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# The Role of Synbiotics in Modulating the Gut–Brain Axis in Attentiondeficit/Hyperactivity Disorder: A Systematic Review

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**Abstract**

ADHD is a neurodevelopmental disorder involving gut microbiota dysbiosis and gut–brain pathways, suggesting synbiotics as a potential adjuvant therapy. Literature searches were conducted on electronic primary databases "PubMed", "EuropePMC", and "ScienceDirect" with a range published between 2020–2025. Studies were selected based on inclusion criteria and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The methodological quality of the included studies was evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for randomized clinical trials. Of the 146 articles identified, five randomized clinical trial studies met the inclusion criteria. The available evidence suggests that synbiotic interventions have varied clinical effects in ADHD patients. More obvious benefits are mainly seen in the symptomatic aspects of inattention, with secondary impacts on impulse control and adaptive function of daily behavior, as well as inflammatory biomarkers and gut microbiota. No serious side effects were reported in any of the included studies. This systematic review suggests that synbiotics have the potential to modulate the two-way gut-brain communication pathway and provide domain-specific clinical benefits in subgroups of ADHD patients with specific clinical or biological characteristics. These findings support the role of synbiotics as adjuvant therapy, but are not enough to recommend it as a single therapy for the entire ADHD patient population in general.

## INTRODUCTION

Attention/hyperactivity deficit disorder (ADHD) is a common neurodevelopmental condition, characterized by persistent attention deficits, hyperactivity, and impulsivity that interfere with academic, social, and occupational functioning (Al-Beltagi et al., 2025; Diale & Eseadi, 2024; Musullulu, 2025; Okeke et al., 2025; Sabir et al., 2024). Although pharmacological therapies and psychosocial interventions have been widely used, most patients achieve only partial symptom control and still experience residual functional impairment or medication side effects. This condition highlights the need for new adjuvant therapy strategies based on the pathophysiological mechanisms underlying ADHD.

In recent years, the gut–brain axis has emerged as a promising biological framework for understanding the pathophysiology of ADHD (Liu et al., 2025; Gandhi et al., 2024; Levy Schwartz et al., 2024). The gut–brain axis represents a two-way communication network that connects the central nervous system and gastrointestinal tract through neurological, endocrine, immune, and metabolic pathways. The gut microbiota plays a role in the modulation of neurotransmission, including the dopaminergic and noradrenergic pathways, as well as in the regulation of neuroinflammatory processes and stress responses relevant to the pathogenesis of ADHD.

A number of studies have reported intestinal microbiota dysbiosis in ADHD patients characterized by changes in composition and decreased microbiota diversity, including a reduced proportion of health-associated genera such as *Bifidobacterium*, *Faecalibacterium*, and *Coprococcus*, as well as a relative increase in some Firmicutes taxa such as *Clostridia*, *Ruminococcaceae*, and *Lachnospiraceae* (Liu et al., 2025; Gandhi et al., 2024; Levy Schwartz et al., 2024; Steckler et al., 2024). This condition is related to changes in immune and metabolic profiles, including decreased production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, both in the circulation and feces. SCFAs are the main metabolites of fermentable substrates fermented by the gut microbiota and play an important role as a metabolic mediator in the gut–brain axis, including in maintaining the integrity of the intestinal barrier, modulating immune responses, and regulating the homeostasis of the intestinal environment. Decreased SCFA levels in ADHD patients were reported to be associated with increased proinflammatory cytokines and were more pronounced in subgroups receiving pharmacological therapy (Liu et al., 2025; Steckler et al., 2024; Yang et al., 2022).

Microbiota-based interventions, including prebiotics, probiotics, and synbiotics, have attracted attention as a potential "psychobiotic" approach. Synbiotics, as a combination of live microorganisms and complementary designed fermentable substrates, theoretically have the advantage of supporting microbial colonization and metabolic activity as well as increasing the production of neuroactive metabolites such as SCFA (Liu et al., 2025; Allahyari et al., 2024).

Although research on the relationship between the gut microbiota and ADHD continues to grow, there is currently no synthesis of evidence that specifically and comprehensively evaluates the role of synbiotics as a modulator of the gut–brain axis in ADHD. Existing reviews generally combine prebiotics, probiotics, and synbiotics within a single analytical framework, thus limiting specific interpretations of the effectiveness of synbiotics. Therefore, this systematic review aims to critically evaluate and integrate the current clinical evidence regarding synbiotic interventions in patients with ADHD. This research provides both theoretical and practical benefits. Theoretically, this study enriches the understanding of the mechanisms of the gut-brain axis in the pathophysiology of ADHD and strengthens the scientific evidence regarding synbiotic potential as a microbiome-based adjuvant therapy modality. Practically, the results of this study are expected to be a reference for clinicians in considering the use of synbiotics as supportive therapy in ADHD patients with certain clinical and biological characteristics, as well as provide direction for future researchers in designing more stratified and mechanism-based clinical trials.

