius* W24, *Lactococcus lactis* W19 (at least 7.5 $\times 10^9$ CFU total)	Depressive (BDI-II; AS; HDRS) and manic (YMRS; MSS) symptoms Cognitive reactivity to sad mood (LEIDS-r) Quality of life (WHOQOL) Inflammatory biomarkers (hs-CRP; IL-6)	Statistically, but not clinically, significant reduction in manic symptoms (YMRS). Significantly reduced LEIDS-r "rumination" subdomain between the first and the third month of the trial, but not in the other five subdomains of the LEIDS-r. No significant improvement in other variables measured.
Reininghaus et al. (2020c) (Austria)	Single Arm Open Clinical trial	BD (DSM-IV)	Euthymic BD (n = 20) *Age (y):* 51.5 ± 11.54 *Females (%):* 45	13	(*Same as*Reininghaus et al., 2020b)	Depressive (BDI-II; HDRS) and manic (YMRS; MSS) symptoms. Neurocognitive performance: - Attention and processing speed (TMT-A; Digit-Symbol test) - Executive functions (TMT-B; MPT) - Working Memory (Digit-Span Test)	Statistically, but not clinically, significant reduction in manic symptoms (YMRS; MSS). No changes in depressive symptoms. Significant improvements in Digit-Symbol (attention/ processing speed) and TMT-B (executive function), but not in TMT-A, MPT or Digit-Span Test
Solis et al. (2002) (Spain)	Cross-over RCT	AN (DSM-IV)	AN female adolescents (n = 27) *Age:* N/A *Gender (% fem):* 100%	20	Fermented food: Yogurt containing *Lactobacillus delbreueckii subsp. Bulgaricus* and *Streptococcus thermophilus* (1125 g) during 10 weeks and then milk (950 g) during 10 weeks vs. Milk 10 weeks and then yogurt 10 weeks	IFN-y levels	Significant increase in IFN-y levels at week 10 in the Yogurt-to-Milk group, remaining unmodified during follow-up. Significant decrease in IFN-y levels at week 10 in the Milk-to-Yogurt group, recovering those levels during the second part of the intervention.

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Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
Nova et al. (2006) (Spain)	RCT	AN (DSM-IV)	AN (n = 30) and healthy (n = 35) female adolescents *Age:* N/A *Gender (% fem):* 100%	10	Fermented food: Yogurt containing *Lactobacillus delbreueckii subsp. Bulgaricus* and *Streptococcus thermophilus* (375 g; 10^7-10^8 CFUs/mL each) vs Semi-skimmed milk (400 mL)	Lymphocyte cells subsets Cytokines (INF-y, TNF-α, IL-6, IL-1, IL-2)	Significant decrease in CD4 + / CD8 + ratio in the AN control group. Significant increase in T lymphocyte subsets in the AN yogurt group. Increase in production of INF-y in both yogurt groups and decrease in both milk groups. No significant changes in the remaining cytokines
Trombetti et al. (2016) (Switzerland/France)	DB RCT	AN (DSM-IV)	Adult AN women (n = 62) *Age (y):* - High-protein: 22.2 ± 0.6 - Low-protein: 22.8 ± 0.9 *Gender (% fem):* - High-protein: 100% - Low-protein: 100%	4 + 4 follow-up	Fermented food: Fresh cheese hight protein product (15 gr protein/150gr cheese) vs. Fresh cheese low protein product (3gr protein/150gr cheese)	*Primary:* serum IGF-I *Secondary:* bone markers, calcium-phosphate metabolism markers (Vitamin D3, osteocalcin, serum calcium, PTH)	No significant increase in IGF-1 levels after intervention or follow-up. Significant increase in IGF-1 after the intervention while adjusting for visit, group, intervention, age and center. No significant between-group changes in secondary outcomes
Zâja et al. (2021) (Croatia)	DB PC RCT	AN (DSM-V)	AN + constipation female patients (n = 31) *Age (y):* - Probiotic: 15.06 ± 2.31 - Placebo: 15.13 ± 1.70 *Gender (% fem):* - Probiotic: 100% - Placebo: 100%	13 + 13 follow-up	Probiotic: *Lactobacillus reuteri* DSM17938 (2×10^8 CFUs)	*Primary:* Relief of constipation (Rome-III criteria) *Secondary:* Stool frequency and consistency, dyspepsia, BMI and weight normalization malnutrition (BMD, Vitamin D3)	No significant differences in relief of constipation, stool frequency and consistency or dyspepsia after intervention. Significant BMI increase and weight normalization in the probiotic group after 6 weeks of follow-up. No significant differences regarding malnutrition parameters (BMD, vitamin D3)
Sepehrmanesh et al. (2021) (Iran)	DB PC RCT	ADHD (DSM-IV-TR)	ADHD Children (n = 34) *Age (y):* - Probiotic: 9.3 ± 1.3 - Placebo: 8.9 ± 1.0 *Gender (% fem):* - Probiotic: 17.6% - Placebo: 23.5%	8	Probiotic: *Lactobacillus reuteri, Lactobacillus acidophilus, Lactobacillus fermentum* and *Bifidobacterium bifidum* (2×10^9 CFUs each)	*Primary:* ADHD symptoms (ADHD-RS) *Secondary:* Anxiety (HAMA) and depressive symptoms (CDI) Inflammation and oxidative stress biomarkers (hs-CRP, GHS, MDA, NO, TAC)	Significant improvement in ADHD symptoms (reduction of the total ADHD-RS, inattention and hyperactivity-impulsivity subscales) in the probiotic group. Significant improvement in some anxiety symptoms (HAMA) but not in depression (CDI) in the probiotic group Significant reduction in serum hs-CRP and plasma TAC increase in the probiotic group. No changes in other biomarkers.
Kumperscak et al. (2020) (Germany)	RCT	ADHD (DSM-V)	ADHD Drug-naïve Children and adolescents (n = 32) *Age (y):* - Probiotic: 11.4 ± 3.2 - Placebo: 12.5 ± 2.3 *Gender (% fem):* - Probiotic: 33.3% - Placebo: 21.4%	13	Probiotic: *Lactobacillus rhamnosuss* GG ATCC53103 (at least 10^{10} CFU)	ADHD symptoms and health-related QoL (ADHD-RS; PesdQL; CBCL) Inflammatory cytokines (IL-1, IL-6, IL-10, IL-12, TNF-α)	Significant improvement in self-perceived QoL (PedsQL Child Self-Report Total Score) but not in parent-perceived QoL (PedsQL Parent-Report or in the TRF of the CBCL) in the probiotic group. No significant changes in ADHD symptoms (ADHD-RS) Significant decrease in some inflammatory

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Table 1 (*continued*)

Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
							cytokines (IL-10, IL-12, TNF-α) between groups
Skott et al. (2020) (Sweden)	RCT	ADHD	Child, adolescent and adult ADHD (n = 182) *Age (y):* - Children: N/A (median=12) - Adults: N/A (median=36) *Gender (% fem):* - Children: 26.5% - Adults: 71.1%	9 + 2 follow-up	Synbiotic: P*ediacoccus pentasaceus*, *Lactobacillus casei ssp paracasei* S19, *Lactobacillus plantarum* 2362 (4 $\times 10^{11}$ CFUs total) + inulin, betaglucan, pectin and resistant starch (2,5 g each)	*Primary:* ADHD symptoms (SNAP-IV –for children-; ASRS – for adults-), autism symptoms (SCQ –for children-, AQ –for adults-), and functioning (WFIRS) *Secondary:* emotion regulation (DERS-16)	No significant differences among groups in ADHD symptoms (SNAP-IV, ASRS). When stratified by sVCAM-1 levels, children with levels above median showed improvement in autism restricted, repetitive and stereotyped behaviours (SCQ) in the synbiotic group. No changes in autism symptoms in the adult group after intervention or in functioning in both groups. No significant changes in emotion regulation (DERS-16)
Eskandarzadeh et al. (2021) (Iran)	DB PC RCT	GAD (DSM-V)	Drug-free GAD patients (n = 37) *Age (y):* - Probiotic: 34.17 ± 6.14 - Placebo: 33.67 ± 6.56 *Gender (% fem):* - Probiotic: 79.2% - Placebo: 83.3%	8	Probiotic: *Bifidobacterium subs. longum, bifidum, lactis* and *Lactobacillus acidophilus* (1.8 $\times 10^{9}$ CFUs total) + Sertraline 25 mg	*Primary:* anxiety symptoms (HAMA) *Secondary:* anxiety symptoms (BAI; STAI) and quality of life (WHO-QOL). Plasma ACTH and serum cortisol	Significantly reduced anxiety symptoms in the probiotic group (HAMA). No significant difference among groups in other anxiety scales (BAI; STAI) or in quality of life (WHO-QOL) No changes in ACTH or cortisol levels
Brenner et al. (2020) (USA)	PC RCT	PTSD (CAPS-5)	PTSD + Mild Traumatic Brain Injury (n = 31) *Age (y):* - Probiotic: 37.9 ± 8.5 - Placebo: 36.7 ± 6.2 *Gender (% fem):* - Probiotic: 0% - Placebo: 0%	8	Probiotic: *Lactobacillus reuteri* DSM17938 (10^{8} CFUs)	Inflammatory biomarkers (hs-CRP, cytokines: IL-6, IL-1 TNF-α, IFN-γ) Stress responsivity (TSST, VAS) Intestinal permeability (IFABP, DAO)	Significantly larger increase in heart beats per minute during the math task part of TSST in the placebo group. No changes during the pre-speech, speech or relaxation parts. No changes in VAS. A trend to decreased levels of hs-CRP, but not in cytokines, in the probiotic group No changes in intestinal permeability
Wu et al. (2021) (Taiwan)	DB PC RCT	TS (DSM-V)	TS children (n = 57) *Age (y):* - Probiotic: N/A (median=9.3) - Placebo: N/A (median=10.4) *Gender (% fem):* - Probiotic: 14.29% - Placebo: 17.24%	8	Probiotic: *Lactobacillus plantarum* PS128 (6 $\times 10^{10}$ CFUs)	*Primary:* Tic severity (YGTSS) *Secondary;* ADHD, OCD, migraine and MDD comorbidities (SNAP-IV; CPT; OCI-R; MIDAS; CDI-TW)	No significant results in tic severity (YGTSS). Significant reduction in SNAP-IV and CPT scales for ADHD in the intervention group. No significant changes in migraine, depression or obsessive symptoms (CDI-TW, OCI-R, MIDAS)
Ho et al. (2021) (Taiwan)	DB PC RCT	Insomnia (DSM-V)	Chronic primary insomnia (n = 40) *Age (y):* - Probiotic: 28.58 ± 6.5 - Placebo: 25.47 ± 4.64 *Gender (% fem):*	4	Probiotic: *Lactobacillus plantarum* PS128 (6 $\times 10^{10}$ CFUs)	*Primary:* changes in sleep EEG (miniature-PSG in different sleep stages: N1, N2, N3 and REM; HRV) *Secondary:* insomnia (PSQI, ISI, VAS, ESS), depressive and anxiety symptoms (BDI-II, BAI, STAI)	Significant decrease in awakenings at N3 (deep sleep stage) at the intervention group but not at other sleep stages (N1, N2 and REM). No changes in HRV. No significant improvement in sleep quality/insomnia parameters (PSQI ISI,

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Table 1 (*continued*)

Study reference / Country	Study Design	Diagnosis (criteria)	Sample and Population Characteristics	Duration (weeks)	Intervention (Type and dosage)	Outcomes (Measurement Instruments)	Main results
			- Probiotic: 79.19% - Placebo: 57.89%				VAS or ESS) Significant reduction in depressive symptoms (BDI-II) in the intervention group. No changes in anxiety (STAI or BAI)
Amadieu et al. (2022) (Belgium)	PC RCT	AUD (DSM-V)	AUD in withdrawl (n = 43) *Age (y):* - Probiotic: 48.4 ± 9.8 - Placebo: 48.0 ± 9.0 *Gender (% fem):* - Probiotic: 50% - Placebo: 23.8%	2.5	Prebiotic: Inulin (from 4 to 16 g)	Liver disease and inflammatory parameters (glucagon, fasting glucose, cholesterol, triglycerides, GLP-1, leptin, ghrelin, PYY) BDNF levels Depressive and anxiety symptoms (BDI, STAI), craving (OCDS) and sociability (sociability score)	Significant increase in serum BDNF levels, but no changes in the remaining biological parameters, in the inulin group. Significant improvement in sociability pleasant score in the inulin group. No significant differences between groups over abstinence, depressive and anxiety symptoms (BDI, STAI, OCDS)

Abbreviations (alphabetically): 3-HAA: 3-hydroxi anthralinic acid; 3-HKYN: 3-hydroxykynureninte; AA: Anthralinic Acid; ACTH: Adrenocorticotropic Hormone; ADHD: Attention Deficit and Hyperactivity Disorder; ADHD-RS: Attention Deficit and Hyperactivity Disorder Rating Scale; AN: Anorexia Nervosa; AQ: Austim Spectrum Quotient; AS: Anhedonia Scale; ASRS: Adult ADHD Self-Report Scale; AUD: Alcohol Use Disorder; BACS: Brief Assessment on Cognition in Schizophrenia; BAI: Beck Anxiety Inventory; BD: Bipolar Disorder; BDI: Beck Depression Inventory; BDNF: Brain Derived Neurotrophic Factor; BMD: Bone Mass Density; BMI: Body Mass Index; BPRS: Brief Psychiatry Rating Scale; CAPS-5: Clinician Administered PTSD scale for DSM-V; CBCL: Child Behavior Checklist; CDI: Children's Depression Inventory; CDI-TW: Children's Depression Inventory, Taiwan Version; CES-D: Centre of Epidemiological Studies – Depression; CGI-I: Clinical Global Impression-Improvement Rating Scale; CGI-S: Clinical Global Impression Severity Rating Scale; CPT: Continuous Performance Test; DAO: D-aminoacid Oxidase; DB: Double-blinded; DERS-16: Dificulties and Emotion Regulation Scale - 16; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, fifth edition; DSSS: Depression Anxiety Stress Scales; ESS: Epworth Sleepiness Scale; FEP: First Episode Psychosis; FOS: Fructooligosacharide; FPG: Fasting Plasma Glucose; GAD: General Anxiety Disorder; GAD-7: Generalized Anxiety Disorder Scale – 7 item; GI: Gastro-intestinal; GI-DQ: Gastrointestinal Discomfort Questionnaire; GLP-1: Glucagon-like Peptide type 1; GLQI: Gastrointestinal Quality of Life Questionnare; GOS: Galactooligosacharide; GSH: Glutathione; GSRS: Gastrointestinal Symptoms Rating Scale; HADS: Hospital Anxiety and Depression Scale; HAMA: Hamilton Anxiety Rating Scale; HC: Healthy controls; HDL-c: High Density Cholesterol; HOMA-IR: Homeostasis Model of Assesment-Insulin Resistance; HRSD: Hamilton Rating Scale for Depression; HRV: Heart Rate Variability; ICD-10: International Classification of Diseases, 10th version; hs-CRP: high sensitivity C Reactive Protein; IBS-QOL: Irritable Bowel Syndrome Quality of Life instrument; ICD: International Statistical Classification of Diseases and Related Health Problems; IFABP: Intestinal Fatty-Acid Binding Protein; IFN: Interferon; IGF-1: Insulin-like Growth Factor-1; IL: Interleukin; IRI: Insulin Resistance Index; ISI: Insomnia Severity Index; KYN: Kynurenine; KYNA: Kynurenic Acid; LEIDS-r: Leiden Index of Depression Sensitivity – Revised; LPCs: Lysophosphatidylcholines; MADRS: Montgomery-Adsberg Depression Rating Scale; MCP-1: Monocyte Chemotactic Protein-1; MDA: Malondialdehyde; MDD: Major Depressive Disorder; mESS: modified Epworth-Sleepiness Scale; MIDAS: Migraine Dissability Assessment; MINI: Mini-International Neuropsychiatric Interview; MIP-1b: Macrophage Inflammatory Protein 1 beta; MPT: Mittenecker Pointing Test; MSS: Mania Self-Rating Scale N/A: Not Available; NFKB1: Nuclear Factor Kappa B subunit 1; NO: Nitric Oxide; OCD: Obsessive-Compulsive Disorder; OCDS: Obsessive-Compulsive Drinking Scale; OCI-R: Obsessive-Compulsive Inventory Revised; OQ45: Outcome Questionnaire 45; PAC-SYM: Patient Assesment of Constipation-Symtoms; PANSS: Positive and Negative Syndrome Scale; PC: Placebo-controlled; PedsQL: Pediatric Quality of Life; PPY: Pancreatic Polipeptide Gamma; PSQI: Pittsburgh Sleep Quality Index; PTH: Parathyroid hormone; PTSD: Post Traumatic Stress Disorder; QIDS-SR16: Quick Inventory of Depression Symptomatology – Self Reported – 16 items; QoL: Quality of Life; QUICKI: Quantity Insulin Sensitivity Check Index; RANTES: Regulated on Activation, Normal T Expressed and Secreted; RCT: Randomized clinical trialREM: Rapid Eye-Movement; RFFT: Ruff Figural Fluency Test; RMBPC: Dementia-Revised Memory and Behaviour Problem Checklist; SAD: Schizoaffective Disorder; SAMe: S-Adenosylmethionine; SCL-90: Derogatis Symptom Cheklist; SCQ: Social Communication Questionnaire; SHAPS: Snaith-Hamilton Pleasure Scale; SNAP-IV: The Swanson, Nolan and Pelham rating scale; STAI1: State-Trait Anxiety Inventory 1; sVCAM-1: soluble Vascular Cell Adhesion Molecule-1; TAC: Total antioxidant capacity; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; TNF: Tumoral Necrosis Factor; TRANCE: TNF-related activation-induced cytokine;; TRF: Teacher Report Form; TS: Tourette Syndrome; TSST: Trier Social Stress Test; VAS: Visual Analogue Scale; VLMT: Verbal Learning Memory Test; vWf: von Willerbrand factor; WFIRS: Weiss Functional Impairment Rating Scale; WHOQOL: The World Health Organization Quality of Life; YGTSS: Yale Global Tic Severity Scale; YMRS: Young Mania Rating Scale; Z-SDS: Zung Self-Rating Depression Scale;

