

Gut Microbiota in Autism Spectrum Disorder, Attention-Deficit Hyperactivity Disorder, and Schizophrenia

Mikrobiota jelitowa w zaburzeniach ze spektrum autyzmu, zespole nadpobudliwości psychoruchowej z deficytem uwagi oraz schizofrenii

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Abstract

Background: The microbiota-gut-brain axis provides a biologically plausible framework for bidirectional communication between intestinal microorganisms and the central nervous system. Human studies have reported gut microbiota differences in autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD), and schizophrenia, but the reproducibility and clinical meaning of these observations remain uncertain.

Objective: To critically summarize human evidence on gut microbiota composition in ASD, ADHD, and schizophrenia, and to assess clinical evidence for probiotic and synbiotic formulations and fecal microbiota transplantation (FMT) in these disorders.

Methods: A focused narrative review was conducted using PubMed and supplementary Google Scholar searches. Publications from 1 January 2012 to 31 December 2024 were considered, and the final search update was completed on 28 February 2025. Forty-two publications were purposively selected and synthesized; original human studies were prioritized whenever available. Evidence was interpreted with attention to study design, sample size, medication exposure, diet, gastrointestinal symptoms, stool characteristics, sequencing and bioinformatics methods, outcome selection, safety reporting, and risk of reverse causality. Because this was a narrative rather than a systematic review, no PRISMA flow diagram, duplicate independent screening, formal study-level risk-of-bias instrument, or new quantitative pooling was used.

Results: Across all three disorders, individual studies and meta-analyses report group-level microbiota differences, but no reproducible disorder-specific microbial signature has been established. In ASD, dietary selectivity, gastrointestinal symptoms, and stool consistency explain an important proportion of reported associations. ADHD studies are generally small and yield conflicting diversity and taxonomic findings. In schizophrenia, associations are influenced by antipsychotic exposure, metabolic status, smoking, diet, and illness chronicity. Controlled trials and meta-analyses have not shown consistent improvement in core symptoms with probiotic or synbiotic products. Early uncontrolled microbiota-transfer studies in ASD suggested possible benefits, but a 2024 randomized placebo-controlled FMT trial did not demonstrate improvement in its primary clinical outcome. Evidence for FMT in ADHD is limited to a case report, and no controlled human efficacy evidence was identified for schizophrenia. FMT carries infectious, procedural, and uncertain long-term risks.

Conclusions: Gut microbiota differences in ASD, ADHD, and schizophrenia should currently be regarded as associated features rather than established causes, diagnostic biomarkers, or validated therapeutic targets. Routine microbiome testing, probiotics or synbiotics for core symptoms, and FMT cannot be recommended as standard treatments for these disorders. Future studies require longitudinal designs, careful control of diet and medication, standardized laboratory methods, preregistered clinical outcomes, adequate power, external validation, and systematic safety monitoring.

Keywords: gut microbiota; microbiome; microbiota-gut-brain axis; autism spectrum disorder; attention-deficit hyperactivity disorder; schizophrenia; probiotics; synbiotics; fecal microbiota transplantation

Strzeszczenie

Wprowadzenie: Oś microbiota–jelita–mózg stanowi biologicznie prawdopodobny model dwukierunkowej komunikacji między mikroorganizmami jelitowymi a ośrodkowym układem nerwowym. Badania z udziałem ludzi wskazują na różnice w składzie mikrobioty jelitowej w zaburzeniach ze spektrum autyzmu (ASD), zespole nadpobudliwości psychoruchowej z deficytem uwagi (ADHD) oraz schizofrenii, jednak powtarzalność i znaczenie kliniczne tych obserwacji pozostają niepewne.

Cel: Krytyczne podsumowanie dowodów naukowych z badań u ludzi dotyczących składu mikrobioty jelitowej w ASD, ADHD i schizofrenii oraz ocena dowodów klinicznych na stosowanie preparatów probiotycznych, synbiotycznych i transplantacji mikrobioty kałowej (FMT) w tych zaburzeniach.

Metody: Przeprowadzono ukierunkowany przegląd narracyjny z wykorzystaniem bazy PubMed oraz uzupełniającego wyszukiwania w Google Scholar. Uwzględniono publikacje od 1 stycznia 2012 r. do 31 grudnia 2024 r., a ostateczną aktualizację wyszukiwania ukończono 28 lutego 2025 r. Celowo wyselekcjonowano i zsyntetyzowano 42 publikacje, priorytetyzując oryginalne badania z udziałem ludzi. Dowody interpretowano z uwzględnieniem projektu badania, wielkości próby, ekspozycji na leki, diety, objawów żołądkowo-jelitowych, charakterystyki stolca, metod sekwencjonowania i bioinformatycznych, doboru punktów końcowych, raportowania bezpieczeństwa oraz ryzyka odwrotnej przyczynowości. Ponieważ był to przegląd narracyjny, a nie systematyczny, nie zastosowano diagramu PRISMA, podwójnej niezależnej selekcji, formalnego narzędzia do oceny ryzyka błędu systematycznego na poziomie badań ani nowej metaanalizy ilościowej.

