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Should we consider microbiota-based interventions as a novel therapeutic strategy for schizophrenia? A systematic review and meta-analysis

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ABSTRACT

Schizophrenia is a chronic psychiatric disorder characterized by a variety of symptoms broadly categorized into positive, negative, and cognitive domains. Its etiology is multifactorial, involving a complex interplay of genetic, neurobiological, and environmental factors, and its neurobiology is associated with abnormalities in different neurotransmitter systems. Due to this multifactorial etiology and neurobiology, leading to a wide heterogeneity of symptoms and clinical presentations, current antipsychotic treatments face challenges, underscoring the need for novel therapeutic approaches. Recent studies have revealed differences in the gut microbiome of individuals with schizophrenia compared to healthy controls, establishing an intricate link between this disorder and gastrointestinal health, and suggesting that microbiota-targeted interventions could help alleviate clinical symptoms. Therefore, this meta-analysis investigates whether gut microbiota manipulation can ameliorate psychotic outcomes in patients with schizophrenia receiving pharmacological treatment. Nine studies (n = 417 participants) were selected from 81 records, comprising seven randomized controlled trials and two open-label studies, all with a low risk of bias, included in this systematic review and meta-analysis. The overall combined effect size indicated significant symptom improvement following microbiota treatment (Hedges' g = 0.48, 95% CI = 0.09 to 0.88, p = 0.004, I^2 = 62.35%). However, according to Hedges' g criteria, the effect size was small (approaching moderate), and study heterogeneity was moderate based on I^2 criteria. This review also discusses clinical and preclinical studies to elucidate the neural, immune, and metabolic pathways by which microbiota manipulation, particularly with *Lactobacillus* and *Bifidobacterium* genera, may exert beneficial effects on schizophrenia symptoms via the gut-brain axis. Finally, we address the main confounding factors identified in our systematic review, highlight key limitations, and offer recommendations to guide future high-quality trials with larger participant cohorts to explore microbiome-based therapies as a primary or adjunctive treatment for schizophrenia.

Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia; B-GOS®, Bimuno®-Galacto-oligosaccharides; BPRS, Brief Psychiatric Rating Scale; CES, Combined Effect Size; CNS, Central Nervous System; GABA, Gamma-Aminobutyric Acid; GBA, Gut-Brain Axis; IBS, Irritable Bowel Syndrome; IDO, Indoleamine 2,3-Dioxygenase; Ig, Immunoglobulin; OL, Open-Label; PANSS, Positive and Negative Syndrome Scale; PAMP, Pathogen-Associated Molecular Pattern; RCT, Randomized Controlled Trial; SCFAs, Short-Chain Fatty Acids; SD, Standard Deviation; SMD, Standardized Mean Difference; SZ, Schizophrenia; TLR, Toll-Like Receptor; Treg, Regulatory T Cells.

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1. Introduction

Schizophrenia (SZ) is a complex and disabling disorder affecting approximately 24 million people worldwide, or about 1% of the population (Marder and Cannon, 2019; Ferrari et al., 2024; Galletly et al., 2016; Keepers et al., 2020). Most patients are diagnosed by the age of forty, with initial symptoms typically appearing in late adolescence or early adulthood (Galletly et al., 2016; Keepers et al., 2020; McCutcheon et al., 2020). Clinically, SZ is characterized by a range of clinical features that can be broadly categorized into several symptom domains (Galletly et al., 2016; Keepers et al., 2020; Remington et al., 2017), including positive (e.g., hallucinations, delusions), negative (e.g., blunted affect, alogia, avolition), and cognitive symptoms, all of which significantly impair functioning and quality of life (Kantrowitz et al., 2023a). Patients with SZ have a life expectancy that is 15–20 years shorter than the general population (Correll et al., 2022a; Ringen et al., 2014) with the metabolic and other side effects of antipsychotics likely contributing to this reduced life span (Kantrowitz et al., 2023b; Huhn et al., 2019).

Unfortunately, currently available antipsychotics do not adequately address primary and persistent negative symptoms (Correll and Schooler, 2020; Kantrowitz, 2017) or cognitive deficits (Saleh et al., 2023) in SZ. Mean recovery rates for patients diagnosed with SZ have remained stable or even declined over time, from before 1941 to after the introduction of atypical antipsychotics, with only 10%–20% of patients achieving full recovery (Jaaskelainen et al., 2013; Taylor and Jauhar, 2019). Additionally, 10%–30% of patients with SZ are refractory to antipsychotic drugs, and another 50%–60% exhibit only a partial response (Kane et al., 2019). As a result, the chronic nature of the disorder, its severe functional impairments, and the limited efficacy of current pharmacological treatments position SZ as one of the leading causes of disability globally, contributing significantly to disability-adjusted life years and driving worldwide efforts to optimize its treatment (Ferrari et al., 2024; Fleischhacker et al., 2014; Dudzik et al., 2024).

Recent advancements in high-throughput genomic sequencing have revealed the complex interplay between the enteric microbiome and the central nervous system (CNS) and its role in psychiatric disorders (Petra et al., 2015; Montiel-Castro et al., 2013; Bistoletti et al., 2020; Cryan et al., 2019; Westfall et al., 2017; Hamamah et al., 2022). This connection occurs through bi-directional communication between gut microbes and the brain, commonly called the gut-brain axis (GBA), involving immunological, endocrine, vagus nerve, and metabolic pathways (Cryan et al., 2019; Dinan et al., 2013; Grenham et al., 2011; Clarke et al., 2014; Pedrazzi et al., 2023, 2024). Indeed, functional gastrointestinal disorders such as irritable bowel syndrome (IBS), gastroesophageal reflux disease, and celiac disease frequently coexist with psychiatric illnesses (Gupta et al., 1997; Severance et al., 2015). Moreover, patients diagnosed with these gastrointestinal disorders have a higher incidence of neuropsychiatric conditions, such as anxiety and depression (Person and Keefer, 2021; Yan et al., 2023; Wu, 2011; Pinto-Sanchez et al., 2015). A recent genome-wide association study demonstrated that patients with psychiatric and gastrointestinal phenotypes share considerable genetic overlap with IBS-related variants (Tesfaye et al., 2023). Specifically, 98% of variants influencing bipolar disorder and 93% affecting SZ are also present in the IBS phenotype. Additionally, more than half of the shared variants between IBS and bipolar disorder (55%) and SZ (56%) show a concordant effect, suggesting their involvement in similar phenotypic traits (Tesfaye et al., 2023).

Regarding SZ, metagenomic analyses have revealed significant differences in the gut microbiome of SZ patients compared to matched healthy individuals, as well as taxonomic variations depending on treatment responses and exposure to different classes of antipsychotics (Murray et al., 2023; Stiernborg et al., 2024; Tsamakis et al., 2022; Schwarz et al., 2018). Additionally, gut microbiome composition and functional profiling in patients with first-episode psychosis suggest that this condition may be associated with gut dysbiosis—that is, an imbalance in the composition of gut microbiota, where beneficial microorganisms are reduced and potentially harmful ones are increased (Cryan et al., 2019)—, which could precede weight gain in these patients (Sen et al., 2024). Although the mechanisms are not yet fully understood, these findings collectively indicate that the enteric microbiome, alongside the host's genetic background and environmental factors, plays a role in the pathophysiology of SZ (Andrioaie et al., 2022). For example, emerging evidence suggests that disruptions in immunological training during early life, caused by enteric dysbiosis, may interact with the host's genetic background and environmental factors during neurodevelopment, potentially contributing to the onset of the disorder (Kelly et al., 2017).

Thus, the potential benefits of modulating the gut microbiome have been investigated over the past few decades as a novel therapeutic target for the treatment of psychiatric disorders (Mosquera et al., 2024; Ng et al., 2019; Minichino et al., 2021). Various dietary supplements, including *(1)* probiotics: live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Mazziotta et al., 2023); *(2)* prebiotics: non-digestible food ingredients that selectively stimulate the growth or activity of beneficial microorganisms in the gut (Gibson and Roberfroid, 1995); and *(3)* symbiotics: combinations of probiotics and prebiotics designed to have synergistic effects, enhancing the survival and colonization of beneficial microorganisms in the gastrointestinal tract (Fekete et al., 2024); have been formulated and have demonstrated specific benefits for mental health, including improvements in cognition, mood, and social behavior (Westfall et al., 2017; Dinan et al., 2013; Fekete et al., 2024; Ansari et al., 2023; Kao et al., 2019; Burokas et al., 2017; Ng et al., 2018).

Several clinical studies since 2014 have investigated gut microbiome modulation as an alternative or adjuvant treatment for SZ (Kao et al., 2019; Dickerson et al., 2014; Severance et al., 2017; Tomasik et al., 2015; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Kelly et al., 2021; Okubo et al., 2019), and two meta-analyses were conducted on the topic in 2019 (Ng et al., 2019) and 2021 (Minichino et al., 2021). However, while the first included only three studies and used follow-up data (Ng et al., 2019), which may introduce bias due to the repetition of the same patient sets (Tendal et al., 2011; Hozo et al., 2005), the second meta-analysis considered more generic treatments (Minichino et al., 2021), such as the use of antibiotics like minocycline, which can cross the blood-brain barrier and exert effects on the CNS independently of the microbiota (Grada et al., 2022; Kim and Suh, 2009). Since then, new studies have been published on the subject, allowing for a more comprehensive analysis to investigate potential effects, as well as to describe current research trends and their limitations.