## RESEARCH METHODS

### Search Strategy

The author was conducted in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA). Literature searches were conducted on three major electronic databases, namely "Pubmed", "ScienceDirect", and

"EuropePMC". The search strategy used a combination of keywords and Medical Subject Headings (MeSH Terms), namely ("Synbiotics" OR "Probiotics" AND "Prebiotics") AND ("ADHD" OR "Attention Deficit Hyperactivity Disorders"). The search was limited to studies involving human subjects. The flow of the study selection is presented in the PRISMA diagram Figure 1.

**Inclusion and Exclusion Criteria**

The studies included in this systematic review met the following inclusion criteria: (1) studies involving patients with Attention-Deficit/Hyperactivity Disorder (ADHD) of all age groups, diagnosed based on the criteria of the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5); (2) studies evaluating the effectiveness of synbiotics defined as the combination of probiotics with fermentable substrates such as inulin, dietary fiber, resistant starches, or other compounds that function as prebiotics; (3) studies that compared interventions with standardized, placebo or no specific intervention protocols; (4) studies that report at least one of the outcomes in the form of clinical effectiveness and/or biomolecular changes; (5) randomized controlled trials (RCTs); (6) studies conducted in the last five years; (7) Full text is available; and (8) studies written in English. Studies are excluded if they meet one of the following criteria: (1) studies evaluating probiotic or prebiotic-only interventions without a combination of the two; (3) study design other than randomized clinical trials; and (4) animal-based or in vitro research.

**Study Selection**

All research articles were filtered based on topic, title, abstract, keywords, and inclusion and exclusion criteria. All authors selected the study individually and blindly to reduce bias and conflicts of interest among individual authors. Full text is downloaded and identified. All duplicate articles are filtered using the Rayyan app. All disagreements between authors are resolved through discussions between authors.

**Data Extraction and Evaluation**

The authors identified all research articles included in this review, including: (1) Authors (Year); (2) State; (3) Study design; (4) Characteristics of the basic population included in the study; (5) Results; (6) Quality assessment of research articles; (7) Sample size; (8) Intervention (Type, Duration, Frequency, and Dose); (9) Control (Type and Dosage). Other secondary research results were screened and incorporated into studies to support the effectiveness of synbiotics in the management of ADHD. This systematic review will report on 2 main types of outcomes, namely clinical effectiveness and biomolecular effectiveness.

**Study Quality Assessment**

All articles were evaluated for quality assessment using the Joanna Briggs Institute (JBI) Critical Appraisal Tools for Randomized Clinical Trials. No articles are excluded based on quality assessment. The articles are evaluated individually by the authors, and differences of opinion are resolved through discussion with the agreement of all the authors. The assessment is presented using a code system. Each answer "Yes" counts as 1 point and "No" as 0 points. A code system with a score range of 1-13 is applied to articles with a randomized clinical trial research design (scores of 10-13 are classified as high quality, 6-9 as medium quality, and less than 6 as low quality). Although all included studies were classified as high quality, some minor limitations were found, particularly regarding the reporting of allocation methods and blinding.