compound and five a combination of a probiotics and other nutraceutical supplements. Overall, *Bifidobacterium* and *Lactobacillus* spp. were the most common bacterial species employed across different probiotic interventions. Moreover, three studies used prebiotics (two inulin, and one galactooligosaccharide (GOS)), two studies used a synbiotic compound and three studies used fermented foods (fermented dairy products). Regarding the trial design, 34 of the 42 studies were placebo-controlled RCTs, four were single-arm clinical trials, three were open clinical trials, and one was an open-label pilot study. Studies are presented below according to the psychiatric disorder examined.

In general, the main outcomes of the studies were changes in the mean score of different psychiatric symptom and other clinical variable scales or biochemical parameters and biomarkers (see Table 1). Of note, only two studies estimated the clinical benefits of psychobiotics based on response rates. Specifically, Miyaoka et al. (2018) and Schaub et al. (2022) estimated a 50% and a 57% reduction in HDRS scores, respectively. Moreover, no study reported remission rates. Also, except from Kao et al. (2019) in SZ, Kumperskcak et al., (2020) in ADHD and Tian et al. (2023) in MDD, none of the studies reported the effect size of the intervention.

3.1. Major depressive disorder

Nineteen studies have examined the efficacy of psychobiotics in patients with MDD. The PROVIT Study (Reiter et al., 2020; Reininghaus et al., 2020a) used a multi-strain probiotic compound plus biotin for 4 weeks and compared them with placebo plus vitamin B7. There were no significant differences in psychiatric symptoms, gastrointestinal (GI) symptoms and oxidative stress biomarkers (Reininghaus et al., 2020a); however, the IL-6 gene expression in blood mononuclear cells was increased in the probiotic group only (Reiter et al., 2020).

In a larger RCT (Arifdjanova et al., 2021), patients treated with escitalopram received a mix of *Bifidobacterium*, *Lactobacillus* and *Streptococcus* strains or placebo. There were no significant differences in depressive symptoms. However, the probiotic was associated with significant changes in several inflammatory biomarkers (see Table 1). In an 8-week RCT, Rudzki et al. compared MDD patients receiving adjunctive *Lactobacillus plantarum 299 v* or placebo. There were no significant changes in depressive or anxiety symptoms between groups. However, the probiotic was associated with significant improvements in attention/processing speed and verbal learning. There were also significant differences in antioxidant capacity in the probiotic group compared with placebo (Rudzki et al., 2019).

In another placebo-controlled RCT, supplementation with a mix of *Lactobacillus* and *Bifidobacterium* was associated with a significant decrease in self-reported depressive symptoms as well as several inflammatory and metabolic parameters (see Table 1) (Akkasheh et al., 2015). Moreover, Saccarello et al. performed a 6-week placebo-controlled RCT with S-Adenosylmethionine (SAMe) and *Lactobacillus plantarum* and found a reduction in depressive, anxiety, and somatic symptoms since week 2 of the study (Saccarello et al., 2020). Also, a multi-strain probiotic compound during four weeks in an RCT showed an improvement in depressive and GI symptoms (Tian et al., 2023). A synbiotic formulation (fructooligosaccharide (FOS) plus *lactobacillus*, *bifidobacterium* and *streptococcus* strains) showed a significant improvement in depressive symptoms in patients treated with fluoxetine during 6 weeks (Ghorbani et al., 2018). Moreover, a significant improvement in depressive symptoms was shown in a 4-week RCT using a multi-strain formulation (Schaub et al., 2022). Moreover, a secondary analysis of this study (Schneider et al., 2023) showed an improvement in verbal learning in the probiotic group.

Other studies, which did not meet the criteria of a double-blinded, placebo-controlled clinical trial, focused on the treatment of MDD (Bambling et al., 2017; Otaka et al., 2021; Miyaoka et al., 2018; Wallace and Milev, 2021; Chen et al., 2021). Bambling et al. assessed the efficacy of a combination of probiotics and SAME + magnesium orotate in treatment-resistant MDD, e.g., to selective serotonin-reuptake inhibitors (SSRI). Depressive symptoms significantly improved at the end of the intervention but a trend to relapse appeared at follow-up. The lack of a control group prevents establishing whether the addition of probiotics achieved preferable outcomes compared to SAMe or magnesium orotate alone (Bambling et al., 2017). A 12-week study showed a decrease in depressive symptoms and insomnia after an intervention with *Lactobacillus casei* in individuals with unipolar or bipolar depression (Otaka et al., 2021). In an open trial comparing *Clostridium butyricum* as adjunctive therapy for treatment-resistant MDD, significant improvements in depressive and anxiety spectrum symptoms were observed (Miyaoka et al., 2018). In another 8-week open-label study, but without a control group, and a different probiotic, a significant improvement in depressive and anxiety symptoms from baseline to week 4 was found, which did not persist at week 8 (Wallace and Milev, 2021). In contrast, an improvement in sleep quality emerged from week 4 until week 8 (Wallace and Milev, 2021). Finally, Chen et al. used adjunctive *Lactobabillus plantarum* in an 8-week, open study. They showed a significant improvement in depressive and somatic symptoms but no changes in biomarkers of inflammation (Chen et al., 2021).