Wyniki: We wszystkich trzech zaburzeniach pojedyncze badania oraz metaanalizy wskazują na różnice w mikrobiocie na poziomie grup, nie ustalono jednak powtarzalnego, swoistego dla danego zaburzenia profilu mikrobiologicznego. W ASD wybiórczość pokarmowa, objawy żołądkowo-jelitowe oraz konsystencja stolca wyjaśniają istotną część raportowanych zależności. Badania nad ADHD obejmują na ogół małe próby i przynoszą sprzeczne wyniki dotyczące różnorodności oraz zmian taksonomicznych. W schizofrenii na obserwowane asocjacje wpływają: stosowanie leków przeciwpsychotycznych,

stan metaboliczny, palenie tytoniu, dieta oraz przewlekłość choroby. Badania z randomizacją i grupą kontrolną oraz metaanalizy nie wykazały spójnej poprawy w zakresie osiowych objawów pod wpływem probiotyków lub synbiotyków. Wczesne, niekontrolowane badania nad transferem mikrobioty w ASD sugerowały potencjalne korzyści, jednak randomizowane badanie z kontrolą placebo z 2024 r. nad FMT nie wykazało poprawy w zakresie pierwszorzędnego punktu końcowego. Dowody na zastosowanie FMT w ADHD ograniczają się do opisu przypadku, a w przypadku schizofrenii nie zidentyfikowano żadnych kontrolowanych badań klinicznych oceniających skuteczność u ludzi. Zabieg FMT wiąże się z ryzykiem infekcyjnym, powikłaniami proceduralnymi oraz niepewnymi konsekwencjami długoterminowymi.

Wnioski: Różnice w mikrobiocie jelitowej w ASD, ADHD i schizofrenii należy obecnie traktować jako cechy współwystępujące, a nie udowodnione przyczyny, biomarkery diagnostyczne czy zwalidowane cele terapeutyczne. Rutynowe badania mikrobiomu, stosowanie probiotyków lub synbiotyków w leczeniu objawów osiowych oraz FMT nie mogą być zalecane jako standardowe metody leczenia tych zaburzeń. Przyszłe badania wymagają projektów podłużnych, rygorystycznej kontroli diety i farmakoterapii, standaryzowanych metod laboratoryjnych, prospektywnie zarejestrowanych klinicznych punktów końcowych, odpowiedniej mocy statystycznej, zewnętrznej walidacji oraz systematycznego monitorowania bezpieczeństwa.

Słowa kluczowe: mikrobiota jelitowa; mikrobiom; oś mikrobiota–jelita–mózg; zaburzenia ze spektrum autyzmu; zespół nadpobudliwości psychoruchowej z deficytem uwagi; schizofrenia; probiotyki; synbiotyki; przeszczepienie mikrobioty jelitowej

Introduction

The human gut microbiota is a complex ecosystem of bacteria, archaea, viruses, fungi, and other microorganisms. It participates in nutrient metabolism, immune regulation, maintenance of epithelial barrier function, and production or transformation of bioactive metabolites. The microbiota-gut-brain axis describes bidirectional communication among the gastrointestinal tract, enteric and central nervous systems, endocrine pathways, immune mechanisms, and microbial products [1]. Large human cohort studies also show associations between microbial functions, quality of life, and depressive symptoms, supporting the relevance of this field while not establishing causality [2].

Interest in neurodevelopmental and psychiatric disorders has been driven by several observations: gastrointestinal symptoms are common in some affected populations; diet and

psychotropic medications can alter gastrointestinal physiology; and experimental models have identified plausible immune, metabolic, and neural pathways. Nevertheless, mechanistic plausibility must be separated from clinical evidence. A microorganism capable of producing a neuroactive compound *in vitro* does not necessarily generate a biologically relevant exposure in humans, and an association between a taxon and a clinical phenotype does not establish that the taxon causes the disorder.

The present review is deliberately restricted to ASD, ADHD, and schizophrenia. These disorders differ in age at onset, clinical presentation, treatment, diet-related behaviors, and common comorbidities; consequently, findings should not be combined into a single generic concept of “mental health.” The objectives are to: (1) summarize the most relevant human observational findings; (2) identify major sources of inconsistency and reverse causality; (3) assess selected clinical evidence concerning probiotics, synbiotics, and FMT, including outcomes and safety; and (4) define conclusions that can and cannot currently be applied in clinical practice.

Methods

This article is a focused narrative review rather than a systematic review. PubMed was searched in January and February 2025 for publications dated from 1 January 2012 through 31 December 2024, and the final search update was completed on 28 February 2025. Google Scholar and reference lists of relevant articles were used as supplementary sources. Supplementary searches paired each disorder with the terms diet, dietary selectivity, gastrointestinal symptoms, stool consistency, stress, medication, antipsychotic, stimulant, sequencing, metagenomics, metabolomics, safety, and adverse events. English – and Polish-language publications were considered.

The core PubMed search combined the following elements: (“gut microbiota” OR “gut microbiome” OR microbiome) AND (“autism spectrum disorder” OR autism OR ASD OR “attention-deficit” OR ADHD OR schizophrenia OR psychosis) AND (2012:2024[dp]). This core string was then combined in separate disorder-specific searches with each of the supplementary terms listed above (e.g., “gut microbiota” AND autism AND “dietary selectivity”) to identify additional records not captured by the broad search. Google Scholar searches used equivalent free-text combinations of the same terms, restricted to the same date range, and were screened only for records not already retrieved from PubMed.