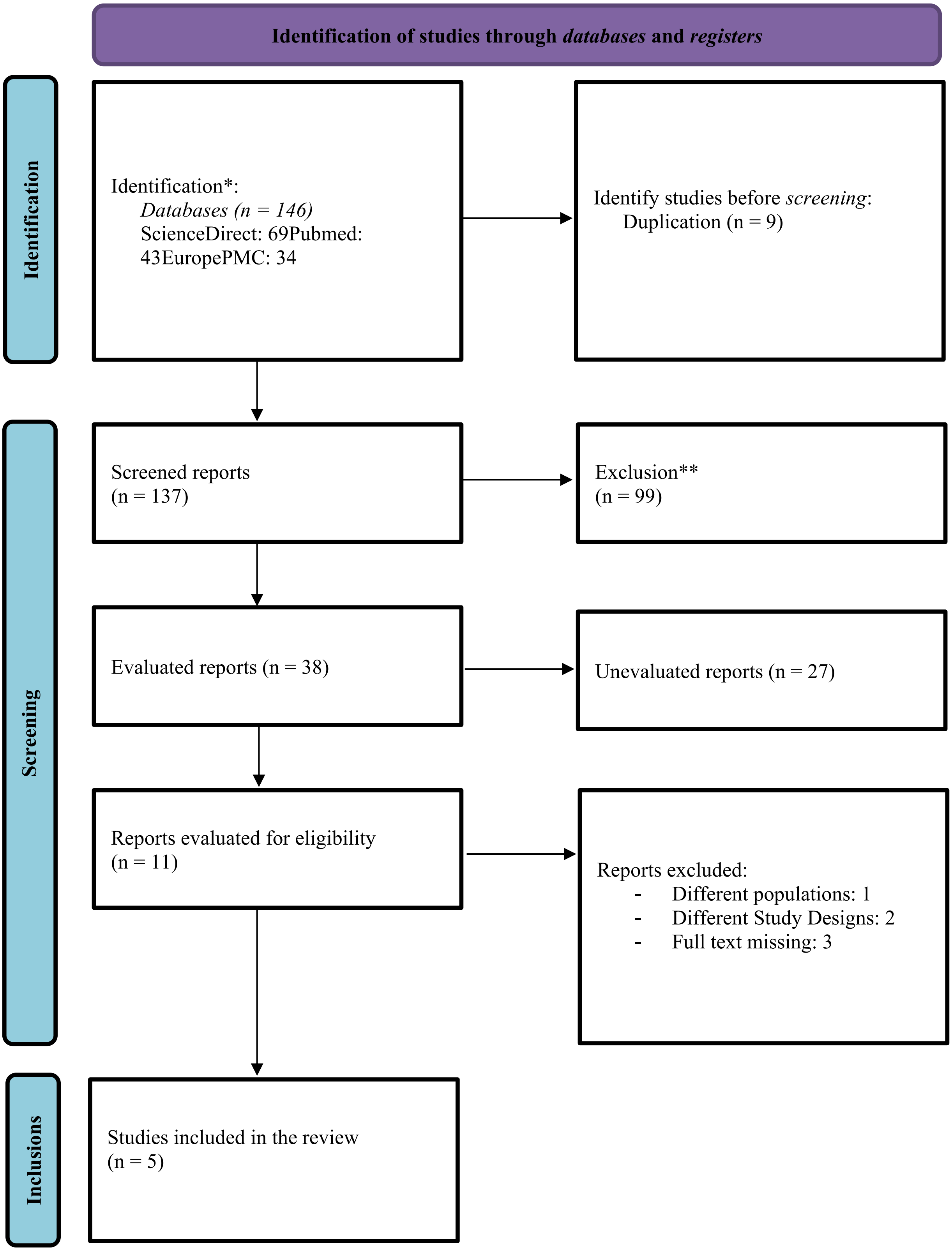


**Figure 1. Flowchart of the "PRISMA Statement Guidelines"**

Source: Authors' illustration based on PRISMA 2020 guidelines

## RESULTS AND DISCUSSION

Based on the literature search, a total of 146 articles were identified from major electronic databases, namely Europe PMC (34 articles), Science Direct (69 articles), and PubMed (43 articles). After the removal of duplicate articles, there are 137 articles left for the screening process. Filtering of titles and abstracts based on topic relevance resulted in 11 articles that met the criteria for full-text assessment.

Furthermore, a full-text feasibility assessment was conducted based on inclusion and exclusion criteria, resulting in five randomized clinical trial studies evaluating synbiotic interventions in patients with ADHD. Other studies were excluded because of population differences, inappropriate research design, limited availability of full texts, or use of languages other than English. The study selection process is presented in the PRISMA flowchart.

All included studies were judged to be of high methodological quality based on the Joanna Briggs Institute (JBI) Critical Appraisal Tools for randomized clinical trials. However, some minor limitations related to reporting of allocation and blinding procedures were still found

**Basic Characteristics of the Study**

A total of five studies were included in the main analysis according to inclusion and exclusion criteria. All studies used a double-camouflaged randomized clinical trial design and were published in English. The studies came from European countries, namely Sweden, Spain, and Italy.

The total number of participants involved in the intervention group was 409 individuals, while the control group consisted of 271 individuals. Age variations, duration of interventions, and synbiotic formulations used were reported in each study. Detailed characteristics of the study, including design, population, intervention, and key outcomes are presented in Tables 1, 2, and 3.