Therefore, this meta-analysis aims to identify studies in literature that have used microbiome-based interventions to ameliorate clinical symptoms in patients undergoing pharmacological treatment for SZ and to analyze whether this approach can yield positive effects in symptom improvement. It also seeks to discuss the characteristics and limitations of the available studies, guiding future research to optimize experimental designs and contribute further to this emerging field. Additionally, preclinical studies are reviewed to explore the potential underlying mechanisms involving the GBA in SZ.

2. Methodology

2.1. Literature search

This study was registered in PROSPERO (CRD42023494067) and conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2010) and the recommendations for carrying out a meta-analysis (Forero et al., 2019). A searchable review question was structured using the PICO tool as follows: Population = Humans diagnosed with SZ (according to the scales

described in the "Diagnostic and Symptoms Instruments" section); Intervention = Direct manipulation of the microbiota (Probiotic, Prebiotic, Symbiotic, Fecal Microbiota Transplantation); Control = No manipulation of the microbiota; Outcome = Primary follow-up scales for SZ. A computerized literature search was performed in the PubMed, Medline, and Embase databases seeking original articles investigating the effect of human gut microbiota manipulation on scores in the primary severity quantifying instruments for SZ using the search strategy described in Supplementary Table 1.

2.2. Eligibility criteria and screening

Clinical studies in any language, from any date, and published in any journal were included if patients were diagnosed with SZ based on diagnose scales applied before and after the intervention. Included studies treated patients with specific microbiota manipulations using prebiotics, probiotics, or symbiotics. Studies that performed microbiota manipulation in conjunction with another co-treatment were allowed, provided that the method of microbiota manipulation was one of those previously mentioned. Microbiota manipulations not targeting specific microorganisms, such as the use of antibiotics, dietary manipulations, exercise, or pharmacological interventions, were excluded. Eligible study designs encompassed Randomized Clinical Trials (RCTs), Non-randomized Controlled Clinical Trials, Open Label Studies (OL), and Phase I, II, III, and IV Clinical Trials. Observational Studies, Cohort Studies, Case-Control Studies, Cross-Sectional Studies, and Longitudinal Studies were not considered, nor were studies unrelated to SZ or those that were reviews or meta-analyses.

2.3. Diagnostic and follow-up instruments

The selected studies were required to diagnose patients according to the DSM or ICD criteria applicable at the time of data collection (Mason et al., 1997; Biedermann and Fleischhacker, 2016). Previous versions of these diagnostic manuals (such as DSM-IV) were also accepted, as no publication year restrictions were applied during our database search. For patient follow-up, studies had to use and report data from at least one of the following scales: Positive and Negative Syndrome Scale (PANSS), Brief Assessment of Cognition in Schizophrenia (BACS), or Brief Psychiatric Rating Scale (BPRS). According to our PROSPERO registration, other scales could also be used for follow-up, such as the Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms, Structured Clinical Interview for DSM Disorders, Global Assessment of Functioning, and Psychotic Symptom Rating Scales. However, only the PANSS, BPRS, and BACS scales were used in the studies found in our analysis, which were explored in greater depth.

The PANSS is a comprehensive tool designed to measure the severity of positive, negative, and general psychopathology symptoms in SZ (Kay et al., 1987). It consists of 30 items, divided into three subscales: Positive Symptoms (7 items), Negative Symptoms (7 items), and General Psychopathology (16 items)(Shafer and Dazzi, 2019; BELL et al., 1992a). The BPRS is commonly used to assess the severity of psychiatric symptoms, including those observed in SZ, and comprises 18 items that address a range of symptoms such as depression, anxiety, hallucinations, and unusual behavior (Hofmann et al., 2022). Compared to the BPRS, the PANSS is distinguished by a significantly larger number of items that more clearly define and measure negative symptoms, as well as enough items to more accurately identify a disorganization factor, since PANSS was developed by combining the 18 items of the BPRS and other 12 items from the Psychopathology Rating Scales (Shafer and Dazzi, 2019). The BACS is specifically designed to assess cognitive function in individuals with SZ (Keefe, 2004; Keefe et al., 2006). It includes tests that evaluate various cognitive domains, such as verbal memory, working memory, motor speed, verbal fluency, attention, and executive functions (Keefe, 2004).

2.4. META-ANALYSIS outcomes

As the primary outcome of our meta-analysis, we analyzed the most recent overall scores available from the follow-up scales after the conclusion of treatment, aiming to investigate the lasting impacts of microbiota manipulation on patient symptoms. When domain-specific data (e.g., positive, negative, general, and cognitive symptoms) were reported separately, we performed stratified analyses. In cases where a study employed more than one scale, both were reported. However, to avoid bias in the meta-analysis including multiple data points from the same study (Hassib et al., 2023), we prioritized data from the most representative scale, following this hierarchy: PANSS > BPRS > BACS. This ranking reflects the degree of domain specificity and relevance to the overall symptomatology of SZ (Shafer and Dazzi, 2019; BELL et al., 1992a; Hofmann et al., 2022; Keefe et al., 2006; BELL et al., 1992b).

2.5. Assessment of study quality

Four pairs of independent reviewers (L.H., B.V., S.H., J.P., I.A., Y.S., A.S., and A.K.) assessed the risk of bias in the studies using Cochrane tools. Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was employed for RCTs (Sterne et al., 2019), while the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool was used for OLs (Sterne et al., 2016). In case of disagreement between members of the group, a third reviewer from another pair was consulted to make the final decision. For RCTs, studies with a high risk of bias would be excluded, while for OLs, only those with a low risk of bias were included. This decision was made because the ROBINS-I tool considers that only OL studies with a low risk of bias have a similar quality to RCTs (Sterne et al., 2016).

2.6. Data extraction, global and stratified meta-analyses

Quantitative data extraction was conducted by pairs of independent reviewers (L.H., B.V., S.H., J.P., I.A., Y.S., A.S., and A.K.) using a predefined data extraction sheet. This sheet encompassed various components, including the study name and year of publication, study design (RCTs or OLs), participant group design (Dependent (DEP) or Independent (IND)), treatment details (type, duration, and co-treatment), severity quantifying instruments used for condition follow-up, patient age range, control group data (n, severity quantifying instrument score (mean ± SD)), treated group data (n, severity quantifying instruments score (mean ± SD)), and microbiota characterization data (technique, treatment-induced alterations). When patient data were collected at multiple time points, we consistently extracted the data from the furthest time point from the beginning of treatment. This approach enables us to explore the potential long-lasting effects of the treatment.

Meta-analysis calculations and figures were conducted using the Meta-essentials Software developed by Suurmond, van Rhee, and Hak (Suurmond et al., 2017). Mean and standardized mean difference (SD) were used for each primary outcome. In cases where SD was not provided in tables, it was derived from raw data in supplementary materials or calculated from the standard error of the mean and participant numbers. The data input into the Meta-essentials' software was structured such that improvements in scale scores (indicating symptom improvement) shifted the graph to the right, while worsening scores (indicating symptom deterioration) turned it to the left, a methodology previously described by our group (Hassib et al., 2023). Additionally, studies were stratified by design (RCT or OL) for subgroup meta-analysis. The random effects model was selected to estimate the combined effect size (CES) using Hedge's g (G) with a 95% confidence interval (95% CI), two-tailed p-value (P), and heterogeneity (I^2) due to the observed heterogeneity among studies (Rodrigues and Klarmann Ziegelmann, 2010; Hak et al.).

CES values were classified as follows: very small (SMD = up to 0.2), small (SMD = between 0.2 and 0.5), moderate (SMD = 0.5–0.8), and

large (SMD higher than 0.8) (Hassib et al., 2023)' (Sullivan and Feinn, 2012). I^2 values ranging from 0% to 100% indicate the proportion of heterogeneity, which is interpreted as low (up to 25%), moderate (between 25% and 75%), or high (above 75%). A 95% confidence interval (95% CI) that excludes the null is considered significant or conclusive, while a 95% CI that includes the null is considered inconclusive. P-values lower than alpha (<0.05) are interpreted as significant.

3. Results

3.1. Search results and bias risk analysis

Out of the 81 articles identified in the database search strategy, 59 underwent screening of their titles and abstracts after removing 22 duplicates. Following this process, nine studies that met the inclusion criteria were included in the present meta-analysis (Kao et al., 2019; Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Kelly et al., 2021; Okubo et al., 2019) (Fig. 1), accumulating 417 participants. All nine studies demonstrated a low risk of bias, with seven RCTs assessed using the ROB2 tool (Kao et al., 2019; Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021) (Supplementary Table 2) and two OLs assessed using the ROBINS-I tool (Kelly et al., 2021; Okubo et al., 2019) (Supplementary Table 3).

3.2. Descriptive analysis

The characteristics of the selected articles on SZ are presented in Table 1.