The core narrative was built from peer-reviewed human case-control and cohort studies, clinical trials, systematic reviews, and meta-analyses addressing gut microbiota compo-

sition, function, or microbiota-targeted interventions in ASD, ADHD, or schizophrenia. Original human studies were prioritized when they directly supported a clinical or microbiological statement; systematic reviews and meta-analyses were used to assess reproducibility across cohorts and trials. Mechanistic reviews were used only for biological context. Animal and *in vitro* studies were not treated as evidence of clinical efficacy or human causality. Conference abstracts, non-peer-reviewed reports, studies without clinically characterized participants, and publications unrelated to the three prespecified disorders were not used in the core clinical synthesis.

Selection was purposive and guided by clinical relevance, methodological informativeness, and representation of conflicting findings rather than by an exhaustive numerical screening process. Forty-two publications met these purposive criteria and form the evidence base synthesized in this review. Duplicate citations encountered across searches were consolidated by bibliographic identity, including DOI, PMID, title, and author information; no numerical deduplication log was maintained. Literature searching and study selection were performed collaboratively by the author team (see Author Contributions). Consistent with a narrative rather than a systematic review, this was not a duplicate-independent process, and disagreements between independent reviewers were therefore not a feature of this narrative method.

Evidence was synthesized qualitatively. Observational studies were interpreted with attention to design, sample size, participant age, diagnostic ascertainment, treatment status, diet, gastrointestinal symptoms, stool consistency and transit, smoking and metabolic factors, specimen handling, sequencing platform, bioinformatics pipeline, multiplicity of analyses, validation, and temporal direction. For intervention studies, the population, formulation or procedure, treatment duration, comparator, primary and secondary outcomes, reported effect estimates, adverse events, and major design limitations were recorded and summarized in Table 2. A formal study-level risk-of-bias instrument was not applied, and no new meta-analysis was undertaken. Accordingly, this review does not present a PRISMA-style numerical selection diagram and should not be interpreted as a systematic review or an exhaustive estimate of treatment effect.

Evidence synthesis

Mechanistic framework and limits of translation

Potential communication routes within the microbiota-gut-brain axis include vagal and enteric signaling, immune mediators, hypothalamic-pituitary-adrenal activity, intestinal

barrier function, and microbial metabolites such as short-chain fatty acids, bile-acid derivatives, and products of tryptophan metabolism [1]. These pathways are biologically plausible, but most direct mechanistic evidence derives from experimental models. Human microbial composition also varies with host genetics, geography, household, socioeconomic conditions, diet, medication, age, and laboratory methods [3,4].

A transdiagnostic meta-analysis of 59 case-control studies involving 1,519 individuals with psychiatric disorders and 1,429 controls found some recurring community-level alterations, but did not identify a validated disorder-specific signature [5]. Methodological choices – including sampling, DNA extraction, sequencing region or platform, taxonomic database, compositional analysis, and correction for multiple testing – can materially affect results [6]. Therefore, isolated taxonomic findings should not be treated as diagnostic biomarkers, and predicted microbial pathways should not be equated with measured metabolites or central nervous system activity.

Autism spectrum disorder

An earlier systematic review found reported differences in the composition and inferred function of intestinal microbiota in ASD, but also substantial inconsistency in the direction and identity of altered taxa [7]. Strati et al. reported microbial differences between children with ASD and controls, including associations with constipation [8]. Such findings supported further research, but the cross-sectional design could not determine whether ASD, diet, bowel function, or another factor accounted for the differences.

Later evidence has sharpened this interpretation. In a cohort of 247 children, Yap et al. found that restricted dietary preferences associated with ASD were linked to microbiome composition, whereas direct ASD-microbiome associations were negligible after relevant factors were considered [9]. A subsequent correction changed parts of the analysis but retained the central conclusion that diet and the behavioral phenotype can mediate apparent microbiome associations [10]. A harmonized multi-cohort analysis involving 690 participants likewise showed that age, sex, and bowel function influenced taxonomic findings and that proposed ASD signatures were not stable across analytical conditions [11]. A 2024 cross-sectional study of 98 children with ASD, ADHD, unaffected siblings, and unrelated controls further illustrated the close relationship between dietary diversity and microbial diversity [12].

Taken together, the human evidence does not support a single ASD microbiome profile. Gastrointestinal symptoms and restricted eating are clinically important in their own

right, but they also create a strong possibility of reverse causality: ASD-related behaviors may change diet and bowel habits, which then alter the microbiota. This does not exclude a modifying role for microbial functions in subgroups, but it prevents attribution of current group-level differences to the cause of ASD.

Attention-deficit hyperactivity disorder

The evidence on the ADHD microbiome is more limited and less consistent than the ASD literature. In a study of 19 participants with ADHD and 77 controls, Aarts et al. reported a greater predicted abundance of bacterial gene functionality encoding cyclohexadienyl dehydratase, an enzyme involved in phenylalanine biosynthesis, together with an association involving neural reward anticipation [13]. The finding was derived from 16S rRNA marker-gene sequencing with PICRUSt-based prediction of bacterial gene function, not from shotgun metagenomics or direct measurements of enzyme activity, phenylalanine production, dopamine production, or central dopamine signaling. Controls were also older than cases in the microbiome sample.