**Common Patterns of Findings**

The findings of this systematic review suggest that the clinical effects of synbiotics on ADHD are uneven across the entire symptom dimension. Clinical improvement tends to be domain-specific, with more consistent benefits on the inattention aspect than on hyperactivity/impulsivity symptoms or overall ADHD total scores. In addition to improvements in inattention, some studies also reported secondary impacts on impulse control and adaptive function of everyday behavior. However, these changes were not always reflected in a decrease in the overall ADHD score, which was often not significantly different than the placebo group.

This pattern suggests that synbiotics are likely to work on specific neurobiological dimensions that are more relevant to attention regulation and executive function, rather than resulting in a comprehensive improvement across the spectrum of ADHD symptoms. Thus, synbiotics are more appropriately positioned as adjuvant therapies with selective effects on specific clinical subdomains.

Immunological and Short Chain Fatty Acid Modulation (SCFA's) Yang et al. (2023) reported that administration of Synbiotic 2000 produced measurable anti-inflammatory effects in children with ADHD, particularly in subgroups receiving stimulant therapy. During the 9-week intervention period, the group of children receiving Synbiotic 2000 showed significant decreases in levels of IL-12/IL-23p40, sICAM-1, and TGF-β3, while the group of children receiving placebo showed no significant changes in the assessed immunological markers. Further stratified analysis showed that the decrease in IL-12/IL-23p40 and sICAM-1 was more pronounced in children receiving stimulant therapy, indicating a targeted synbiotic effect in subgroups with high endothelial activation and basal immunity (Yang et al., 2023).

At the metabolic level, administration of Synbiotic 2000 significantly improved plasma propionic acid levels in children compared to placebo. In addition, levels of major short-chain fatty acids (SCFAs), including formic acid, acetate, and propionate, showed a negative correlation with endothelial activation markers sICAM-1 and sVCAM-1. In vitro, SCFAs have also been shown to inhibit IL-1-induced ICAM-1 expression in vascular smooth muscle cells. These findings support a mechanistic model in which synbiotic-induced recovery of SCFA levels contributes to the suppression of endothelial inflammation in ADHD, especially in individuals with low SCFA levels and increased adhesion molecules at baseline conditions (Yang et al., 2023).

The decline in SCFA production capacity has significant immunological implications. Under normal physiological conditions, SCFAs play a role in maintaining the integrity of the intestinal barrier, providing a source of energy for colon epithelial cells, as well as modulating the immune response through activation of G protein-bound receptors and inhibition of histone deacetylase, which collectively suppress proinflammatory pathways. When SCFA levels decrease, the risk of developing low-level systemic inflammation becomes more likely. In individuals with ADHD, this condition is reflected through increased vascular and immune activation markers in plasma, including sICAM-1, sVCAM-1, IL-12/IL-23p40, and sIL-2R, and is supported by meta-analysis findings showing increased levels of IL-6 and associated proinflammatory cytokines. Some studies have also reported that in children with ADHD, especially those receiving psychostimulant therapy, SCFA concentrations are negatively correlated with sICAM-1 and sVCAM-1. In vitro exposure of human vascular smooth muscle cells to physiological concentrations of formic acids, acetate, and propionate decreased IL-1-induced ICAM-1 expression, demonstrating the direct anti-inflammatory role of these metabolites at the endothelial interface (Silva et al., 2020; Sankarganesh et al., 2025; Lewis et al., 2025).

Through vascular and immune pathways, gut microbiota dysbiosis can channel its impact to the central nervous system. Persistent increases in endothelial adhesion molecules, such as ICAM-1 and VCAM-1, facilitate leukocyte transmigration and are associated with increased permeability of the blood-brain barrier as well as activation of microglia, a mechanism that has been reported in a variety of neuropsychiatric conditions and is now also identified in ADHD. Simultaneously, changes in microbiota metabolism, including disruptions in catecholamine pathways and short-chain fatty acid (SCFA) signaling, have the potential to disrupt dopaminergic and noradrenergic transmission in the corticostriatual and frontolimbic pathways, which play important roles in attention, reward processing, and emotion regulation.

Clinical evidence is beginning to reflect such mechanistic linkages, where symptom cluster analyses identified the presence of different microbiota and metabolic markers between dimensions of inability to concentrate and hyperactivity/impulsivity, while lower propionate levels were consistently associated with higher severity of ADHD symptoms (Lewis et al., 2025; Xiao et al., 2025; Tsukuda et al., 2021; Wang et al., 2025).