Among the articles examined, 77.5% employed the PANSS (Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Okubo et al., 2019) tool for assessing patients' symptoms, with the remaining 22.5% opting for the BACS (Kao et al., 2019) or BPRS (Kelly et al., 2021) (see Fig. 2A). In terms of study design, the majority (77.5%) were randomized controlled trials (RCTs) (Kao et al., 2019; Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi

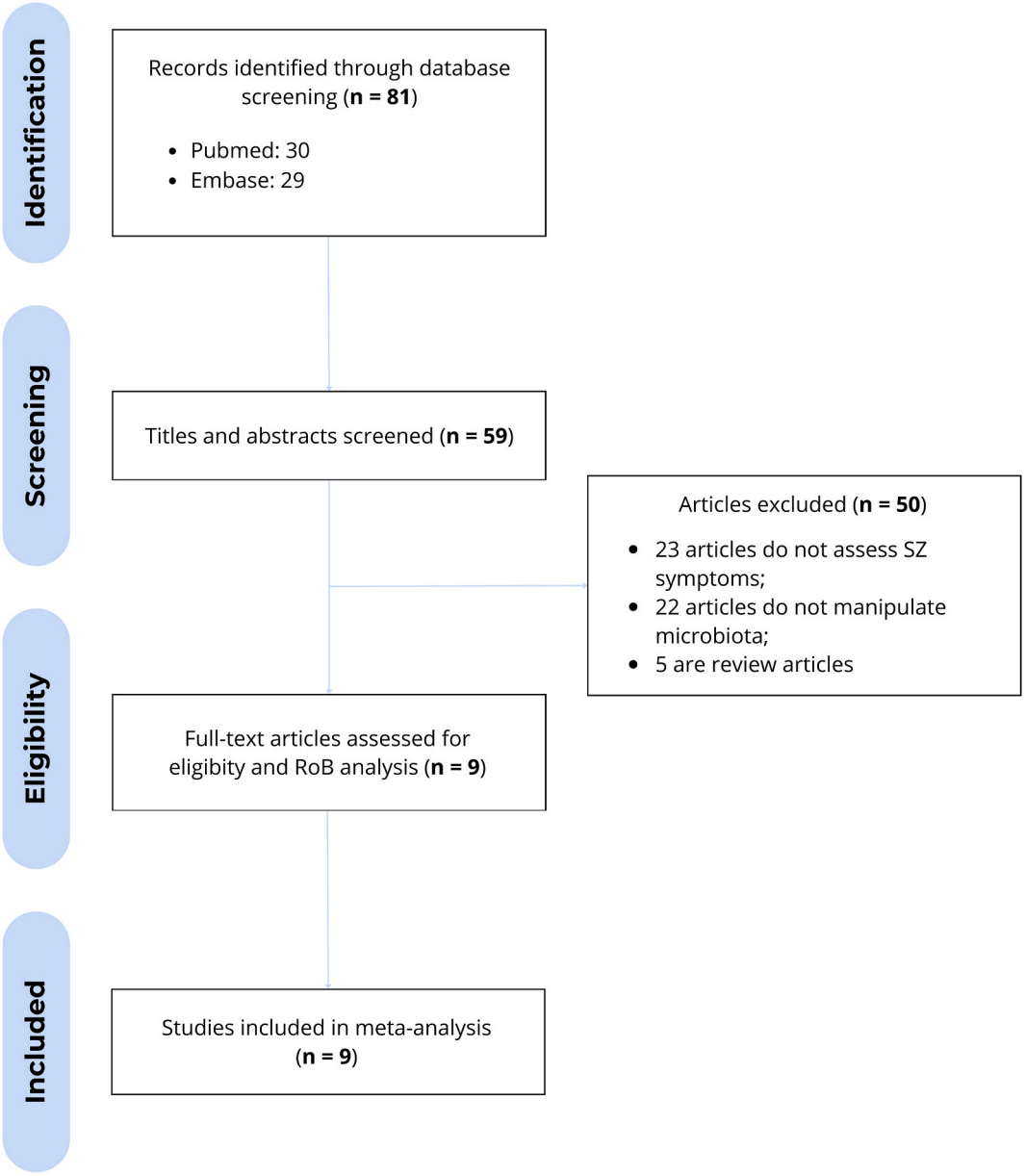

Fig. 1. PRISMA flow diagram of the study.

Table 1
Data collection from studies on Schizophrenia.

Study	Study Design	Groups Design	Treatment (Type, Duration)	Co-treatment	Baseline BMI CTL (kg/m^2)	Baseline BMI TRT (kg/m^2)	Baseline BMI P	Substance Use	Diagnose Scale	Follow-Up Scale (s)	Therapy resistance history	Patients Age	Patients Sex	Patients Country/Region	Domains of Predominant Symptoms at Baseline	Follow-Up Scale Overall Score: Control Group n_i score (Mean±SD)	Follow-Up Scale Overall Score: Treatment Group n_i score (Mean±SD)	Follow-Up Scale Positive Symptoms: Control Group n_i score (Mean±SD)	Follow-Up Scale Positive Symptoms: Treatment Group n_i score (Mean±SD)	Follow-Up Scale Negative Symptoms: Control Group n_i score (Mean±SD)	Follow-Up Scale Negative Symptoms: Treatment Group n_i score (Mean±SD)	Follow-Up Scale General Symptoms: Control Group n_i score (Mean±SD)	Follow-Up Scale General Symptoms: Treatment Group n_i score (Mean±SD)	Microbiota Characterization (Techniques; Alterations)
Dickerson, 2014	RCT	IND	Probiotic Blend; 14 weeks	Antipsychotics	N/P			Patients diagnosed with substance dependence or substance use disorder (DSM-IV), or with a history of intravenous drug use, were excluded	DSM-IV	PANSS	NI	18-65 years	Male/Female	United States	Absence of dominance between domains according to the PANSS	27; F value: 1.28	31; F value: 1.28	27; F value: 1.13	31; F value: 1.13	27; 1.80	31; 1.80	27; 0.99	31; 0.99	N/P
Ghaderi, 2019	RCT	IND	Probiotic Blend; 12 weeks	Vitamin D; Antipsychotics	24.5±3.7	23.1±2.8	ns	Any patient diagnosed with substance or alcohol addiction (except caffeine or nicotine) within the last 6 months of screening were excluded	DSM-IV-TR	PANSS; BPRS	NI	25-65 years	Male/Female	Iran	Absence of dominance between domains according to the PANSS	30; 85.5 ± 14.1	30; 78 ± 11.3	30; 19.3 ± 5.3	30; 22.3 ± 4.8	30; 27.0 ± 3.8	30; 23.9 ± 5.0	30; 39.2 ± 9.5	30; 31.7 ± 5.7	N/P
Jamilian, 2021	RCT	IND	Probiotic Blend; 12 weeks	Selenium	24.5±3.0	25.1±4.4	ns	NI	DSM-IV-TR	PANSS; BPRS	NI	18-60 years	Male/Female	Iran	Absence of dominance between domains according to the PANSS	26; 79.2 ± 9.3	25; 77.8 ± 10.8	26; 18.0 ± 4.2	25; 19.5 ± 4.6	26; 26.3 ± 3.7	25; 26.9 ± 3.7	26; 34.9 ± 6.5	25; 31.4 ± 8.4	N/P
Kao, 2019	RCT	IND	Prebiotic; 12 weeks	Antipsychotics	32.5±3.4	32.3±3.5	ns	NI	NI	BACS	NI	18-60 years	Male/Female	United Kingdom	NI	25; 33.83 ± 7.5	24; 36.17 ± 6.86	N/P	N/P	N/P	N/P	N/P	N/P	N/P
Kelly, 2021	OPL	DEP	Probiotic; 2 weeks	Antipsychotics	N/P			All participants were cigarette smokers	DSM-5	BPRS	All participants were considered treatment resistant	18-64 years	Male/Female	United States	NI	5; 14 ± 0.9	5; 12.2 ± 1.5	N/P	N/P	N/P	N/P	N/P	N/P	N/P
Mujahid, 2022	RCT	IND	Probiotic (NI); 6 weeks	Risperidone	21.5±3.2	225±4.4	ns	Patients who use psychotropic drugs, alcohol, and narcotics were excluded.	DSM-5	PANSS	NI	20-45 years	Male/Female	Indonesia	NI	21; 82.9 ± 9.59	21; 72.2 ± 6.28	NI	NI	NI	NI	NI	NI	N/P
Okubo, 2019	OPL	DEP	Probiotic SS; 4 weeks	Antipsychotics	25.7±5.4 *			Patients who consumed significant doses of alcohol (i.e., > 500 mL of beer per day) or had a history of drug use (excluding nicotine) were excluded. Among the 29 participants, 11 were smokers.	DSM-5	PANSS; BPRS	NI	>20 years	Male/Female	Japan	NI**	29; 15 ± 2	29; 13 ± 2	NI	NI	NI	NI	NI	NI	16s MG; Increased levels of Parabacteroides observed in responsive patients.
Severance, 2016	RCT	IND	Probiotic Blend; 14 weeks	Antipsychotics	32.2+6.6	31.7+5.3	ns	Patients with a history of intravenous drug use and a diagnosis of substance abuse or dependence in the past 3 months (excluding nicotine) were excluded. Twenty percent of the participants were smokers.	DSM-5	PANSS	NI	18-65 years	Male/Female	United States	NI	26; 67 ± 12	30; 67.1 ± 11.7	NI	NI	NI	NI	NI	NI	N/P
Yang, 2021	RCT	IND	Probiotic Blend; 12 weeks	Olanzapine	21.4±1.6	20.7± 1.7	ns	Patients diagnosed with substance dependence or substance use disorder were excluded	DSM-5	PANSS	NI	18-55 years	Male/Female	China	NI	34; 55.56 ± 8.53	33; 55.33 ± 8.89	NI	NI	NI	NI	NI	NI	N/P