Prehn-Kristensen et al. reported lower alpha diversity in 14 boys with ADHD than in 17 controls [14], whereas another small case-control study of 17 children with ADHD and 17 controls found taxonomic differences but no alpha diversity difference [15]. Richarte et al. studied 100 medication-naïve adults with ADHD and 100 controls and reported compositional differences. A microbiota-based classifier showed 74% sensitivity and 71% specificity within the study dataset [16]. These values are insufficient for clinical use, and the classifier lacked independent external validation.

A systematic review and meta-analysis of eight studies, comprising 316 participants with ADHD and 359 controls, found no robust or consistent taxonomic signature. An apparent Shannon-diversity result was sensitive to individual studies, and evidence concerning *Blautia* was based on a limited number of datasets [17]. The conflicting diversity results, small pediatric samples, and variation in age, diet, geography, gastrointestinal symptoms, and medication status preclude causal inference. Stimulants may also affect appetite and food intake, so treated and untreated populations should not be combined without careful adjustment.

Schizophrenia and psychosis

In first-episode psychosis, Schwarz et al. compared 28 patients with 16 controls and identified preliminary microbiota associations with symptom severity and treatment response [18]. The small sample size and observational design made these findings hypothesis-

generating. In a larger metagenome-wide association study, Zhu et al. compared 90 medication-free patients with schizophrenia and 81 controls. A microbial classifier had an area under the receiver operating characteristic curve of 0.896 in the discovery sample and 0.765 in a separate sample of 45 patients and 45 controls [19]. External testing strengthened the report, but case-control discrimination is not equivalent to diagnosis, prospective prediction, or proof that the microbiome causes schizophrenia.

A systematic review and meta-analysis found compositional and functional alterations across psychosis and schizophrenia studies, alongside high clinical and methodological heterogeneity and limited consistency for individual taxa [20]. Medication and illness characteristics are especially important. In a 2024 study of 97 individuals with schizophrenia, microbiome differences were most pronounced in treatment-resistant and clozapine-treated groups [21]. Clozapine exposure, constipation, metabolic disease, diet, smoking, and chronicity can all influence the observed profile. Consequently, microbiota differences in chronic treated populations cannot be assumed to represent the biology of untreated schizophrenia.

Selected human evidence

Table 1 summarizes representative human studies that illustrate both the reported associations and their limitations. The table is selective rather than exhaustive.

Table 1. Selected human evidence on gut microbiota in ASD, ADHD, and schizophrenia

Disorder and study	Design and sample	Main finding relevant to this review	Principal limitation
ASD; Strati et al. [8]	Cross-sectional case-control study in children	Group-level compositional differences; constipation was associated with microbial features	Single cohort; cross-sectional design; gastrointestinal phenotype may explain part of the association
ASD; Yap et al., including correction [9,10]	Cohort study of 247 children	Restricted dietary preferences linked the ASD phenotype to microbiome composition; the direct ASD-microbiome association was negligible after relevant modelling	Observational design; correction required reanalysis; residual confounding remains possible
ASD; West et al. [11]	Harmonized multi-cohort analysis of 690 participants	Proposed taxonomic differences varied according to age, sex, and bowel function	Heterogeneous source cohorts and metadata; no causal inference
ASD/ADHD; Kurokawa et al. [12]	Cross-sectional study of 98 children, including affected groups, siblings, and unrelated controls	Dietary and microbial diversity differed across groups, emphasizing diet-microbiome coupling	Small subgroups; cross-sectional design; multiple comparisons

Disorder and study	Design and sample	Main finding relevant to this review	Principal limitation
ADHD; Aarts et al. [13]	Case-control study of 19 participants with ADHD and 77 controls	16S-based prediction of increased phenylalanine-related bacterial gene function and an association with reward anticipation	Function predicted using PICRUSt rather than measured directly; age imbalance; small ADHD group
ADHD; Prehn-Kristensen et al. [14]	Case-control study of 14 boys with ADHD and 17 controls	Lower alpha diversity in participants with ADHD	Very small, male-only sample; limited generalizability
ADHD; Wan et al. [15]	Case-control study of 17 children with ADHD and 17 controls	Taxonomic differences, but no difference in alpha diversity	Very small sample size; no longitudinal assessment
ADHD; Richarte et al. [16]	Case-control study of 100 medication-naïve adults with ADHD and 100 controls	Compositional differences; within-dataset classifier sensitivity of 74% and specificity of 71%	No independent external validation; cross-sectional design
ADHD; Wang et al. [17]	Systematic review and meta-analysis of eight studies, including 316 participants with ADHD and 359 controls	No stable disorder-specific microbial profile; diversity findings were sensitive to the included studies	Few heterogeneous studies; limited taxon-level replication
Psychosis; Schwarz et al. [18]	Case-control study of 28 participants with first-episode psychosis and 16 controls	Preliminary associations with symptom severity and treatment response	Small sample size; exploratory analyses; possible treatment – and life-style-related confounding
Schizophrenia; Zhu et al. [19]	Metagenomic study of 90 medication-free patients and 81 controls; external sample of 45 patients and 45 controls	Classifier AUC of 0.896 in the discovery sample and 0.765 in the external sample	Case-control classification does not establish causality or clinical diagnostic utility
Schizophrenia; Vasileva et al. [21]	Cross-sectional study of 97 participants with schizophrenia	More pronounced microbiota differences in treatment-resistant and clozapine-treated groups	Effects of treatment, constipation, metabolic status, diet, and illness severity are difficult to disentangle