ADHD is also associated with low-degree inflammatory states and SCFA deficiency, and Synbiotic 2000 appears to work primarily on these biological communication pathways, in line with stratification-based adjuvant therapy approaches. Studies show that adults with ADHD report higher baseline levels of sICAM-1 and sVCAM-1 as well as lower plasma SCFA levels compared to healthy individuals or control groups. Meanwhile, children with ADHD showed increased levels of IL-12/IL-23p40, sICAM-1, sVCAM-1, and sIL-2R accompanied by decreased levels of formic acid, acetate, and propionate, reflecting more pronounced vascular-immune activation and more severe SCFA deficiency in pediatric patients with ADHD.

In subgroups with prominent inflammatory profiles, especially in children receiving stimulant therapy or having high baseline levels of sVCAM-1, administration of Synbiotic 2000 was associated with decreased IL-12/IL-23p40, sICAM-1, and IL-2R, as well as a tendency to increase propionate levels. Higher levels of SCFAs (formic acid, acetate, and propionic) were consistently correlated with decreased levels of sICAM-1/sVCAM-1, and were shown to suppress IL-1-induced ICAM-1 expression in in vitro models. These findings support a mechanism by which synbiotic-triggered SCFA modulation can directly suppress vascular inflammation (Yang et al., 2023).

Nevertheless, clinical trials show that these biological changes do not consistently translate into broad or large improvements in the core symptom scores of ADHD. In contrast, the observed clinical benefits tend to be domain-specific. Synbiotic 2000 is reported to reduce autistic spectrum traits in children as well as improve emotional regulation in adults with ADHD, especially in individuals with higher rates of vascular inflammation. Another randomized controlled study evaluating synbiotics or probiotics in children who had never received pharmacological therapy showed moderate improvements in attention, inhibition, irritability, and daily functioning with no consistent effect on the entire dimension of ADHD symptoms.

**Clinical Implications**

Overall, these findings support the view that synbiotics should be positioned as adjuvant interventions that target a portion of the dysbiosis-SCFA-inflammation pathophysiological chain in a subgroup of patients with biologically defined ADHD, i.e. individuals with increased adhesion molecules, proinflammatory cytokines, SCFA deficiency, and predominance of emotional or autistic symptoms, rather than as a single, broad-spectrum therapy for the entire population of patients with ADHD (Yang et al., 2023; Skott et al., 2020; Arteaga-Henríquez et al., 2024; Trezzi et al., 2025).

**Table 1. Effectiveness of Synbiotics in Regulating Intestinal Microbiota Dysbiosis in ADHD Patients**

| No. | Author (Year) | Country | Study Design | Populasi | Results | Quality Assessment |
|---|---|---|---|---|---|---|
| 1 | Yang et al. (2023) | Sweden | Randomised double-blind controlled trial | Subjects with a diagnosis of ADHD (based on ICD-10 or DSM-5), age 5–55 years | • The pediatric intervention group showed significant decreases in IL-12/IL-23p40, sICAM-1, and TGF-β3 from baseline to 9 weeks compared to placebo.• In adults, there was a suggestive decrease in sVCAM-1 (95% CI: | 12/13 |

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|---|---|---|---|---|---|---|
| | | | | | −0.245; −0.007; p = 0.039) and sIL-2Rα (95% CI: −0.145; −0.017; p = 0.015).• Significant decreases in IL-6 (95% CI: −0.359; −0.011; p = 0.037) in the adult intervention group.• SCFAs increased, in particular propionic acid (95% CI: 0.006; 0.699; p = 0.046). | |
| 2 | Nil Novau-Ferré et al. (2025) | Spain | Randomised double-blind controlled trial | Subjects aged 5–14 years with a diagnosis of ADHD or ASD (DSM-5) | • 21 genera of microbes (out of 5 classes) and 1 class (Clostridia) were found that distinguish ADHD and ASD; 13 of them were more in ADHD.• The classification model showed high accuracy (AUC 0.939; 95% CI: 0.937–0.941), sensitivity 0.872, and specificity 0.923.• In ADHD, Firmicutes were more dominant: Clostridia (84.6%), Bacilli and Coriobacteriia were lower (7.69%).• The intervention increased the abundance of Odoribacter, while Eggerthellaceae (uncultured) and Escherichia-Shigella were lower.• In ADHD children, 73 categories of KO were positively correlated with intervention-modulated taxa. | 12/13 |

Source: Extracted from Yang et al. (2023) and Nil Novau-Ferré et al. (2025)