Finally, four RCTs have examined the efficacy of pre/probiotics in MDD with comorbidities (Majeed et al., 2018; Zhang et al., 2021; Vaghef-Mehrabany et al., 2021; Vaghef-Mehrabani et al., 2023). An intervention with *Lactobacillus coagulans* improved both depressive and GI symptoms in patients with depression and inflammatory bowel disease (IBD) (Majeed et al., 2018). In addition, *Lactobacillus paracasei* improved some specific constipation symptoms, but no other GI symptoms, in patients with MDD (Zhang et al., 2021). Another RCT focused on the treatment of women with MDD and obesity (Vaghef-Mehrabany et al., 2021; Vaghef-Mehrabani et al., 2023). Participants following a caloric restriction and inulin supplementation did not improve depressive or anxiety symptoms (Vaghef-Mehrabany et al., 2021).

3.2. Schizophrenia

Two placebo-controlled RCTs were carried out in the same center (Ghaderi et al., 2019; Jamilian and Ghaderi, 2021) using a multi-strain probiotic (containing *Lactobacillus* and *Bifidobacterium spp*) combined with vitamin D (Ghaderi et al., 2019) or selenium (Jamilian and Ghaderi, 2021). In both studies the probiotic intervention was associated with a significant improvement in psychiatric symptoms and a significant improvement in several parameters of oxidative stress and cardiometabolic risk. Additional changes in other biomarkers were observed (see Table 1).

The results of another 14-week, placebo-controlled RCT using an adjunctive *Lactobacillus* and *Bifidobacterium* compound were published in three articles (Dickerson et al., 2014; Tomasik et al., 2015; Severance et al., 2017). There were no significant differences in psychotic symptoms. However, patients in the probiotic group were less likely to develop severe bowel difficulty over the trial (Dickerson et al., 2014). Regarding immunomodulatory effects, there was a significant reduction in the von Willebrand factor and a trend to increased levels of different biomarkers (see Table 1) (Tomasik et al., 2015). Moreover, a significant reduction in Candida albicans IgG levels was found when patients were stratified by gastrointestinal problems (Severance et al., 2017). In addition, Mujahid et al. performed a 6-week RCT comparing add-on therapy with a probiotic or placebo. The probiotic group showed a more significant reduction in psychotic symptoms and IL-6 compared to placebo. (Mujahid et al., 2022).

Other studies have focused on non-psychotic symptoms in SZ patients. Okubo et al. (2019) found significant improvements in depression and anxiety symptoms as well as significant changes in inflammatory cytokines in an open-label, single-arm study with *Bifidobacterium breve* (see Table 1) (Okubo et al., 2019). Yang et al. (2021) investigated the effect of probiotics on olanzapine-induced metabolic side effects in an open trial with a multi-strain probiotic. In this case, the initial weight

gain and BMI reduction were not consistent at the end of the trial (Yang et al., 2021). Moreover, Huang et al. performed three different 12-week RCTs published in two articles (Huang et al., 2022a, 2022b). The first study used a probiotic plus olanzapine and the second one used a probiotic plus dietary fiber and olanzapine, both versus olanzapine alone. The probiotic was associated with a decrease in insulin resistance in both studies, but significant differences in weight gain were observed only with the combination of probiotic and fiber (Huang et al., 2022a). The third study (Huang et al., 2022b) was an RCT comparing four different groups: probiotic plus dietary fiber, probiotic alone, dietary fiber alone and placebo. Both weight and BMI decreased in the probiotic plus dietary fiber group and increased in the placebo group. Significant differences in several metabolic parameters were also observed (see Table 1).

Finally, one study used a GOS mixture prebiotic in a placebo-controlled trial focused on cognitive performance. Compared to placebo, the prebiotic was associated with improved cognitive performance, which was likely driven by enhanced executive functioning (Kao et al., 2019).

3.3. Bipolar disorder

Three RCTs have been conducted in patients with acute mania (Dickerson et al., 2018; Eslami Shahrbabaki et al., 2020; Zeng et al., 2022). On the one hand, an adjunctive probiotic mix showed a significant improvement in time to all psychiatric rehospitalizations and fewer days hospitalized, but no significant effect was observed on mood symptoms. Moreover, the preventive effect of probiotics was greater in patients with higher levels of systemic inflammation at baseline (Dickerson et al., 2018). On the other hand, first manic episode patients receiving a mix of probiotics showed a significantly higher improvement in manic symptoms, which in turn was positively correlated with a decrease in some oxidative stress biomarkers (Zeng et al., 2022). However, in another trial of inpatients with mania, the probiotic intervention did not improve mood symptoms, compared to placebo (Eslami Shahrbabaki et al., 2020).

In addition, the results of a pilot study in euthymic patients were published in two articles (Reininghaus et al., 2020a, 2020b). Patients received treatment as usual (TAU) and a multi-strain probiotic. They found a significantly reduced cognitive reactivity to sad mood, but not in depressive symptoms or quality of life, between the first and the third month of the trial (Reininghaus et al., 2020a). Moreover, significant changes were found in some tests of attention/processing speed and executive functions, but not in working memory (Reininghaus et al., 2020b).

3.4. Anorexia nervosa

The results of four trials have been published so far on eating disorders (Solis et al., 2002; Nova et al., 2006; Trombetti et al., 2016; Žaja et al., 2021). However, none focused on changes of psychopathology, but instead on biochemical and immunological parameters or physical symptoms associated with anorexia nervosa. In a 20-week, cross-over design trial, the consumption of yogurt was associated with an increase in interferon gamma (INF-γ) levels when compared to milk intake in female adolescents hospitalized for anorexia nervosa (Solis et al., 2002). Another 10-week RCT also compared the effects of yoghurt containing *Lactobacillus* and *Streptococcus* strains versus semi-skimmed milk on hospitalized patients with anorexia nervosa and healthy controls. Similarly, the yogurt intervention showed an increased IFN-γ production compared to milk in the anorexia nervosa group. In both groups, increased IFN-γ levels were observed after yoghurt intake (Nova et al., 2006). Trombetti et al. assessed changes in Insulin-like Growth Factor I (IGF-I) levels, which are usually lower in anorexia nervosa patients and can lead to a decrease in bone mineral mass (Trombetti et al., 2016). Patients received either a high-protein dairy product or a low-protein dairy product. High-protein dairy was not associated with a significant increase in IGF-1 levels in patients with anorexia nervosa, but there was a significant increase after adjusting for visit, group, intervention, age, and center (Trombetti et al., 2016). Finally, Zaja et al. investigated the efficacy of *Lactobacillus reuteri* in individuals with anorexia nervosa with comorbid constipation. A significant BMI increase and weight normalization was observed in the probiotic group, but there was no significant difference in constipation reduction between the groups (Žaja et al., 2021).

3.5. Attention hyperactivity deficit disorder

Three placebo-controlled RCTs investigated ADHD outcomes (Sepehrmanesh et al., 2021; Kumperscak et al., 2020; Skott et al., 2020). A multi-strain probiotic was associated with a significant reduction in ADHD symptoms and an improvement in inflammatory and antioxidant parameters (Sepehrmanesh et al., 2021). Moreover, children and adolescents receiving *Lactobacillus rhamnosus* over three months had improved quality of life and reductions in some inflammatory cytokines, but no significant difference in ADHD symptoms (Kumperscak et al., 2020). Finally, a synbiotic did not improve ADHD symptoms. However, when patients were stratified by levels of soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1), the synbiotic was associated with improved autism-spectrum symptoms in children with elevated sVCAM-1 levels (Skott et al., 2020).

3.6. Anxiety disorders

Two placebo-controlled RCTs have been published on anxiety disorders to date (Eskandarzadeh et al., 2021; Brenner et al., 2020). Drug-naïve patients with GAD received sertraline plus either a multi-strain probiotic compound or placebo during eight weeks. The intervention was associated with a higher decrease in anxiety symptoms, but it was not consistent in all different instruments used to assess them (Eskandarzadeh et al., 2021). Another RCT focused on the probiotic intervention with *Lactobacillus reuteri* in male patients with PTSD and co-occurring mild traumatic brain injury (Brenner et al., 2020). The placebo group showed a higher autonomic stress response in comparison to the treatment group.