BACS: Brief Assessment of Cognition in Schizophrenia; **BMI**: Body Mass Index; **BPRS**: Brief Psychiatric Rating Scale; **CTL**: Control; **DEP**: Dependents; **IND**: Independents; **MG**: Metagenomics; **NI**: Not Informed; **N/P**: Not Performed; **NS**: Non-Significant; **OPL**: Open-Label; **PANSS**: Positive and Negative Syndrome Scale; **RND**: Randomized; **RCT**: Randomized Controlled Trial; **SS**: Single Strain; **TRT**: Treatment. * Since this is a study with dependent groups (repeated measures design), only a single mean is reported at baseline (prior to treatment). ** This study analyzed and reported only the items from the PANSS scale related to anxiety and depressive symptoms (items 1, 2, 3, 4, and 6 of the general psychopathology subscale), which range from 5 to 35. The BPRS scale was applied only at baseline.

et al., 2019; Mujahid et al., 2022; Yang et al., 2021), contrasting with the 22.5% representing OLs (Kelly et al., 2021; Okubo et al., 2019) (see Fig. 2B). Furthermore, the utilization of independent participant groups was prevalent, accounting for 77.5% of the studies (Kao et al., 2019; Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021), whereas 22.5% relied on dependent groups (Kelly et al., 2021; Okubo et al., 2019), where participants acted as their controls (see Fig. 2D). Regarding microbiota manipulation, 55.5% of the investigations employed blends of probiotics (Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Yang et al., 2021), incorporating multiple microorganisms. Conversely, 11.11% utilized a single strain (Okubo et al., 2019), 11.11% did not specify the probiotic employed (Mujahid et al., 2022), and 22.23% utilized prebiotics (Kao et al., 2019; Kelly et al., 2021) (see Fig. 2C).

3.3. Impact of microbiota-based interventions on schizophrenia symptoms

The overall CES in the meta-analysis (Fig. 3) was significantly associated with improvements in patients' symptoms following gut microbiota treatment via oral administration of probiotics or prebiotics (Hedges g = 0.48, 95% CI = 0.09 to 0.88, p = 0.004, I^2 = 62.35%; Fig. 3 - Green Dots). According to the Hedges g criteria, the effect size was small (close to moderate), and heterogeneity among studies was moderate based on the I^2 criteria. When stratified by study design (RCT or OL), the CES of RCT studies tended towards symptom improvement; however, it did not reach statistical significance (Hedges g = 0.35, 95% CI = −0.04 to 0.74, p = 0.03, I^2 = 53.79%; Fig. 3 - Blue Dots). As only two of the nine studies identified were OL (Fig. 3 - Red Dots), conducting a meta-analysis for this design was not feasible. Similarly, we stratified our analysis based on the type of microbiota manipulation (probiotic blend, single-strain probiotic, or prebiotic) due to the low number of articles in each category.

Only three of the nine studies (Dickerson et al., 2014; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019) reported symptomatology outcomes separately for different domains (positive, negative, and general), rather than providing only an overall result, which poses a significant limitation to our domain-stratified analysis. Based on the available data, no improvement or worsening effect was observed in any of the three domains assessed using the PANSS scale: positive (Hedges' g = −0.21, 95% CI = −1.34 to 0.92, p = 0.43, I^2 = 66.68%), negative (Hedges' g = 0.30, 95% CI = −0.76 to 1.35, p = 0.22, I^2 = 59.97%), or general (Hedges' g = 0.55, 95% CI = −0.23 to 1.33, p = 0.007, I^2 = 43.00%).

Of the nine studies, four were conducted in Western (Kao et al., 2019; Dickerson et al., 2014; Severance et al., 2017; Kelly et al., 2021) countries and five in Eastern (Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Okubo et al., 2019) countries, which have distinct dietary impacts on the gut microbiota, as highlighted by several studies (Govender and Ghaia; Shin et al., 2019; Soldá et al., 2024). As diet is a potential confounding factor, we stratified our analysis according to the participants' ethnic dietary patterns. While no significant improvement or worsening of symptoms was observed when stratified by diet type, we noted that studies involving Eastern patients tended to favor symptom improvement (Hedges' g = 0.58, 95% CI = −0.08 to 1.25, p = 0.015, I^2 = 72.26%) compared with studies involving Western patients (Hedges' g = 0.32, 95% CI = −0.44 to 1.08, p = 0.182, I^2 = 40.98%).

4. Discussion

Several studies have highlighted the critical role of the GBA in mental health, indicating that gut dysbiosis in patients with neuropsychiatric disorders, including SZ, can lead to structural and functional damage not only in the gastrointestinal tract but also at a systemic and central level, thereby exacerbating Severe Mental Illness symptoms (Cryan et al., 2019; Severance et al., 2015; Cani, 2018). Disruption of intestinal homeostasis increases gut permeability, facilitating microbial translocation, triggering local inflammatory responses, and further altering the microbiota, thereby worsening both gastrointestinal and neuropsychiatric symptoms through GBA signaling (Montiel-Castro et al., 2013; Cryan et al., 2019). Current antipsychotic treatments face limitations, with many patients failing to achieve full recovery (Taylor and Jauhar, 2019), and a significant number are either refractory or responding only partially (Kane et al., 2019). Additionally, some patients who respond well to antipsychotics may discontinue treatment due to adverse effects such as weight gain (Dickerson et al., 2014). Therefore, introducing an adjunctive agent with a novel mechanism of action could enable dose reduction of existing medications, improving tolerability (Dudzik et al., 2024; Correll et al., 2022b). Manipulation of the gut microbiota has thus been proposed as a potential strategy to restore microbial composition in SZ patients, to improve gastrointestinal, immunological, metabolic, and cognitive functions (Kao et al., 2019; Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Kelly et al., 2021; Okubo et al., 2019).

4.1. Studies characteristics and confounding factors

Seven out of the nine studies employed the PANSS scale (Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Okubo et al., 2019); however, several studies reported an overall PANSS score by summing the positive, negative, and general symptom sub-scales (Severance et al., 2017; Mujahid et al., 2022; Yang et al., 2021; Okubo et al., 2019). This

approach presents our first limitation, as it diminishes the ability to capture the treatment's impact on specific symptom domains and introduces the risk of bias against interventions that improve certain symptoms while potentially worsening others. For example, a patient showing improvement in positive symptoms but a deterioration in negative symptoms may present minimal change in the overall score.

All studies included in this analysis underwent bias assessment using the appropriate Cochrane tools and were classified as low risk, thereby enhancing the quality and reliability of the results by minimizing the likelihood of distortion due to systematic errors or selection bias. Several factors supported the inclusion of OL studies in the analysis: (1) according to Cochrane's ROBINS-I tool, OL studies with a low risk of bias are considered comparable in quality to RCTs (Sterne et al., 2016); (2) studies with dependent groups reduce individual variability between groups, potentially increasing sensitivity to detect differences (Moser, 2019); and (3) we aimed to provide a comprehensive review of high-quality studies to identify patterns and limitations that could guide future research. Nonetheless, we also conducted an analysis stratified by experimental design. Although microbiota manipulation based solely on RCTs showed a trend toward symptom improvement, it did not result in a statistically significant effect on symptom amelioration. Thus, additional data from new RCTs are necessary to evaluate the therapeutic potential of microbiota manipulation in SZ patients.

Several important confounding factors were identified across the studies and should be addressed in future analyses. One notable limitation is the absence of data on sex differences. None of the included studies stratified their results based on the sex of participants, despite well-documented differences in gut microbiota composition between males and females (Liao et al., 2021; Haro et al., 2016; Wu et al., 2022a; del Castillo-Izquierdo et al., 2022). This omission may obscure critical sex-specific responses to microbiota-based interventions, limiting the potential for a more personalized approach to SZ treatment. Future research should prioritize sex-stratified analyses to better understand these differential effects and enhance the precision of microbiota-targeted therapies.

Substance use, reported in seven of the nine studies, represents another potential confounder. Although most studies excluded patients with substance use disorders, the consumption of substances such as alcohol and tobacco—commonly used by individuals with SZ (Lv et al., 2023; Mallet et al., 2019)—can significantly impact gut health and microbiota composition (Kuo et al., 2024; Gui et al., 2021). For example, alcohol use is associated with increased intestinal permeability ("leaky gut syndrome")(Kuo et al., 2024), which can exacerbate gut dysbiosis and potentially interfere with the efficacy of microbiota-based interventions (Kuo et al., 2024). Ideally, future studies investigating microbiota-targeted treatments should exclude patients who use these substances. If exclusion is not feasible, complementary interaction analyses should be performed using raw data to assess whether substance use interferes with the observed symptomatology.

Another potential confounding factor that should be considered in future studies, ideally analyzed through controlled RCTs, is participants' diet. In this review, no significant differences were found in analyses stratified by the nationality (Eastern or Western); however, studies involving Eastern participants tended to report greater improvements. Ethnicity plays an important role in shaping microbiota composition (Dwiyanto et al., 2021; Li et al., 2022; Deschasaux et al., 2018), and one major factor that differs between ethnic groups—and significantly influences gut microbiota—is the diet (Govender and Ghaib; Low et al., 2021; Yao et al., 2023). Dietary patterns could have impacted the outcomes, as Western diets, typically high in fat and low in fiber, are known to affect negatively gut microbiota (reduced microbial diversity and an increased risk of dysbiosis) (Govender and Ghaib; Low et al., 2021), whereas Eastern diets, which are generally richer in fiber, show more beneficial effects (more diverse and stable microbiota, enhancing the production of beneficial Short Chain Fatty Acids (SCFAs) and other metabolites that contribute to gut health and systemic anti-inflammatory effects) (Govender and Ghaib; Low et al., 2021). Without controlling dietary patterns, it becomes challenging to fully attribute changes in SZ symptoms solely to microbiota-based treatments.