**Table 2. Effectiveness of Synbiotics in Managing Clinical Symptoms of ADHD Patients**

| No. | Author (Year) | Country | Study Design | Populasi | Results | Quality Assessment |
|---|---|---|---|---|---|---|
| **1** | Skott et al. (2020) | Sweden | Randomised double-blind controlled trial | Subjects with a diagnosis of ADHD (based on ICD-10 or DSM-5), | • There was no significant difference in total ADHD symptoms between the intervention and placebo (children: 0.142 vs 0.211; adults: 0.180 vs 0.174).• Decrease in hyperactivity/impulsivity | 12/13 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | age 5–55 years | symptoms over time (children: 95% CI 0.068–0.305; adults: 95% CI 0.060–0.221).• Better effect on total function (WFIRS-PC in children; WFIRS-SA in adults).• Improvement in participation in purposeful behavior (95% CI: −2.07 to −0.014; $\eta^2 = 0.040$).• Improvements in clarity, objectives, strategies, and rejection compared to placebo. | |
| **2** | Gara Arteaga-Henríquez et al. (2020) | Europe | Randomised double-blind controlled trial | Subjects aged 18–65 years with high chronic irritability and meeting ADHD criteria (ICD-10/DSM-5) | • Significant decrease in emotional regulation disorders (DERS-16: 3.6; 95% CI: 0.3–6.8; p = 0.03).• Decreased emotional symptoms (SDQ: 0.6; 95% CI: 0.05–1.2; p = 0.03).• Decreased concentration difficulty (ADHD-RS: 1.8; 95% CI: 0.4–3.2; p = 0.01).• Improvement in function (FAST: 2.7; 95% CI: 0.2–5.2; p = 0.03).• Decreased stress levels (PSS: 0.6; 95% CI: 0.05–1.2; p = 0.03) and social relationship problems. | 12/13 |
| **3** | Trezzi S. et al. (2024) | Italy | Randomised double-blind controlled trial | Subjects aged 6–16 years with ADHD (ICD-10 or DSM-5) | • Significant decrease in commission errors ($p < 0.001$) and improved performance (d') on Go-NoGo tasks (p = 0.003).• Improvements in reaction time variability, false alarms, missed responses, as well as continuous attention and shifting attention tasks.• Significant time effects on various indicators: ADHD Index (p = 0.006), Emotional-Ability CGI (p = 0.021), Restless-Impulsive CGI (p = 0.029), total and subscale DSM ($p < 0.05$). | 12/13 |

Source: Extracted from Skott et al. (2020), Arteaga-Henríquez et al. (2024), and Trezzi et al. (2024)

**Table 3. Various Synbiotic Strains for ADHD Patients**

| No. | Author (Year) | Intervention Sample (n) | Probiotics | Probiotic Dosage | Prebiotics | Prebiotic Dosage | Frequency | Duration | Control Sample (n) | Control Type | Duration |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Yang et al. (2023) | 182 | Pediococcus pentosaceus 5-33:3/16:1; Lactobacillus casei ssp. paracasei F19; Lactobacillus plantarum 2362 | $4 \times 10^{11}$ CFU | Beta-glucan, inulin, pectin, resistant starch | 2.5 g | 1x/day | 9 weeks | 61 | Placebo (maltodextrin, oligosaccharides without prebiotic effect) | 9 weeks |
| **2** | Skott et al. (2020) | 99 | Pediococcus pentosaceus 5-33:3/16:1; Lactobacillus casei ssp. paracasei F19; Lactobacillus plantarum 2362 | $4 \times 10^{11}$ CFU | Beta-glucan, inulin, pectin, resistant starch | 2.5 g | 1x/day | 9 weeks | 83 | Placebo (maltodextrin, oligosaccharides without prebiotic effect) | 9 weeks |
| **3** | Gara Arteaga-Henríquez et al. (2024) | 90 | Pediococcus pentosaceus 5-33:3/16:1; Lactobacillus casei ssp. paracasei F19; Lactobacillus plantarum 2362 | $4 \times 10^{11}$ CFU | Beta-glucan, inulin, pectin, resistant starch | 2,5 g | 1x/day | 10 weeks | 90 | Placebo (maltodextrin, oligosaccharides without prebiotic effect) | 10 weeks |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| **4** | Trezzi S. et al. (2024) | 21 | Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacterium animalis subsp. lactis | 3 × $10^{11}$ CFU | Acacia fibre with prebiotic activity | 1500 mg | 1x/day | 16 weeks | 20 | Different prebiotics (acacia fiber + standard components of prebiotic activity) | 16 weeks |
| **5** | Nil Novau-Ferré et al. (2025) | 17 | Lactiplantibacillus plantarum, Levilactobacillus brevis | 100 mg | Maltodextrin | 1939.5 mg | 1x/day | 12 weeks | 17 | Placebo (maltodextrin, oligosaccharides without prebiotic effect) | 12 weeks |