Abbreviations: ADHD – attention-deficit hyperactivity disorder; ASD-autism spectrum disorder; AUC – area under the receiver operating characteristic curve

Diet, stress, genetics, and other confounders

Environmental effects on the human microbiome are substantial. In a large population analysis, shared environment and lifestyle explained more microbial variation than host genetic ancestry [22]. Controlled dietary work also demonstrates that marked changes in diet can alter the gut microbiome rapidly [23]. Host genetic effects exist, but are generally modest and taxon-specific rather than deterministic [24]. Human studies of psychological

stress report possible microbiota associations, yet vary in stress measures, populations, and analytical methods, and remain unable to establish a uniform causal pathway [25].

The most important confounders differ by disorder. In ASD they include food selectivity, restricted diets, constipation, diarrhea, supplements, and caregiver-mediated lifestyle. In ADHD they include age, stimulant exposure, appetite, dietary patterns, sleep, and physical activity. In schizophrenia they include antipsychotic medications, especially clozapine; constipation; smoking; obesity and metabolic disease; socioeconomic conditions; diet; and chronicity. Antibiotics, proton-pump inhibitors, laxatives, metformin, and other drugs should also be recorded. Stool consistency and intestinal transit require explicit assessment because they are strongly related to microbial composition.

Microbiota-targeted interventions

Probiotics and synbiotics are strain-, formulation-, dose-, and duration-specific. A result obtained with one organism or combination cannot be generalized to all products sold under the same broad label. FMT is a substantially different intervention: it transfers a complex donor-derived biological community and requires donor screening, standardized preparation, traceability, and surveillance for infectious and other adverse outcomes.

ASD

In a six-month randomized, placebo-controlled study of 85 preschool children with ASD, Santocchi et al. found no significant overall between-group improvement in the prespecified primary outcome, the Autism Diagnostic Observation Schedule calibrated severity score. Subgroup findings involving gastrointestinal status were exploratory, and 63 participants completed the trial [26]. No serious adverse events were reported. Two probiotic recipients experienced transient abdominal pain and diarrhea during the first ten days, continued treatment, and completed the trial [26]. A 2023 meta-analysis of seven probiotic trials found no statistically significant pooled improvement in ASD symptoms (standardized mean difference [SMD] – 0.24, 95% confidence interval [CI] – 0.60 to 0.11; $p=0.18$), with small samples and substantial clinical and methodological variability [27].

Microbiota Transfer Therapy was initially studied in 18 children with ASD using an open-label regimen that included vancomycin, bowel cleansing, acid suppression, and repeated donor microbiota administration [28]. A two-year follow-up described persistent gastrointestinal and behavioral improvements in the same cohort [29]. Because there was no randomized control group, the contribution of the microbiota product cannot be sepa-

rated from natural change, concomitant components, expectation effects, regression to the mean, or altered care during follow-up.

Another 2024 single-arm study administered oral lyophilized FMT to 38 children with ASD once every four weeks over 12 weeks and assessed participants through week 20 [30]. From baseline to final follow-up, parent – or clinician-rated scores decreased by 23% for the Autism Behavior Checklist, 10% for the Childhood Autism Rating Scale, and 6% for the Social Responsiveness Scale. Vomiting and fever occurred in two participants and resolved within 24 hours [30]. The absence of a placebo group, the small single-center sample size, reliance on within-person changes, and short follow-up prevent attribution of these changes to FMT.

More informative evidence came from a 2024 randomized, double-blind, placebo-controlled oral FMT trial in 103 children with ASD [31]. The primary endpoint, the Social Responsiveness Scale-2 T-score, did not differ significantly between groups at weeks 9 and 17, and there was no between-group difference in the Aberrant Behavior Checklist. A secondary Vineland-3 socialization-domain difference favored FMT by 5.05 points (95% CI 0.31 to 9.79), but this should be interpreted as secondary evidence in the context of a negative primary outcome. Adverse events occurred in 12 of 52 participants (23.1%) receiving FMT and 7 of 51 (13.7%) receiving placebo; no grade 3 or serious adverse events were reported in this trial [31].

ADHD

In a nine-week randomized, double-blind trial completed by 182 children and adults with ADHD, Synbiotic 2000 and placebo produced similar reductions in ADHD symptoms, and neither group showed a statistically significant improvement in daily functioning. Findings involving restricted and repetitive behaviors in children and emotion regulation in adults were secondary or subgroup observations and did not establish an effect on core ADHD symptoms [32].

A 2024 meta-analysis of seven randomized trials involving 379 children and adolescents found no significant benefit of probiotics over placebo for total ADHD symptoms (SMD 0.25; $p=0.12$), inattention (SMD 0.14; $p=0.30$), or hyperactivity/impulsivity (SMD 0.08; $p=0.54$) [33]. The trials differed in formulation, use as stand-alone or add-on treatment, duration, and outcome measures, and the pooled sample remained too small to assess rare harms.