3.7. Tourette syndrome

An 8-week, placebo-controlled RCT with *Lactobacillus plantarum* was conducted in children with Tourette syndrome. While the severity of tics improved in both groups, ADHD symptoms decreased in the intervention group only, and no significant changes were observed in comorbid obsessive-compulsive symptoms (Wu et al., 2021).

3.8. Insomnia

Ho et al. assessed the efficacy of *Lactobacillus plantarum* in individuals with chronic primary insomnia in an RCT. Sleep was measured objectively using miniature polysomnography and subjectively through different evaluation instruments. An objective improvement in sleep quality at non-REM stage 3, but not in other sleep stages, was observed. Subjective sleep symptoms did not significantly improve, whereas depressive symptoms did so (Ho et al., 2021).

3.9. Alcohol use disorder

One RCT examined the effect of supplementation with inulin or placebo for 17 days in patients with AUD undergoing alcohol withdrawal. Inulin supplementation did not elicit additional benefits over abstinence, depressive and anxiety symptoms or in liver disease and inflammatory parameters but it improved sociability. Only serum BDNF levels increased significantly in the inulin group (Amadieu et al., 2022).

3.10. Safety and tolerance

None of the studies reported significant problems regarding the safety or tolerance of the intervention used.

3.11. Risk of bias and quality assessment

After assessing the risk of bias using RoB 2 tool for RCTs, 34 out of 39 articles showed a low risk of bias while four showed some concerns and one of them high risk of bias (see Table 2). ROBINS-I tool was used for evaluating the risk of bias in eight non-randomized studies. Among them, five articles showed a low risk of bias, two presented some concerns and one showed high risk of bias (see Table 3).

When using the PEDro Scale for quality assessment for 39 articles comprising 34 RCTs, all of them showed good statistical parameters quality, while there were some concerns regarding de internal validity of the studies. Despite all of them were described as randomized, three out o 39 articles did not stated clearly that the allocation was concealed from the evaluators. .

4. Discussion

To the authors' knowledge this is the most comprehensive and updated systematic review of clinical trials examining the efficacy of probiotics, prebiotics, synbiotics and fermented foods in a wide range of psychiatric disorders. Moreover, the study selection was restricted to clinical populations fulfilling standardized diagnostic criteria, e.g., DSM or ICD.

So far, MDD is the disorder most studied and with the greatest supporting evidence, especially probiotics containing *Bifidobacterium* and *Lactobacillus* spp. This is consistent with the conclusions of meta-analyses that probiotics may improve depressive symptoms in subclinical and especially in clinical populations (Liu et al., 2019; El Dib et al., 2021; Misera et al., 2021; Alli et al., 2022). The most recent meta-analisys investigating the use of pyschobiotics in MDD across 13 clinical trials (Zhang et al., 2023) shows an overall improvent of depressive symptoms with probiotics but discrete results with prebiotic or synbiotic interventions. Here we expand these results with evidence based on a larger number of 19 clinical trials. Moreover, recent clinician guidelines provisionally recommend adjunctive probiotics in MDD (Sarris et al., 2022). In this review, 10 of 15 studies showed potential benefits for depressive symptoms as measured with different validated instruments (Akkasheh et al., 2016; Bambling et al., 2017; Miyaoka et al., 2018; Majeed et al., 2018; Ghorbani et al., 2018; Otaka et al., 2021; Wallace and Milev, 2021; Chen et al., 2021; Schaub et al., 2022; Tian et al., 2023).

We discuss below the clinical efficacy of psychobiotics as well as their impact on key biological pathways involved in the pathogenesis of psychiatric disorders.

4.1. Effects of psychobiotics on psychiatric symptoms and other clinical outcomes

As expected, given the variety of diagnoses covered in this systematic review, the aims and the main outcomes were heterogeneous across the selected trials. Focusing on core psychopathological symptoms, three studies showed that psychobiotics could improve psychotic symptoms in individuals with SZ (Ghaderi et al., 2019; Jamilian and Ghaderi, 2021, Mujahid et al., 2022), whereas two other trials did not (Dickerson et al., 2014; Yang et al., 2021). Of note, in two of the positive studies probiotics were combined with nutraceuticals such as vitamin D3 (Ghaderi et al., 2019) and selenium (Jamilian and Ghaderi, 2021). Overall, previous reviews of clinical trials do not support the use of probiotics as add-on treatments in SZ (Samochowiec and Misiak, 2021). Moreover, the conclusions of the only existing meta-analysis reviews of pre/probiotics in SZ may be hindered by the substantially lower number of studies included (Minichino et al., 2021). In BD, probiotics were associated with an improvement in symptoms of mania in one out of three studies (Zeng et al., 2022). Moreover, patients with BD receiving probiotics showed a significant improvement in time to all psychiatric rehospitalizations and fewer days hospitalized (Dickerson et al., 2018). Interestingly, none of the five studies on BD was exclusively focused on bipolar depression. Despite assessing depressive symptoms, none revealed significant improvements in that outcome.

Regarding anxiety disorders, the only study conducted in GAD showed a decrease in clinician-rated, although not in self-reported, anxiety symptoms (Eskandarzadeh et al., 2021). In ADHD, one out of three studies (Sepehrmanesh et al., 2021) reported improvement in inattention and hyperactivity, which are core symptoms of ADHD, whereas two other trials with psychobiotics reached negative results (Kumperscak et al., 2020; Skott et al., 2020). In addition, a potential improvement in deep sleep stage was found according to objective measures but it was not consistent with the subjective experience of patients with insomnia (Ho et al., 2021). Finally, no benefits of psychobiotics were described in core clinical symptoms of Tourette syndrome (Wu et al., 2021) and abstinence in AUD (Amadieu et al., 2022).

Moreover, psychobiotics have been associated with improvements in non-core symptoms across several psychiatric disorders. One study showed an improvement in anxiety and depressive symptoms associated with SZ (Okubo et al., 2019) and another described a decreased cognitive reactivity to sad mood during the euthymic phase of BD (Reininghaus et al., 2020c). Also, in ADHD, a synbiotic was associated with decreased autism symptoms, but only in patients with baseline elevated sVCAM-1 levels. Of note, in some autism studies, sVCAM-1 levels correlate to the severity of behavioral impairments and associated symptoms and quantitative clinical traits (Ashwood et al., 2011; Onore et al., 2009). Moreover, children with ADHD showed a reduction in anxiety symptoms (Sepehrmanesh et al., 2021) and patients with Tourette syndrome improved ADHD symptoms (Wu et al., 2021) after probiotic intervention. Finally, depressive symptoms improved in insomnia patients (Ho et al., 2021), which is consistent with another study that tested the same probiotic strain, *Lactobacillus plantarum* PS128, in patients with MDD (Chen et al., 2021).

Neurocognitive function is a core dimension across psychiatric disorders and a major predictor of patients' functional outcomes (Millan et al., 2012). Neurocognitive performance was assessed in several trials and diagnoses. A prebiotic supplement was associated with improved cognition in SZ (Kao et al., 2019). Moreover, treatment with probiotics has been associated with improvements in processing speed and executive cognition in BD (Reininghaus et al., 2020b) and in processing speed and verbal learning and memory in MDD (Rudzki et al., 2019; Schneider et al., 2023). These findings are consistent with previous evidence supporting pro-cognitive effects of psychobiotics in both clinical (Desmedt et al., 2019; Kim et al., 2021) and preclinical studies (Savignac et al., 2015). Nevertheless, conflicting meta-analytic evidence exists about the efficacy of psychobiotics to improve human cognition (Marx et al., 2020; Lv et al., 2021).

Moreover, several studies have focused on the potential of probiotics and prebiotics to mitigate the side effects of psychotropic drugs. Specifically, four studies, published across three articles (Yang et al., 2021; Huang et al., 2022a, 2022b), explored the efficacy of specific probiotic strains in conjunction with olanzapine to prevent weight gain in individuals with SZ. Despite the somewhat inconsistent findings, when dietary fiber was added to the combination, a reduction in weight gain and insulin resistance was observed (Huang et al., 2022a, 2022b).