Source: Extracted from Yang et al. (2023), Skott et al. (2020), Arteaga-Henríquez et al. (2024), Trezzi et al. (2024), and Nil Novau-Ferré et al. (2025)

**Core Symptoms of ADHD and Function**

In contrast to the relatively consistent biological effects, parallel clinical trials conducted by Skott et al. found no synbiotic-specific benefit on the assessment of ADHD core symptoms or overall function in a mixed sample of children and adults with ADHD. Both the groups receiving Synbiotic 2000 and placebo showed a comparable decrease in total scores of ADHD symptoms, inability to concentrate, and hyperactivity/impulsivity (SNAP-IV/ASRS) over the 9-week intervention period, with overlapping confidence intervals and no meaningful differences between groups.

Similarly, impairment of daily functioning assessed using WFIRS-PC/SA showed improvement over time in the adult group, but not in children, and the changes did not differ between the synbiotic and placebo groups. These findings suggest that the observed improvements are non-specific and are most likely related to placebo effects or time factors (Skott et al., 2020).

Follow-up analysis identified the presence of small but potentially significant synbiotic-specific effects on certain secondary domains. In adult populations, Synbiotic 2000 selectively decreased difficulty in performing goal-oriented behaviors based on the DERS-16 scale. In addition, in a subgroup of adults with high levels of sVCAM-1, synbiotic interventions were associated with improved overall emotion regulation as well as on several specific subscales including emotion clarity, goal orientation, regulatory strategies, and rejection and acceptance of emotions, compared to placebo.

In children, the administration of synbiotics was associated with a statistically significant reduction in limited, repetitive, and stereotyped behaviors assessed using the Social Communication Questionnaire (SCQ). This effect was most pronounced in a subgroup of children with high levels of sVCAM-1 and in children who had not received ADHD treatment.

Overall, these findings suggest that synbiotics may provide selective clinical benefits on aspects of emotion regulation and autistic traits in a subgroup of patients with ADHD with a specific inflammatory profile, although they did not result in a significant improvement in overall ADHD symptom scores compared to placebo (Skott et al., 2020).

**Regulation of Emotions, Irritability, and Transdiagnostic Benefits**

The clinical trial conducted by Gara Arteaga-Henríquez et al. expands on previous findings in adult populations with ADHD and/or threshold personality disorder characterized by high chronic irritability. In transdiagnostic samples enriched with emotion regulation disorders, synbiotic interventions showed superiority over placebo in the primary outcome of end-of-treatment response rates. This response was defined based on the combined criteria of ARI-S and CGI-I, which reflected a clinically significant decrease in irritability.

In addition, the group that received synbiotics also showed greater improvements in a variety of secondary outcomes, including emotion regulation (DERS-16), emotional symptoms (SDQ), inability to concentrate (ADHD-RS), overall functioning (FAST), perceived stress levels (PSS), and relationship problems with peers, with small to moderate effect sizes. These findings suggest that the benefits of synbiotics in this population are not limited to the core symptoms of ADHD, but also encompass broader affective and functional dimensions (Arteaga-Henríquez et al., 2024).

Exploratory biomarker analysis revealed that lower baseline levels of RANK-L were associated with a better or higher probability of synbiotic response. In contrast, higher baseline levels of IL-17A predicted greater improvements in emotion regulation only in the placebo group, especially in individuals receiving dopaminergic treatment. This pattern suggests that the effectiveness of synbiotics is likely influenced by the initial inflammatory profile and that modulation of the IL-23/IL-17 communication pathway may interact with dopaminergic therapy in determining emotion regulation outputs.

When considered in conjunction with the findings from Skott et al. (2020), the results of clinical trials by Arteaga-Henríquez et al. (2024) support the role of synbiotics as a promising adjuvant therapy for chronic irritability and emotion regulation disorders. Both dimensions are transdiagnostic in nature and are often not fully captured by conventional ADHD symptom scales, thus highlighting the potential clinical value of synbiotics beyond the repair of ADHD core symptoms alone (Arteaga-Henríquez et al., 2024).

**Cognitive Performance and Modulation of Microbiota by Microbiota Intervention**

The study by Trezzi et al. evaluated synbiotic-based supplementation in children with ADHD and reported significant improvements in neurocognitive performance over time. These improvements include reduced commission errors, improved signal detection, reduced reaction time variability, reduced false alarms and missed responses, and improved continuous attention and attention switching capabilities. However, this improvement was observed in both the intervention and the comparison group, with no significant differences between groups.