In a 12-week double-blind trial, 102 children receiving methylphenidate were included in a modified intention-to-treat analysis of add-on *Bifidobacterium bifidum* Bf-688 (5×10^9

colony-forming units/day) or placebo. Core ADHD symptom scores improved in both groups without an additional between-group benefit from the probiotic. Some computerized attention and gastrointestinal outcomes favored the intervention, but these were secondary or exploratory and do not establish efficacy for core ADHD symptoms [34]. A small three-month trial in university students with ADHD reported signals in hyperactivity, gastrointestinal symptoms, and academic or behavioral measures with a multi-strain probiotic, but only 60 participants were analyzed; the single-center sample size and multiple outcomes limit confirmation [35].

Human FMT evidence in ADHD was limited to a report of a 22-year-old woman who underwent FMT for recurrent *Clostridioides difficile* infection and coincidentally reported improvement in ADHD symptoms [36]. A single uncontrolled case treated for another indication cannot establish efficacy, estimate risk, or support FMT as an ADHD intervention.

Schizophrenia

In a 14-week randomized, placebo-controlled trial involving 65 individuals with schizophrenia, supplementation with *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* Bb12 did not improve Positive and Negative Syndrome Scale scores. The probiotic group was less likely to report severe bowel difficulty (hazard ratio 0.23, 95% CI 0.09 to 0.61; $p=0.003$), suggesting a possible gastrointestinal rather than antipsychotic effect [37]. Four serious adverse events occurred in three participants: three events in the probiotic group, comprising two psychiatric hospitalizations and one hospitalization for dehydration, and one psychiatric hospitalization in the placebo group. Overall adverse-event frequencies were similar, and no probiotic recipient discontinued treatment because of an adverse event [37].

A systematic review of three clinical studies found no significant effect of probiotics on schizophrenia symptoms (SMD -0.0884 , 95% CI -0.380 to 0.204 ; $p=0.551$), with similarly negative analyses for positive and negative symptoms [38]. A broader review of add-on strategies identified 28 randomized double-blind trials, of which 21 investigated antibiotics, four investigated other antimicrobial agents, three investigated prebiotic or probiotic approaches, and none investigated FMT [39]. Its pooled conclusions were driven mainly by antibiotic trials and do not constitute direct evidence that probiotics or FMT treat schizophrenia. No controlled human FMT efficacy study for schizophrenia was identified within the review period.

Table 2 presents selected clinical evidence with the most relevant outcome hierarchy, safety information, and interpretive limitations. It is not an exhaustive trial inventory.

Table 2. Selected clinical evidence for probiotics, synbiotics, and fecal microbiota-based interventions

Population and study	Intervention and follow-up	Clinical result	Safety and evidential interpretation
Preschool children with ASD; randomized trial, 85 enrolled/63 completed [26]	De Simone Formulation probiotic vs placebo for 6 months	No significant overall between-group effect on the primary ADOS calibrated severity score; subgroup observations were exploratory	No serious adverse events; transient abdominal pain/diarrhea in 2 probiotic recipients; attrition and subgroup analyses limit certainty
Children with ASD; meta-analysis of 7 probiotic trials [27]	Heterogeneous products and durations	ASD symptom effect: SMD – 0.24 (95% CI – 0.60 to 0.11; p=0.18)	Small, heterogeneous trials; product-specific safety and efficacy cannot be generalized
Children with ASD and gastrointestinal symptoms; open-label MTT, n=18 [28,29]	Vancomycin, bowel cleanse, acid suppression, then intensive and maintenance donor microbiota; 8-week treatment and 2-year observational follow-up	Gastrointestinal and behavioral scores improved over time	No control group; multi-component regimen; same small cohort at follow-up; cannot establish efficacy
Children with ASD; single-arm oral lyophilized FMT, n=38 [30]	One FMT course every 4 weeks for 12 weeks; follow-up to week 20	From baseline: Autism Behavior Checklist – 23%, CARS – 10%, and SRS – 6% at final follow-up	No control group; vomiting/fever in 2 participants, resolving within 24 hours; within-person changes cannot establish efficacy
Children with ASD; randomized oral FMT trial, n=103 [31]	Donor-derived capsules vs placebo during two treatment periods; assessment to week 17	No difference in primary SRS-2 outcome or Aberrant Behavior Checklist; secondary Vineland-3 socialization difference 5.05 points (95% CI 0.31 to 9.79)	Adverse events: 23.1% FMT vs 13.7% placebo; no grade 3/serious events; negative primary outcome governs interpretation
Children and adults with ADHD; randomized synbiotic trial, n=182 completed [32]	Synbiotic 2000 vs placebo for 9 weeks	Similar ADHD symptom improvement in both groups; no significant effect on daily functioning	Secondary/subgroup signals do not establish core-symptom efficacy; trial not powered for rare harms
Children/adolescents with ADHD; meta-analysis of 7 randomized trials, n=379 [33]	Heterogeneous probiotic formulations, stand-alone or add-on	Total symptoms SMD 0.25 (p=0.12); inattention 0.14 (p=0.30); hyperactivity/impulsivity 0.08 (p=0.54)	No significant core-symptom benefit; heterogeneity and limited safety power
Children with ADHD receiving methylphenidate; randomized trial, modified intention-to-treat n=102 [34]	B. bifidum Bf-688, 5 x 10 ⁹ CFU/day, vs placebo for 12 weeks	No added benefit on core ADHD rating scales; exploratory attention and gastrointestinal signals	Does not support treatment of core ADHD symptoms; rare harms could not be assessed
University students with ADHD; randomized trial, 67 randomized/60 analyzed [35]	Multi-strain probiotic, 8 x 10 ⁹ CFU/day, vs placebo for 3 months	Signals in selected hyperactivity, gastrointestinal, and functional outcomes	Small single-center trial with multiple outcomes; replication required