While body mass index (BMI) was a concern due to the influence of metabolic factors on both SZ (Deng et al., 2024; Wu et al., 2022b) and gut microbiota (Komodromou et al., 2024; Pinart et al., 2021), none of the studies included in this review reported significant differences in BMI between control and intervention groups at baseline. This suggests that BMI was not a confounding factor in the outcomes, allowing for a more focused assessment of microbiota-targeted interventions. However, given the well-documented association between metabolic disturbances, SZ, and gut microbiota composition (Misiak et al., 2024; Xing et al., 2023; Fan et al., 2022), the long-term impact of BMI changes during and after treatment remains an important area for future investigation.

Another notable aspect is the prior treatment status of participants. In all studies, patients were receiving some form of antipsychotic medication or standard SZ treatment at the time of microbiota intervention. While this reflects real-world clinical settings (Marder and Cannon, 2019; Galletly et al., 2016; Keepers et al., 2020), it complicates the interpretation of the isolated effects of microbiota manipulation. Only one study explicitly identified participants as treatment-resistant (Kelly et al., 2021), a crucial subset for whom new therapeutic approaches are most urgently needed (Polese et al., 2019; Correll and Howes, 2021). The lack of consistent reporting on treatment resistance across studies limits the ability to assess the efficacy of microbiota interventions in this population. Given that treatment-resistant SZ is often associated with more severe symptomatology and poorer clinical outcomes, particularly regarding negative symptoms (Correll et al., 2019; Iasevoli et al., 2018), future research should prioritize stratification by treatment response status. Stratified presentation of symptom data by domains will be essential to determine whether microbiota-based therapies provide distinct benefits for these patients.

The diversity of interventions also complicates the interpretation of results. The studies employed a variety of microbiota-based treatments, including multi-strain probiotics, single-strain probiotics, and prebiotics, each with potentially distinct mechanisms of action due to the different strains affected (Bienenstock et al., 2015a; Wang et al., 2020). The limited number of studies in each category hindered our ability to perform a meaningful subgroup analysis. Therefore, future meta-analyses would benefit from a more standardized approach to microbiota interventions facilitating a clearer understanding of which specific treatments provide the greatest clinical benefit. Below, we outline the main findings of the studies analyzed concerning the type of microbiota manipulation used.

4.2. *Effects of different gut microbiota manipulation techniques*

1) Probiotics

In the present meta-analysis, seven studies (Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Okubo et al., 2019) treat their patients with probiotics, featuring *Lactobacillus* and/or *Bifidobacterium*, except for Yang et al. (2021), who also included *Enterococcus* in the treatments, and Mujahid et al. (2022), who did not specify the microorganism used. Both the *Lactobacillus* and *Bifidobacterium* genera are well-established probiotics, widely available commercially, and valued for their excellent tolerability. These genera are frequently used in numerous clinical and preclinical studies (O et al., 2016; Dempsey and Corr, 2022) and, although their potential central effects are currently under debate (Xu et al., 2022; Rastogi and Singh, 2022; Lebovitz et al., 2019; Liu et al., 2016; Yunes et al., 2016; Wang et al., 2011; Engevik et al., 2021), they have long been recognized for their beneficial impact on gut health (O' et al., 2016; Dempsey and Corr, 2022; Powell et al., 2017), which was the primary reason they were selected in the earliest

study identified in our literature search (Dickerson et al., 2014).

4.2.1. Historical overview

The use of probiotics as adjuvant to the treatment of SZ received notoriety after the groundbreaking study conducted by Dickerson and colleagues in 2014 (Dickerson et al., 2014). They performed a randomized, placebo-controlled, double-blind clinical trial to investigate the effects of probiotic manipulation, primarily focusing on the improvement of gastrointestinal symptoms. Over fourteen weeks, patients received a probiotic blend containing *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *Lactis* strain Bb12, alongside their prescribed antipsychotic medication. The probiotic supplementation was well-tolerated and led to improvements in gastrointestinal symptom severity. However, the probiotic treatment did not result in any significant changes in SZ symptoms.

4.2.2. Probiotics and inflammation

In a subsequent follow-up of these same patients (Tomasik et al., 2015), the investigation focused on whether probiotic treatment altered levels of fourty-seven inflammatory mediators. The probiotics exhibited immunomodulatory properties, primarily affecting the IL-17 family of cytokines, which are associated with bowel inflammation (Akiyama and Sakuraba, 2021), complementing the findings of the previous trial (Dickerson et al., 2014). Other studies have also examined the impact of probiotic supplementation on inflammatory markers in patients with SZ (Tomasik et al., 2015; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Okubo et al., 2019). Low-grade inflammation has been proposed as part of the etiology of this mental disorder (Corsi-Zuelli et al., 2017), suggesting a possible mechanism through which probiotics exert their beneficial effects (Mujahid et al., 2022; Okubo et al., 2019). Some studies have shown that probiotic treatment attenuated the inflammatory response in patients with SZ, as evidenced by reductions in standard inflammatory markers such as C-reactive protein levels (Jamilian and Ghaderi, 2011; Ghaderi et al., 2019). Meanwhile, other studies have focused on specific immune-derived mediators, primarily cytokines (Tomasik et al., 2015; Mujahid et al., 2022; Okubo et al., 2019). The most recent study (Mujahid et al., 2022) demonstrated that adjuvant therapy with probiotics improved clinical symptoms in patients with SZ receiving risperidone. This effect was associated with decreased blood IL-6 levels, a pro-inflammatory cytokine linked to SZ development and dysbiosis (Wu et al., 2022c; Zhou et al., 2021).

Given the significant individual heterogeneity, much more data on mental disorders is needed to predict which patients will respond to specific probiotic treatments. For instance, Okubo and colleagues demonstrated that the *Bifidobacterium breve* A-1 administration improved the severity of anxiety and depressive symptoms in patients with SZ through a mechanism not associated with changes in the inflammatory cytokine TNF levels (Okubo et al., 2019). Patients who responded to the treatment showed higher relative abundance of *Parabacteroides* in the gut microbiome and increased levels of the mediators TRANCE and IL-22, related to gut epithelial barrier function. The baseline lipid and energy metabolism of the microbiota of SZ patients that are “responders” to *B. breve* A-1 treatment increased compared to “non-responders” (Yamamura et al., 2021). Additionally, in a randomized study, Severance et al. (2015) indicated that the presence of *Candida albicans* in males was associated with worsening of positive SZ symptoms. In the same study, probiotic supplementation appeared to benefit seronegative patients for *C. albicans*.

4.2.3. Probiotics and metabolism

The potential of probiotics to mitigate metabolic disturbances induced by neuroleptic medication has been explored in some of the studies reviewed in this analysis. (Jamilian and Ghaderi, 2011; Yamamura et al., 2021). For instance, a recent randomized, double-blind, placebo-controlled trial demonstrated that probiotic supplementation containing *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*, alongside selenium co-supplementation, improved both clinical and metabolic symptoms in patients with chronic SZ (Jamilian and Ghaderi, 2011). In this study, probiotic and selenium co-supplementation yielded beneficial metabolic effects, including reductions in fasting glucose, insulin levels, insulin resistance, and improvements in the quantitative insulin sensitivity check index. The treatment also enhanced antioxidant capacity and exhibited potential anti-inflammatory effects. Similarly, Ghaderi et al. (2019) found that the same probiotic combination, co-supplemented with vitamin D, improved clinical symptoms, total antioxidant capacity, and inflammatory status in patients with SZ. Additionally, this treatment improved the metabolic profile by reducing fasting plasma glucose, insulin concentrations, insulin resistance, triglycerides, total cholesterol, and the total-/HDL-cholesterol ratio.

Second-generation antipsychotics generally present a lower propensity for causing extrapyramidal side effects compared to first-generation drugs (Leucht et al., 2009). However, in addition to an increased incidence of gastrointestinal complaints (Dickerson et al., 2014), second-generation antipsychotics are also associated with a higher risk of metabolic-related disorders, particularly in children and adolescents (Yang et al., 2021; Leucht et al., 2009). In light of this concern, Yang and colleagues conducted a randomized controlled study to investigate whether co-treatment with probiotics containing *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* (known for their beneficial effects on host metabolism)(Hanchi et al., 2018) could mitigate olanzapine-induced weight gain and increased appetite (Yang et al., 2021). The probiotic treatment successfully prevented olanzapine-induced weight gain during the initial phase of treatment and delayed the increase in appetite. However, these significant differences did not persist until the end of the treatment, which contrasts with previous studies that reported *Lactobacillus* species reduced body weight and abdominal fat (Kadooka et al., 2010). This discrepancy may be attributed to the use of different probiotic strains across studies. Additionally, no significant difference in the reduction of clinical symptoms was observed between the groups receiving or not probiotics.