Patient-centered outcomes, such as quality of life (QoL), have also been examined in some trials. Probiotic supplementation has been associated with improved QoL in MDD at a trend level (Bambling et al., 2017; Otaka et al., 2021) and children and adolescents with ADHD (Kumperscak et al., 2020), but not in BD (Reininghaus et al., 2020b) or GAD (Eskandarzadeh et al., 2021). Conversely, virtually no study included measures of social functioning to assess if the potential benefits

Table 2
Risk of bias assessment of randomized studies – RoB 2.

Reference	RoB arising from randomization process	Effect of assignment to intervention	Effect of adhering to intervention	Missing outcome data	RoB in measurement of the outcome	Rob in selection of the reported result	Overall risk of bias
Akkasheh et al., 2016	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Amadieu et al. 2022	SC	HIGH	HIGH	LOW	LOW	SC	HIGH
Arifdjanova et al., 2021	LOW	SC	SC	LOW	SC	SC	SC
Brenner et al. 2020	SC	SC	SC	LOW	LOW	SC	SC
Dickerson et al. 2014	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Dickerson et al. 2018	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Eskandarzadeh et al. 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Eslami Shahrbabaki et al. 2020	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Ghaderi et al. 2019	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Ghorbani et al., 2018	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Huang et al. 2022a	LOW	SC	SC	LOW	LOW	LOW	SC
Huang et al. 2022b	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Ho et al. 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Jamilian et al. 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Kao et al. 2019	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Kumperscak et al., 2020	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Majeed et al., 2018	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Miyaoka et al., 2018	SC	SC	SC	LOW	LOW	SC	SC
Mujahid et al., 2022	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Nova et al., 2006	LOW	SC	SC	LOW	LOW	LOW	SC
Reininghaus et al., 2020a	LOW	LOW	LOW	SC	LOW	LOW	LOW
Reiter et al., 2020	LOW	LOW	LOW	SC	LOW	LOW	LOW
Rudzki et al., 2019	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Saccarello et al., 2020	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Schaub et al., 2022	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Schneider et al., 2023	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Sepehrmanesh et al., 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Severance et al. 2017	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Skott et al., 2020	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Solis et al., 2002	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Tian et al. 2023	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Tomasik et al. 2015	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Trombetti et al., 2016	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Vaghef-Mehrabany et al., 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Vaghef-Mehrabany et al., 2023	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Wu et al. 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Žaja et al., 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Zeng et al. 2022	LOW	LOW	LOW	LOW	SC	SC	LOW
Zhang et al., 2021	LOW	LOW	LOW	LOW	LOW	SC	LOW

Abbreviations: RoB 2 = Revised Cochrane risk-of-bias tool for randomized trials, SC = some concerns.

of psychobiotics translate also onto patients' daily functioning. Only one trial (Skott et al., 2020) assessed functioning in ADHD patients but there were no between-group differences after the intervention with a synbiotic.

Regarding other kinds of symptoms associated with psychiatric disorders, a probiotic was found to have an indirect improvement in autonomic response to stress, as there was a larger increase in heartbeats per minute during the TTST task in the placebo group, in individuals with PTSD and comorbid mild head trauma (Brenner et al., 2020). This is a stress responsivity standard laboratory assessment used in individuals with mental health conditions (Lemyre and Tessier, 2003; Gold et al., 2004).

4.2. *Effects on biochemical parameters and biomarkers*

Several trials examined metabolic, biochemical, molecular, and other biological outcomes after treatment with psychobiotics and fermented foods. Three studies reported benefits for glucose metabolism as probiotics supplementation was associated with decreased fasting glucose, reduced insulin serum levels or reduced insulin resistance. Of

Table 3
Risk of bias assessment of non-randomized studies - ROBINS-I.

Reference	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Bambling et al., 2017	HIGH	LOW	SC	LOW	LOW	SC	HIGH	HIGH
Chen et al., 2021	SC	LOW	SC	LOW	LOW	SC	LOW	SC
Okubo et al., 2019	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Otaka et al., 2021	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Reininghaus et al., 2020b	LOW	LOW	LOW	LOW	LOW	SC	LOW	LOW
Reininghaus et al., 2020c	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Wallace et al., 2021	LOW	LOW	LOW	LOW	LOW	SC	LOW	LOW
Yang et al., 2021	SC	LOW	LOW	LOW	LOW	SC	SC	SC

Abbreviations: ROBINS-I = Risk of bias in non-randomized studies – of Interventions, SC = some concerns.

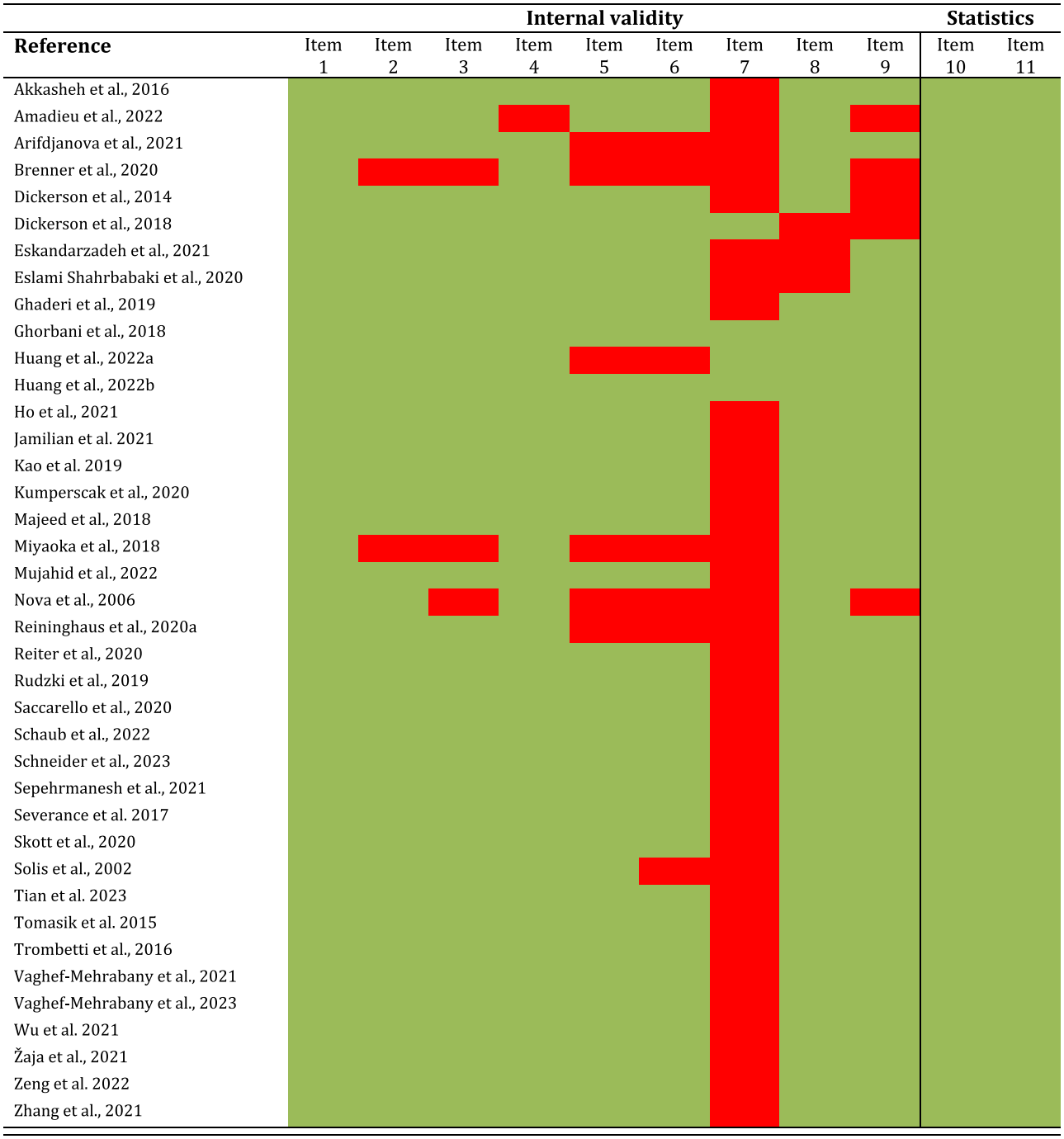
note, they used the same probiotic species, e.g., *Lactobacillus acidophilus and Bifidobacterium bifidum* (Akkasheh et al., 2016; Ghaderi et al., 2019; Jamilian and Ghaderi, 2021). These results converge with meta-analytic evidence that the consumption of probiotics in general may confer modest benefits to improve glycemic control in humans (Ruan et al., 2015). Moreover, one trial examining a protein-fortified dairy product in women with anorexia nervosa found an increase in IGF-1 levels in a stratified analysis for some of the periods of the intervention, but not during the whole intervention and follow-up (Trombetti et al., 2016). Fermented foods have gained recognition due to their potential synbiotic capacity as they usually contain probiotics and prebiotics in various combinations, as well as beneficial bacterial metabolites (Aslam et al., 2020). IGF-1 is a biomarker for bone mineral mass loss, which is relevant in anorexia nervosa (Grinspoon et al., 2002).