Population and study	Intervention and follow-up	Clinical result	Safety and evidential interpretation
Adult with ADHD and recurrent <i>C. difficile</i> infection; case report, n=1 [36]	FMT for recurrent <i>C. difficile</i> ; microbiome profiling before and after	Coincidental improvement in reported ADHD symptoms	No comparator; treatment was for another indication; no efficacy or safety inference for ADHD
Adults with schizophrenia; randomized trial, n=65 [37]	<i>L. rhamnosus</i> GG plus <i>B. animalis</i> Bb12 vs placebo for 14 weeks	No PANSS improvement; lower risk of severe bowel difficulty, HR 0.23 (95% CI 0.09 to 0.61)	Four serious events across both groups; overall AE rates similar; possible gastrointestinal benefit, not antipsychotic efficacy
Schizophrenia; systematic review of 3 probiotic studies [38]	Probiotic supplementation vs placebo	Symptoms: SMD – 0.0884 (95% CI – 0.380 to 0.204; p=0.551)	Very small evidence base; no demonstrated benefit for positive, negative, or overall symptoms
Schizophrenia; broader systematic review/meta-analysis, 28 trials [39]	21 antibiotic, 4 other antimicrobial, 3 pre/probiotic, and 0 FMT trials	No effect of probiotics alone on negative symptoms; findings mainly reflected non-probiotic strategies	Does not support routine microbiome-targeted treatment; no human FMT efficacy evidence

Abbreviations: ADOS, Autism Diagnostic Observation Schedule; AE, adverse event; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CARS, Childhood Autism Rating Scale; CFU, colony-forming units; CI, confidence interval; FMT, fecal microbiota transplantation; HR, hazard ratio; MTT, Microbiota Transfer Therapy; PANSS, Positive and Negative Syndrome Scale; SMD, standardized mean difference; SRS, Social Responsiveness Scale.

Clinical status and safety of FMT

Current gastroenterology guidance recommends or suggests fecal microbiota-based therapies only for selected gastrointestinal indications, principally recurrent *Clostridioides difficile* infection after standard antimicrobial treatment [40]. ASD, ADHD, and schizophrenia are outside these guideline-supported indications. The guideline did not evaluate FMT as a treatment for the core symptoms of these neurodevelopmental or psychiatric disorders, so its gastrointestinal recommendations must not be extrapolated to them.

FMT can transmit pathogens despite donor screening. Transmission of extended-spectrum beta-lactamase-producing *Escherichia coli* caused invasive infections in two recipients and contributed to one death in a documented report [41]. Route-specific procedural risks also matter: colonoscopic delivery can involve sedation, bleeding, or perforation, whereas upper-gastrointestinal delivery can involve regurgitation and aspiration [42]. Oral capsules avoid an invasive delivery procedure but do not eliminate the risk of pathogen transmission, transfer of antimicrobial-resistance determinants, or uncertain delayed ecological and metabolic effects.

Accordingly, FMT for ASD, ADHD, or schizophrenia should be undertaken only in appropriately designed, ethically approved clinical trials with regulated donor screening, product preparation, traceability, adverse-event surveillance, predefined stopping rules, and long-term follow-up. It should not be offered as a routine, do-it-yourself, or commercial treatment for core neurodevelopmental or psychiatric symptoms.

Discussion

The central finding of this review is not the absence of microbiota associations, but their limited specificity and uncertain direction. Across ASD, ADHD, and schizophrenia, group-level differences have repeatedly been reported. However, the taxa, diversity metrics, and predicted functions vary among cohorts, and results often change when diet, bowel function, medication, age, or analytical choices are considered. The transdiagnostic meta-analysis by Nikolova et al. [5] and the disorder-specific syntheses in ASD [7,11], ADHD [17], and psychosis [20] converge on heterogeneity rather than a stable diagnostic profile.

Concrete findings demonstrate why causal language is premature. In ASD, the corrected analysis by Yap et al. [9,10] placed restricted eating upstream of much of the observed microbiome variation, while the multi-cohort analysis by West et al. [11] showed sensitivity to age, sex, and bowel function. In ADHD, reduced alpha diversity in one very small study [14] was not reproduced in another [15], and the meta-analytic diversity signal was not robust in sensitivity analyses [17]. The Aarts et al. finding [13] was based on 16S-derived functional prediction, not direct demonstration that gut microorganisms increase dopamine synthesis. In schizophrenia, findings in medication-free participants [19] reduce but do not eliminate confounding, whereas the strong differences associated with treatment resistance and clozapine exposure [21] show how illness course and therapy may shape microbial profiles.

Microbial classifiers should also be interpreted cautiously. Even external discrimination between existing cases and controls does not demonstrate prospective diagnostic performance, specificity against other psychiatric disorders, resistance to geographic and technical shifts, or added value beyond clinical assessment. No gut microbiome test is currently validated for diagnosing ASD, ADHD, or schizophrenia.