2) Prebiotics

The remaining two studies incorporated prebiotics, namely oligofructose-enriched inulin (Kelly et al., 2021) or Bimuno®-Galacto-oligosaccharides (B-GOS®)(Kao et al., 2019). Kelly demonstrated that treatment with the oligofructose-enriched inulin, a prebiotic molecule converted by bacteria (e.g., *Bifidobacteria*) to the SCFA butyrate, improves psychiatric symptoms in drug-resistant patients with SZ (Kelly et al., 2021). Similar improvements were observed by Kao and colleagues (Kao et al., 2019) with the prebiotic B-GOS®. The treatment conferred significant cognitive benefits in patients diagnosed with psychosis, consistent with previous findings in rats, where the neurocognitive improvements were associated with increased N-methyl-D-aspartate receptor activity (Gronier et al., 2018).

Prebiotics primarily exert their effects through the modulation of the gut microbiota, selectively promoting the growth of probiotic microorganisms (Neri-Numa and Pastore, 2020; Yoo et al., 2024; Pujari et al., 2021). While inulin may have some direct effects on the gut, such as influencing intestinal motility and reducing oxidative stress in response to lipopolysaccharide exposure, these effects remain closely tied to its interaction with the microbiota (Guarino et al., 2017). B-GOS®, on the other hand, not only selects probiotic microorganisms (Davis et al., 2011; Grimaldi et al., 2016), but also exerts effects independently of the microbiota (Del Fabbro et al., 2020). These effects include binding to toll-like receptors on immune cells, such as monocytes and macrophages, modulating cytokine production, and influencing immune cell maturation, thereby directly affecting immune responses (Del Fabbro et al., 2020). Thus, while prebiotics such as inulin primarily act by selectively promoting probiotic microorganisms, others like B-GOS®

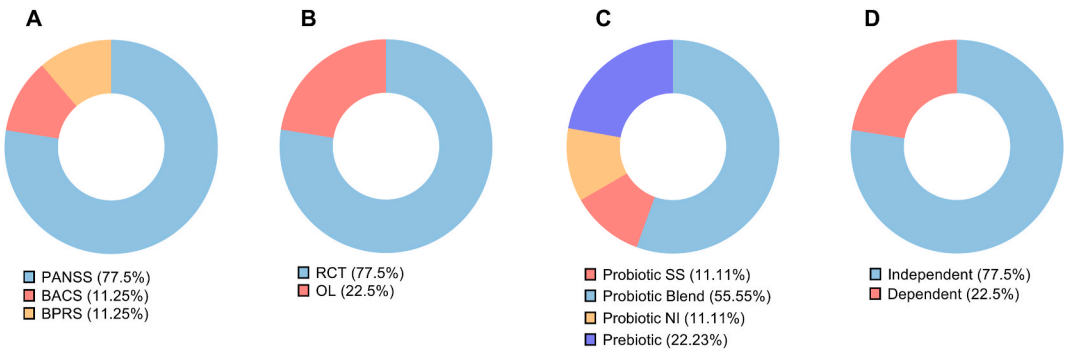

Fig. 2. Descriptive analysis of studies on Schizophrenia: **(A)** Severity Quantifying Instruments used (%); **(B)** Study design (%); **(C)** Microbiota manipulation methods employed (%); **(D)** Study group design (%). **PANSS**: Positive and Negative Syndrome Scale; **BACS**: Brief Assessment of Cognition in Schizophrenia; **BPRS**: Brief Psychiatric Rating Scale; **RCT**: Randomized Controlled Trial; **OL**: Open-Label; **SS**: Single Strain; **NI**: Not Informed.

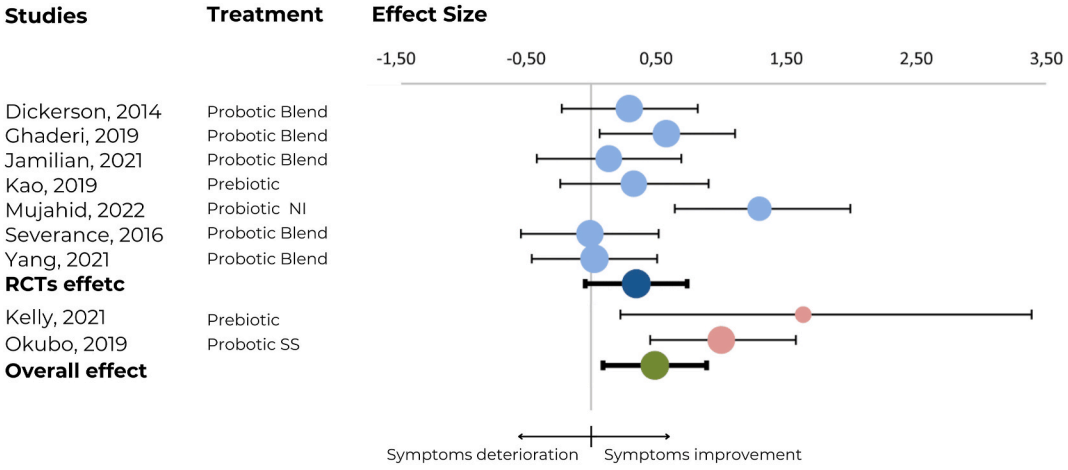

Fig. 3. Forest plot graph of microbiota manipulation on symptoms of schizophrenia according to the severity quantifying instrument (follow-up scale). In blue: Randomized Controlled Trials; In red: Open Label Studies; In green: Overall Effects. **SS**: Single Strain; **NI**: Not Informed. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

may act synergistically with these microorganisms via GBA (Raval and Archana, 2024; Han et al., 2024), through the potential mechanisms discussed below. In the future, as more studies are published on this topic, it will be possible to investigate whether these additional mechanisms, beyond the selection of microorganisms, indeed produce a significant synergistic effect with therapeutic potential.

4.3. Potential mechanisms underlying the benefits of gut microbiota manipulation in gastrointestinal and central schizophrenia symptoms

As previously discussed, 7 of the 9 studies presented here treated patients with *Lactobacillus* and/or *Bifidobacterium* (Dickerson et al., 2014; Severance et al., 2017; Jamilian and Ghaderi, 2011; Ghaderi et al., 2019; Mujahid et al., 2022; Yang et al., 2021; Okubo et al., 2019). The remaining two studies used inulin (Kelly et al., 2021) or B-GOS (Kao et al., 2019), prebiotics known to increase the populations of these same genera (Wu et al., 2024; Azcarate-Peril et al., 2017). Several preclinical models provide mechanistic insights into how these microorganisms may act on the CNS (Xu et al., 2022; Lebovitz et al., 2019; Yunes et al., 2016; Cao et al., 2018; Liang et al., 2015; Nishida et al., 2017; Qiu et al., 2021; Zhao et al., 2020; Xie et al., 2020; Ranuh et al., 2019) demonstrating that this communication is bidirectional occurring via three axes (Cryan et al., 2019): (1) neural, (2) immune, and (3) metabolic (Fig. 4). These axes do not function independently but interact dynamically, forming the GBA. *Lactobacillus* and *Bifidobacterium* are among the most extensively studied genera in literature and have been shown to influence these pathways (Dinan et al., 2013; Roy et al., 2023), as discussed below.

4.3.1. GUT health

Regarding gut health, the *Lactobacillus* and *Bifidobacterium* genera have species that enhance the survival of gut epithelial cells by inhibiting pro-apoptotic pathways through the recognition of Pathogen-Associated Molecular Pattern (PAMP) by Toll-Like Receptors (TLR) (Yan and Polk, 2002; Hughes et al., 2017). They are also crucial for improving the integrity of the intestinal epithelium preventing leaky gut syndrome (Rastogi and Singh, 2022). Although not yet defined in terms of cause and effect, leaky gut syndrome is often observed in individuals with SZ (Ishida et al., 2022) and other neuropsychiatric disorders (Petra et al., 2015). This pathological alteration can lead to increased bacterial translocation into the systemic circulation, contributing to the systemic pro-inflammatory state observed in these patients (Petra et al., 2015; Ishida et al., 2022).

4.3.2. Immune pathways

As previously mentioned, the *Lactobacillus* and *Bifidobacterium* genera may enhance the health of individuals with SZ by improving metabolic function and modulating inflammatory responses via immunomodulatory properties (Bistoletti et al., 2020). Specifically, they promote the clonal expansion of immunoglobulin A (IgA)-producing B lymphocytes, which are critical for mucosal immunity, and stimulate the differentiation of regulatory T (Treg) lymphocytes (Mazziotta et al.,

2023), which regulates the Th17 response (Parker et al., 2020; Chen et al., 2015) and modulate central immune activity (Choi et al., 2022). Additionally, probiotics inhibit the expression of JAK and NF-Kb genes (Mazziotta et al., 2023; Kropp et al., 2021), leading to a reduction in pro-inflammatory cytokine production (Kropp et al., 2021), while simultaneously inducing the release of anti-inflammatory cytokines (Mazziotta et al., 2023). Collectively, these processes activate defense mechanisms against pathogens, promote immune tolerance, and regulate immune responses, resulting in extra-intestinal effects, including CNS homeostasis (Ribeiro et al., 2019).

These changes may occur via (1) recognition of PAMPs from these bacteria by specific TLRs of the immune system, regulating the NF-κB signaling system (Ulevitch, 1999); (2) Histone Deacetylase inhibition via SCFAs (Liu et al., 2023); (3) SCFA receptors activations, such as GPR41, GPR43, and GPR109A, generating anti-inflammatory effects on macrophages and antigen-presenting cells inducing FoxP3+ T-cell and IL-10 production (Liu et al., 2023; Singh et al., 2014).