Many studies also assessed changes in several molecular biomarkers that have been involved in the pathophysiology of mental illnesses, such as biomarkers of inflammation/ immune dysfunction, oxidative stress, and neurotrophins (Müller et al., 2018). In preclinical studies, probiotics have been shown to reduce the levels of pro-inflammatory cytokines such as IL-1 β (Ait-Belgnaoui et al., 2014), IL-6 and TNFα (Ait-Belgnaoui et al., 2012). This represents a relevant approach to gain a better understanding of the pathways contributing to the clinical benefits of psychobiotics in human clinical populations. In studies of SZ, probiotics supplementation has been associated with significant reductions in peripheral levels of the *pro-inflammatory biomarkers* hs-CRP (Ghaderi et al., 2019; Jamilian and Ghaderi, 2021), IL-6 (Mujahid et al., 2022) and TNF-α (Okubo et al., 2019), although not in all studies with probiotics (Tomasik et al., 2015; Kao et al., 2019) or prebiotics (Kao et al., 2019). In ADHD, probiotics were associated with decreased levels of hs-CRP (Sepehrmanesh et al., 2021), and IL-10, IL-12 and TNF-α (Kumperscak et al., 2020). In MDD, probiotics were also related to significant reductions in pro-inflammatory status, indexed by hs-CRP (Akkasheh et al., 2016), IL-6 and TNF- α (Zhang et al., 2021; Arifdjanova et al., 2021), as well as to increased IL-6 gene expression (Reiter et al., 2020). However, negative results were observed with the prebiotic inulin in MDD (Vaghef-Mehrabani et al., 2023) and a single-strain probiotic in PTSD (Brenner et al., 2020). In addition, a multistrain probiotic was not associated with reductions in inflammatory biomarkers (hs-CRP, IL-6) in a small, open study of euthymic patients with BD (Reininghaus et al., 2020b). Collectively, the positive findings converge with the immunomodulatory and anti-inflammatory properties of psychobiotics across health and disease (Da Silva Borges et al., 2020; Kazemi et al., 2020), reinforcing the possibility of selecting psychobiotics based on a defined mechanism of action (Bambury et al., 2018; Long-Smith et al., 2020). Studies of anorexia nervosa also focused on immune parameters. Dairy products containing probiotics were reported to improve IFN-γ levels (Solis et al., 2002; Nova et al., 2006), which hyperproduction leads to inflammatory diseases (De Benedetti et al., 2021). These results are consistent with the involvement of the gut microbiome and the therapeutic potential of fermented foods for anorexia nervosa (Rocks et al., 2021).

Regarding oxidative stress, adults with SZ and children with ADHD showed an increased total antioxidant capacity after receiving a probiotic containing *Lactobacillus and Bifidobacterium* strains (Ghaderi et al., 2019; Jamilian and Ghaderi, 2021; Sepehrmanesh et al., 2021). However, no significant differences with placebo in oxidative stress biomarkers were observed after probiotic intake in patients with MDD (Akkasheh et al., 2016) and BD (Zeng et al., 2022). As for neurotrophins, a significant increase in BDNF levels was shown in AUD patients supplemented with inulin (Amadieu et al., 2022). In addition, a trend towards increased levels of BDNF using a combination of *Lactobacillus ramnosus* and *Bifidobacterium animalis* was reported in SZ (Tomasik et al., 2015). However, a short-term supplementation with a multistrain probiotic did not differ from placebo with regard to changes in BDNF levels in individuals with MDD (Schneider et al., 2023). Overall, these results are in line with the efficacy of psychobiotics to modulate oxidative stress biomarkers and BDNF across several non-psychiatric diseases (Foshati et al., 2022; Naseri et al., 2023). It has been also reported that the antidepressant effects of probiotics may result from increases in neurotrophins and decreases in inflammation, although the evidence is still limited (Nikolova et al., 2021).

In MDD, Rudzki et al. found that *Lactobacillus plantarum* 299 v may decrease kynurenine concentrations and contribute to cognitive performance (Rudzki et al., 2019). The neurotoxic molecules derived from the degradation of tryptophan along the kynurenine are believed to play a significant role in the pathophysiology of MDD (Marx et al., 2021), with strong evidence for microbial regulation of this pathway (Kennedy et al., 2017; Purton et al., 2021). This converges with previous preclinical studies showing that probiotics can improve depressive symptoms (Desbonnet et al., 2008). It is interesting to highlight the implication of some tryptophan catabolites in the immune-inflammatory response that is activated in MDD, BD or SZ (Almulla et al., 2022a,

Table 4
Quality Assessment of Randomized Controlled Trials – PEDro Scale.



Abbreviations: PEDro Scale = Physhiotherapy Evidence Database; Item 1: eligibility criteria were specified; Item 2: subjects were randomly allocated to groups; Item 3; allocation was concealed; Item 4: the groups were similar at baseline regarding the most important prognostic indicators; Item 5: there was blinding of all subjects; Item 6: there was blinding of all therepist who administered the theraphy; Item 7: there was blinding of all assessors who measured at least one key outcome; Item 8: measures of at least one key outcome were obtained for more tan 85% of the subjects initially allocated to groups; Item 9: all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to trear"; Item 10: the results of between-group statistical comparisons are reported for at least one key outcome; Item 11: the study provides both point measured and measures of variability for at least one key outcome.

2022b) although the evidence is mixed (Marx et al., 2021; Brum et al., 2023). Also, the role of BDNF in the modulation of the GBA. BDNF is involved in neuronal plasticity and survival and has been related to the pathophysiology of psychotic and mood disorders (Angelucci et al., 2005; Autry and Monteggia, 2012; Manchia et al., 2022; Travica et al., 2022).

4.3. Limitations

When interpreting the results of the present review, several limitations must be considered. First and foremost, it must be highlighted that the vast majority of studies do not provide information regarding effect size to estimate whether their positive results are clinically significant.

Only Kao et al. (2019), in SZ, Kumperskcak et al., (2020) in ADHD and Tian et al. (2023) in MDD reported significant positive outcomes after intervention with a moderate-large effect size. The rest of the studies reported outcomes as changes in the mean score of different clinical scales and biochemical/biomarker parameters regardless the effect size. This might undermine the statistical power of the studies and diminish the clinical relevance of the findings.