The intervention literature does not yet convert association into therapeutic efficacy. The pooled probiotic effect on ASD symptoms was not statistically significant [27]. In ADHD, a relatively large synbiotic trial showed equal improvement with active product and placebo [32], and a seven-trial meta-analysis did not find a significant benefit for

total symptoms, inattention, or hyperactivity/impulsivity [33]. The schizophrenia probiotic trial did not improve PANSS scores [37], and the disorder-specific systematic review found an effect estimate close to zero [38]. Gastrointestinal benefits, when present, should not be described as treatments for the core psychiatric or neurodevelopmental disorders.

FMT evidence is even less mature. The early ASD microbiota-transfer reports were uncontrolled and involved a multicomponent procedure [28,29]. A second uncontrolled study also reported within-person improvements but could not separate an intervention effect from placebo effects, maturation, regression to the mean, or changes in concurrent care [30]. The later placebo-controlled FMT trial was negative for its primary endpoint [31]; a favorable secondary socialization result is hypothesis-generating and should not override the primary analysis. ADHD evidence is limited to one case treated for recurrent *C. difficile* infection [36], and the schizophrenia intervention review identified no FMT trials [39]. Describing FMT as “promising” without this outcome hierarchy would therefore overstate the evidence.

At present, clinical care should focus on evidence-based assessment and treatment of each disorder and on standard evaluation of coexisting gastrointestinal symptoms. A clinician may address constipation, diarrhea, nutritional restriction, or medication adverse effects according to established practice, but should not present correction of an undefined “dysbiosis” as a treatment for the core disorder. Over-the-counter probiotic products differ in organisms, dose, viability, manufacturing, and evidence; the benefit from one formulation cannot be extrapolated to another.

Future observational studies should recruit sufficiently large and clinically well-characterized cohorts, ideally before treatment or at defined treatment stages. Longitudinal sampling is needed to establish temporal order. Diet, stool consistency, intestinal transit, gastrointestinal diagnoses, antibiotics, psychotropic medications, other microbiome-active drugs, smoking, sleep, physical activity, body composition, and socioeconomic variables should be measured prospectively. Laboratory protocols and bioinformatics workflows should be standardized and reported in enough detail for replication. Functional claims should rely on measured metabolites or validated metagenomic and metabolomic data rather than taxonomic inference alone.

Future trials require preregistered primary outcomes, adequate allocation concealment and blinding, intention-to-treat analyses, clinically interpretable effect estimates with confidence intervals, correction for multiple secondary outcomes, and longer follow-up. Products and donor-derived preparations must be fully characterized. Trials should distinguish effects on core psychiatric or neurodevelopmental symptoms from effects on gastro-

intestinal symptoms and should prospectively monitor adverse events. Independent replication and external validation are essential before a microbiota-based biomarker or intervention can enter routine care.

Limitations of this review

This is a focused narrative rather than a systematic review. It used PubMed and supplementary Google Scholar searching, was limited to English – and Polish-language publications through December 2024, and did not use duplicate independent screening, a study-level formal risk-of-bias instrument, or quantitative pooling. Selection was purposive and emphasized studies most informative for clinical interpretation, so relevant publications may have been missed. Table 1 and Table 2 are representative rather than exhaustive. The numerical results quoted from individual studies and meta-analyses should be interpreted in the context of their original protocols and analyses. These limitations preclude claims of exhaustive evidence retrieval or a new pooled treatment estimate.

This review was not prospectively registered in PROSPERO or an equivalent registry. Prospective registration is not a standard requirement for narrative reviews, but its absence should be considered when assessing the reproducibility of the study-selection process described above.

Funding sources and potential conflicts of interest in the individual primary studies and trials cited here (for example, industry sponsorship of probiotic or synbiotic products) were not systematically extracted or reported. This is a relevant limitation, because sponsorship can be associated with more favorable reported outcomes in nutrition and supplement trials; readers should consult the original publications for this information before drawing product-specific conclusions.

The cited studies also used markedly heterogeneous outcome measures — including the ADOS, SRS/SRS-2, CARS, Autism Behavior Checklist, Aberrant Behavior Checklist, Vineland-3, and PANSS — which differ in what they capture, their responsiveness to change, and their score ranges. This heterogeneity, distinct from the heterogeneity of the study populations discussed above, limits direct numerical comparisons of effect sizes across studies and contributes to the difficulty of pooling results in existing meta-analyses.

Conclusions

Human studies support associations between gut microbiota features and ASD, ADHD, and schizophrenia, but they do not establish a causal microbial mechanism or a repro-

ducible disorder-specific signature. Diet, gastrointestinal function, medications, lifestyle, geography, specimen processing, sequencing, and bioinformatics methods account for substantial variability and may produce or modify observed associations.

Probiotic, synbiotic, and microbiota-transfer studies remain insufficient to support treatment of core ASD, ADHD, or schizophrenia symptoms. Controlled trials and meta-analyses have generally shown negative or inconsistent primary clinical outcomes, and favorable secondary findings require replication. FMT is not standard treatment for these disorders and carries clinically important safety concerns; outside established gastrointestinal indications, it should be restricted to properly regulated clinical research.

The field remains scientifically relevant, particularly for identifying biologically defined subgroups and understanding interactions among diet, gastrointestinal symptoms, medications, and host physiology. Clinical translation, however, requires longitudinal evidence, reproducible multi-cohort findings, validated functional measurements, and adequately powered controlled trials.

Disclosure

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