4.3.3. Neural Pathways

Both pathogenic (Wang, 2002) and non-pathogenic (Perez-Burgos et al., 2013) bacteria have been shown to activate different brain nuclei in a vagus nerve-dependent manner. The exact mechanisms and receptors through which microorganisms activate vagal afferents have been increasingly uncovered and discussed in recent years (Buckley et al., 2018; Kaelberer et al., 2018; Singh et al., 2020; Pradhananga et al., 2020). In 2018, Buckley and O'Malley (Buckley et al., 2018) demonstrated that ex vivo exposure of a distal colon section to peptidoglycan —the main component of the cell wall of gram-positive bacteria— but not lipopolysaccharide —the main component of the cell wall of gram-negative bacteria— triggers vagal nerve firing. This suggests that vagal sensory system respond selectively to different bacterial signals (Kaelberer et al., 2018; Singh et al., 2020). Furthermore, cysteine proteases from commensal bacteria increase the excitability of vagal afferent neurons by activating protease-activated receptor 2 and modulating sodium conductance (Pradhananga et al., 2020). Studies in germ-free animals have also highlighted the importance of the *Lactobacillus* genus in maintaining the function of primary afferent neurons in the enteric nervous system, enhancing their excitability, reducing calcium and potassium channel activity, and decreasing slow after-hyperpolarization in intrinsic primary afferent neurons (Kunze et al., 2009), thereby influencing nerve signaling to the CNS.

Through this vagal activation, different strains of *Lactobacillus* have been shown to induce central changes with behavioral impacts in animal models (Perez-Burgos et al., 2013; Sgritta et al., 2019; Bercik et al., 2011). For instance, *Lactobacillus* species improve social deficits in various behavioral models of autism in mice, including genetic, environmental, or idiopathic models (Sgritta et al., 2019; Buffington et al., 2016). This improvement is vagus nerve-dependent and is mediated by synaptic potentiation in the ventral tegmental area in an oxytocin-dependent manner (Sgritta et al., 2019). Similarly, this vagus-dependent behavioral modulation has also been observed with *Bifidobacterium* in anxiety-related behavior (Bercik et al., 2011).

4.3.4. Metabolic pathways

The *Lactobacillus* and *Bifidobacterium* genera can also modulate various neurotransmitter systems (Bistoletti et al., 2020; Bin-Khattaf et al., 2022; O et al., 2015). Cao et al. demonstrated that the supernatant of *Lactobacillus* and *Bifidobacterium* cultures increases the expression of serotonin receptors in intestinal epithelial cells, contributing to the regulation of serotonin levels in the gut (Cao et al., 2018). This effect has also been described in the brain (Yunes et al., 2016; Zhao et al., 2020), suggesting that probiotics enhance central serotonergic function (Engevik et al., 2021; Ranuh et al., 2019). Additionally, by inhibiting the activity of the indoleamine 2,3-dioxygenase enzyme (Valladares et al., 2013; Martin-Gallausiaux et al., 2018), these genera increase systemic serotonin circulation while reducing kynurenine levels both systemically (Valladares et al., 2013) and in the brain (Xu et al., 2022)' (Tian et al., 2019). Similar effects have been observed with other neurotransmitters that regulate the excitatory/inhibitory balance in the brain (Bistoletti et al., 2020)'(Bin-Khattaf et al., 2022). Both *Lactobacillus* and *Bifidobacterium* express glutamate decarboxylase and produce gamma-aminobutyric acid (GABA)(Yunes et al., 2016). For microorganisms, GABA is involved in pH homeostasis and energy generation (Otaru et al., 2021)'(Karatzas et al., 2010), whereas in humans, GABA acts as the primary inhibitory neurotransmitter in the brain (Yunes et al., 2016). Preclinical studies have demonstrated that species from the *Bifidobacterium* (Bin-Khattaf et al., 2022) and *Lactobacillus* (Bravo et al., 2011) genera can increase brain GABA levels and their receptors expression, in a vagus nerve dependent pathway (Bravo et al., 2011). Finally, some species of the *Lactobacillus* genus have also been identified as glutamate producers (Bistoletti et al., 2020)increasing the brain levels of this excitatory neurotransmitter.

Both the *Lactobacillus* and *Bifidobacterium* genera have species capable of producing SCFAs (O' et al., 2016)'(Dempsey and Corr, 2022), mainly acetate, propionate, and butyrate, which have anti-inflammatory effects modulating immune responses (Dalile et al., 2019; Silva et al., 2020; Smith et al., 2013). These molecules are products of the fermentation of dietary fiber by gut microorganisms, (Dalile et al., 2019). These SCFAs bind to different G protein-coupled receptors, affecting a wide range of metabolic and biochemical processes, and regulating gene expression (Silva et al., 2020)'(Lin et al., 2015). Locally, SCFAs provide energy for colonocytes (Dalile et al., 2019) and strengthen the intestinal barrier by promoting the expression of tight junction proteins such as claudins and occludins (Wang et al., 2012). SCFAs can also cross epithelial barriers, such as the intestinal barrier, blood-brain barrier, and placenta, via monocarboxylate transporters (Moschen et al., 2012), allowing them to exert systemic and central effects modulating inflammation, gene expression in the brain, myelination, and neural signaling, improving brain function and behavior (Cryan et al., 2019)' (Dinan et al., 2013)' (Grenham et al., 2011)' (Dalile et al., 2019).

Due to their broad effects, SCFAs have garnered significant attention (den Besten et al., 2013)'(Mann et al., 2024). However, it is important to acknowledge that the gut microbiota produces other metabolites with systemic and central actions, including neuromodulators (e.g., tryptophan, kynurenic acid), bile acids, vitamins, phenols, indoles, and polyamines (Cryan et al., 2019). For example, preclinical studies suggest that *Lactobacillus plantarum* PS128 may reduce anxiety-like behavior by increasing dopamine levels in the prefrontal cortex and modulating serotonin and dopamine levels in the striatum (Liu et al., 2016)'(Zhao et al., 2020).

4.4. Other relevant microorganisms

In addition to the *Lactobacillus* and *Bifidobacterium*, other microorganisms could also be involved with SZ (Yuan et al., 2019). In this regard, a recent systematic review (McGuinness et al., 2022) observed that 79% of studies comparing the microbiota of healthy individuals with patients with SZ found beta diversity differences with increased *Prevotella* and decreased *Bacteroides, Haemophilus*, and *Streptococcus*. Other studies have also demonstrated a significant increase in the *Lachnospiraceace* sp. in SZ patients (Nguyen et al., 2021). In this study, the authors also analyzed the microbiota of Major Depressive Disorder and Bipolar Disorder patients. Across all three conditions, a reduction in *Ruminococcaceae, Ruminococcus, Haemophilus*, and *Coprococcus* was noted, along with an increase in *Eggerthella, Flavonifractor*, and *Veillonella*. Interestingly, the *Lactobacillus* genus was also frequently higher in patients than controls in all three disorders. This aligns with the findings of Murray and colleagues, who conducted a meta-analysis investigating alterations in the gut microbiota composition of SZ patients (Murray et al., 2023). They observed that the most frequently reported genera with increased relative abundance in first-episode psychosis and SZ groups (reported in at least four studies) were *Bifidobacterium*,

Lactobacillus, *Megasphaera*, and *Veillonella* (Murray et al., 2023). While the latter two are recognized as potentially pathogenic (Murray et al., 2023), the first two are well-known for their benefits to gut and brain health, as extensively discussed in this study.

In this context, two important points must be considered: (1) several in vitro and preclinical studies have demonstrated the antimicrobial effects of antipsychotics, which may select for certain microorganisms, thereby favoring an increase in *Lactobacillus* and *Bifidobacterium* (Cussotto et al., 2019, 2021; Davey et al., 2012). Among the sixteen groups analyzed in Murray's study, five observed an increase in *Lactobacillus* and *Bifidobacterium*, with two of these studies reporting antipsychotic use among participants. Therefore, it is possible that the observed changes are not a direct reflection of the disorder's biology, but rather a consequence of pharmacological treatment. (2) The microbiota is composed of a vast array of microorganisms that interact both with each other and with the host, potentially acting synergistically