Beyond that, there are other limitations that must be taken into account. Firstly, the effects of probiotics are likely strain-specific and there is much heterogeneity in the probiotics and prebiotics used in each study. Some examined a single probiotic strain (Miyaoka et al., 2018; Rudzki et al., 2019; Okubo et al., 2019; Otaka et al., 2021; Chen et al., 2021; Brenner et al., 2021; Žaja et al., 2021; Kumperscak et al., 2021; Wu et al., 2021; Ho et al., 2021) while many trials used multiple species. Indeed, the variability in the duration of use and dose of different bacterial strains and strain cocktails have previously been acknowledged as important contributors to heterogeneity in results in other disorders like IBS, and as a complicating factor in the evaluation by meta-analysis of efficacy (Mazurak et al., 2015). The rationale for the selection of specific strains is also not often clearly articulated. Moreover, several studies combined a probiotic with nutraceuticals such as vitamin D (Ghaderi et al., 2019), biotin (Reiter et al., 2020; Reininghaus et al., 2020a), selenium (Jamilian and Ghaderi, 2021), magnesium orotate (Bambling et al., 2017) or SAMe (Saccarello et al., 2020) and none of those studies included a control group with the nutraceutical only. Therefore, their results are not completely free from bias. Also, the varying doses of the same psychobiotics supplement used across studies might explain the different results. For instance, Vaghef-Mehrabany et al. did not find any significant benefits with inulin 10 mg, while other studies suggest that higher doses might have influenced these outcomes (Causey et al., 2000; Vaghef-Mehrabany et al., 2021).

Second, there is evidence that diet, smoking, substance misuse, physical exercise or sleep may influence the composition of human gut microbiota and thus confound the results of psychobiotics trials (Donoso et al., 2023); however, few studies (Okubo et al., 2019) consider dietary and other lifestyle behaviours of patients as relevant variables that may influence treatment response. Third, many studies have a limited number of participants. Indeed, only two studies recruited more than 100 subjects (Arifdjanova et al., 2020; Skott et al., 2020) and three of them have less than 20 (Bambling et al., 2017; Chen et al., 2021; Otaka et al., 2021). Fourth, the duration of the supplementation is also heterogeneous across studies and seven have a short intervention period of 4 weeks or less (Reiter et al., 2020; Reininghaus et al., 2020a; Ho et al., 2021; Schaub et al., 2022; Amadieu et al., 2022; Schneider et al., 2023). The lack of significant outcomes in some trials might likely result from supplementation falling short of a critical duration to achieve a meaningful impact on the human brain and MGBA functioning (Ng et al., 2023). Also, there is not a current consensus regarding the optimal duration of these interventions as this is still a developing area (Wallace and Milev, 2017; Mörkl et al., 2020). Fifth, probiotics and prebiotics are frequently used as an adjuvant therapy. In most studies, previous or co-adjuvant psychopharmacologic treatments are heterogeneous. In fact, as other previous meta-analysis have pointed out, antidepressants might have antimicrobial effect and may interact with probiotics (Chait et al., 2020; Nikolova et al., 2021). Sixth, the use of different instruments to assess the severity of symptoms in each disorder is also heterogeneous. For instance, depressive symptoms are measured by clinician-rated scales or self-reported with questionnaires, such as Beck Depression Inventory (BDI), Children Depression Scale (CDI), Hamilton's Depression Rating Scale (HDRS), Quick Inventory of Depression Symptomatology – Self Reported – 16 items (QIDS-SR16) or Montgomery-Adsberg Depression Rating Scale (MADRS). Seventh, given the variety of diagnoses covered in this review, the studies have different designs and assess different variables. Then, even if some of the studies used the same probiotic at the same dosage, results are difficult to compare. For instance, Wu et al. and Ho et al. both used *Lactobacillus plantarum* PS128 but they did not assess the same outcomes (Ho et al., 2021; Wu et al., 2021). Eighth, despite this review covers a wide scope of psychiatric conditions in this topic, it excludes conditions such as autistic spectrum disorders, dementia and other neurodegenerative disorders. Lastly, information regarding the probiotic used, the strain or the dosage was lacking in some studies (Arifdjanova et al., 2021; Yang et al., 2021; Huang et al., 2022a, 2022b; Mujahid et al., 2022; Zeng et al., 2022). Altogether, the variety of specific psychobiotics, clinical diagnoses, study outcomes and assessments precluded conducting a meta-analysis of current evidence.

Despite these limitations, the present systematic review has several strengths. First, we believe that our search was comprehensive in terms of the number of accessed bibliographic databases, interventions (all currently considered as psychobiotics) and diseases. Indeed, we systematically included all psychiatric diagnoses, except ASD and dementia. To our knowledge, the present review includes the highest number of clinical trials and the widest scope of psychiatric conditions in this topic. For instance, eleven trials on SZ and five trials in BD were identified, whereas recent systematic reviews of pre/probiotics in these diseases included only three and two trials, respectively (Minichino et al., 2021; Obi-Azuike et al., 2023). Second, our search was restricted to clinical populations fulfilling strict diagnostic criteria. We purposely excluded clinical trials examining psychobiotics in healthy populations. In doing that, we believe that the present results are more meaningful to inform clinical use. Third, the efficacy of psychobiotics was examined through a wide range of outcomes including clinical variables (core psychiatric symptoms as well as neurocognitive performance and physical parameters), and a wide set of biological markers. Lastly, we believe this review may contribute to current clinical guidelines (Sarris et al., 2022).

4.4. Future research

Future research might try to replicate the results of those studies showing more consistent outcomes using the same psychobiotics intervention during longer periods of supplementation and in larger samples. We encourage investigators and scientific societies to define protocols in order to standardize these clinical trials. Adjuvant psychopharmacologic treatment should be ideally standardized and diet/nutrition and other lifestyle behaviours must be always taken into account as potential confounders. The study population should be properly phenotyped and defined and interventions might be addressed to specific subtypes of diagnosed patients, e.g., study stratification based on inflammation cutoffs in studies with strains that have anti-inflammatory or immunomodulatory potential. There should be different control groups with healthy subjects for both intervention and placebo groups in the studies. In interventions using different co-adjuvants, different study arms should be considered in order to avoid biases. Patient-centered outcomes, especially measures of social functioning, should be included in future trials. In addition, molecular and other biological markers should be studied in tandem with clinical outcomes in order to elucidate the mechanisms underlying the potential benefits of psychobiotic interventions for psychiatric disorders.

There are also some gaps in the current evidence that should be considered. So far, no clinical trials have been conducted on conditions such as social anxiety disorder, despite preliminary evidence of microbiome changes (Butler et al., 2023). The same applies to substance use disorders other than AUD, despite growing preclinical evidence supporting that the manipulation of MGBA with pre and probiotics is a promising strategy for substance addiction (Qin et al., 2021). Furthermore, most of the studies do not take into account the distinct inflammation profiles between men and women when interpreting their results, as previously noted in some prior research. Certainly, this is a factor that should be considered in future investigations (Vemuri et al., 2019; Kim et al., 2023). New next-generation probiotics may also be considered in future studies (O'Toole et al., 2017). Finally, besides the

use of the specific psychobiotics evaluated here, other MGBA-regulating interventions, such as whole diets (Jacka et al., 2017; Berding et al., 2023) and faecal microbiota transplantation (Green et al., 2023; Keubler et al., 2023; Vasiliu, 2023), should be more widely studied.

5. Conclusions

MDD is the psychiatric disorder that has received most research attention so far.

Except for MDD, where probiotics are listed in the current World Federation of Societies of Biological Psychiatry (WFSBP) treatment guidelines with nutra- and phytoceuticals, (Sarris et al., 2022), current evidence is scarce to support interventions with prebiotics, synbiotics and fermented foods in the treatment of other mental disorders. Potential benefits of psychobiotics for core and non-core symptomatic outcomes as well as neurocognitive functioning have been described across disorders. In addition, several studies found an improvement in immune and inflammatory biomarkers, which could explain those benefits and may be particularly relevant to patient populations with comorbid inflammatory diseases. Future research should focus on generating evidence for those less-studied disorders through larger-scale studies and consider dietary and other lifestyle behaviours of patients as they can influence the gut microbiota composition.

CRediT authorship contribution statement

Carlos Ribera wrote the first draft of the paper and contributed to literature research, risk of bias and quality assessment, analyses and interpretation. Vicent Balanzá-Martínez contributed to literature research, analyses and interpretation. Joan Vicent Sánchez-Ortí assessed the risk of bias and quality of the different studies. Wolfgang Marx, Gerard Clarke and Sabrina Mörkl contributed to the interpretation of the results and discussion and reviewed the manuscript.

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