Age-rated ADHD indexes, including Conners' Parent Rating Scale (CPRS) and DSM-based scales, also showed declines during the intervention period. However, there was no consistent evidence that one synbiotic formulation was superior to another, nor was there significant difference between groups in changes in plasma SCFA or branched-chain fatty acids

(BCFA) levels. These findings indicate that synbiotic-based interventions or a combination of prebiotics or probiotics may support aspects of attention control and inhibition processes in children with ADHD, while highlighting the challenges of separating the effects mediated by the microbiota from the effects of task exercise, neurocognitive maturation, or participant expectations in short-term clinical trials (Trezzi et al., 2025).

The study by Nil Novau-Ferré et al. provides additional biological context by describing differences in gut microbiota profiles between ADHD and autism spectrum disorder (ASD), as well as evaluating probiotic interventions in mixed pediatric samples. At baseline or initial condition, as many as 21 genera and classes of Clostridia distinguished ADHD from ASD with high accuracy (AUC 0.939), with relative excess of taxa related to Firmicutes, especially Clostridia, in the ADHD group.

In the ADHD subgroup, probiotic administration was associated with increased abundance of *Odoribacter* as well as a decrease in the uncultivable genus *Eggerthellaceae* and *Escherichia–Shigella*. These changes were accompanied by a positive correlation between the modulated taxa and a number of KEGG orthology pathways, indicating changes in biologically relevant microbiota function. Although this study did not use synbiotics and was not designed to evaluate the clinical outcomes of ADHD in detail, the findings support the biological feasibility that targeted microbiota interventions can functionally modify ADHD-related microbiota signatures, and potentially synergize with synbiotic formulations in a more targeted clinical context (Novau-Ferré et al., 2025).

**Integrative Interpretation and Clinical Implications**

Based on the synthesis of various available clinical trials, a relatively consistent pattern emerged that Synbiotic 2000 reliably modulates immune markers, such as IL-12/IL-23p40, sICAM-1, sVCAM-1, sIL-2R, and microbiota metabolites in the form of short-chain fatty acids (SCFAs). These biological effects are prominent in children and adults with ADHD who exhibit increased vascular-immune activation or are receiving stimulant therapy. However, clinical advantage over placebo was primarily seen in specific domains of specific behaviors, including autism-like traits in children, emotion regulation and irritability in adults, and goal-oriented functions and behaviors in subgroups with higher levels of inflammation, and was not reflected in improvements in overall ADHD symptom severity (Yang et al., 2023; Arteaga-Henríquez et al., 2024).

These findings support a stratified and mechanism-based view of understanding the role of synbiotics in ADHD and related disorders. Patients with an "inflammatory" profile or emotion regulation disorder, characterized by elevated endothelial adhesion molecules (e.g. sVCAM-1, sICAM-1), or chronic irritability, appear to be the group most likely to benefit clinically. In contrast, ADHD samples that were not selected based on specific biological or clinical characteristics tended to show a strong placebo response with limited symptom improvement.

From a clinical perspective, synbiotics should be positioned as an adjuvant intervention, particularly in children with signs of inflammation and adults with ADHD and/or borderline personality disorder accompanied by prominent irritability. Meanwhile, in the future, clinical trials will need to integrate immunological profile characteristics and basic microbiome, longer follow-up periods, and relevant mechanistic outputs to improve the identification of potential responders and optimize synbiotic clinical composition and indications (Yang et al., 2023; Arteaga-Henríquez et al., 2024; Skott et al., 2020; Novau-Ferré et al., 2025).

## CONCLUSION

Based on the available evidence, synbiotic interventions show varying clinical effects in patients with ADHD. Synbiotics have the potential to modulate immune signals and gut microbiota metabolism. More consistent benefits are mainly seen in aspects of emotion regulation, certain cognitive function, as well as inflammatory biomarkers and microbiota, compared to overall improvement in ADHD symptoms. These findings suggest that synbiotic biological effects tend to be more consistent compared to overall improvement in ADHD symptom-based clinical outcomes. More meaningful clinical effects tend to emerge when interventions are targeted at specific subgroups of patients, particularly individuals with phenotypes related to inflammation or emotion regulation disorders. Therefore, synbiotics are more appropriately considered as adjuvant therapy than single therapy. Further research needs to emphasize characterization of immunological and basic microbiome profiles, long-term monitoring, as well as mechanism-based clinical trials to identify respondents, optimize formulations, and determine the clinical context of synbiotic use.

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