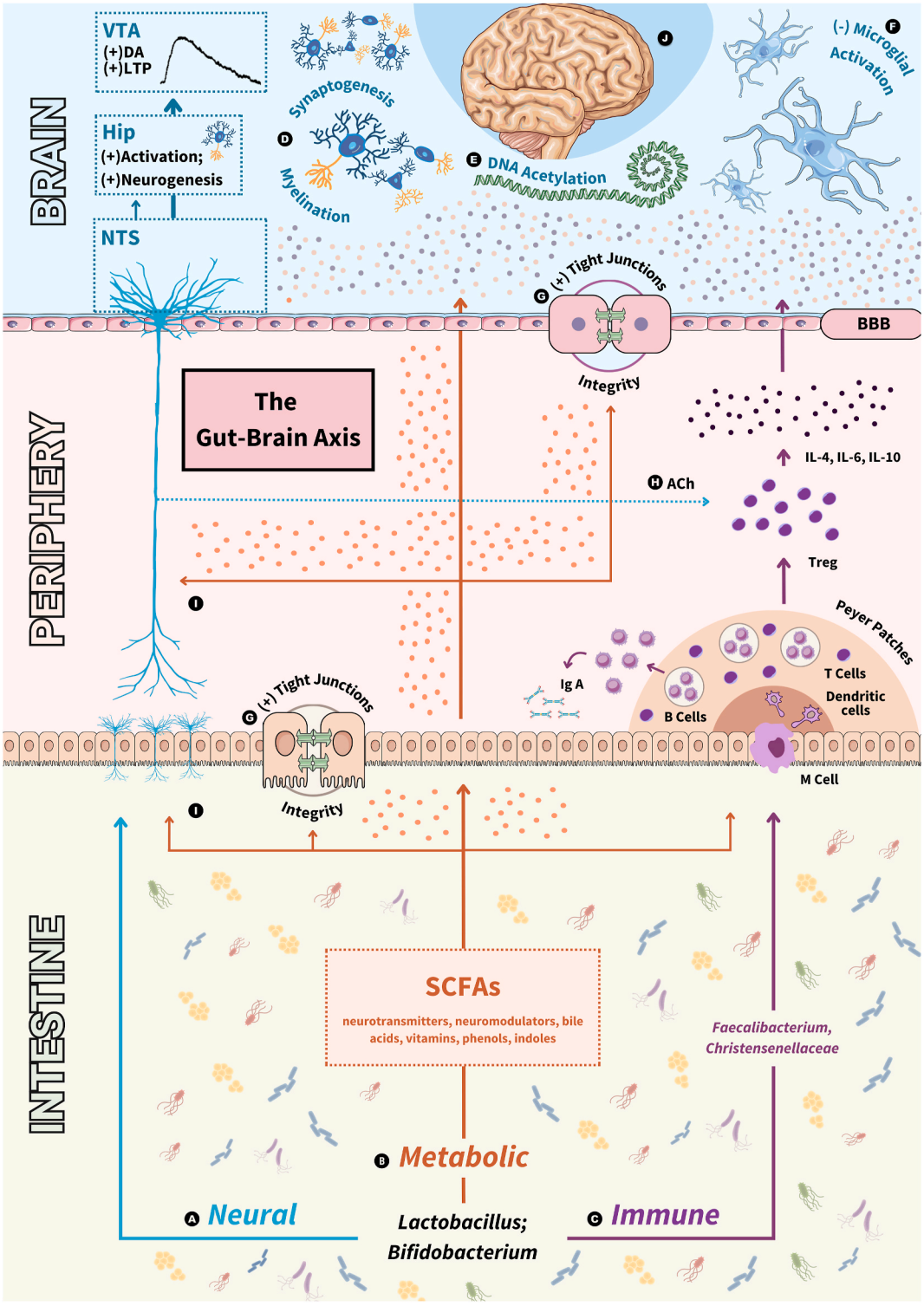

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Fig. 4. The Gut-Brain Axis. **A – Neural Pathway:** bacterial components activate the vagus nerve altering activity in the nucleus tractus solitarius (NTS), ventral tegmental area (VTA) and hippocampus (Hip). *Lactobacillus* and *Bifidobacterium* promote neuronal activation and hippocampal neurogenesis, as well as long-term potentiation (LTP) and increased dopamine (DA) release in the VTA in a vagus-dependent manner, modulating social behavior in rodents. Vagal activation can also modulate the immune pathway (**C**) through the suppression of the inflammatory response via acetylcholine (ACh) release and activation of nicotinic receptors on macrophages and other immune cells (**H**). **B – Metabolic Pathway:** Gut microbiota (*Lactobacillus*, *Bifidobacterium*) produces bioactive compounds, including short-chain fatty acids (SCFA), which act on metabolic pathways via interactions with different receptors, such as GPR41 (FFAR3), GPR43 (FFAR2), GPR109a (HCAR2), OR51E2 (human), and OLFR78 (mouse), expressed on enteroendocrine and immune cells, regulating gut motility and epithelial integrity.(**G**), and modulating endocrine and immune responses, promoting the production of anti-inflammatory cytokines. Additionally, SCFAs can regulate vagal activity through G protein-coupled receptors (GPCRs) (**I**) such as GPR41 and GPR43. Transported into systemic circulation by monocarboxylate transporters (MCT1 and MCT4), SCFAs can reach various organs, including the brain, crossing the blood-brain barrier (BBB) via MCTs (MCT1 and MCT2) to exert central effects (**D, E, F**). SCFAs can also exert central effects regulating synaptogenesis and myelination (**D**), reducing microglial activation (**F**), and regulating gene expression due to their ability to inhibit histone deacetylases. (E). **C – Immune Pathway:** In Peyer's patches, antigens presentation to immune cells induces both mucosal immune responses, including the production of IgA by B lymphocytes, and the differentiation of naive T lymphocytes into anti-inflammatory cytokines-producing regulatory T lymphocytes, which exert protective effects in the central nervous system. In these structures, *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*, and *Christensenellaceae* can generate systemic anti-inflammatory responses after the presentation of their components to lymphocytes, exerting various regulatory effects in the central nervous system (**D, F**). Collectively, these distinct mechanisms demonstrate the capacity for *in vivo* modulation of social behavior in rodents (**J**).

or oppositely[200–202]. It is almost contradictory to think that just one or two species of microorganisms could independently generate a significant impact on the host's physiology without considering the environment in which they exist (Wang et al., 2024): it is essential to consider their interactions with other microorganisms, as well as confounding factors such as diet and substance use (Wang et al., 2024)'(Selber-Hnatiw et al., 2017). While it is natural to discuss and study microorganisms separately in the context of mechanism investigation, it is also essential to remember that these microorganisms interact with thousands of other microbes in the gut (Bienenstock et al., 2015b)'(Wang et al., 2024)' (Selber-Hnatiw et al., 2017). This perspective led to discussions about the need to ensure the overall health of microbiota and has spurred the development of therapeutic approaches that target a broader range of microorganisms, from using blends of probiotic strains (Wang et al., 2020)' (Arnold et al., 2019; Billeci et al., 2023; Santocchi et al., 2020; Shaaban et al., 2018) to fecal microbiota transplants (Li et al., 2019, 2021; Khoruts, 2017; de Groot et al., 2017; Parker et al., 2022; Goo et al., 2020; Xiao et al., 2021), which have traditionally been used to treat gut-related conditions and are now being explored for neuropsychiatric disorders such as depression and autism (Li et al., 2019, 2021; Khoruts, 2017; de Groot et al., 2017; Parker et al., 2022; Goo et al., 2020; Xiao et al., 2021). Other limitations of the studies comparing the microbiota of healthy individuals with those diagnosed with SZ include the different methodologies employed, such as distinct treatments and the fecal collection, DNA extraction, and sequencing techniques. Nevertheless, these studies emphasize the importance of identifying new taxa that could serve as future therapeutic options for treating SZ. For example, the *Coprococcus* genus, which is diminished in patients with SZ (McGuinness et al., 2022), has garnered attention as a therapeutic target for SZ due to its potential impact on various neuropsychiatric disorders, such as depression and Parkinson's disease, via modulation of dopamine metabolism (Notting et al., 2023).

The *Ruminococcus* genus is also being considered as a potential target in neuropsychiatric disorders, with its reduced presence observed in several studies (McGuinness et al., 2022). It influences dopamine biosynthesis, reducing tyrosine hydroxylase activity (Hamamah et al., 2022) and tyrosine (Williams et al., 2014). Interestingly, antidepressants from different classes reduce *Ruminococcus* species through their antimicrobial activities (Luki et al., 2019). Moreover, the co-treatment with *Ruminococcus* reduced the duloxetine therapeutic effect. This study demonstrates the complexity of the interactions between microbiota, medication treatment, and behavior, reinforcing the need for a more cautious approach to data interpretation in the development of microbiota therapeutic strategies in neuropsychiatric disorders.

5. Limitations

The primary limitations of this study include small sample sizes and substantial heterogeneity among the included studies. The high heterogeneity primarily stemmed from differences in the methods and duration of microbiota manipulation, the instruments used to diagnose and assess SZ symptoms, and other confounding factors (Table 1). Additionally, included open-label studies may introduce biases, and the combined analysis of different assessment scales could also obscure specific treatment effects on individual symptoms. Consequently, given the limited number of published studies, the current evidence is not robust enough to recommend microbiota manipulation as a therapeutic intervention yet.

6. Conclusion

The analysis of the current literature does not allow us to recommend microbiome-based therapy for patients with SZ yet. However, it highlights the potential of these interventions to improve clinical outcomes when used as an adjunct to pharmacological treatments. More robust studies in this area are needed, specifically high-quality studies with larger participant cohorts, refined probiotic formulations, and controls for various confounding factors (such as sex, diet, and substance use). These studies should also present data across different symptom domains to better assess the full potential of microbiota-based interventions in SZ treatment. This would enable future analyses with reduced heterogeneity and greater precision in controlling symptom domains, ultimately improving the quality and specificity of the findings and paving the way for exploring this potential and innovative therapeutic approach.

CRediT authorship contribution statement

Lucas Hassib: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Alexandre Kanashiro:** Writing – original draft, Formal analysis, Data curation. **João Francisco Cordeiro Pedrazzi:** Writing – review & editing, Formal analysis, Data curation. **Bárbara Ferreira Vercesi:** Resources, Data curation. **Sayuri Higa:** Resources, Data curation. **Íris Arruda:** Resources, Data curation. **Yago Soares:** Resources, Data curation. **Adriana de Jesus de Souza:** Resources, Data curation. **Alceu Afonso Jordão:** Writing – review & editing. **Francisco Silveira Guimarães:** Writing – review & editing. **Frederico Rogério Ferreira:** Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100923.

Data availability

Data will be made available on request.

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